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# Dengue
## Clinical and public health ramifications

### Background

Dengue virus infection is spread by the mosquito vector *Aedes aegypti* and causes significant morbidity and mortality worldwide. In Australia, it is an important cause of fever in the returned traveller and recent outbreaks have occurred in northern Queensland. A comprehensive understanding of the clinical and public health ramifications of dengue infection is essential for general practitioners.

### Objective

The aim of this article is to review the pathophysiology, clinical manifestations, complications, laboratory investigations and public health consequences of dengue infection.

### Discussion

Dengue should be considered as a differential diagnosis of fever in a returned traveller, including in patients who have travelled to northern Queensland within 3 months of an outbreak. Clinical manifestations vary from asymptomatic infection to serious disease. Typical symptoms last 7 days and may include: fever, headache, myalgia, fatigue, abnormal taste sensation, arthralgia, maculopapular rash and anorexia. Around 1% of patients will get the more severe form of the illness, dengue haemorrhagic fever. Recommended diagnostic tests depend on the time since the onset of symptoms. Management involves symptomatic treatment and monitoring for complications. Dengue haemorrhagic fever requires hospitalisation. Prompt notification to public health authorities and advice to patients about prevention of spread are a key role of the GP.

■ **Dengue virus infection is spread primarily by the mosquito vector *Aedes aegypti* and causes significant morbidity and mortality worldwide. It is an important cause of fever in the returned traveller.[1] In addition, recent outbreaks of dengue fever in northern Queensland[2] highlight other important implications of this infection for Australian general practitioners beyond the assessment and management of the returned international traveller.**

Historically, *A. aegypti* mosquitoes were widespread in the north of Australia and were known to occur as far south as the Victorian border. Since the 1970s however, spread of the mosquito has been limited to northern Queensland.[2] In recent years, returned and international travellers carrying the virus have infected the local mosquito population resulting in outbreaks of dengue fever in northern Queensland.[2] These outbreaks are a significant public heath concern, particularly given that dengue transmission has the potential to again spread further south.[3]

## Epidemiology

Dengue fever is fast becoming a major international public health concern. Reasons for this include an increased frequency of epidemics and changing geographic distribution of both virus and vector.[4]

Dengue is endemic to over 100 countries and occurs in tropical and subtropical regions. Significant outbreaks have been reported in South East Asia, the Americas, Africa and far north Queensland.[5] South East Asia, Thailand, Vietnam and Indonesia report the highest number of cases.

Modelling suggests that global warming will increase the amount of land with a climate suitable for dengue fever transmission, potentially placing a higher proportion of the global population at risk.[6]

## Pathophysiology

Dengue fever is caused by one of 4 arbovirus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) from the Flaviviridae family. A viraemic

human is the source of infection for an adult mosquito, which can transmit the virus further within the mosquito population after 8–10 days.[7]

In humans, the intrinsic incubation period is 3–14 days, commonly 4–7 days. A patient with dengue is infectious for mosquitoes from just before to just after the febrile period.[8] Infection with one dengue serotype confers lifelong immunity to that serotype but may result in an increased risk of complications if subsequently infected with another serotype.[9]

## The vector

The primary mosquito vector, *A. aegypti*, evolved as a domestic mosquito. It prefers to breed in artificial water holding containers, although natural containers such as palm fronds and bromeliads may also act as breeding sites. It is a day biter and is most active just after sunrise and just before sunset.[8]

*A. aegypti* is present in urban areas of northern Queensland with extension as far south as Gladstone. Another less efficient but potential vector is the *A. albopictus*, or the 'Asian tiger mosquito', which is present in the Torres Strait. Efforts to eradicate this mosquito have been to date, unsuccessful. Spread of this mosquito, which is more tolerant of colder conditions, could result in outbreaks of dengue occurring further south.[3]

## Clinical features

Clinical manifestations of dengue fever vary from asymptomatic infection to serious disease.[10] Most commonly, dengue fever manifests as a debilitating illness lasting around 7 days. Symptoms include:
- sudden onset of fever
- retro-orbital headache
- myalgia
- fatigue
- abnormal taste sensation
- arthralgia
- maculopapular rash, and
- anorexia.

A petechial rash or minor bleeding may occur in uncomplicated dengue fever; thrombocytopenia occurs in 25–50% of cases.[11] Early in the disease the clinical picture may be nonspecific. Children tend to experience milder illness than adults.[10]

## Complications

Dengue haemorrhagic fever (DHF) is a severe immune mediated complication of dengue virus infection occurring in up to 1% of cases.[9] The mortality rate for untreated DHF is 10–20%.[5] Children,[10] people with a history of dengue infection from another serotype, and individuals with a certain genetic profile are more likely to develop DHF if infected with the virus.[9]

Dengue haemorrhagic fever occurs because of increased blood vessel permeability and plasma leakage. It typically occurs on day 3–4 of the illness. Dengue haemorrhagic fever can deteriorate into shock typified by hypotension, narrowed pulse pressure and decreased organ perfusion – 'dengue shock syndrome' (DSS). Left untreated it has a high case fatality rate.[5] In developed countries, with adequate treatment, this should be less than 1%.

The World Health Organization (WHO) has clinical and laboratory criteria for diagnosis of DHF. The WHO clinical criteria require a fever lasting 2–7 days with evidence of haemorrhagic manifestations (eg. a positive tourniquet test or bleeding from venipuncture sites).[11] A tourniquet test is performed by applying a blood pressure cuff to the patient's arm, inflated to a pressure halfway between the diastolic and systolic blood pressure for 5 minutes. A positive test is indicated by the development of petechiae at the site of cuff application. The WHO laboratory criteria relate to thrombocytopenia (platelets <100 x 109/L) and haemoconcentration (20% rise in haematocrit or 20% fall after rehydration).[11]

## Pathology tests

Dengue infection is a differential diagnosis of fever in either a returned traveller or resident of an area experiencing a dengue outbreak. It is important therefore that appropriate testing for other differential diagnoses such as malaria are undertaken, depending on the clinical picture. Exclusion of malaria as a diagnosis in a returned traveller who is febrile requires three negative blood films.[9]

### Dengue diagnostic testing

Diagnostic testing for dengue is not straightforward; appropriate testing relies on a reliable history of the date of onset of symptoms.

#### Serum dengue PCR

This test can detect dengue virus up to day 10 of the illness and should be ordered in suspected cases as early as possible in the course of the illness.[12] Importantly, polymerase chain reaction will not usually be performed if a doctor only writes 'dengue serology' on the pathology form. There is the risk in such instances of not diagnosing an early infection.

#### Serum dengue NS1 antigen

This test has a high specificity and moderate sensitivity for dengue. It is positive early in the course of the illness and may prove to be useful early in the patient's clinical illness in areas of low endemicity. However, it is not in widespread use at present.[13]

#### Serology

Serum IgM appears after 4–5 days of infection. Serum IgG does not become positive until about the seventh day of the illness. A patient whose serum is IgG positive for dengue early in their illness has probably been previously exposed to another serotype of dengue. General practitioners managing such patients should have a heightened awareness of the risk for DHF. Cross reactivity between other flavivirus and IgG may occur; patients with previous dengue

or other flavivirus infection may have a reduced IgM response and elevated, early IgG response which is given a nonspecific diagnosis, eg. 'acute flavivirus infection'.[9]

### Practice point

If a patient presents in the first 10 days of illness the GP should request dengue PCR and dengue serology on the acute sample and dengue serology only in the convalescent phase. A GP may just order dengue serology on patients presenting after day 10 of the illness.

### Additional pathology tests in patients with confirmed or suspected dengue infection

In addition to diagnostic tests, a full blood examination, with particular attention to haematocrit and platelets, is beneficial as a baseline for comparison in cases of DHF. It is prudent to repeat these on day 3–4.

## Management

Management of dengue fever is symptomatic and includes rest and adequate oral analgesics as required. Nonsteroidal anti-inflammatory drugs (NSAIDS) should be avoided because of the increased risk of bleeding.[14] Dengue haemorrhagic fever and/or DSS require hospital admission and management.

From a practical perspective, DHF should be suspected in any patient with dengue who has a rapid clinical deterioration. *Table 1* lists 'red flags' which should trigger hospital referral.[15] Warning signs of deterioration should be given to patients; encouraging them to return if they occur. The cornerstone of hospital management of DHF and DSS is rapid volume expansion.

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Table 1. Red flags that indicate if a patient with dengue should be referred to hospital[15]

- Significant bleeding
- Fall in blood pressure
- Dehydration and postural hypotension
- A rise in haematocrit ≥20% above baseline
- Platelet count <80 000 cells per cubic mm
- Severe vomiting or diarrhoea
- Severe abdominal pain
- Elderly patients with comorbidities who are unwell

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### The northern Queensland outbreak

Tropical public health services first became aware of an outbreak of dengue 3 (DEN-3) in the Cairns area in November 2008. The outbreak is thought to have originated from a traveller infected in Indonesian Borneo who did not seek medical attention while unwell.[16] This outbreak extended south to Townsville, and north to Port Douglas and the tip of Cape York Peninsula. The outbreak resulted in 931 confirmed cases in tropical Queensland. A concurrent dengue 1 (DEN-1) outbreak occurred in the Townsville area. On 4 September 2009 Queensland Health declared tropical Queensland dengue free.

A dengue outbreak is considered to have finished after 3 months have passed since the last case of local transmission. Dengue should therefore be considered as a diagnosis in a returned traveller experiencing fever, including those who have travelled to northern Queensland within 3 months of an outbreak.

Information relating to dengue outbreaks in northern Queensland is available on the Queensland Health website (see *Resource*).

## Prevention

The GP has an active role to play in prevention of the spread of dengue. Dengue is a notifiable disease and notification is mandatory in most Australian states and territories.[7] Early notification to public health authorities in cases of positive laboratory results indicating dengue infection or clinical suspicion of disease will enable public health units in areas susceptible to local transmission to launch environmental health actions and other vector control activities. As the spectrum of dengue related illness may be broad and relatively nonspecific, particularly early in the infection, it is imperative that GPs working in areas of potential transmissibility notify the public health unit immediately on suspicion that a patient has dengue.

In addition to prompt notification, GPs can assist in the prevention of further spread by advising patients suspected of having dengue to undertake the preventive activities listed in *Table 2*. This will assist patients to minimise the risk of transmitting the virus to others.

## Summary of important points

- Northern Queensland remains susceptible to repeated outbreaks of dengue infection. Clinical suspicion for dengue should be maintained in any traveller returning from either a dengue endemic country or northern Queensland.
- Laboratory testing of suspected cases should be tailored to the date of onset of symptoms.

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Table 2. Activities to prevent transmission of the dengue virus[17]

| Activities to reduce mosquito breeding | Activities to prevent mosquito bites |
|---|---|
| • Weekly removal of receptacles that encourage breeding (eg. tyres, pot plant bases, palm fronds)<br>• Weekly flushing of permanent receptacles (eg. dog bowls, bromeliads)<br>• Application of repellent surface spray to areas that may harbour mosquitoes (eg. under beds, behind furniture, within closets) | • Wearing long trousers and long sleeved light coloured clothing<br>• Appling tropical strength repellent containing DEET (diethyltoluamide or diethylmethylbenzamide) or repellents which contain picaridin every 4 hours during daylight hours<br>• Using screened accommodation |

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- Dengue hemorrhagic fever and dengue shock syndrome are medical emergencies. Prompt referral to hospital is essential if either is suspected.
- People intending to travel to areas of dengue transmission should be advised on how to avoid mosquito bites.
- A comprehensive public health response is necessary to combat dengue outbreaks in areas where the vector is present. General practitioners remain at the frontline of dengue surveillance systems and preventive activities.

## Resource
Queensland Health. Defend against dengue. Available at www.health.qld.gov.au/dengue/default.asp.

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## Acknowledgment

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