CLINICAL PRACTICE GUIDELINES

DECEMBER 2003 MOH/P/PAK/ 69.03(GU)

MANAGEMENT OF DENGUE INFECTION IN ADULT

MINISTRY OF HEALTH MALAYSIA ACADEMY OF MEDICINE MALASIA

GUIDELINE DEVELOPMENT AND OBJECTIVES

Rationale and Process of Guideline Development

Dengue infection is an infectious viral disease spread by the bite of the aedes mosquito. It is a common viral infection in the tropics. The severe from is manifested by bleeding complications and sometimes shock which my lead to death. Although dengue infection has been identified for many decades, the management of patients varies widely. More than two fifth of the world's population live in areas potentially at risk for dengue. It is one of the commonest causes for admission in our country. Because travelers to endemic areas like ours are also at risk, health care providers should have an understanding of the spectrum of infection, diagnosis, and appropriate management to prevent complications and mortality.

The clinical practice guidelines on " Management of Dengue Infections in Adult Patients" was prepared by a committee of physicians, pediatricians, virologists, intensivists and anaesthetists, public health specialists and haematologists from the public and private sector using a standard methodology based on a systematic review of evidence.

Objectives

The aim of the guideline is to present evidence based recommendations to assist health care professionals in understanding the clinical spectrum of Dengue infection, to established the diagnosis of dengue fever to manage the patients comprehensively.

Clinical Question

The clinical question of these guidelines are

I. How is Dengue infection diagnosed ?
II. How can patients with Dengue infection be managed appropriately?
III. How to prevent deterioration of the patients into dengue shock syndrome?

Target Population

These guidelines are developed to apply to all adult patients who are seen with history of fever at outpatient and inpatient.

Target Group

These guidelines are developed for all health care providers.

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in very case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in December 2003 and will be reviewed in December 2005 or sooner if new evidence becomes available

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Available on the following website : http://www.moh.gov.my/medical/cpg.htm
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- All members of the committee for their contributions in drawing up the guideline.
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- All those who had provided valuable input and feedback.

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LEVELS OF EVIDENCE SCALE

I	Evidence obtained from at least one properly randomized controlled trial
II – 1	Evidence obtained from well-design controlled trials without randomization
II – 2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II – 3	Evidence obtained from multiple time series with or without the intervention.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

(U.S. / Canadian Preventive Services Task Force)

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1. INTRODUCTION

1.1 Epidemiology of dengue fever in Malaysia

The geographical spread, incidence and severity of dengue fever (DF) and dengue haemorrhagic fever (DHF) are increasing in the Americas, South-East Asia, the Eastern Mediterranean and the Western Pacific. Some 2,500 million to 3,000 million people live in areas where dengue viruses can be transmitted. It is estimated that 50 million infections occur each year, with 500,000 cases of DHF and at least 12,000 deaths.[1] LE -III

In Malaysia, dengue fever was first reported in 1902 in Penang[2] and has become a major public health problem especially since the appearance of the first DHF outbreak (also in Penang) in1962.[3] Rapid industrial and economic developments over the last two decades have brought about massive infrastructure development, creating man-made environment for breeding of Aedes mosquito. Most cases (70 – 80 %) are among the urban population, with the highest incidence in the working and school going age group, correlating with the relatively high Aedes Index in construction sites, factories and school.[4] LE -III

1.2 Virology

There are four serotypes of dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4). Dengue virus is present in the blood in the early acute phase only, generally for 1-5 days. The incubation period varies between 3 to 10 days with an average of 4-6 days.[5] The 4 serotypes of the Dengue virus may all circulate concurrently in the same season but in different geographical regions. The trends in circulating dengue viral serotypes in Malaysia have been found to predominate in a cyclical pattern[7]. From 1990 – 1995, DEN-3[8] was the predominant serotype , followed by DEN-2 in 1997-2000. In 2001, DEN-3 reappeared, predominant over DEN-2. LE -III

2. DIAGNOSIS OF DENGUE INFECTION

2.1 Clinical presentations

Dengue virus infection may present in four different clinical syndromes.

1. Undifferentiated fever
2. Classic dengue fever
3. Dengue Haemorrhagic fever [DHF]
4. Dengue Shock Syndrome [DSS]

Pointers to the clinical diagnosis of dengue infection

1. high continuous fever of 3 days or more
2. headache, backache and retro-orbital pain
3. abdominal pain, vomiting, loose stools
4. petechial haemorrhage and /or spontaneous bleeding
5. rash-generalised flushing /maculopapular / confluent rash with small islands of normal skin
6. Hepatomegaly
7. fall into platelet count that precedes or occurs simultaneously with a rise in the haematocrit
8. normal WBC or luekopenia with relative lymphocytosis
9. normal ESR (<20 mm first hour)

Note: **All criteria need not be present at the same time**

Other sign and symptoms included flush face, sore throat, cough, cutaneous hyperaesthesia, and taste aberrations. Rare presentations of infection include jaundice, parotitis, and cardiomyopathy. Unusual neurological presentations include menoneuropathies, polyneuropathies, encephalitis , and transverse myelitis [13,14,15]. Encephalopathy occurs occasionally and may result from liver failure, or electrolyte imbalances. Recovery may be prolonged and include depression.[19] LE -III LE -III

2.1.1 Classic Dengue Fever (DF).

- Probable an acute febrile illness with two or more of the following manifestation.
  - headache
  - retro-orbital pain
  - myalgia
  - arthralgia
  - rash
  - haemorrhagic manifestations
  - leucopenia; **and**
- supportive serology (refer laboratory diagnosis) **or**
- occurrence at the same location and time as other confirmed cases of DF

2.1.2 Dengue Haemorrhagic Fever (DHF)

1. Fever, or history of fever preceding week. The critical stage is reached at the end of the febrile phase of illness, accompanying or shortly after a rapid drop in temparature, when varying degrees of circulatory disturbances occur.

2. Evidence of plasma leakage is the hallmark, menifested by:
   a. haemoconcentration (equel to or greater than 20% above avarage for age, sex and population. In Malaysia, a haemotocrit or packed cell volume > 40 in female and > 45 in male has been agreed upon)
   b. a drop in haemotocrit following volume replacement.
   c. signs of plasma leakage evidanced by pleural effusion, ascites and hypoprotienemia.

3. Haemorrhagic tendencies such as:
   a. a positive torniquet test
   b. petechiae, ecchymoses, or purpura
   c. bleeding from the mucosa, gastrointestinal tract, injection sites or other locations

4. Thrombocytopenia (100,000/mm^3 or less)

2.1.3 Dengue Shock Syndrom (DSS)

Criteria fro DHF must be present, and in addiction, evidence off circulatory failure manifested by:
- rapid and weak pulse
- Narrow pulse pressure less than 20mmHg, or hypetension
- cold clammy skin and restlessnes

It is important to differentiate DF from DHF as some cases of DHF may progress to DSS

* Variable thrombocytopenia is seen in DF
* Haemorrhagic tendency may also be seen in DF
* Thrombocytopenia with concurrent haemoconcerntration differentiates DHF from classic DF
* Increased capillary permeability is the main pathophysiology that differentiates DHF/DSS from DF

WHO grading of DHF / DSS

Grade I
In the presence of haemoconcentration, fever and non-specific constitutional symptoms, a positive torniquet test is the only haemorrhagic manifestation

Grade II
Spontaneous bleeding in addition to the manifestation from Grade I

Grade III*
Circulatory failure, pulse pressure less than 20 mmHg but systolic pressure is still normal

Grade IV*
Profound shock, hypotension or unrecordable blood pressure.

*Grades III and IV are classified as DSS

Dengue infection is a **notifiable** disease, based on clinical features, even before there is laboratory confirmation.

2.2 Laboratory Diagnosis

The WHO laboratory criteria for confirmation of dengue fever are as follow[5]. LE -III

- Demonstration of a four-fold or greater, charge in reciprocal IgG antibody titres to one or more dengue virus antigens, or positive detection of dengue specific IgM by enzyme immunoassay .
- Isolation of dengue virus from serum, liver biopsy or cerebrospinal fluids.
- Positive polymerase chain reaction (PCR) test from serum, cerebrospinal fluid or liver biopsy specimen in cases where there is a problem in diagnosis.
- If the patient dies early in the disease, persistent efforts should be made to get autopsy specimens for detection of dengue virus antigen, virus isolation and PCR tests. Post mortem liver biopsy can be done if a full autopsy is refused.

Laboratory tests include

1) Serology
2) Virus isolation
3) Molecular technique (Amplification and detection of dengue ribonucleic acids by RT-PCR.[9] LE -III

1) Serology test:

Dengue IgM

Dengue IgM should be requested in all cases. This is the most practical method available for the laboratory diagnosis of dengue infection. The serological test of choice is the *Enzyme Linked Immunosorbent Assay (ELISA)*, which is simpler, faster and is also the mainstay of most hospital laboratories in this country. Some points worth considering with respect to ELISA IgM are as follows:

- Dengue – specific IgM appears in both primary &' secondary infections
- Only about 60% of dengue infection may be diagnosed on day 5 or 6 of illness with single serum by IgM test, while it is 100% with paired sera (7-14 days apart)
- IgM is more specific for flavivirus infection than IgG
- IgM testing can be done in one day (turnaround time of 5 hours)
- The interpretation of serological results must be carefully considered with respect to clinical features of the illness and NOT interpreted in isolation.
- A positive dengue IgM result indicates acute disease or recent past infection (up to 90 days)

Simple rapid tests such as the strip assays are available for the rapid detection of specific IgM and IgG . The commercial kits available are:

a. Dengue IgM Dot Enzyme Immunoassay - available in state laboratories; these are costly but useful during an epidemic situation*.
b. Pan Bio Dengue IgM ELISA LE -III
c. Pan Bio Dengue Rapid (5 min) Immunochromatographic test[11]

**Note : These tests are re-evaluated from time to time.*

2) Virus isolation

This is the *most definitive method* for the diagnosis of dengue infection, but is only performed in a few research laboratories because it is laboratories, time consuming, costly and is sensitive only if the blood is collected in the early acute phase of illness.

3) Molecular technique (PCR)

This technique is available as a research tool in very few laboratories.

4) Autopsy Specimens

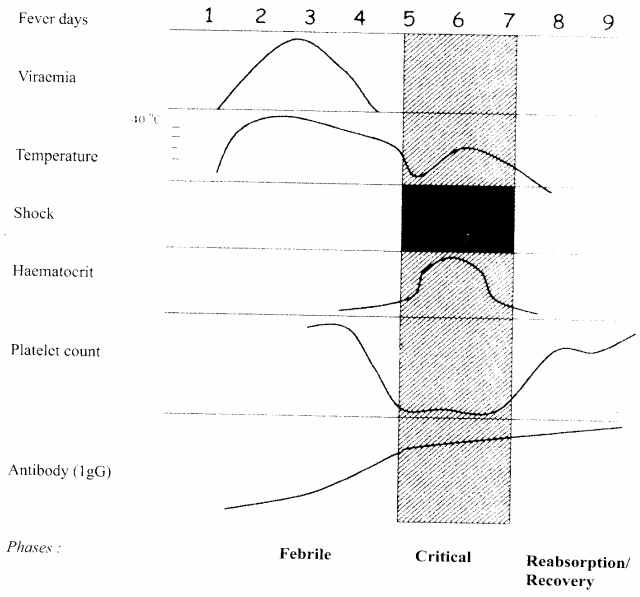
Post mortem specimens include biopsies from the lymph nodes, spleen, liver, brain, which should be collected in a sterile bottle/container (no preservatives required), and transported in dry ice. It is important to communicate with the relevant virology laboratory prior to dispatch of specimen. If delay in transport is anticipated, the sample should be stored at - 70°C, or in dry ice.

3. PATHOPHYSIOLOGY OF DENGUE HAEMORRHAGIC FEVER

The main characteristics of DHF are vasculopathy, thrombocytopaenia and coagulopathy. The pathophysiology of dengue haemorrhagic fever is indicated in Appendix 1.

4. CLINICAL COURSE OF DENGUE HAEMORRHAGIC FEVER

- It is important to recognize the febrile phase, critical phase and reabsorption / recovery phase so that appropriate hydration can be instituted.
- The patient's clinical condition should be monitored until at least 24 hours after defervescence because of the risk of shock. Fluid intake / infusion should be monitored during reabsorption / recovery phase.



5. CRITERIA FOR HOSPITALISATION

Along with a suspicion of dengue infection, the following are the criteria for hospitalisation :

- Lethargy and restlessness
- Generalised flushing
- Innability to tolerate orally / vomiting
- Oliguria

- Diarrhoea / frequent loose stools
- Abdominal pain / tenderness, hepatomegaly
- Evidence of plasma leakage, pleural effusion,ascites
- Bleeding in any form
- Rapid and weak pulse / cold extremities
- Narrowing of pulse pressure (<20mmHg) or hypotension
- Haematocrit > 40% or rising haematocrit
- Platelet <100 x 10/L

The patient must be assessed in totality and NOT by the absence or presence of any feature / criterion in isolation.

A lower threshold be used for the elderly, in pregnancy, patients with liver disease, peptic ulcer disease or multiple co-morbid conditions [cardiovascular, pulmonary, metabolic, renal , immuno-suppressed conditions] and patients who who are living alone.

6. MANAGEMENT OF DENGUE INFECTION

6.1 Management of Classical Dengue Fever

The treatment is the same as for other acute uncomplicated viral infections:

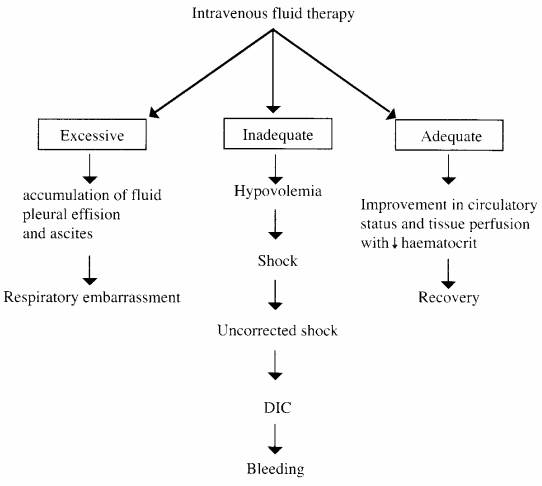
- Plenty of oral fluids
- Paracetamol for relief of fever and bodyache
- Aspirin & NSAIDs (antiplatelet effect) to be avoided
- Intra-muscular injections to be avoided
- Further medical advice to be sought if there is deterioration.

There are no specific therapeutic agents for dengue. Steroids, anti-virals, or intravenous immunoglobulins (IVIG) have no proven role[19]. LE -III

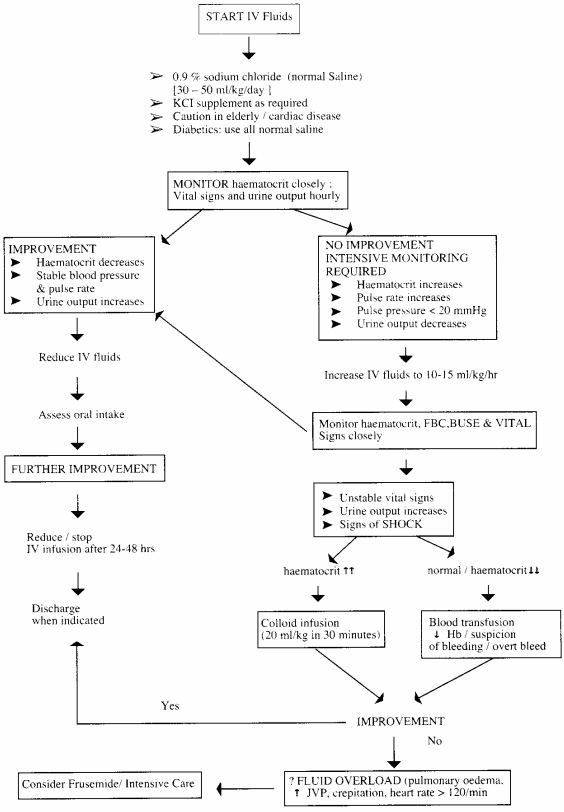
6.2 Management Algorithm of Dengue Haemorrhagic Fever

All cases of DHF should preferably be admitted to a high dependency area in order to ensure better monitoring and management. Intravenous fluids should be started. After 24 – 48 hours of onset of increase in vascular permeability , plasma leakage stops. It is very important that fluid therapy be managed carefully.

A general algorithm of events is as follows:



6.3 Management Algorithm of DHF / DSS



Notes:

- When pulse rate and volume and blood pressure are improving, it should be ensure that fluid is reduced to maintenance level.
- Reabsorption of extravasated fluid occurs when capillary leakage ceases.
- There is no evidence that colloids are superior to crystalloids, nor is there evidence on which type of colloids and at what stage of management they are to be used[19]. LE -III

6.4 Criteria for referral to intensive care unit

1. Early in the shock syndrome or established shock syndrome
2. Mechanical ventilation is required
3. Evidence of any organ failure

6.5 Management of bleeding in DF/DHF/DSS

There is no correlation between platelet count and bleeding. Bleeding manifestations in dengue infection are multifactorial. Most of the bleeding in DHF /DSS occurs as a result of prolonged shock secondary to inadequately corrected plasma leakage. Some patients with pre-existing peptic ulcers may develop haemorrhage in the course of DF. However there is no good evidence on how these patients are to be treated.

6.6 Blood products in dengue infection

1. Blood transfusion (packed red cells) is indicated in significant bleeding* (falling haematocrit / haemoglobin) in an unstable patient
   * Significant bleeding includes:
     a. extensive mucosal bleeds
     b. upper GIT bleeding
     c. impending intracranial haemorrhage (headaches, fundal haemorrhages)

2. Platelet transfusion is generally avoided unless:
   a. there is significant bleeding regardless of the severity of thrombocytopaenia
   b. platelet count < 10,000/mm^3 with impending or established CNS bleed or continues bleeding from a pre- existing peptic ulcer which needs a procedure such as gastroscopy

3. in established disseminated intravascular coagulopathy (low serum fibrinogen, reduce platelets along with prolonged PT and APTT**) with significant bleeding, infusion of cryoprecipitate (1 unit per 10 kg body weight), fresh frozen plasma (15ml/kg) and platelet concentrates (4-6 unit random platelet concentrate) are required.

Notes:

There is no good evidence on platelet transfusion based on a low platelet count with or without bleeding in dengue infection in the adult population. Similarly, there are no randomised prospective studies to show that the administration of fresh frozen plasma or platelet concentrates have improved the outcome in DHF/DSS in adult.

7. CRITERIA FOR DISCHARGING PATIENTS WITH DENGUE INFECTION

The following criteria should be met before patients recovering from DHF/DF are discharged.

- absence of fever for at least 24 hours without the use of antipyretics
- at least 2 days after recovery from shock
- rising platelet count of more than 50,000 per mm^3
- stable haematocrit
- visible clinical improvement
- return of appetite
- good urine output

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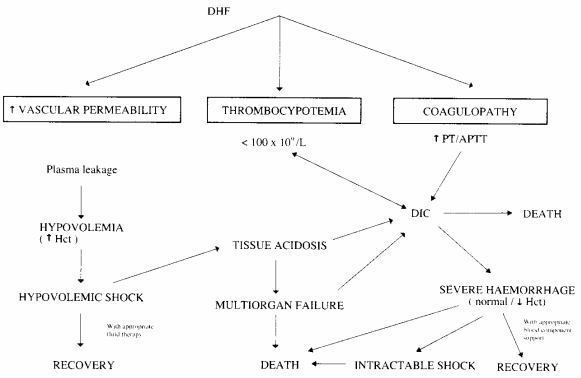
Appendix 1

Appendix 1

PATHOPHYSIOLOGY OF DENGUE HAEMORRHAGIC FEVER



a. Vasculopathy

Basic pathology is vasculopathy which causes inccreased vasculur permability. This leads to plasma leakege which result in haematocrit. The haematocrit in DHF is usually > 40%, but may be as high as 55-60%. [16] LE -III
A positive tourniquet test in early ssign in capilary fragility.

b. Thrombocytopenia

Thrombocytopenia s caused by multiple factors either from maturation arrest of megakaryocytes to immune destruction or consumption of platlet. The platlet count begins to fall in the febrile stage and is lowest in the shock stage. It can reach a nadir of less than $10x10^9$L. It then starts to rise by the second afebrile day and normalizes by 7 days[17] Platelet dysfunction also LE -III
has been reported.[18]