Dengue

Synonyms: breakbone fever, dengue fever, dengue haemorrhagic fever, dengue shock syndrome, dandy fever, seven-day fever, duengero, ki denga pepo (Swahili, meaning 'sudden overtaking by a spirit')

Dengue is a notifiable disease in the UK. See the See also separate Viral Haemorrhagic Fevers article.

Dengue is a mosquito-borne viral haemorrhagic fever (VHF) transmitted by female mosquitoes mainly of the species Aedes aegypti and, to a lesser extent, Ae. albopictus. Human to human direct spread does not occur.

Dengue is most commonly a self-limiting flu-like illness of low mortality which can be asymptomatic. Illness is characterised by an abrupt onset of fever often accompanied by severe headache and pain behind the eyes, muscle pain, joint pains, nausea, vomiting, abdominal pain and loss of appetite; however, symptoms can range from mild or non-existent to severe. Severe dengue involves haemorrhagic symptoms and organ failure, sometimes leading to shock and death. Severe dengue tends is extremely rare in travellers.

The number of annual infections is in the hundreds of millions globally, and a significant proportion are severe, including many which are fatal. Second infections carry particular risk. There is no treatment other than supportive care, although good supportive care has a dramatic impact on mortality.

Dengue is rarely diagnosed in the UK, although it should be on the differential diagnosis of travellers with unexplained pyrexia returning from an affected area. It should rise high on the list of differential diagnosis if there are features suggesting bleeding, hypovolaemia, increased vascular permeability, or organ failure.

The global impact of dengue has markedly increased over the last few decades and about half the world's population is now at risk. Dengue is considered a major and emergent concern.

Classification[1]

Dengue is a single disease with several different clinical presentations. It was previously classified into dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). However, there is overlap between these manifestations, as dengue is a spectrum of disease. In 2009 the World Health Organization (WHO) revised the classification according to levels of severity.

NB: apart from text dealing with dengue fever historically, to encompass the disease's different clinical presentations, this article will refer to 'dengue'.

The WHO classification encompasses two clinical entities, one of which is further divided:

- **Non-severe dengue** - fever followed by recovery characterises non-severe dengue. It is subdivided into:
  - **Dengue without warning signs** - fever with two of the following: nausea/vomiting, rash, aches and pains, positive tourniquet test, leukopenia.
  - **Dengue with warning signs** - the above plus any of: abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets. Those who deteriorate to develop severe dengue tend to have warning signs. They are likely to recover with intravenous rehydration.
- **Severe dengue** - this is dengue with severe plasma leakage, severe bleeding, or organ failure. There may be shock, respiratory distress or organ damage. Further deterioration of dengue with warning signs is classified as severe dengue. A second subsequent infection with a different serotype of the dengue virus increases the risk of developing severe dengue.

The 2009 classification is more sensitive to the diagnosis of severe dengue, and this helps triage and case management. Some argue that the definitions need to be more specific, so classification may evolve further[2].

**Epidemiology[2]**

- Dengue is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia and the Western Pacific. The Americas, Southeast Asia and the Western Pacific regions are the most seriously affected. There have been outbreaks in the Southern States of the USA.
- In endemic areas dengue occurs annually when rainfall is optimal for mosquito breeding.
- These areas are additionally at periodic risk for epidemic dengue. Dengue epidemics require the coincidence of large numbers of vector mosquitoes and large numbers of people with no immunity.
- Local pockets of increased risk are related to rainfall, temperature and rapid urbanisation.
- A century ago dengue tended to occur in small epidemics in seaports. Globalisation and urbanisation has allowed the disease to grow from localised outbreaks to pandemic status.
- Dengue incidence has increased dramatically in the last few years. This is in part because of increased reporting. 3.2 million cases were reported in 2015. However, cases are massively under-reported: the WHO suggests there are 284-528 million cases per year.
- The WHO recognises dengue as a major and emergent concern.
- 90% of severe dengue cases occur in children aged <15 years: it is a leading cause of hospitalisation and death, particularly in children, in affected regions. This is particularly true in Southeast Asia, whereas in the Americas young adults seem to be affected by severe dengue as frequently as children.
- Infection provides lifelong immunity only against the infecting viral serotype.
- Secondary infection with a different serotype increases the risk of developing severe dengue.
- Pandemics in 1998 and 2001 are thought to have been due to the emergence of a new subtype of the DEN-3 virus.
- Dengue is an important cause of fever in returning travellers. Since 2010 there have been an average of 350-400 imported cases of dengue fever in England, Wales and Northern Ireland each year[3].

**The organism**

The dengue virus is a single-stranded RNA positive-strand virus of the family *Flaviviridae*, genus Flavivirus. This genus includes also the West Nile virus, tick-borne encephalitis virus, yellow fever virus and several other viruses which may cause encephalitis. Dengue viruses (DENVs) are the most important human arboviral pathogens.

Four related serotypes of the dengue virus are well described: DEN-1, DEN-2, DEN-3 and DEN-4. A fifth serotype, DEN-5, has been isolated in some human cases although appears at present to occur predominantly in monkeys in Southeast Asia. However, it provides an indication of possible evolvement of further challenges to vaccination[4].

**History of dengue fever[5]**

- Dengue virus is relatively new to human populations. The four main serotypes originated in monkeys and independently jumped to humans in Africa or Southeast Asia less than 800 years ago.
- Dr Benjamin Rush (a signatory of the American Declaration of Independence) coined the name 'breakbone fever' in 1780. This was the first clear description of dengue fever in English, and was during the first simultaneous reported epidemics in Asia, Africa and North America.
- Ashburn and Craig showed that the agent responsible was ultramicroscopic and non-filterable, confirming in 1906 that it could be transmitted by mosquitoes.
- The first epidemic in Europe occurred Greece in 1928.
- Dengue fever remained a relatively minor, geographically restricted disease until the middle of the 20th century. The disruption of the second world war - in particular the coincidental transport of *Aedes* mosquitoes around the world in cargo - is thought to have played a crucial role in the dissemination of the virus.
Severe dengue fever was first documented in the 1950s during epidemics in the Philippines and Thailand. In the 1980s large numbers of cases began to appear in the Caribbean and Latin America, where highly effective Aedes control programmes had been in place until the early 1970s.

**Transmission**[6]

Dengue virus is transmitted by the bite of an infected Aedes mosquito.

- The female Ae. aegypti (the most important vector) mosquito is semi-domesticated, preferring to lay its eggs in man-made water containers, feeding in daylight in the early morning or late afternoon. (The male Aedes mosquito is not a blood feeder and does not bite.) Antimalarial measures are largely ineffective against dengue.
- The mosquito, recognisable by its stripy legs, also transmits *chikungunya fever*, *yellow fever* and *Zika virus*.
- In order for transmission to occur, the mosquito must feed on a person during the five-day period when large amounts of virus are in the blood; this period usually begins before the person becomes symptomatic.
- After entering the mosquito, the virus will require an additional 8-12 days of incubation before it can then be transmitted to another human.
- The mosquito remains infected for the remainder of its life, which might be days or a few weeks.

**Risk factors**

**For contracting dengue virus**

- High population density.
- Urban living.
- Poor public hygiene.
- Exposure to mosquitoes in endemic areas.

**For developing severe dengue[7]**

- **Age** - 95% of severe dengue occurs in the those aged under 15 years.
- **Repeated dengue infections** - infection with a secondary serotype is a risk factor for the development of severe disease[8].
- **Genetic factors** - disease severity and outcome appear related to variation at multiple gene loci involved in immune response[9].
- **Viral genotypes** - some strains may be more virulent.
- **Nutritional status** - malnourished children are less likely to develop severe dengue than well nourished children, due to impaired cellular immunity but, where they do, the disease is more likely to be severe.

**Pathophysiology[10]**

Infection by any of the four serotypes may range from asymptomatic to life-threatening. The pathological effects are immune-mediated[11]. The development of severe disease seems to involve a complex interplay of host immunity and genetic predisposition combined with certain viral virulence factors[11].

- Patients become infected once bitten by infected mosquitoes.
- The virus passes to lymph nodes and replicates, mainly in monocytes and macrophages. It then spreads to the circulation and other tissues.
- Incubation period is 2-7 days.
- Initial immune activation leads to a flu-like illness of varying severity (dengue and severe dengue can be very similar at the start of the illness).
- There is a tendency to haemorrhage associated with severe thrombocytopenia: this can also be seen in non-severe dengue.
- Proliferation of T cells and the production of cytokines may lead to vascular endothelial cell dysfunction and to plasma leakage. When severe this capillary leak characterises severe dengue. It causes an increase in haematocrit, hypoalbuminaemia, pleural effusions and ascites.
- In severe cases there may be multiple organ failure.
Multiple organ dysfunction can also result from direct viral damage to organs, particularly heart, brain and liver.

Recovery from infection by one dengue serotype provides full lifelong immunity only against that serotype. Cross-immunity to the other serotypes is partial and temporary.

Subsequent infections by other serotypes increase the risk of developing severe dengue.

Infants can develop severe dengue infection during their primary infection due to transplacental transfer of maternal antibodies to a different serotype from an immune mother. These amplify the infant’s immune response to the primary infection.

The pathogenesis of severe dengue is thought to be immune-mediated. Recent evidence suggests cross-reactive high pro-inflammatory cytokine producing T cells predominate in severe dengue. Studies also suggests that there may be a genetic susceptibility to severe disease[11].

Presentation[1, 2]

Presentation varies with the severity of the illness. Dengue can be asymptomatic.

In symptomatic presentations, following an incubation period of 4-10 days, the illness begins abruptly, going through three phases - febrile, critical and recovery:

Febrile phase
Initial symptoms consist of a high fever (39.5-41°C/104°F), which may be biphasic and which is accompanied by two or more of:

- Severe headache.
- Pain behind the eyes.
- Muscle and joint pains, which are typically severe.
- Nausea, vomiting.
- Swollen glands.
- Rash (typically morbilliform or confluent, although there may also be petechiae).

Symptoms usually last for 2-7 days. In non-severe dengue the illness does not enter a critical phase beyond this, and recovery occurs. This is often characterised by return of appetite and by profound itching. There is commonly peeling of the skin, giving rise to potential confusion with Kawasaki disease.

Signs

- Rash is initially generalised, macular and blanching, fading after 1-2 days. It may return as a maculopapular, morbilliform rash with sparing of palms and soles. Desquamation may follow.
- Tender muscles.
- Positive torniquet test. This can be performed by inflating a blood pressure cuff on the upper arm to a pressure midway between the systolic and diastolic pressures, for five minutes. The test is considered positive when ≥20 petechiae per 2.5 cm² are seen. Even in profound shock it can be negative or just mildly positive.

Critical phase
Some patients move into a critical phase in which warning symptoms appear and there is a risk of progression to severe dengue. During this phase increased vascular permeability may develop, heralding the onset of severe dengue.

Warning signs may develop 3-7 days after the first symptoms in conjunction with a sudden decrease in temperature (below 38°C/100°F) and include:

- Severe abdominal pain.
- Persistent vomiting.
- Rapid breathing.
- Bleeding gums.
- Fatigue.
- Restlessness.
- Blood in vomit.
• If severe dengue develops, patients may become profoundly shocked and may also become encephalopathic.

Signs

Non-severe dengue

• Rash is initially generalised, macular and blanching, fading after 1-2 days. It may return as a maculopapular, morbilliform rash with sparing of palms and soles. Desquamation may follow.
• Tender muscles.
• Positive tourniquet test. This can be performed by inflating a blood pressure cuff on the upper arm to a pressure midway between the systolic and diastolic pressures, for five minutes. The test is considered positive when ≥20 petechiae per 2.5 cm$^2$ are seen. Even in profound shock it can be negative or just mildly positive.

Non-severe dengue with warning signs

This may also include:

• Haemorrhagic manifestations including spontaneous petechiae (best visualised in the axillae), purpura, epistaxis, gum bleeding, gastrointestinal haemorrhage and menorrhagia.
• Cardiovascular signs include hypotension, narrow pulse pressure, poor capillary refill and relative bradycardia.
• Hepatomegaly and lymphadenopathy may occur.

Severe dengue

This may also include:

• Pleural effusion, ascites and pericarditis due to plasma leakage.
• Periorbital oedema and proteinuria.
• Maculopathy and retinal haemorrhage[12],
• Progress, in severe cases, to profound hypovolaemic shock.
• Central nervous system involvement, in severe cases - eg, encephalopathy.
• Hepatitis with altered liver function.
• Myocarditis with impairment of cardiac function.
• Severe bleeding, especially from the gastrointestinal tract (previously referred to as 'dengue haemorrhagic fever').
• Hypovolaemic shock.

Recovery phase

Fatigue and depression may last for weeks, particularly in adults. Where there has been plasma leakage, the recovery phase involves rapid fluid resorption over 2-3 days, and fluid overload may occur; this may result in cerebral oedema. Severe itching and a slow heart rate are common during recovery. There may be another rash which may be maculopapular or vasculitic, followed by peeling of the skin.

Differential diagnosis

There is a long list of differential diagnoses, including many causes of febrile illness, of flu-like illness and of shock. A careful history will rule some conditions out.

• Malaria.
• Typhoid fever.
• Typhus.
• Scrub typhus.
• HIV seroconversion.
• Infectious mononucleosis.
• Coxsackievirus and other enteroviruses.
• Rickettsial infections.
• Measles.
• Rubella.
Severe dengue
As above, plus any cause of shock, including septic shock and toxic shock syndrome.

Investigations
- FBC may show high PCV with low platelets. There may be paradoxical lymphocytosis (>15% circulating white cells) but overall leukopenia.
- Clotting studies can reveal prolongation of APTT and PT. Fibrin degradation products may be elevated.
- U&E may show electrolyte disturbance. LFTs can be elevated - especially AST.
- Severe cases may show reduced bicarbonate due to acidosis.
- Infection may be confirmed by isolation of virus in serum and detection of IgM and IgG antibodies by ELISA, monoclonal antibody or haemagglutination.
- PCR-based techniques are increasingly being used.
- X-rays may be useful to exclude other sources of sepsis/assess complications. CXR may show abnormalities, such as pleural effusion, in the first week.[13]
- Blood cultures and repeated malaria films should be checked in the traveller returning with a high fever.

Management[10, 14, 15]
There is no specific treatment for dengue. The patient can quickly become severely unwell and close monitoring of clinical signs and laboratory measurements is needed. Supportive medical care by experienced teams lowers mortality dramatically. Management principles include:
- Fever control with paracetamol, tepid sponging and fans.
- Intravenous fluid resuscitation with close monitoring, observing for increased capillary permeability. Monitor CVP and urine output, electrolytes, packed cell volume, platelets and LFTs.
- High-volume and aggressive colloid/crystalloid infusion under expert guidance may be needed. Inotropes and renal support may be necessary.
- Secondary bacterial infections may occur and require treatment.
- Haemorrhage and shock require FFP and platelets.
- Those with severe dengue are likely to require intensive care, where available.

Prognosis
- Dengue is typically a self-limiting flu-like disease.
- The vast majority have no serious sequelae and the return of appetite is a good marker of recovery[14]. However, recovery can be associated with prolonged fatigue and depression.
- The overall mortality rate is less than 1%.
- Severe dengue has a mortality rate of 50% if untreated; however, this is reduced to less than 5% if appropriately treated[14].
- Most severe dengue and most deaths occur children aged under 15 years; however, in recent years the numbers of deaths in young adults has increased, particularly in Asia.
Complications

- Hepatic failure
- Encephalopathy
- Myocarditis
- Disseminated intravascular coagulation
- Septicaemia

Prevention

- In late 2015 the first dengue vaccine, Dengvaxia® (CYD-TDV) by Sanofi Pasteur, was registered in several countries for use in individuals aged 9-45 years living in endemic areas [2].
- The WHO recommends that countries should consider introduction of the dengue vaccine CYD-TDV only in geographical settings where epidemiological data indicate a high burden of disease [16].
- Other tetravalent live-attenuated vaccines are under development in phase III clinical trials. Other vaccine candidates (based on subunit, DNA and purified inactivated virus platforms) are at earlier stages of clinical development.
- Any vaccine must be protective against all the subtypes of the disease. There have been concerns regarding the potential of live vaccines to undergo recombination with flaviviruses [17].
- Dengue prevention and control also depends on effective vector control measures.
- Anti-mosquito public health measures, such as reducing breeding sites, good sewage management, house design and use of insecticides, may help. Effective mosquito control is virtually non-existent in many endemic countries.
- Mosquito nets are unhelpful, as the Aedes mosquito is mainly day-biting.
- Repellents may reduce the risk by reducing the overall number of bites, especially those containing N,N-diethyl-3-methylbenzamide (DEET).
- Unlike the other VHF’s, dengue cannot be aerosolised and thus is not regarded as a likely agent of bioterrorism.

Further reading & references

- Teixeira MG, Barreto ML; Diagnosis and management of dengue. BMJ. 2009 Nov 18;339:b4338. doi: 10.1136/bmj.b4338.
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- Dengue Vaccine; WHO position paper: World Health Organization Weekly Epidemiological Record, 29 July 2016

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