

PRIMARY CARE MANAGEMENT OF DENGUE / DENGUE HAEMORRHAGIC FEVER DURING AN OUTBREAK

ADVISORY BY THE CFPS DENGUE WORKSHOP – NUMBER 1

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INTRODUCTION

Objective

The objective of this advisory is to provide a collation of information for family physicians who face the challenge of managing patients in the early and undifferentiated phase of the illness. Please supplement the information with updates from the Ministry of Health and other information as these become available.

GENERAL CONSIDERATIONS

Epidemiology

Present situation

Dengue infection is endemic in Singapore with new cases reported throughout the year (Figure 1). The majority of cases are acquired locally (99%). The majority of those infected are age 15 and above. The highest incidence is among young adults in the 15 to 24 years age groups. Children under age of 5 have the lowest incidence¹ (Figure 2).

The vector

The bite of *Aedes* mosquitoes (mainly *Aedes aegypti*) infected with the dengue virus transmits the disease. The dengue virus is therefore an arthropod-borne virus or arbovirus. The mosquito becomes infected when it feeds on an infected host that has viraemia, usually during the time of the fever. The virus develops in the mosquito for about 8 to 10 days where the virus migrates to the salivary glands. After this period of time, the mosquito becomes a vector that can transmit the virus. Once infected the mosquito remains infected for the duration of its life span which is estimated to be about 2 to 4 weeks. Infected mosquitoes can pass on the virus to the next generation of mosquitoes by transovarian transmission (vertical transmission) but this is considered rare and does not contribute significantly to human transmission.

Aedes aegypti is one of the most efficient transmitters of arboviruses because it lives in close proximity to humans, often indoors. This species of mosquito is difficult to eradicate because its eggs can withstand desiccation for as long as a year.

Aedes aegypti is a day-biting species with increased biting activity for 2 hours after sunrise and several hours before sunset. It is a domestic breeder and breeds in water containers, discarded tyres, coconut shells, and overhead tanks.

Pathophysiology

Dengue virus

Dengue (DF) and dengue hemorrhagic fever (DHF) are caused by one of four closely related, but antigenically distinct, virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), of the genus *Flavivirus*.

Immunity

Infection with one of these serotypes provides immunity to only that serotype for life, so persons living in a dengue-endemic area can have more than one dengue infection during their lifetime. If an individual develops immunity to one subtype and then tries to launch an immune response to another subtype then they will develop DHF/DSS. Work has been done on a tetravalent vaccine that will attempt to give the individual immunity to all four of the subtypes at the same time.

Figure 1. Weekly incidence of vector borne disease

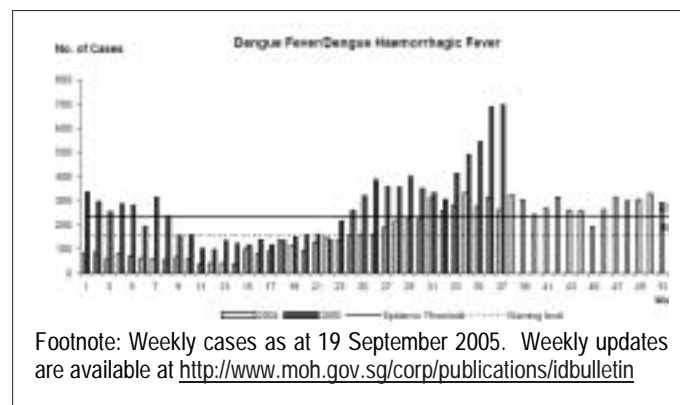
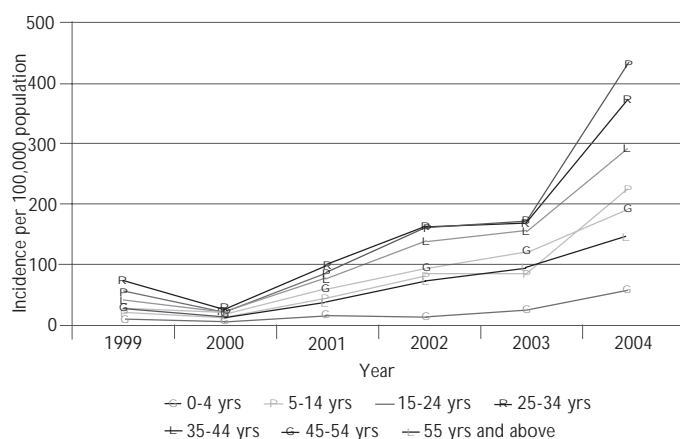


Figure 2. Age-specific dengue incidence in males, 1999-2004



Mechanism of complications

It is useful to understand why certain individuals develop DHF/DSS. The Dengue virus has been shown to have 4 subtypes. These 4 subtypes are different strains of dengue virus that have 60-80% homology between each other. The major difference for humans lies in subtle differences in the surface proteins of the different dengue subtypes.

After a person is infected with dengue, he or she develops an immune response to that dengue subtype. The immune response produces specific antibodies to that subtype's surface proteins that prevent the virus from binding to macrophage cells (the target cell that dengue viruses infect) and gaining entry. However, if another subtype of dengue virus infects the individual, the virus will activate the immune system to attack it as if it was the first subtype.

The immune system is tricked because the 4 subtypes have very similar surface antigens. The antibodies bind to the surface proteins but do not inactivate the virus. The immune response attracts numerous macrophages, which the virus proceeds to infect because it has not been inactivated. This situation is referred to as Antibody-Dependent Enhancement (ADE) of a viral infection. This makes the viral infection much more acute. The body releases cytokines that cause the endothelial tissue to become permeable which results in hemorrhage and plasma loss from the blood vessels.

Increased vascular permeability leads to plasma loss from the vascular compartment. This results in haemoconcentration, low pulse pressure. When the plasma loss becomes critical, shock ensues.

Both quantitative and qualitative platelet defects can develop. Therefore bleeding time can be prolonged even when platelet counts are above 100,000 per cubic millimeter.

In the liver there is focal necrosis of hepatocytes, swelling, appearance of Councilman bodies and hyaline necrosis of Kupffer cells.

CLINICAL DIAGNOSIS

Clinical features help the doctor to make a decision on the likelihood that a febrile illness will be self-limiting or will deteriorate into a potentially life threatening situation. Bearing in mind that illnesses can have atypical presentations, making a diagnosis is a challenging task that requires knowledge, skills, experience and deductive thinking.

Clinically dengue infection presents as a spectrum of clinical syndromes ranging from the asymptomatic to the very severe.

(1) Asymptomatic

Many infected individuals remain asymptomatic. This may be one reason why dengue remains endemic and makes isolation of cases ineffective. The percentage of patients who are asymptomatic in a given community varies:

- κ A two-year study using a cluster investigation method was conducted in West Jakarta, Indonesia to demonstrate the detection of dengue cases prior to onset of clinical illness.

Among 785 adult and child volunteers enrolled, 17 (2.2%) post-enrollment dengue (PED) infections were identified. Eight PED cases were asymptomatic and nine were symptomatic².

- κ In another study dengue seroconversion was tested among 104 Israeli young adults who traveled to tropical countries for at least 3 months. Seven seroconverted during travel; four had immunoglobulin IgM antibodies; one was symptomatic with borderline IgM and a rise in IgG; two others (1.9%) had a rise in IgG titers, without detectable IgM. Of the four with IgM, three had fever. Out of the 3 febrile cases, two had chills, headache, and protracted fatigue. One patient had an asymptomatic infection¹.

(2) Undifferentiated Viral Fever

Infants and younger children may present with an undifferentiated febrile illness sometimes accompanied by a non-specific maculopapular rash. Older children and adults may have just a mild febrile illness.

(3) Dengue Fever (DF)

This is the classic severe febrile syndrome that is recognized as dengue infection. The clinical features are:

- κ *Fever: acute onset, lasts 2-7 days.* Onset of fever is abrupt and rises rapidly. It sometimes has two peaks and hence is referred to as "saddle-backed".
- κ *Headache, backache, myalgia.* Headache can be severe. There is retro-orbital pain. Pain in the muscles, bone and joints may also be prominent, hence it is referred to in the Chinese language as "the bone pain and blood fever syndrome".
- κ *Rash: maculopapular or flush; petechiae with islands of sparing.*
- κ There may be nausea and vomiting.
- κ *Thrombocytopenia.*

Complications: Dengue fever can be accompanied by bleeding complications such as epistaxis, gum bleeding, hematuria and even menorrhagia. It can also result in severe life-threatening gastrointestinal bleeding especially among patients who are already at risk of developing gastrointestinal bleeding. The pathophysiological process of such bleeding complications is probably different from that of dengue hemorrhagic fever.

(4) Dengue Hemorrhagic Fever (DHF)

There are 4 major clinical features that define dengue hemorrhagic fever (DHF):

- κ *Fever.* The fever is high plus
- κ *Bleeding manifestations* (e.g. petechiae, ecchymosis, epistaxis, gum bleeding, haematemesis, melena) plus
- κ *Thrombocytopenia* ($<100 \times 10^9/L$) plus
- κ *Evidence of increased capillary permeability* (Haematocrit increased by $>20\%$ above baseline; Pleural effusion; Hypoalbuminaemia)

Neurological disturbances (e.g., seizures, cranial nerve signs and coma) may also occur.

Children with DHF present with a characteristic syndrome. The fever usually rises suddenly accompanied by flushing of

the skin. The fever is usually high (> 39 degree Celsius). It usually remains high for 2 to 7 days. Febrile fits can occur in infants and younger children.

Constitutional symptoms similar to DHF such as loss of appetite, vomiting, nausea, headache, myalgia, arthralgia, bone pain usually comes with the fever. The conjunctiva may become injected. Epigastric discomfort and generalized abdominal pain may be a symptom. Tenderness of the right hypochondrium may be present.

Sore throat and an injected pharynx on examination may mislead one to diagnose pharyngitis. However coryza and coughing are infrequent. Absence of such symptoms should be taken into consideration to help distinguish dengue infection from a febrile upper respiratory tract infection.

A positive tourniquet test indicates presence of hemorrhagic phenomenon. The patient may present with easy bruising and prolonged bleeding at venepuncture sites after taking of blood for tests. Petechiae may present anywhere but characteristically over the limbs and soft palate. They appear usually in the early part of the illness. Epistaxis, gum bleeding and even mild gastrointestinal bleeding can occur but they are infrequent.

Tourniquet test: The tourniquet test assesses capillary fragility. Inflate the blood pressure cuff to a point midway between the systolic and diastolic blood pressures for five minutes. After deflating the cuff, wait for the skin to return to its normal color, and then count the number of petechiae visible in a one-inch-square area on the ventral surface of the forearm. Twenty or more petechiae in the one-inch square patch constitutes a positive test⁴.

Hepatomegaly is more commonly detected in pediatric cases. The liver if palpable is usually only mildly enlarged. This occurs usually in the early febrile phase. The liver may be tender and is not usually associated with jaundice.

(5) Dengue shock syndrome (DSS)

κ *All the above plus*

κ *Evidence of circulatory failure* manifested by hypotension, narrowed pulse pressure (< 20 mmHg) and impaired organ perfusion (rapid and weak pulse, cold clammy skin and altered mental status).

DHF that deteriorate into shock is called Dengue Shock Syndrome (DSS). About one third of the patients with DHF will develop shock. It usually occurs around the time when the fever subsides. The patient can rapidly go into shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.

The signs are: cool blotchy skin which is also clammy; circumoral cyanosis may be present; the pulse rate increases and is weak due to a narrow pulse pressure (< 20mm Hg); blood pressure is low and falls; the patient is lethargic initially and becomes restless as the condition deteriorates; pleural effusion and ascites may be clinically detectable.

If shock is not recognized and treated in time, the patient passes into a state of profound shock when pulse becomes imperceptible and blood pressure unrecordable. The patient

usually remains conscious even at a very late stage of shock. Both the onset and progression of shock is rapid. If uncorrected, the patient typically dies within 12 to 24 hours. Late correction can result in a stormy and complicated course with the development of metabolic acidosis, gastrointestinal bleeding, intracranial hemorrhage and convulsions from metabolic causes.

Timely correction with volume replacement results in rapid recovery. Convalescence, even in cases of profound shock who are treated early, is short and uneventful. Good prognostic signs are return of appetite and good urine output.

Case fatality ratio (CFR): This is high in DHF and DSS and in untreated or mistreated shock cases have been as high as 40-50%; with good physiological fluid replacement therapy, rates should be about 3.5%. CFR is low in dengue fever by itself.

RED FLAGS

Family physicians are often in a situation where they have to identify the potentially serious cases amongst large numbers of cases in their early and undifferentiated stage of the disease. A helpful strategy is to identify red flags which are situations where extra caution is needed. In a dengue outbreak, the following can be red flags:

Abdominal Pain

Nonspecific complaints of epigastric and generalized abdominal discomfort are not uncommon. However acute abdominal pain is a frequent complaint shortly before the onset of shock. When it occurs just around the time of the fever subsiding, suspicion must be raised.

Narrow Pulse Pressure

A narrow pulse pressure may be an early detectable sign of circulatory disturbance in dengue infection.

Hepatomegaly

There is no correlation between severity of illness and size of a palpable liver. However a palpable liver is more likely to be present in shock than non-shock cases.

Bleeding phenomenon

Bleeding phenomenon to watch out for and to monitor are epistaxis, bleeding gums, gastrointestinal bleeding and menorrhagia. Presence of easy bruising, petechiae and a positive tourniquet test indicate the presence of hemorrhagic phenomenon. The patient may have developed DHF.

Rising hematocrit and falling platelet count

This is detectable in primary care monitoring of blood investigations. They indicate development of DHF. This phenomenon tends to occur just before the subsidence of fever and the onset of shock.

Subsiding fever with increasing distress

In DHF, the critical phase of illness often occurs at the end of the febrile period. After days of fever, a rapid fall in temperature may be accompanied by signs of circulatory failure of variable levels of distress.

The unusual and the elderly

Dengue can present atypically like an encephalitis, as alacalculous cholecystitis, severe vomiting or diarrhea, or as fulminant hepatitis. The elderly are more likely than youths and younger adults to develop severe illness. Their clinical evaluation must include a careful assessment of increased capillary permeability and occult haemorrhage in order to avoid complications from delayed identification and treatment of severe dengue infection⁵.

MANAGEMENT STRATEGY

Investigations at the primary care level

The strategy for investigation at the primary care level is directed mainly towards determining the likelihood that a febrile illness is a dengue infection. If dengue is provisionally diagnosed the main purpose of investigations is then to determine the likelihood of the development of complications of circulatory failure and hemorrhagic phenomenon and whether the patient requires hospitalization.

A system should be in place for blood investigation results to be reviewed as early as possible because delay in acting on abnormal results can have adverse consequences.

Daily total white cell count and platelet count

Leucopenia helps in the clinical diagnosis of dengue fever. Platelet count helps in the monitoring of patients for the development of complications. A platelet count of < 80,000 cells per cubic mm is a criteria for hospital referral and admission. Apart from absolute numbers, trends and clinical correlations should be taken into consideration. A rising hematocrit and falling platelet counts is ominous.

Hematocrit

A base line level should be established early in the patient encounter. A rise in hematocrit $\geq 20\%$ above baseline is a criteria for hospital referral and admission. Apart from absolute readings, trends and clinical correlations should be taken into consideration. A rising hematocrit and falling platelet counts is ominous.

Dengue serology and confirmatory tests

Five basic serological tests are used for diagnosis of dengue infection: haemagglutination-inhibition (HI), complement fixation (CF), neutralization test (NT), IgM-capture enzyme-linked immunosorbent assay (Mac-ELISA), and Dot Blot Immunoassay. Mac-ELISA appears to be the most important serological test for a rapid diagnostic technique. However, further standardization is required⁶.

Laboratory tests for confirmatory diagnosis of dengue infection include:

- o isolation of the virus,
- o demonstration of a rising titre of specific serum dengue antibodies, and;
- o demonstration of a specific viral antigen or RNA in the tissue or serum.

Isolation of the virus is the most definitive approach, but presently such tests are more suitable for tertiary and research centres.

Serological tests are simpler and more rapid, but cross-reactions with antibodies to other flaviviruses may give false positive results. In addition, accurate identification of the infecting dengue virus serotype is not possible with most serological methods. Specimen for serological tests should be collected in the following manner:

- o Collect a specimen as soon as possible after the onset of illness or attendance at a clinic (acute serum).
- o Collect a specimen shortly before discharge from outpatient follow-up or the hospital or, in the event of a fatality, at the time of death (convalescent serum).

The optimal interval between the acute and the convalescent serum is 10 days. Serial (paired) specimens are required to confirm or refute a diagnosis of acute flavivirus or dengue infection.

New technologies available for the laboratory diagnosis of dengue infection include immunohisto-chemistry on autopsy tissues and polymerase chain reaction (PCR) to detect viral RNA in the tissue or serum.

A number of serologic test kits for anti-dengue IgM and IgG antibodies have become available in the past few years, some producing results within minutes. Unfortunately most of these tests are not well validated. It is important to note that these kits should not be used in the clinical setting to guide management of DF/DHF cases because many serum samples taken in the first five days after the onset of illness will not have detectable IgM antibodies. The use of a rapid test alone is not sufficient to diagnose dengue infection even if antibodies are detected. A negative test does not preclude the possibility of dengue infection. There are concerns that reliance on such tests to guide clinical management may result in an increase in case fatality rates⁴.

Medications

Avoid the use of NSAIDs in the management of pain and fever when there is a possibility of dengue infection as this will increase the likelihood of hemorrhagic complications.

Paracetamol is metabolized by the liver and is hepatotoxic in high doses. As the liver can be adversely affected in a dengue infection, the dosage of paracetamol should be kept low.

General advice

Dengue patients that do not need hospitalization should be given medical leave to rest at home and advised to maintain

good hydration⁷. As viraemic patients can serve as reservoirs of infection, patients and household members should be advised on precautionary measures against mosquito bites including the use of insect repellents and mosquito coils⁵.

Follow-up

Mild and stable cases with good home environment and access to follow-up should be monitored closely at home. Patients should be advised to monitor for gum bleeding, epistaxis, easy bruising, malena, hematemesis and menorrhagia. They should also be educated and advised to seek emergency treatment if they develop severe abdominal pain or symptoms of circulatory failure.

Patients should be reviewed at least once a day. Assessments at such visits should include general condition, circulatory sufficiency, presence of hemorrhagic phenomenon and hydration. Blood investigations should include total white cell count, hematocrit and platelet count. Patients should be referred to the hospital if they fulfill the admission criteria or when it is no longer safe to manage the case in an outpatient setting.

Hospital referral and admission criteria

The clinical course of DHF can be modified by early diagnosis and prompt correction of plasma loss. Early and appropriate referral is important. The admission criteria recommended by the MOH's committee of experts are as follows⁵:

Presence of **any ONE** of the following justifies referral to hospital

- o Significant bleeding
- o Fall in blood pressure
- o Dehydration and postural hypotension
- o A rise in hematocrit $\geq 20\%$ above baseline
- o Platelet count $< 80,000$ cells per cubic mm
- o Severe vomiting or diarrhea
- o Severe abdominal pain
- o Elderly patients with co-morbidities who are unwell

Notification

Prompt notification even of suspect cases is important to allow public health measures to be implemented. The criteria for suspect dengue fever is as follows⁵:

A suspect case of dengue fever is defined as an **acute febrile illness** with **2 or more** of the following features: headache, eye pain, myalgia, arthralgia, rash, haemorrhagic manifestations, leucopenia.

PREVENTIVE MEASURES

Insect repellents

The active ingredients in repellents (usually a compound known as DEET) repel but do not kill mosquitoes. Most repellents are only effective a short distance away from the site of application (estimated to be about 4 cm). Although neck,

wrists and ankles are often mentioned as target areas for application all exposed skin is at risk. Care must be taken to avoid mucous membranes (nose and eyes). When applied on the skin, the repellent effect may last from 15 minutes to 10 hours, depending on a number of factors including climate and humidity, the formulation of the product, the concentration of the formulation and the species of the biting insect. Applying repellents on clothing extends their duration of effectiveness.

Insecticide spraycans

Insecticide spraycans are effective for an immediate knockdown and killing effect on the mosquitoes in range of the spray. There is however hardly any residual effect. Spraying a room with an insecticide spraycan will help to free it from mosquitoes soon after the spray. However it will not keep the room mosquito free. The use of spraycans can be made more effective by combining with a mosquito coil or mosquito net. Spraying is useful in reducing mosquito population and killing mosquitoes that are harbouring indoors. Killing of mosquitoes that carry the virus is better than just repelling it.

Mosquito coils

Mosquito coils are actually insecticide vaporizers, usually with a synthetic pyrethroid as the active ingredient. Under usual conditions, one coil is effective for a normal bedroom for one night. Air currents in well ventilated rooms have a diluting effect on the insecticide. The coils tend to burn faster and shorten the period of effectiveness. Some versions place the insecticide mat on an electrically heated grid and the insecticide evaporates from the substrate. The smoke from coils deters the mosquitoes from entering the room, while those inside are expelled or their host finding ability is affected. A significant proportion of them are knocked down and killed. Studies indicate that the allethrin group of chemicals are metabolised in mammals rapidly and there were no reports of accumulation of these compounds in animal tissues. They are highly biodegradable and disintegrate in sunlight. Nevertheless prolonged use is best avoided. The lighted mosquito coil can be a fire hazard and precaution must be taken.

Protective clothing

Protective clothing can be effective but their practicality is limited in our hot and humid climate. The thickness of the material is critical, and no skin should be left exposed, unless treated with a repellent. Clothing is a good substrate for the application of repellents for certain insecticides such as synthetic pyrethroids. The effectiveness of the repellent is extended.

Air-conditioning

Air-conditioning is fairly effective in keeping mosquitoes and other flying insects out of a room. This is only effective when the room is closed to the surrounding. Mosquitoes that are already in the room remain unless they are killed off by insecticides.

RECOMMENDED READING AND SOURCES OF INFORMATION

Dengue Information Websites

Singapore

- κ MOH Weekly Infectious Disease Bulletin at:
<http://www.moh.gov.sg/corp/publications/iddbulletin>.
- κ Answers to Frequently Asked Questions for the public:
<http://www.moh.gov.sg/corp/about/faqs/illness.do>.
- κ Areas with cases of dengue in Singapore:
http://www.moh.gov.sg/dengue_hotspots

International Health Organisations

- κ World Health Organisation website on Dengue
<http://www.who.int/topics/dengue/en/>
<http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/index.html>
- κ US Centres for Disease Control website on Dengue
<http://www.cdc.gov/ncidod/dvbid/dengue/index.htm>

Further reading

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http://www.moh.gov.sg/cmaweb/attachments/publication/ENB01Q_05.pdf
- κ Clinical Case Definition for Dengue Haemorrhagic Fever. In: Management of dengue epidemic (SEA/DEN/1), 1997.
http://w3.whosea.org/en/Section10/Section332/Section366_1153.htm
- κ Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. 2nd Edition Geneva: World Health Organisation, 1997.
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5. Garcia-Rivera EJ & Rigau-Perez JG. Dengue severity in the elderly in Puerto Rico. *Pan Am J Public Health* 2003; 13(6):362-8.
6. WHO Regional Office for South East Asia
http://w3.whosea.org/en/Section10/Section332/Section554_2566.htm
7. Ministry of Health. Professional Circular 18A/2005, 21 Sep 2005.