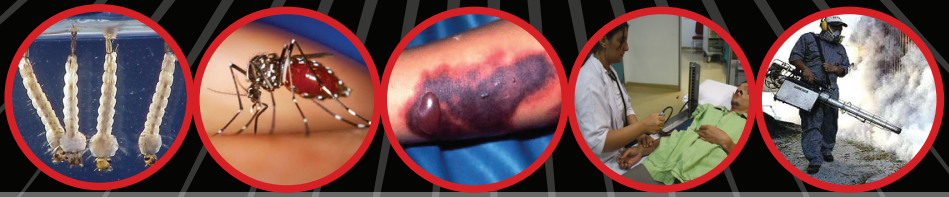
CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/209.10 (GU)

MANAGEMENT OF DENGUE INFECTION IN ADULTS

(Revised 2nd Edition)



MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

These are Clinical Practice Guidelines on Management of Dengue Infection in Adults (Revised 2nd Edition) 2010. The CPG supersede the previous CPG on Management of Dengue Infection in Adults (2nd Edition) 2008.

These guidelines are meant to be guides for clinical practice, based on the best available evidence at the time of develoment. Adherence to these guidelines may not necessary guarantee the best outcome in every case. Every healthcare 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

These guidelines were issued in 2010 and will be reviewed in 2014 or sooner if new evidence becomes available.

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Electronic version available on the following websites :

http://www.moh.gov.my

http://www.acadmed.org.my

GUIDELINES DEVELOPMENT AND OBJECTIVE

GUIDELINES DEVELOPMENT

The development group for these guidelines consisted of a family medicine specialist, an emergency medicine specialist, a general physician, infectious disease physicians, intensivists, haematologists, public health physicians, a virologist and a nursing sister from the Ministry of Health and Ministry of Higher Education, Malaysia. During the process of development of these guidelines, there was active involvement of a review committee.

The previous edition of CPG (2003) was used as the basis for the development of these present guidelines.

These guidelines provide:

a. A detailed description of the clinical course of dengue illness which reflects the dynamism and systemic nature of dengue that have crucial bearing on the patient's management.

b. A detailed description of the basic pathophysiological changes of severe dengue (i.e. plasma leakage and hypovolemia/shock) and provide guidance on the recognition of these changes and appropriate action of management.

c. A brief discussion on WHO Classification (1997) and its limitations.

d. Some useful guides on the differential diagnoses that can be confused with dengue or vice versa; they were described according to the stage of disease.

e. A more focused guide on the disease monitoring in accordance with the dynamic changes as the disease progresses.

f. Emphasis on the importance of monitoring the plasma leakage (clinical signs of plasma leakage and haematocrit (HCT) and haemodynamic status of the patients.

g. Clearer algorithm on fluid management in severe dengue.

h. Emphasis on the importance of recognising or suspecting significant occult bleed with some useful guides.

i. A more systematic approach on the recognition of signs of recovery.

Literature search was carried out at the following electronic databases: International Health Technology Assessment Website, PUBMED, Cochrane Database of Systemic Reviews (CDSR), Journal full text via OVID search engine, Comprehensive; Database of Abstracts of Reviews of Effectiveness,

Cochrane Controlled Trials Registered, CINAHL via EBSCO search engine. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Reference was also made to other guidelines – WHO Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control, WHO Geneva, 1997; Guidelines, Guidelines for DHF Case Management, Bangkok, Thailand 2002; Guidelines on Clinical Management Of Dengue Fever / Dengue Haemorrhagic Fever 2005 Sri Lanka; WHO Regional Publication SEARO, 1999; Guidelines for Treatment of Dengue Fever/Dengue Hemorrhagic Fever in Small Hospitals, WHO Regional Office for SE Asia, New Delhi, 1999. There were very few studies carried out on dengue patients in the adult population. Many of the studies included in these guidelines are based upon the management of dengue in children. The findings of these studies were then extrapolated on to the adult population, taking into consideration our local practices.

The clinical questions were divided into major subgroups and members of the development group were assigned individual topics within these subgroups. The group members met a total of 15 times throughout the development of the guidelines. All literature retrieved were appraised by at least two members and presented in the form of evidence tables and discussed during group meetings. All statements and recommendations formulated were agreed by both the development group and review committee. Where the evidence was insufficient the recommendations were derived by consensus of the development group and review committee.

The articles were graded using the modified version of the criteria used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guidelines was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVES

GENERAL OBJECTIVES

To provide evidence-based guidance in the management of dengue infection in adult patients

SPECIFIC OBJECTIVES

- To improve recognition and diagnosis of dengue cases and provide appropriate care to the patients
- To identify severe dengue and carry out more focused close monitoring and prompt appropriate management
- To provide guidance on appropriate and timely fluid management and the use of blood and blood products
- To improve on early and accurate notification of dengue cases for prompt public health intervention

CLINICAL QUESTIONS

Please refer to Appendix 6

TARGET POPULATION

Adult patients with dengue fever, dengue haemorrhagic fever or dengue shock syndrome and other forms of severe dengue.

TARGET GROUP/USER

These guidelines are applicable to primary care doctors, public health personnel, nurses, assistant medical officers, physicians and critical care providers involved in treating adult patients with dengue fever, dengue haemorrhagic fever or dengue shock syndrome and other forms of severe dengue.

HEALTHCARE SETTINGS

Both outpatient and inpatient settings

CLINICAL INDICATORS FOR QUALITY MANAGEMENT

PRIMARY INDICATORS

i. Case fatality rate (DF & DHF)
   Numerator: No of DF & DHF/DSS death
   Denominator: No of DF & DHF cases (clinically diagnosed)
   National target (9th Malaysian Plan):< 0.2%

ii. DHF fatality rate
   Numerator: No of DHF/ DSS death
   Denominator: No of DHF/ DSS cases (clinically diagnosed)
   National target (9th Malaysian Plan):<1.0%

SECONDARY INDICATORS

1. Appropriateness of usage of blood and blood components

(a) Numerator : No of DF/DHF cases received platelet concentrates
Denominator : No of DF/DHF cases with significant bleeding

(b) Numerator : No of DF/DHF cases received Fresh Frozen Plasma
Denominator : No of DF/DHF cases with significant bleeding

(c) Numerator : No of DF/DHF cases received Whole blood/ Packed cells
Denominator : No of DF/DHF cases with significant bleeding
Denominator : No of DF/DHF cases with no or insignificant bleeding

Note : All dengue deaths should be audited at individual hospitals/state/national level

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TABLE OF CONTENTS

1. EPIDEMIOLOGY

Dengue is one of the most important arthropod-borne viral diseases in terms of human morbidity and mortality. Dengue has become an important public health problem. It affects tropical and subtropical regions around the world, predominantly in urban and semi urban areas.

The number of reported dengue fever (DF) and dengue haemorrhagic fever (DHF) cases in Malaysia shows an increasing trend (Figure 1). The incidence rate also shows an upward trend from 44.3 cases/100,000 population in 1999 to 181 cases/100,000 population in 2007 (Figure 2). This exceeds the national target for the incidence rate of DF and DHF which is less than 50 cases/100,000 population. Dengue fever accounts for almost 95% of all reported cases. The serologically confirmed cases are approximately 40-50% of these cases at the time of notification. This relatively low percentage of seropositivity is due to lack of convalescent samples (second blood specimen) being sent for confirmation.

The incidence rate is higher in the age group of 15 years and above (Figure 2). The highest incidence rate is among the working and school-going age groups. An increase of dengue deaths in the adult population has been observed since 2002 (Figure 3). The case fatality rates for both DF and DHF however remain well below 0.3% since 2002 (Figure 4).

Most of the dengue cases reported were from urban areas (70 – 80%) where there is a high density of its population and rapid development activities factors which favour dengue transmission.

Figure 1 : Number of Dengue Cases, Malaysia 1995-2007

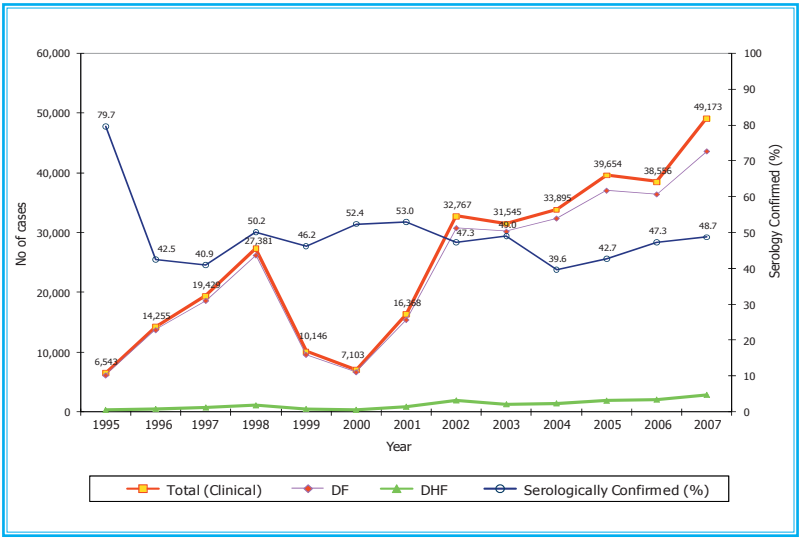


Figure 2 : Dengue Incidence Rate by Age Group in Malaysia, 1999-2007

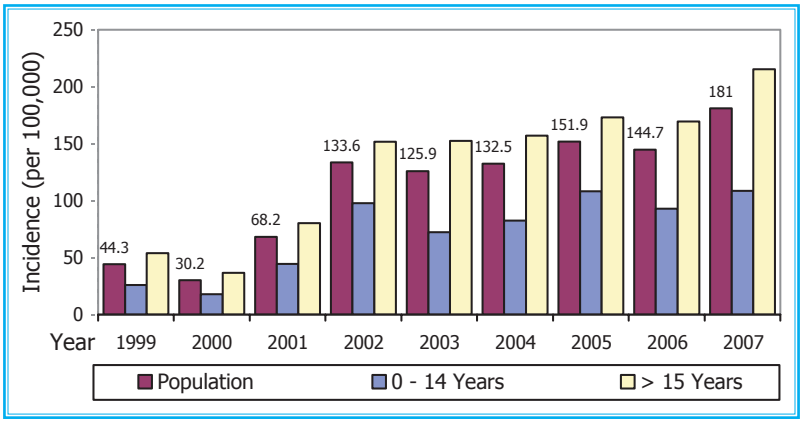


Figure 3 : Dengue Deaths by Age Group in Malaysia, 1999-2007

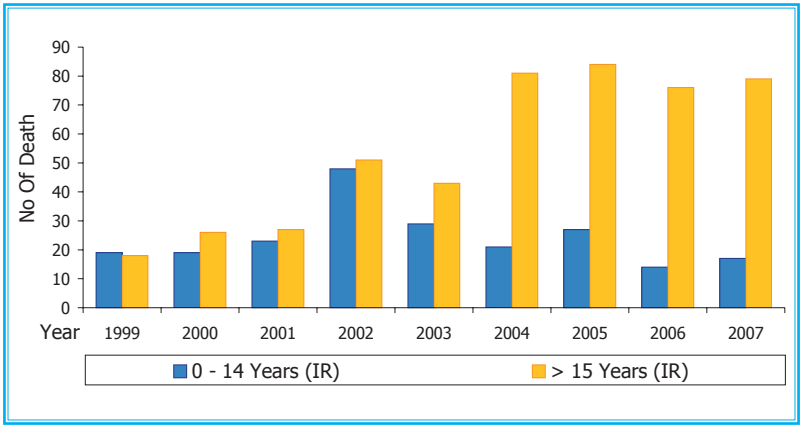
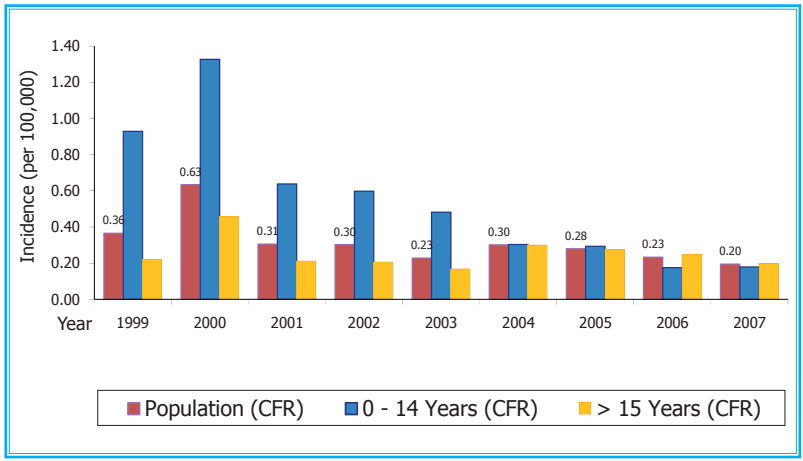


Figure 4 : Dengue Case Fatality Rate (CFR) by Age in Malaysia, 1999-2007

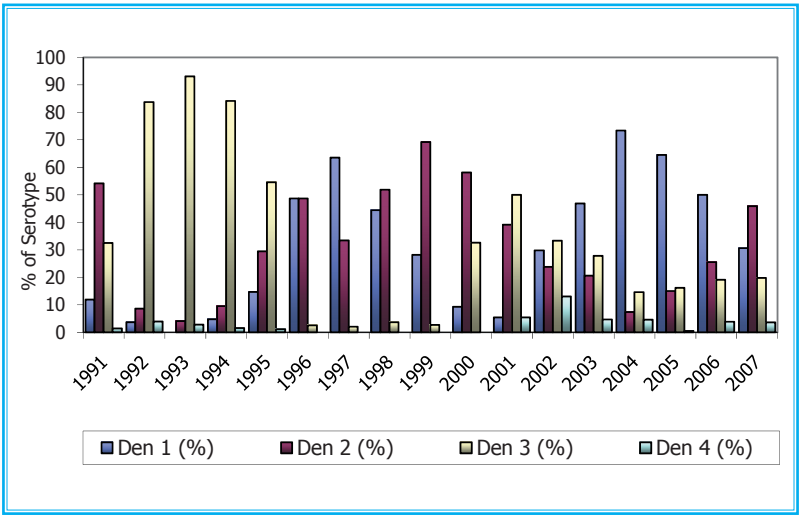


2. VIROLOGY

Dengue infection is caused by dengue virus which is a mosquito-borne flavivirus. It is transmitted by Aedes aegypti and Aedes albopictus. There are four distinct serotypes, DEN-1, 2, 3 and 4. Each episode of infection induces a life-long protective immunity to the homologous serotype but confers only partial and transient protection against subsequent infection by the other three serotypes. Secondary infection is a major risk factor for DHF due to antibody-dependent enhancement. Other important contributing factors for DHF are viral virulence, host genetic background, T-cell activation, viral load and auto-antibodies.

All four serotypes can be isolated at any one time but the predominant circulating dengue virus will show a sinusoidal pattern (Figure 5). For example, DEN-3 was the predominant serotype in the early 90s with a peak in 1993, and then subsequently declined. It then re-emerged, reaching the peak in 2001. Other serotypes had been observed to be co-circulating at the same time

Figure 5 : Percentage of Dengue Serotype in Malaysia, 1991-2007



3. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

3.1 SPECTRUM OF DENGUE INFECTION

The incubation period for dengue infection is 4-7 days (range 3-14).2 It may be asymptomatic or may result in a spectrum of illness ranging from undifferentiated mild febrile illness to severe disease, with or without plasma leakage and organ impairment. Symptomatic dengue infection is a systemic and dynamic disease with clinical, haematological and serological profiles changing from day to day. These changes accelerate by the hour or even minutes during the critical phase, particularly in those with plasma leakage (refer to section 3.3).

Understanding the systemic and dynamic nature of dengue disease as well as its pathophysiological changes during each phase of the disease will produce a rational approach in the management of dengue

3.2 CLINICAL COURSE OF DENGUE INFECTION

Dengue infection is a dynamic disease. Its clinical course changes as the disease progresses. After the incubation period, the illness begins abruptly and will be followed by 3 phases: febrile, critical and recovery phase (refer Figure 6). [3, 4]

i. Febrile Phase

Typically, patients develop high grade fever suddenly. This acute febrile phase usually lasts 2-7 days and often accompanied by facial flushing, skin erythema, generalised body ache, myalgia, arthralgia and headache.[3,4] Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. These clinical features are indistinguishable between DF and DHF.[5]

Mild haemorrhagic manifestations like positive tourniquet test or petechiae and mucosal membrane bleeding may be seen in DF and DHF.[5,6] Per vaginal bleeding is common among young adult females. Massive vaginal bleeding and gastrointestinal bleeding may occur during this phase but are not common.[7, 6] The findings of an enlarged and tender liver are more suggestive of DHF.[5]

The earliest abnormality in the full blood count is a progressive decrease in total white cell count. This should alert the physician to a high index of suspicion of dengue especially when there is positive history of neighborhood dengue. This disease should be notified as early as possible to prevent disease from assuming epidemic proportion.

ii. Critical Phase

The critical phase occurs towards the late febrile phase (often after 3rd day of fever) or around defervescence (usually between 3rd to 5th day of illness but may go up to 7th day) when a rapid drop in temperature may coincide with an increase in capillary permeability in some patients. In other viral infections, the patient's condition improves as the temperature subsides, but the contrary happens in DHF. At this point the patient will either become better if no or minimal plasma leak occurs, or worse if a critical volume of plasma is lost.[3, 4, 8, 9]

The critical phase lasts about 24-48 hours. (refer Figure 6) Varying circulatory disturbances (refer to Table 1) can develop. In less severe cases, these changes are minimal and transient. Many of these patients recover spontaneously, or after a short period of fluid or electrolyte therapy. In more severe forms of plasma leakage, the patients may sweat, become restless, have cool extremities and prolonged capillary refill time. The pulse rate increases, diastolic blood pressure increases and the pulse pressure narrows. Abdominal pain, persistent vomiting, restlessness,

altered conscious level, clinical fluid accumulation, mucosal bleed or tender enlarged liver are the clinical warning signs of severe dengue or high possibility of rapid progression to shock.[9, 10, 11] The patient can progress rapidly to profound shock and death if prompt fluid resuscitation is not instituted.

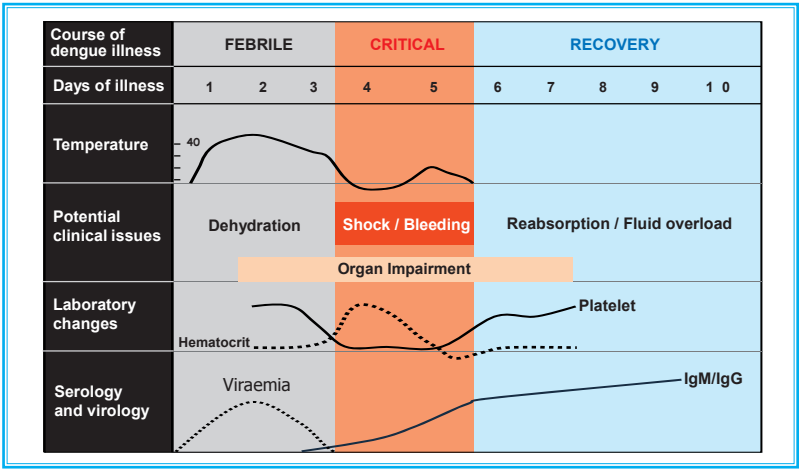
It is important to note that thrombocytopaenia and haemoconcentration (evidenced by a raised haemotocrit (HCT) from baseline or a drop in HCT after rehydration) are usually detectable before the subsidence of fever and the onset of shock. Refer to 3.5.1 for further details. The HCT level correlates well with plasma volume loss and disease severity. However, the levels of HCT may be equivocal when there is frank haemorrhage, early and excessive fluid replacement or untimely HCT determinations.

Leucopaenia with relative lymphocytosis, clotting abnormalities, elevation of transminases [typically the level of aspartate aminotransaminase (AST) is about 2-3 times the level of alanine aminotransaminase (ALT)], hypoproteinaemia and hypoalbuminaemia are usually observed.[3, 4, 5]

iii. Recovery Phase

After 24-48 hours of defervescence, plasma leakage stops and is followed by reabsorption of extravascular fluid. Patients' general well being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilises and diuresis ensues. Some patients may have a classical rash of "isles of white in the sea of red".[3] Some may experience generalised pruritus. Bradycardia and electrocardiographic changes are not uncommon during this stage. It is important to note that during this phase, HCT level stabilises or drops further due to haemodilution following reabsorption of extravascular fluid. The recovery of platelet count is typically preceded by recovery of white cell count (WCC).

Figure 6 : CLINICAL COURSE OF DHF[12]



Note : Onset of defervescence usually occurs between day 3 to day 5 of illness

- Clinical deterioration often occurs during the **critical phase** (plasma leakage) and it is therefore crucial to recognise the onset of this phase.
- The onset of **critical phase** is marked by plasma leakage and usually occurs around the onset of defervescence.
- Evidence of plasma leakage includes raised HCT (early marker), haemodynamic instability, fluid accumulation in extravascular space (rather late marker) or hypoproteinemia.
- Abdominal pain, persistent vomiting, restlessness, altered conscious level, clinical fluid accumulation, tender enlarged liver or mucosal bleed are the clinical warning signs of severe dengue or high possibility of rapid progression to shock.

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3.3 PATHOPHYSIOLOGY OF PLASMA LEAKAGE IN DENGUE HAEMORRHAGIC FEVER (DHF)/DENGUE SHOCK SYNDROME (DSS)

The primary pathophysiological abnormality seen in DHF and DSS is an acute increase in vascular permeability that leads to leakage of plasma into the extravascular compartment, resulting in haemoconcentration and hypovolaemia or shock.[13,3,4] Hypovolaemia leads to reflex tachycardia and generalised vasoconstriction due to increased sympathetic output.[14,15] Clinical manifestations of vasoconstriction in various systems are as follows :

a. Skin - coolness, pallor and delayed capillary refill time

b. Cardiovascular system - raised diastolic blood pressure and a narrowing of pulse pressure

c. Renal system - reducing urine output

d. Gastrointestinal system - vomiting and abdominal pain

e. Central nervous system – lethargy, restlessness, apprehension, reduced level of consciousness

f. Respiratory system – tachypnoea (respiratory rate >20/min)

In patients whose consciousness is not obtunded, intense thirst is another prominent symptom. At the same time, the inadequate perfusion of the tissue leads to increased anaerobic glycolysis and lactic acidosis. If the hypovolaemia is not corrected promptly, the patient will progress to a refractory shock state. By then, the tissue perfusion would not respond to vasopressor drugs, even if the blood pressure and intravascular volume were to be restored and cardiac output would remain depressed. The resultant lactic acidosis further depresses the myocardium and worsens the hypotension.[15] The common late complications of prolonged shock are massive bleeding, disseminated intravascular coagulopathy (DIC) and multi-organ failure which are often fatal.

The following table is the summary of the continuum of various pathophysiological changes in a patient who progresses from normal circulatory state to hypovolaemic shock.

Table 1 : A continuum of pathophysiological changes from normal circulation to compensated and decompensated/ hypotensive shock (Adapted from[15])

Normal Circulation	Compensated shock	Decompensated / Hypotensive shock
Clear consciousness	Clear consciousness – shock can be missed if you do not touch the patient	Change of mental state – restless, combative or lethargy
Brisk capillary refill time (<2 sec)	Prolonged capillary refill time (>2 sec)	Mottled skin, very prolonged capillary refill time
Warm and pink extremities	Cool extremities	Cold, clammy extremities
Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral pulses
Normal heart rate for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Normal blood pressure for age	Normal systolic pressure with raised diastolic pressure Postural hypotension	Hypotension/unrecordable BP
Normal pulse pressure for age	Narrowing pulse pressure	Narrowed pulse pressure (<20 mmHg)
Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ hyperpnoea/ Kussmaul's breathing
Normal urine output	Reduced urine output	Oliguria or anuria

The pathogenetic mechanism responsible for the increased vascular permeability in DHF/DSS is not known. There are no apparent destructive vascular lesions to account for this increased vascular permeability but on post-mortem (microscopically), perivascular oedema and loss of integrity of endothelial junctions with endothelial dysfunction are found.[16, 17] Abnormal immune response involving the production of cytokines or chemokines, activation of T-lymphocytes and disturbances of haemostatic system are the major changes seen in DHF. Mediators including C3a, C5a, tumour necrosis factor-α, interleukin 2, 6 and 10, interferon-α and histamine are elevated.[4, 18]

Secondary infection with a heterotypic dengue virus is associated with increased risk of developing DHF. It is believed to be due to the antibody-dependent enhancement phenomenon.[19,20,21] The sub-neutralising concentration of the cross-reacting antibody from the previous infection may opsonise the virus and enhance its uptake and replication in the macrophage or mononuclear cells. The level of T-cell activation is also enhanced. Profound T-cell activation with cell death during acute dengue infection may suppress or delay viral elimination, leading to the higher viral loads and increased immunopathology found in patients with DHF.[4, 18]

Increased vascular permeability is the primary pathophysiological abnormality in DHF/ DSS.

Increased vascular permeability leads to plasma leakage and results in hypovolaemia/ shock.

3.4 TOURNIQUET TEST

In DHF grade 1, a positive tourniquet test serves as the only indicator of haemorrhagic tendency. The sensitivity of the test varies widely from as low as 0% to 57%, depending on the phase of illness the test was done and how often the test was repeated, if negative. In addition 5-21% of patients with dengue like illness had positive tourniquet test but subsequently have negative dengue serology.[22, *Level 1*]

A recent study demonstrated that there was 95.3% positive preditive value if fever, positive tourniquet test, leucopenia/ thrombocytopaenia/ haemoconcentration were used as screening criteria.[23, *Level 8*]

The tourniquet test may be useful as an additional tool when the diagnosis is in doubt, especially when the platelet count is still relatively normal.

How to perform tourniquet test

Inflate the blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 minutes.

A positive test is when 20 or more petechiae per 2.5 cm (1 inch) square are observed.

Recommendation

The tourniquet test may be helpful in the **early febrile phase** (less than three days) in differentiating dengue from other febrile illnesses. **(Grade C)**

3.5 WHO DENGUE CLASSIFICATION

Based on current WHO dengue classification scheme (refer Appendix 1), the key differentiating feature between DF and DHF is the presence of plasma leakage in DHF. However, in the early febrile phase of dengue infection, the symptoms can overlap and one cannot differentiate DF and DHF.

DHF is further classified as mild (grades I and II) or severe (grades III and IV), the presence of shock being the main difference. Grades III and IV are classified as Dengue Shock Syndrome (refer Appendix 1).

(Note : The existing WHO dengue classification is being reviewed and revised)

3.5.1 Limitations of WHO classification [22, *Level 1*]

It has been observed that the existing WHO classification scheme has several limitations as the disease has spread to new regions and infected older age groups. For example:

1. Dengue with shock without fulfilling all the 4 criteria for DHF
   There have been many case reports of patients with severe dengue with shock who do not fulfil all the 4 criteria for DHF. These patients would have been classified as dengue fever if the WHO criteria are to be strictly applied.
2. Severe organ impairment
   Patients with severe organ impairment such as liver, respiratory, cardiac and brain dysfunction are not captured as having severe disease based on the existing classification.

3. Plasma leakage in DHF

   The requirement of 20% increase in HCT as one of the evidence of plasma leakage is difficult to fulfill due to several issues:

   a. Baseline HCT is not available in most patients and therefore, the interpretation of plasma leak can only be made retrospectively

   b. Early fluid administration may affect the level of HCT

   c. Bleeding will affect the HCT level

4. The existing classification scheme is often not useful for disease management because the correct disease classification can only be made towards the end of the illness.

> Patients can present with severe dengue without fulfilling **ALL** the 4 criteria (refer Appendix 1) for DHF/DSS.

3.5.2 Suggested WHO Classification 2009

The classification into levels of severity has a high potential for being of practical use in the clinicians' decision as to where and how intensively the patient should be observed and treated (i.e. triage, which is particularly useful in outbreaks).

Figure 7: Suggested Dengue Classification and Level of Severity

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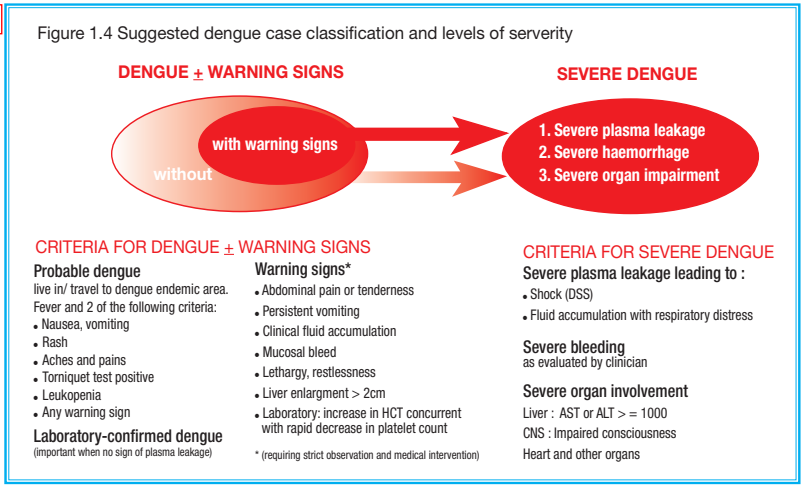

Source: World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

3.6 OTHER IMPORTANT MANIFESTATIONS

Severe bleeding or organ impairment might occur without plasma leakage. The Following manifestations are important in dengue infection but are often under- recognised or misdiagnosed:

1. Acute abdomen :
   Acute abdominal pain is a common symptom in dengue infection. It can be due to hepatitis, acalculous cholecystitis and shock, and occasionally misdiagnosed as acute appendicitis.[24, *Level 8*; 25, *Level 8*] The history of onset of fever before the abdominal pain, and laboratory findings of leucopenia, thrombocytopenia, or prolonged APTT with normal PT help to differentiate acute abdominal pain due to dengue infection from other surgical causes.[24, *Level 8*] Furthermore, in patients with shock, the abdominal pain is relieved by intravenous fluid therapy.

2. Hepatitis and liver failure :
   Hepatitis is common in patients with DF/DHF and may be mild or severe regardless of the degree of plasma leakage. In some cases, liver failure may occur.[22, *Level 1*] The patients with liver failure have a high propensity to bleed, especially gastrointestinal bleeding. [26, *Level 8*; 11, *Level 8*]

3. Neurological manifestation :
   Patients with dengue infection may have neurological manifestations, (<1%) mainly encephalitis or encephalopathy.[27, *Level 8*] Other rare manifestations include myelitis and Guillain Barré Syndrome. [28, *Level 8*]

4. Haemophagocytic syndrome
   This is an uncommon syndrome and is due to overt active cytokine productions as a result of the activation of T cells and macrophages system following dengue virus infection. This “cytokine storm” induces the severe vascular injuries, followed by the immense plasma leakage leading to cellular oedema, cellular damage, necrosis and cell death. This syndrome should be looked for in patients with unusual progressive cytopenia and multiorgan complications. Serum LDH and serum ferritin are often markedly elevated as well. Definitive diagnosis can be made by performing bone marrow biopsy which demonstrates haemophacytosis activity.

3.7 DIAGNOSTIC CHALLENGES

Clinical features of dengue infection are rather non-specific and mimic many other diseases, therefore can be easily misinterpreted. A high index of suspicion and appropriate history taking, particularly with regards to a recent stay in dengue hotspots, are useful for early and accurate diagnosis of dengue. In addition, a dengue patient may have a co-infection with another pathogen.

Using a syndromic approach, Tables 2 and 3 provide quick and helpful references to the differential diagnoses which vary at different stages of dengue disease.

FEBRILE PHASE

Table 2 : Differential diagnoses for dengue illness during febrile phase

Clinical syndrome	Differential diagnoses
Flu-like syndrome	Influenza Measles Chikungunya Adenovirus Infectious mononucleosis Acute HIV seroconversion illness
Rash	Rubella Measles Scarlet fever Meningococcal infection Chikungunya Drug
Diarrhea	Rotavirus Food poisoning
Neurological manifestation	Meningoencephalitis Febrile seizures

CRITICAL PHASE

Table 3: Differential diagnoses for dengue illness during critical phase

Clinical syndrome	Differential diagnoses
Acute abdomen	Acute appendicitis Acute cholecystitis Perforated viscus Viral hepatitis Diabetic ketoacidosis
Shock	Septic shock
Respiratory distress (Kussmaul's breathing)	Diabetic ketoacidosis Renal failure Lactic acidosis
Leucopaenia & thrombocytopenia ± bleeding	Acute leukaemia Immune thrombocytopaenia purpura Thrombotic Thrombocytopenic purpura Malaria / Leptospirosis / Typhoid / Typhus Bacterial sepsis SLE Acute HIV seroconversion illness

4. DISEASE NOTIFICATION

All suspected dengue cases must be notified by telephone to the nearest health office within 24 hours of diagnosis, followed by written notification within a week using the standard notification format.[29] Any delay in notification will increase the risk of dengue transmission in the locality of the residence. In 2007, 98.4% of dengue cases were notified by public and private hospitals with only 1.6% from the government and private clinics. The average day of illness at the time of notification was about 4-5 days after the onset of illness even though patients might have presented themselves to the healthcare facilities at day 1-3 day of fever.

Notification should be done as soon as a clinical diagnosis of dengue is suspected; serological confirmation is not necessary. Notified cases will be followed up by the health authorities for the verification of case definition and preventive measures. It is also important to note that re-notification has to be done if the diagnosis has been changed from DF to DHF or DF to other diagnosis.

Failure to notify is liable to be compounded under the Prevention and Control of Infectious Diseases Act, 1988 (Act 342).[30]

5. LABORATORY INVESTIGATIONS

5.1 DISEASE MONITORING LABORATORY TESTS

Full Blood Count (FBC)

1. White cell count (WCC) :
   In the early febrile phase WCC is usually normal but will decrease rapidly as the disease progresses.[5, *Level 8*] This trend of leucopenia should raise the suspicion of possible dengue infection.

2. Haematocrit (HCT) :
   A rising HCT is a marker of plasma leakage in dengue infection and helps to differentiate between DF and DHF but it can be masked in patients with concurrent significant bleeding and in those who receive early fluid replacement.[22, *Level 1*] Setting the patient's baseline HCT in the early febrile phase of disease will be very useful in the recognition of a rising HCT level.

3. Thrombocytopaenia :
   Thrombocytopaenia is commonly seen in dengue infection.[22, *Level 1*] In the early febrile phase, platelet count is usually within normal range but it will decrease rapidly as the disease progresses to the late febrile phase or at defervescence and it may continue to remain low for the first few days of recovery.

   There is a significant negative correlation between disease severity and platelet count [3, *Level 9*; 31 *Level 8*] but it is not predictive of bleeding.[32, *Level 8*; 33, *Level 1*; 34, *Level 6*; 35, *Level 8*; 36, *Level 8*]

Liver Function Test

Elevated liver enzymes is common and is characterised by greater elevation of the AST as compared to the ALT.[37, *Level 8*] The frequency and degree of elevation of the liver enzymes are higher with DHF compared to DF.[38, *Level 8;* 37, *Level 8*]

Leucopaenia followed by progressive thrombocytopaenia is suggestive of dengue infection.
A rising HCT accompanying progressive thrombocytopaenia is suggestive of DHF.
There is no local data available on the normal range of HCT in adults. In the absence of a baseline HCT level, a HCT value of >40% in female adults and >46% in male adults should raise the suspicion of plasma leakage.

Recommendation
The baseline HCT and WCC should be established as early as possible in all patients with suspected dengue. **(Grade A)**
Serial FBC and HCT must be monitored as the disease progresses. **(Grade A)**

5.2 DIAGNOSTIC TESTS

Definitive diagnosis of dengue infection can only be confirmed in the laboratory. However, the interpretation of laboratory diagnostic results should be done in the clinical context. Laboratory confirmatory tests include antibody detection (serology), virus isolation, detection of virus genetic materials (polymerase chain reaction -PCR) and detection of dengue virus protein (NS1 antigen).

5.2.1 DENGUE SEROLOGY TESTS

Haemagglutination Inhibition Test

The haemagglutination Inhibition (HI) test has been the gold standard for serological diagnosis. However, because it is labour intensive and requires paired samples for interpretation, this test is now being used mainly for research purposes to differentiate between primary and secondary dengue infections.

Dengue IgM test

The IgM capture enzyme-linked immunosorbent assay (ELISA) is the most widely used serological test. This antibody titre is significantly higher in primary infections, compared to secondary infections. Once the IgM is detectable, it rises quickly and peaks at about 2 weeks after the onset of symptoms, and it wanes to undetectable levels by 60 days. However in some patients, it may persist for more than 90 days. A positive result thus has to be intepreted and correlated cautiously with the clinical picture. If the dengue IgM test is the only available diagnostic test in the hospital, then establishing a negative IgM early in the illness, and demonstrating a positive serology later will be essential to exclude false negative results.

In one study, IgM was detected in only 55% of patients with primary dengue infections between day 4-7 onset of fever, and it became positive in 100% of the patients after day 7. However, in secondary dengue infections, IgM was detected in only 78% of patients after day 7.[39, Level 7]. In another study, 28% of secondary dengue infections were undiagnosed when IgM was the only test performed.[4, *Level 9*; 40, *Level 8;* 41, *Level 8*]

Indirect IgG ELISA test

In primary and secondary dengue infection, dengue IgG was detected in 100% of patients after day 7 of onset of fever. Therefore dengue IgG is recommended if dengue IgM is still negative after day 7 with the negative IgG in the initial test sample.[*39, level 7; 40, level 8; , level 8*]

Recommendation
In order to establish serological confirmation of dengue illness a seroconversion of dengue IgM needs to be demonstrated. Therefore a dengue IgM should be taken as soon as the disease is suspected. **(Grade C)**
Dengue IgM is usually positive after day 5-7 of illness. Therefore a negative IgM taken before day 5-7 of illness does not exclude dengue infection. **(Grade B)**
If dengue IgM is negative before day 7, a repeat sample must be taken in recovery phase. **(Grade B)**
If dengue IgM is still negative after day 7 with negative IgG tested at less then 7 days, dengue IgG is recommended for diagnostic confirmation. **(Grade C)**

Simple rapid tests such as the strip assays (immunochromatography test) are available for qualitative detection of dengue IgM and IgG (e.g. Pan Bio Dengue IgM ELISA and Dengue IgM Dot Enzyme Immunoassay).

The yield of rapid tests was shown to be higher when samples were collected later in the convalescent phase of infection, with good specificity and could be used when ELISA test were not available [43, *Level 1*] But the result had to be interpreted in the clinical context because of false positive and negative results.[44, *Level 8*; 45, *Level 8; 41, Level 8;* 46, *Level 8*] It is recommended that the dengue IgM Capture ELISA test be done after a rapid test, to confirm the status.[44, *Level 8*]

Note : False positive dengue serology

Serological tests for dengue have been shown to cross-react with:

- other flavivirus – Japanese Encephalitis.[47, *Level 9;* 41, *Level 8*]
- non-flavivirus – *malaria, leptospirosis*, *toxoplasmosis, syphilis*[48, *Level ;* 45, *Level 8*]
- connective tissue diseases – rheumatoid arthritis[44, *Level 8*]

5.2.2 VIRUS ISOLATION

Virus isolation is the most definitive test for dengue infection. It can only be performed in the lab equipped with tissue culture and other virus isolation facilities. It is useful only at the early phase of the illness. Generally, blood should be collected before day 5 of illness; i.e. before the formation of neutralizing antibodies.

During the febrile illness, dengue virus can be isolated from serum, plasma and leucocytes. It can also be isolated from post mortem specimens. The monoclonal antibody immunofluorescence test is the method of choice for identification of dengue virus. It may take up to two weeks to complete the test and it is expensive.

Note: Virus isolation has a poor yield if compared with molecular tests. It is most probably due to the viability of the virus and the quality of the samples.[49, *Level 8*]

5.2.3 POLYMERASE CHAIN REACTION (PCR)

Molecular tests such as the reverse transcriptase – ploymerase chain reaction (RT- PCR) are useful for the diagnosis of dengue infection in the early phase (< 5 days of illness). It was shown to have a sensitivity of 100% in the first 5 days of disease, but reduced to about 70% by day 6, following the disappearance of the viraemia.[50, *Level 8*; 42, *Level 8;* 51, *Level 8*]

An additional advantage of RT- PCR is the ability to determine dengue serotypes [52, *Level 7*; 42, *Level 8;* 53, *Level 8*; 49, *Level 8*; 54, *Level 8*]

Limitations of RT- PCR are:

a) This test is only available in a few centres with facilities and trained personnel (e.g. IMR, HKL, National Public Health Laboratory and University Malaya Medical Centre).
b) The test is expensive
c) The specimen requires special storage temperatures and short transportation, time between collection and extraction (refer Appendix 1)

In view of these limitations, the use of RT- PCR should only be considered for in-patients who present with diagnostic challenges in the early phase of illness.

5.2.4 NON-STRUCTURAL PROTEIN-1 (NS1 Antigen)

NS1 antigen is a highly conserved glycoprotein that seems to be essential for virus viability. Secretion of the NS1 protein is a hallmark of flavivirus infecting mammalian cells and can be found in dengue infection as well as in yellow fever and West Nile virus infection. This antigen is present in high concentrations in the sera of dengue infected patients during the early phase of the disease.[55, *Level 8*; 56, *Level 8*]

The detection rate is much better in acute sera of primary infection (75%-97.3%) when compared to the acute sera of secondary infection (60% - 70%).[57, *Level 8*; 58, *Level 8*; 59, *Level 8*; 60, *Level 8*] The sensitivity of NS1 antigen detection drops from day 4-5 of illness onwards and usually becomes undetectable in the convalescence phase.[61, *Level 8*; 60, *Level 8;* 58, *Level 8*; 59, *Level 8*]

Recommendation
PCR can be used as a diagnostic tool in early dengue infection **(Grade B)**. It is not recommended as a routine diagnostic test due to limited availability and cost. **(Grade C)**
NS1 Ag is a new diagnostic tool that may be useful in the early phase of dengue infection. It is not useful in the convalescence phase. However, this test is still undergoing evaluation. **(Grade C)**

Please refer to Appendix 2 for methods of sample collection for dianostic tests

6. INVESTIGATION OF POST MORTEM CASE

Suitable samples for viral isolation and PCR should be obtained from the liver, lung, thymus, spleen, lymph nodes, CSF, pleural fluid and brain tissues in a patient suspected to have died of DF/DHF.[2, *Level 9*; 62,*Level 9*] However PCR is a more sensitive method.[62 *Level 9* ; 63, *Level 7* ; 64, *Level 8*]

For serological confirmation of dengue illness a seroconversion of dengue IgM needs to be demonstrated. In a patient who has died suspected of dengue, a repeat dengue serology together with the samples mentioned above should be obtained.

Caution : Massive blood transfusion may affect the test results mentioned above.

Recommendation
A repeat dengue serology should be obtained at the time of death. **(Grade C)**
Suitable specimens for virus isolation and/ or RT-PCR and/ or antigen detection are recommended for confirmation of diagnosis. **(Grade C)**

Please refer to Appendix 2 for methods of sample collection.

7. MANAGEMENT OF DENGUE INFECTION

7.1 OUTPATIENT MANAGEMENT

The management of dengue infection is **symptomatic and supportive.** A stepwise approach as suggested in Table 4 can be useful.

Dengue is a dynamic disease and management issues vary according to the 3 phases of the clinical course (refer to section 7.4). It is crucial to recognise plasma leakage, shock early or severe organ impairment. This can be achieved by frequent clinical and laboratory monitoring.

Dengue patients who are managed in the outpatient setting should be provided with a disease monitoring record (refer to Appendix 4) to ensure that all relevant information is available to all health care providers.

Primary care providers with no immediate haematocrit facilities should refer patient to the nearest health facility for further management.

Table 4 : A Stepwise Approach On Outpatient Management of Dengue Infection

It is important to evaluate every patient in a stepwise manner as in the following :

Step 1: Overall assessment

1. History
   - Date of onset of fever/ illness
   - Oral intake
   - Assess for alarm signs – refer to Table 5
   - Diarrhoea
   - Bleeding
   - Change in mental state/seizure/dizziness
   - Urine output (frequency, volume and time of last voiding)
   - Other important relevant histories:
     - Family or neighbourhood history of dengue
     - Jungle trekking and swimming in waterfall (consider leptospirosis, typhus, malaria)
     - Recent travel
     - Recent unprotected sexual or drug use behaviour (consider acute HIV seroconversion illness)
     - Co-morbidities (consider sepsis particularly in patients with diabetes mellitus)

2. Physical examination
   i. Assess mental state and Glasgow Coma Scale (GCS) score
   ii. Assess hydration status
   iii. Assess haemodynamic status
      - Skin colour
      - Cold/ warm extremities
      - Capillary filling time (normal <2 seconds)
      - Pulse rate
      - Pulse volume
      - Blood pressure
      - Pulse pressure
   iv. Look out for tachypnoea/ acidotic breathing/ pleural effusion
   v. Check for abdominal tenderness/ hepatomegaly/ ascites
   vi. Examine for bleeding manifestation
   vii. Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

3. Investigations
   i. FBC and HCT
   ii. Dengue serology

Step 2 : Diagnosis, disease staging and severity assessment

Based on evaluations in history, physical examination±FBC and HCT, the clinicians should be able to determine:

1. Dengue diagnosis (provisional)
2. The phase of dengue illness if dengue is suspected (febrile/critical/recovery)
3. The hydration and haemodynamic status of patient (in shock or not)
4. Whether the patient requires admission

Step 3 : Plan of management

1. Notify the district health office via phone followed by disease notification form
2. If admission is indicated (refer to admission criteria) :
   - Stabilise the patient at primary care before transfer (refer to intravenous fluid regime)
   - Communicate with the receiving hospital/ Emergency & Trauma Department before transfer
3. If admission is not indicated (refer to Table 6) :
   - Daily or more frequent follow up is necessary especially from day 3 of illness onwards until the patient becomes afebrile for at least 24 - 48 hours without antipyretics
   - Refer to Home Care Advice Leaflet for Dengue Patients in Appendix 3

Adapted from[2, *Level 9*; 3, *Level 9*; 4, *Level 9*]

Table 5 : Warning signs [8, level 8, 9, level 8]

- **Abdominal pain or tenderness**
- **Persistent vomiting**
- **Clinical fluid accumulation (pleural effusion, ascites)**
- **Mucosal bleed**
- **Restlessness or lethargy**

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- **Tender enlarged liver**
- **Laboratory : Increase in HCT concurrent with rapid decrease in platelet**

Table 6 : Clinical and Laboratory Criteria for Patients Who Can be Treated at Home

1. Able to tolerate orally well, good urine output and no history of bleeding
2. Absence of clinical alarm signals (refer Table 5)
3. Physical examination:
   - Haemodynamically stable
     - pink, warm extremities
     - normal capillary filling time (normal <2 seconds)
     - good pulse volume
     - stable blood pressure
     - normal pulse pressure (> 20mmHg)
     - no disproportionate tachycardia
   - No tachypnoea or acidotic breathing
   - No hepatomegaly or abdominal tenderness
   - No bleeding manifestation
   - No sign of pleural effusion ascites
   - No alterations in mental state and full GCS score
4. Investigation:
   - Stable serial HCT
   - In the absence of a baseline HCT level, a HCT value of >40% in female adults and >46% in male adults should raise the suspicion of plasma leakage. Therefore admission may be required

Adapted from [65, *Level 9;* 66, *Level 9;* 67, *Level 9*]

7.2 PATIENT TRIAGING AT EMERGENCY & TRAUMA / OUTPATIENT DEPARTMENT

The purpose of triaging patients is to determine whether they require urgent attention. This is to avoid critically ill patients being missed upon arrival.

[68, *Level 9;* 65 *Level 9*; 69, *Level 9;* 70, *Level 9*]

Triage Checklist:

1. History of fever
2. Abdominal pain
3. Vomiting
4. Dizziness/ fainting
5. Bleeding

Vital parameters to be taken :
Mental state,blood pressure, pulse, temperature, cold or warm peripheries

7.3 CRITERIA FOR HOSPITAL REFERRAL / ADMISSION

7.3.1 Referral from primary care providers to hospital

The decision for referral and admission must not be based on a single clinical parameter but should depend on the **Total Assessment** of the patient.

Referral from primary care providers to hospital

1. Symptoms :
   - Alarm signals (refer to Table 5)
   - Bleeding manifestations
   - Inability to tolerate oral fluids
   - Reduced urine output
   - Seizure
2. Signs :
   - Dehydration
   - Shock (refer to Table 1)
   - Bleeding
   - Any organ failure
3. Special Situations :
   - Patients with co-morbidity e.g.Diabetes, Hypertension, Ischaemic Heart Disease, Coagulopathies, Morbid Obesity, Renal Failure, Chronic Liver disease, COPD,
   - Elderly (more than 65 years old)
   - Pregnancy
   - Social factors that limit follow-up e.g. living far from health facility, no transport, patient living alone, etc
4. Laboratory Criteria: Rising HCT accompanied by reducing platelet count

7.3.2 Referral From hospitals without specialist to hospitals with specialists

Early consultation with the nearest physician should be initiated for **ALL DHF** or **DF** with organ dysfunction/ bleeding.

Prerequisites for transfer

1. All efforts must be taken to optimise the patient's condition before and during transfer.
2. The Emergency Department **and/or** Medical Department of the receiving hospital must be informed prior to transfer.
3. Adequate and essential information must be sent together with the patients that includes fluid chart, monitoring chart and investigation results.

7.4 DISEASE MONITORING

7.4.1 Principles of Disease Monitoring

1. Dengue is a systemic and dynamic disease. Therefore disease monitoring is governed by different phases of the disease.
2. The critical phase (plasma leakage) may last for 24-48 hours. Monitoring needs to be intensified and frequent adjustments in the fluid regime may be required.
3. Recognition of onset of reabsorption phase is also important because intravenous fluid regime needs to be progressively reduced/ discontinued at this stage.

7.4.2 Outpatient Disease Monitoring

Every patient suspected of dengue attending the outpatient/ emergency and trauma department should be assessed in stepwise manner as recommended in Table 4**.**

Daily or more frequent follow up is necessary especially from day 3 of illness, until the patient becomes afebrile for at least 24- 48 hours without antipyretics. A disease monitoring record has been developed and it is recommended to be used for outpatient care (refer to Appendix 4.).

7.4.3 Inpatient Disease Monitoring

Immediately after admission every patient with suspected dengue should be reviewed thoroughly similar to the stepwise approach in outpatient (refer to Table 4). The plan of management and monitoring should be based on the phase of the disease and the haemodynamic status of the patient.

Table 8 summarises the parameters and frequency of monitoring according to the different phases of the illness.

Table 7: Issues of Monitoring According to Different Phases Of Dengue Illness

Phases of illness	Issues :
Febrile	- Differentiation of dengue illness from other febrile illnesses. - Not possible to differentiate DF from DHF.
Critical	- Plasma leakage occurs as patient progresses to late febrile phase or as temperature begins to defervescence (T < 38.0 °C). - Clinical deterioration occurs during this phase due to plasma leakage. - Plasma leakage results in haemoconcentration and hypovolemia/ shock. - Excessive plasma leakage due, in part, to intravenous fluid therapy may cause respiratory distress. - Bleeding can be precipitated by prolonged shock and shock can be perpetuated by bleeding. - May mimic acute abdomen of other causes. - May be confused with septic shock or other forms of shock.
Reabsorption	- Cessation of plasma leakage. - Reabsorption of fluid from extravascular compartment. - Haemodilution occurs following fluid reabsorption. - Hypervolaemia and pulmonary oedema if intravenous fluid therapy is continued.

Table 8 : Parameters and Frequency of Monitoring According to Different Phases of Dengue Illness

Parameters for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Recovery phase
Clinical Parameters			
General well being **Appetite/ oral intake** **Warning signs** **Symptoms of bleeding** **Neurological/ mental state**	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Haemodynamic status • *Pink/ cyanosis* • *Extremities (cold/warm)* • *Capillary refill time* • *Pulse volume* • *PR* • *BP* • *Pulse pressure* **Respiratory status** • *RR* • *SpO_2*	4-6 hourly depending on clinical status	2-4 hourly depending on clinical status **In shock** Every 15-30 minutes till stable then 1-2 hourly	4-6 hourly
Signs of bleeding, abdominal tenderness, ascites and pleural effusion	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Urine output	4 hourly	2-4 hourly **In shock** Hourly	4-6 hourly
Parameters for monitoring	**Frequency of monitoring**		
	Febrile phase	**Critical phase**	**Recovery phase**
Clinical Parameters			
FBC + HCT	Daily or more frequently if indicated	4-12 hourly depending on clinical status **In shock** Repeated before and after each attempt of fluid resuscitation and as indicated	Daily
BUSE/ Creatinine **LFT** **RBS** **Coagulation profile** **HCO_3/ TCO_2/ Lactate**	As indicated	At least daily or more frequently as indicated **In shock** Crucial to monitor acid-base balance/ ABG closely	As indicated

Adapted from [2, *Level 9*; 65, *Level 9*]

7.5 FLUID MANAGEMENT

7.5.1 Dengue with Warning Signs (refer to Table 5)

Recognising and monitoring for warning signs are crucial in identifying patients who may deteriorate into severe dengue.

- All patients with warning signs should be considered for monitoring in hospitals.
- Common pitfalls in fluid therapy:
  * Treating patient with unnecessary fluid bolus based on raised
  * HCT as the sole parameter without considering other clinical parameters
  * Excessive and prolonged fixed fluid regime in stable patients
  * Infrequent monitoring and adjustment of infusion rate
  * Continuation of intravenous fluid during the recovery phase

Cases of dengue with warning signs will probably recover with early intravenous rehydration. Some cases will deteriorate to severe dengue. If the patient has dengue with warning signs, the action plan should be as in Table 9a.

Table 9a: Action Plan for Patient who has Dengue with Warning Signs

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• Obtain a baseline HCT before fluid therapy.
• Give crystalloids solution (such as 0.9% saline).
• Start with 5-7 ml/kg/hour for 1-2 hours, then reduce to 3-5 ml/kg/hr for 2-4 hrs and then reduce to 2-3 ml/kg/hr or less according to the clinica response.
• If the clinical parameters are worsening and HCT is rising, increase the rate of infusion.
• Reassess the clinical status, repeat the HCT and review fluid infusion rates accordingly

7.5.2 Non-Shock Patients (DHF Grade I & II)

There are no studies that have looked at fluid therapy in non shock dengue patients. Increased oral fluid intake may be sufficient in some patients who are haemodynamically stable and not vomiting. However IV fluid (0.9% saline is recommended) is indicated in patients with increasing HCT (indicating on-going plasma leakage) despite increased oral intake. IV fluid therapy should also be considered in patients who are vomiting and not tolerating orally.[71, level 9; 65, level 9]

The normal maintenance requirement for IV fluid therapy in such patients could be calculated based on the formula in Table 9b. Frequent adjustment of maintenance fluid regime is often needed during the critical phase. Often 1.2-1.5 times the normal maintenance will be required during the critical phase. If the fluid infusion rate exceeds more than the maintenance requirement, the infusion rate should be reviewed within 4 to 6 hours.

A rising HCT AND/ OR haemodynamic instability indicates on-going plasma leakage and will require an increase in the IV fluid infusion rate. If patients deteriorate and progress to shock, fluid resuscitation is indicated (refer to the section on 7.5.3).[71, level 9; 65, level 9]

Reduce or consider discontinuation of IV fluid therapy when patients begin to show signs of recovery (usually after 24-48 hours of defervescence, or the HCT drops in a stable patient).

Table 9b : Calculations for normal maintenance of intravenous fluid infusion

* **Normal maintenance fluid per hour can be calculated based on the following formula (Equivalent to Halliday-Segar formula) :** 4 mL/kg/h for first 10kg body weight + 2 mL/kg/h for next 10kg body weight + 1 mL/kg/h for subsequent kg body weight * For overweight/obese patients calculate normal maintenance fluid based on ideal body weight (Adapted from [2, Level 9])
Ideal bodyweight can be estimated based on the following formula: [72, Level 9] Female: 45.5 kg + 0.91(height -152.4) cm Male: 50.0 kg + 0.91(height -152.4) cm

Recommendation Encourage adequate oral fluid intake**. (Grade C)**
IV fluid is indicated in patients who are vomiting or unable to tolerate oral fluids. **(Grade C)**
IV fluid is also indicated in patients with increasing HCT (indicating on-going plasma leakage) despite increased oral intake. (**Grade C)**
Crystalloid is the fluid of choice for non shock patients**. (Grade C)**

7.5.3 Dengue Shock Syndrome (DSS) (DHF Grade III & IV)

Dengue shock syndrome is a medical emergency. Recognition of shock in its early stage (compensated shock) and prompt fluid resuscitation will give a good clinical outcome.[73, Level 2] Refer Table 1 for details. However, failure to recognise the compensated shock phase will ultimately lead to decompensated (hypotensive) shock and a more complicated disease course.

Pulse pressure of < 20 mmHg and systolic pressure < 90 mmHg are late signs of shock in adults.

All patients with dengue shock should be managed in high dependency intensive care units. Fluid resuscitation must be initiated promptly and should not be delayed while waiting for admission to ICU or high dependency unit.

Following initial resuscitation there maybe recurrent episodes of shock because capillary leakage can continue for 24-48 hours.

IV fluid therapy is the mainstay of treatment for dengue shock. [2, Level 9; 73, Level 2; 74, Level 2] To date, only three randomised controlled trials studying different types of fluid regime in DSS in children aged from 5 to 15 years of age are available.[73, Level 2; 74, Level 2; 75, Level 2] Our recommendations are extrapolated from these studies. These studies showed no clear advantage of using any of the colloids over crystalloids in terms of the overall outcome. However,

colloids may be preferable as the fluid of choice in patients with intractable shock in the initial resuscitation. Colloids seem to restore the cardiac index and reduce the level of HCT faster than crystalloids in patients with intractable shock. [74] *Level 2* The choice of colloids includes gelatin solution (e.g. Gelafusine) and starch solution (e.g. Voluven).

Principles for fluid resuscitation

The volume of initial and subsequent fluid resuscitation depends on the degree of shock and can vary from 10-20 mL/kg ideal body weight. The volume and rate of fluid replacement should be carefully titrated to the clinical response to maintain an effective circulation while avoiding an over-replacement.

Improvement in the following parameters indicates adequate fluid resuscitation:

Clinical parameters

- Improvement of general well being/mental state
- Warm peripheries
- Capillary refill time <2sec
- BP stable
- Improving pulse pressure
- Less tachycardic
- Increase in urine output
- Less tachypnoiec

Laboratory parameters

- Decrease in HCT
- Improvement in metabolic acidosis

If the first two cycles of fluid resuscitation with crystalloids (about 40 ml/kg) fails to establish a stable haemodynamic state and HCT remains high, colloids should be considered for the third cycle [2, *Level 9*; 65, *Level 9*] (refer to Algorithm for fluid management for DSS).

If the repeat HCT drops after two cycles of fluid resuscitation and the patient remains in shock, one should suspect significant bleed (often occult) and blood transfusion should be instituted as soon as possible (refer to Algorithm for fluid management for DSS).

In patients with persistent shock despite three cycles of fluid resuscitation (60ml/kg IV fluid), other causes of persistent shock must be considered, the commonest being significant bleeds (often occult) for which blood ± blood products transfusion needs to be instituted promptly, (refer to Algorithm for fluid management for DSS).Other possible causes of persistent shock include sepsis and cardiogenic shock (due to myocarditis or ischaemic heart disease).

Fluid therapy has to be judiciously controlled to avoid fluid overload which could result in massive pleural effusion, pulmonary oedema or ascites.

[2, *Level 9*; 65, *Level 9*]

Refer to the Algorithm A and Algorithm B for details.

Recommendation
For initial resuscitation • Crystalloids are the fluid of choice in patients with DSS. **(Grade A)** • Colloids may be preferred as the fluid of choice in patients with severe shock. **(Grade B)**
• When two cycles of initial resuscitation with crystalloids fail to restore haemodynamic stability, colloids should be considered.**(Grade C)**

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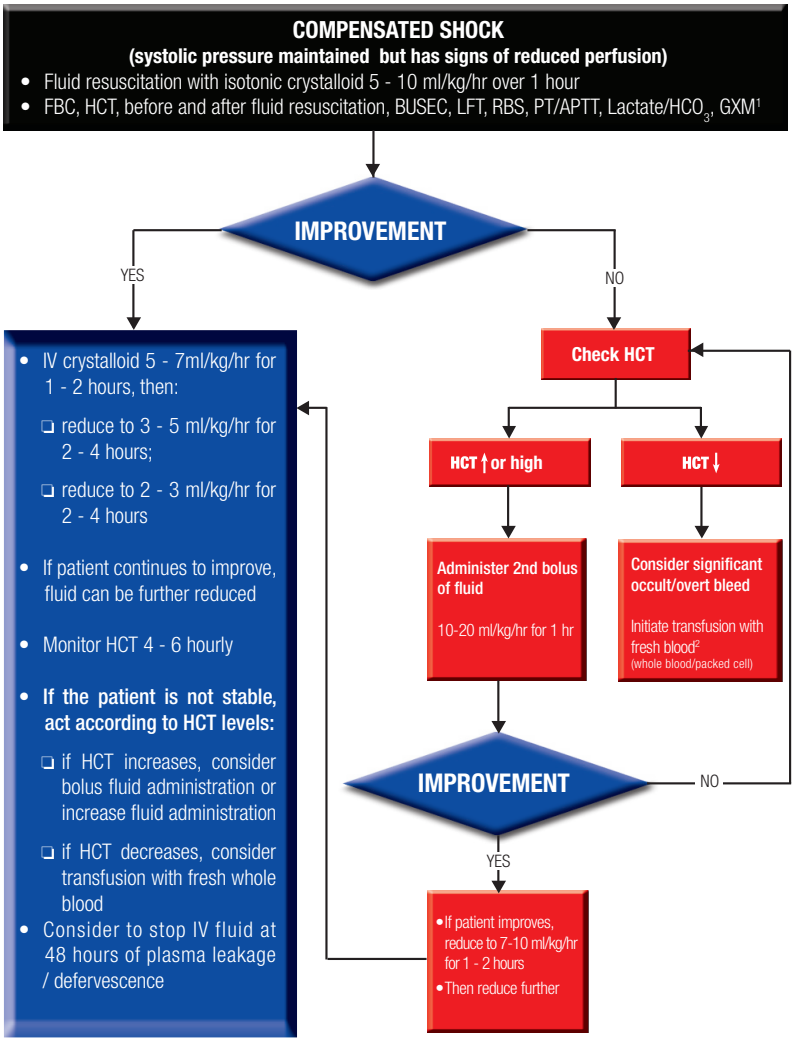
ALGORITHM A - FLUID MANAGEMENT IN COMPENSATED SHOCK



HCT = haematocrit

[1]GXM: require first stage cross match or emergency O

[2]fresh blood: less than 5 days

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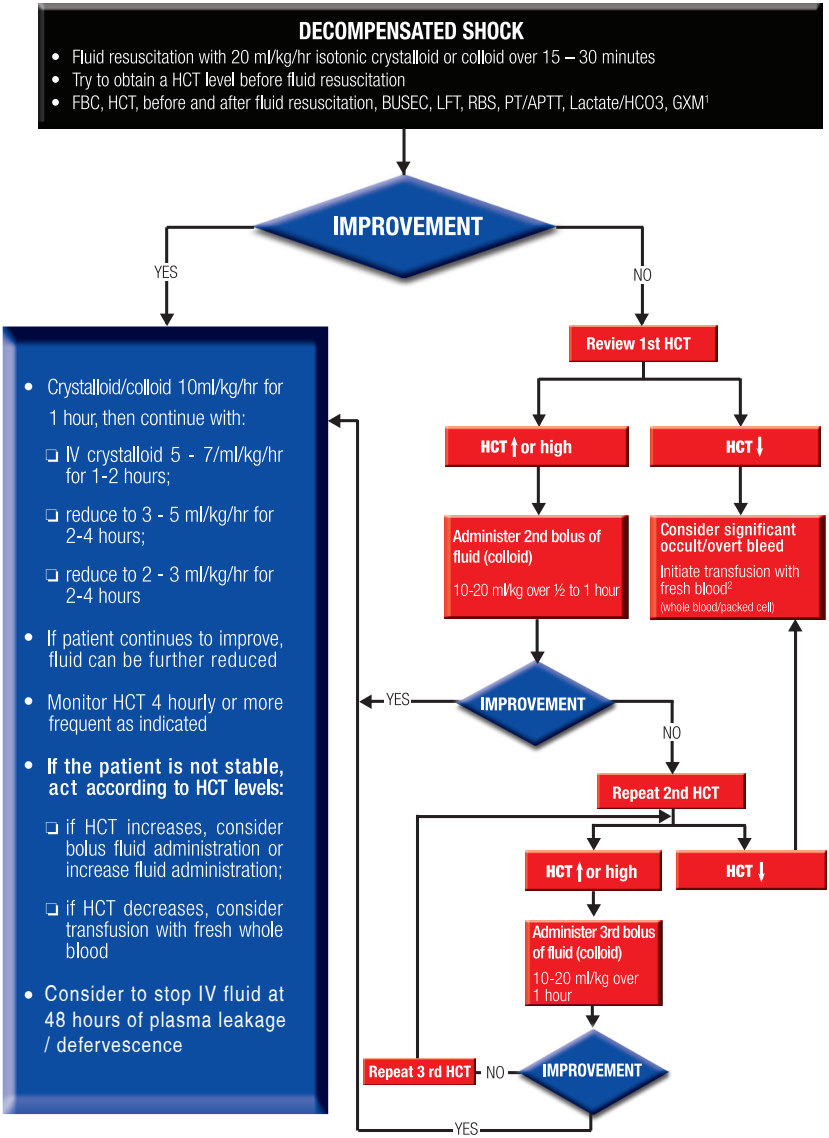
ALGORITHM B - FLUID MANAGEMENT IN DECOMPENSATED SHOCK



HCT = haematocrit

[1]GXM: require first stage cross match or emergency O

[2]fresh blood: less than 5 days

7.6 MANAGEMENT OF BLEEDING/HAEMOSTASIS

7.6.1 Haemostatic Abnormalities in Dengue Infection

The haemostatic changes that occur in dengue infection are a result of endothelial activation.[76 level 9; 77, level 8; 78, level 5] This leads to thrombocytopaenia and coagulation activation which are an intrinsic part of the disease.[76, level 9; 77, level 8; 78, level 5]

Thrombocytopaenia and coagulation abnormalities do not reliably predict bleeding in dengue infection.[34, level 6; 33, level 1; 36, level 8]

Markers of endothelial activation such as elevated levels of thrombomodulin, tissue factor and Von Willebrand factor are more often seen in severe dengue.[79, level 6; 80, level 6] Increased levels of these proteins may promote microvascular thrombosis and end-organ damage.[81, level 9]

7.6.2 How to Recognise Significant Occult Bleeding?

Bleeding is considered significant when it results in haemodynamic instability. Bleeding from the gums or per vagina, epistaxis and petechiae are common but will usually cease spontaneously and are often not significant.[2, level 9] Significant bleeding or disseminated intravascular coagulation usually occurs following prolonged shock and acidosis.[32, level 8]

Suspect significant occult bleeding in the following situations:
Haematocrit not as high as expected for the degree of shock to be explained by plasma leakage alone. [32, level 8]
A drop in haematocrit without clinical improvement despite adequate fluid replacement (40-60 ml/kg).[32, level 8; 66, level 9]
Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.[32, level 8]

7.6.3 Management of Bleeding in Dengue

Mild bleeding such as from the gums, per vagina, epistaxis or petechiae, usually cease spontaneously and do not require blood transfusion.[2, level 9]

Transfusion of blood and blood components in dengue is indicated when there is evidence of significant bleeding.[32, level 8]

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Transfusion of blood in patients with significant bleeding

- Transfused 5-10ml/kg of fresh-packed red cells or 10-20 ml/kg of fresh whole blood at an appropriate rate and observe the clinical response.
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in HCT after blood transfusion.

Recommendation
Patients with mild bleeding such as from the gums or per vagina, epistaxis and petechiae do not require blood transfusion. **(Grade C)**
Blood transfusion with whole blood or packed cell (preferably less than 1 week) ± blood component is indicated in significant bleeding. **(Grade C)**

7.6.4 Management of Upper Gastrointestinal Bleeding

No studies have looked at the use of proton pump inhibitor in upper GIT bleeding in dengue.

Endoscopy and endoscopic injection therapy in upper GIT haemorrhage increases the risk of bleeding and must be avoided.[82, *Level 7*]

Generally, most of the GIT bleed will improve after 48-72 hours of the defervescence. A persistent bleed beyond this time will require further investigation.

Recommendation
Endoscopy and endoscopic injection therapy in upper GIT haemorrhage should be avoided. **(Grade C)**
Blood transfusion with whole blood or packed cell (as fresh as is available, preferably less than one week old) ± blood components is indicated in significant bleeding. **(Grade C)**

7.6.5 The Role of Prophylactic Transfusions in Dengue

Prophylactic transfusion with platelets and fresh frozen plasma do not produce sustained changes in the coagulation status and platelet count in patients with DHF/DSS.[83, *Level 8 ;* 84, *Level 8*]

Prophylactic transfusion with platelets and fresh frozen plasma do not change or reduce the bleeding outcome in DHF. [83, *Level 8*; *84*, *Level 8* ; 36, *Level 8*]

Inappropriate transfusion of blood components increases the risk of pulmonary oedema and respiratory embarrassment.[83, *Level 8*]

Recommendation
There is no role for prophylactic transfusion with platelets and fresh frozen plasma in dengue patients. (**Grade C)**

7.6.6 The Role of Adjunctive Therapy in Dengue

There is insufficient evidence to support the use of recombinant activated factor VII in dengue patients with significant bleeding.[85, *Level 3*; 86, *Level 9* The coagulation system is activated in dengue and infusion of activated factor concentrates may increase the risk of thrombosis.[87, *Level 9*]

There is insufficient evidence to support the use of intravenous immunoglobulin[88, *Level 3*] and steroids[89, *Level 1*] in the management of dengue patients.

However there are anedoctal reports,[72, *Level 9*] that demonstrated a dramatic response when pulse methylprednisolone and high dose immunoglobulin G (lgG) was used in the early phase of haemophagocytic syndrome.

7.7 INTENSIVE CARE MANAGEMENT

The management of DSS in the intensive care unit (ICU) follows the general principles of management of any critically ill patient in the ICU. However, certain aspects which are of particular relevance to the management of DSS are discussed here. There are several papers reviewing dengue patients who were admitted to ICU. Several indications for ICU care were observed as listed in the box below. [10, *Level 8*, 90, *Level 8;* 91, *Level 8*]

Indications for referral to Intensive Care:

1. Recurrent or persistent shock
2. Requirement for respiratory support (non-invasive and invasive ventilation)
3. Significant bleeding
4. Encephalopathy or encephalitis

7.7.1 Indications for respiratory support (non-invasive and invasive ventilation)

The main objectives of respiratory support are to support pulmonary gas exchange and to reduce the metabolic cost of breathing.

In general, respiratory support should be considered early in a patient's course of illness and should not be delayed until the need arises. The decision to initiate respiratory support should be based on clinical judgement that considers the entire clinical situation.[92, *Level 9*]

In patients with metabolic acidosis, respiratory support should be considered despite the preservation of relatively normal arterial blood pH. When $PaCO_2$ is higher than expected to compensate for the acidosis, the patient should be promptly intubated.

Formula to calculate the expected $PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$ mmHg

In patients with encephalopathy and GCS of <9, intubation is often required to protect the airway.[93, *Level 9 ;* 94, *Level 9*]

Indications for mechanical ventilation:

- Respiratory failure
- Severe metabolic acidosis
- Encephalopathy

7.7.2 Indications for haemodynamic support

In dengue, hypotension is usually due to plasma leakage or internal bleeding. Fluid resuscitation is crucial and should be initiated first. However, vasopressor (e.g. dopamine, noradrenaline) may be considered when a mean arterial pressure is persistently <60 mmHg despite adequate fluid resuscitation. [95, *Level 9*]

CAUTION : While vasopressors increase the blood pressure, tissue hypoxia may be further compromised by the vasoconstriction.

Formula : MAP (Mean Arterial Pressure)
= DBP + 1/3 (SBP - DBP)

DBP = diastolic blood pressure
SBP = systolic blood pressure

7.7.3 Guide on safety and risk of invasive procedures

a. Central venous catheter (CVC) insertion

Volume resuscitation does not require a CVC if sufficient peripheral intravenous access can be obtained (e.g. 14- or 16-gauge intravenous catheters). In fact, peripheral intravenous catheterisation may be preferable because a greater flow rate can be achieved through a shorter catheter, assuming the catheters are of equal diameter.[96, *Level 8*] When a CVC of 8.5 French or larger (i.e. an introducer) is used, the length of tubing becomes the rate limiting factor, not the CVC.

There are no studies on dengue patients with regards to invasive procedures and bleeding risks. In general, thrombocytopaenia and other bleeding diathesis are relative contraindications to CVC placement as high femoral, low internal jugular, and subclavian venous punctures are difficult to compress and confer an increased risk of uncontrolled bleeding. However, studies have shown that the incidence of bleeding in patients with coagulopathy varies (0 - 15.5%).[97, *Level 8*; 98, *Level 8*; 99, *Level 8*; 100, *Level 8*; 101, *Level 8*]

When CVC is indicated in dengue patients (e.g. poor peripheral venous access, requirement of vasopressors) it should be inserted by an experienced operator and under ultrasound guidance if available.[102, *Level 8;* 103, *Level 1*]

There are multiple insertion sites to choose from: femoral vein, external jugular vein, internal jugular vein, subclavian vein, brachial vein and cephalic vein. However, because the subclavian vein and artery are not accessible to direct compression, the subclavian site is least appropriate for a patient with a bleeding diathesis[104, *Level 9*; 105, *Level 9*]

Recommendation
Volume resuscitation does not require a central venous catherisation (CVC) if sufficient peripheral intravenous access can be obtained. **(Grade C)**
When CVC is indicated, it should be inserted by a skilled operator, preferably under ultrasound guidance if available. **(Grade C)**
Subclavian vein cannulation should be avoided as far as possible. **(Grade C)**

b. Arterial catheter insertion

Intra-arterial cannulation is useful as it enables continuous arterial pressure monitoring and repeated arterial blood gas sampling. It has a very low incidence of bleeding (1.8 – 2.6%)[106, *Level 8*]

Recommendation
An arterial catheter should be inserted in DSS patients who require intensive monitoring and frequent blood taking for investigations. **(Grade C)**

c. Gastric tube

If a gastric tube is required, the nasogastric route should be avoided. Consider orogastric tube as this is less traumatic.

d. Pleural tap and chest drain

Intercostal drainage of pleural effusions should be avoided as it can lead to severe haemorrhage and sudden circulatory collapse.[107, *Level 9*]

Recommendation
Intercostal drainage for pleural effusion is not indicated to relieve respiratory distress. Mechanical ventilation should be considered. (**Grade C)**

8. DISCHARGE CRITERIA

The following should be taken into consideration before discharging a patient.[65, *Level 9*; 66, *level 9*]

- Afebrile for 48 hours
- Improved general condition
- Improved appetite
- Stable haematocrit
- Rising platelet count
- No dyspnoea or respiratory distress from pleural effusion or ascites
- Resolved bleeding episodes
- Resolution/recovery of organ dysfunction

9. PREVENTION OF DENGUE TRANSMISSION IN HOSPITALS

Patients are viraemic and hence potentially infectious during the febrile phase.[108, *Level 8*; 109,*Level 8*] There are a few small studies that demonstrate higher levels and prolonged duration of viraemia in patients with DHF.[110, *Level 6*; 111, *Level 8*]

There are no scientific studies that address the efficacy of mosquito repellents or mosquito netting in reducing dengue transmission in hospitalised patients. However several community studies have shown that the use of mosquito netting/screening was efficacious in preventing transmission of dengue in the community.[112, *Level 3*; 113, *Level 8*]

Generally, repellent products with higher concentrations of DEET (N,N-diethyl-m-toluamide) were found to have longer repellence times.[114, *Level 8*]

A consensus dengue guideline advised the use of mosquito netting or repellent day and night for hospitalised dengue patients to reduce nosocomial infection.[66, *Level 9*]

10. VACCINATION

There is no effective vaccine available for dengue.[115, *Level 8*; 116, *Level 9*]

11. DENGUE IN PREGNANCY

There are very few studies addressing the management of dengue in pregnancy. Generally the presentation and clinical course of dengue in pregnant women is similar to that in non-pregnant individuals. [118, *Level 8*] [117, *Level 8*;] However, the signs and symptoms may be confused with other complications of pregnancy such as toxaemia, **H**aemolysis, **E**levated **L**iver **E**nzymes, **L**ow **P**latelets (HELLP) syndrome.[119, *Level 9*]

There are some reports of an increased incidence of prematurity, in-utero death and abruptio placenta in these women.v [117, *Level 8;* 120, *Level 8*]

The following physiological changes in pregnancy may make the diagnosis and assessment of plasma leakage challenging :

- Elevation of HCT in dengue is masked by haemodilution due to increase in plasma volume especially in the 2nd and 3rd trimester. Serial HCT measurement is crucial for disease monitoring in pregnancy.
- The detection of third space fluid accumulation is difficult due to the presence of gravid uterus.
- Baseline blood pressure is often lower and pulse pressure wider
- Baseline heart rate may be higher.

Management of infected pregnant patients close to delivery :

- Risk of bleeding is at its highest during the period of plasma leakage (critical phase).
- If possible, avoid Lower Segment Caesarean Section (LSCS) or induction of labour during critical phase (plasma leakage).[119, *Level 9*]
- Procedures/manoeuvres that may provoke or augment labour should be avoided during this critical phase.

Care for the mother should be provided in a multidisciplinary way in an area of the hospital where there are trained personnel available to handle labour and its complications.

The baby should be observed for vertical transmission of dengue after delivery.[119, *Level 9*]

Recommendation
All pregnant women with suspected dengue infection must be admitted. **(Grade C)**

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APPENDICES

WORLD HEALTH ORGANIZATION CLASSIFICATION OF DF AND DHF (1997) [2, Level 9]

CASE DEFINITION FOR DENGUE FEVER

Given the variability in the clinical illness associated with dengue infection, it is not appropriate to adopt a detailed clinical definition of dengue fever. Rather, the need for laboratory confirmation is emphasised.

The following classifications are proposed:

- *Probable* – an acute febrile illness with two or more of the following manifestations:
  - headache
  - retro-orbital pain
  - myalgia
  - arthralgia
  - rash
  - haemorrhagic manifestations
  - leukopenia

AND

- supportive serology(a reciprocal haemagglutination-inhibition antibody titre ≥ 1280, a comparable IgG enzyme-linked immunosorbent assay (ELISA) titre or a positive IgM antibody test on a late acute or convalescent-phase serum specimen)

OR

- occurrence at the same location and time as other confirmed cases of dengue fever
  - Confirmed – a case confirmed by laboratory criteria (see below).
  - Reportable – any probable or confirmed case should be reported.

Laboratory criteria for confirmation of dengue fever are

- Isolation of the dengue virus from serum or autopsy samples: or
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titres to one or more dengue virus antigens in paired serum samples; or
- Demonstration of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence or ELISA;

OR

- Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR).

CASE DEFINITION FOR DENGUE HAEMORRHAGIC FEVER

The following must **ALL** be present :

- Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic.
- Haemorrhagic tendencies, evidenced by at least one of the following :
  - a positive tourniquet test
  - petechiae, ecchymoses or purpura
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
  - haematemesis or melaena.
- Thrombocytopenia (100,000 cells per mm^3 or less).
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in the HCT equal to or greater than 20% above average for age, sex and population;
  - a drop in the HCT following volume-replacement treatment equal to or greater than 20% or baseline;
  - signs of plasma leakage such as pleural effusion, ascites and hypoproteinaemia.

CASE DEFINITION FOR DENGUE SHOCK SYNDROME

All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by :

- Rapid and weak pulse, and
- Narrow pulse pressure [<20mmHg (2.7 kPa)]

OR manifested by :

- Hypotension for age, and
- Cold, clammy skin and restlessness.

Grade I : Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test and / or easy bruising.

Grade II : Spontaneous bleeding, in addition to the manifestations of Grade I patients, usually in the form of skin or other haemorrhages.

*Grade III : Circulatory Failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension with the presence of cold, clammy skin and restlessness.

*Grade IV : Profound shock with undetectable blood pressure or pulse.

Note : * i. Grades III and IV are classified as Dengue Shock Syndrome
ii. The WHO classification is being reviewed and revised.

METHODS OF SAMPLE COLLECTION

1. Dengue Serology (ELISA)

i. Draw 3-5 ml of blood into a plain tube without anti-coagulants.
ii. Clot at ambient temperature
iii. Dispatch to the laboratory within 4 hours of collection for serum separation by centrifugation.

Note : Haemolysed or icteric or lipaemic specimens invalidate certain test. If such specimens are received, the samples will be rejected to assure results are of clinical value.

2. Viral Particles Detection (PCR)

Blood

i. Collect 3-5 ml of blood into plain tube.
ii. Send directly to virology lab within 2 hours of sampling. If this is delayed, centrifuge and aliquot serum into sterile tube. Keep the sample in a freezer at -70ºC and put in ice when sending to virology lab the next day.

Cerebrospinal fluid (CSF)

i. Collect a minimum of 0.5 ml (5 drops) of CSF into s sterile bijoux bottle.
ii. Pack in ice for transport
iii. Send directly to virology lab within 2 hours after being taken.
iv. Send together with serum sample

Post-mortem tissue sample

Tissue specimens should be placed in a sterile container and sent immediately to the lab. The specimens should be “snap” frozen in liquid nitrogen or in a -70 ºC bath such as dry ice/alcohol as quickly as possible after collection. Once frozen, the tissue specimen can be stored at -70ºC until detection by PCR.

3. Viral Isolation

Blood

i. Draw 3-5 ml of blood into a plain tube without anti-coagulants

CSF

i. Collect at least 1 ml of CSF specimen in a sterile plan screw capped container (universal or Bijou Bottle).Do not add in VTM or freeze.
ii. Pack the specimen individually in biohazard plastic bag and keep in 4ºC or in cold box with ice.
iii. Send to the lab within 24 hours after collection.

Tissue or post mortem tissue

i. Put the tissue in sterile container screw capped tight to avoid drying of tissue. Do not add in VTM
ii. Packed the specimen individually in biohazard plastic bag and keep in 4ºC or in cold box with ice.
iii. Send to the lab within 24 hours after collection
- Inform the laboratory processing the samples that the case was fatal
- Obtain a blood sample to attempt virus isolation and serology
- Obtain tissue samples for separate tests of virus isolation and immunohistochemistry

HOME CARE ADVICE LEAFLET FOR DENGUE PATIENTS

Front View

HOME CARE ADVICE FOR DENGUE PATIENTS

WHAT SHOULD BE DONE?

- Adequate bed rest
- Adequate fluid intake (more than 5 glasses for an average person)
  - Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley water.
  - Plain water alone is not sufficient and may cause electrolyte imbalance. (Nicaragua 2003, Level 8)
- Take paracetamol (not more than 4 gram per day)
- Tepid sponging
- If possible, use mosquito repellent or rest under a mosquito net even during day time to prevent mosquito bites
- Look for mosquito breeding places in and around the home and eliminate them

WHAT SHOULD BE AVOIDED?

- Do not take non steroidal anti-inflammatory (NSAIDS) e.g. aspirin/mefenamic acid (ponstan) or steroids. If you are already taking these medications please consult your doctor.
- Antibiotics are not required

Back View

THE DANGER SIGNS OF DENGUE INFECTION

(IF ANY OF THESE ARE OBSERVED, PLEASE GO IMMEDIATELY TO THE NEAREST HOSPITAL)

1. **Bleeding**
   for example :
   - Red spots or patches on the skin
   - Bleeding from nose or gums
   - Vomiting blood
   - Black coloured stools
   - Heavy menstruation / vaginal bleeding
2. **Frequent vomiting**
3. **Severe abdominal pain**
4. **Drowsiness or irritability**
5. **Pale, cold or clammy skin**
6. **Difficulty in breathing**

Adapted from [66, *Level 9*; 9, *Level 8*]

DENGUE MONITORING RECORD

DENGUE MONITORING RECORD

Patient's Name : ..... I/C No. : .....

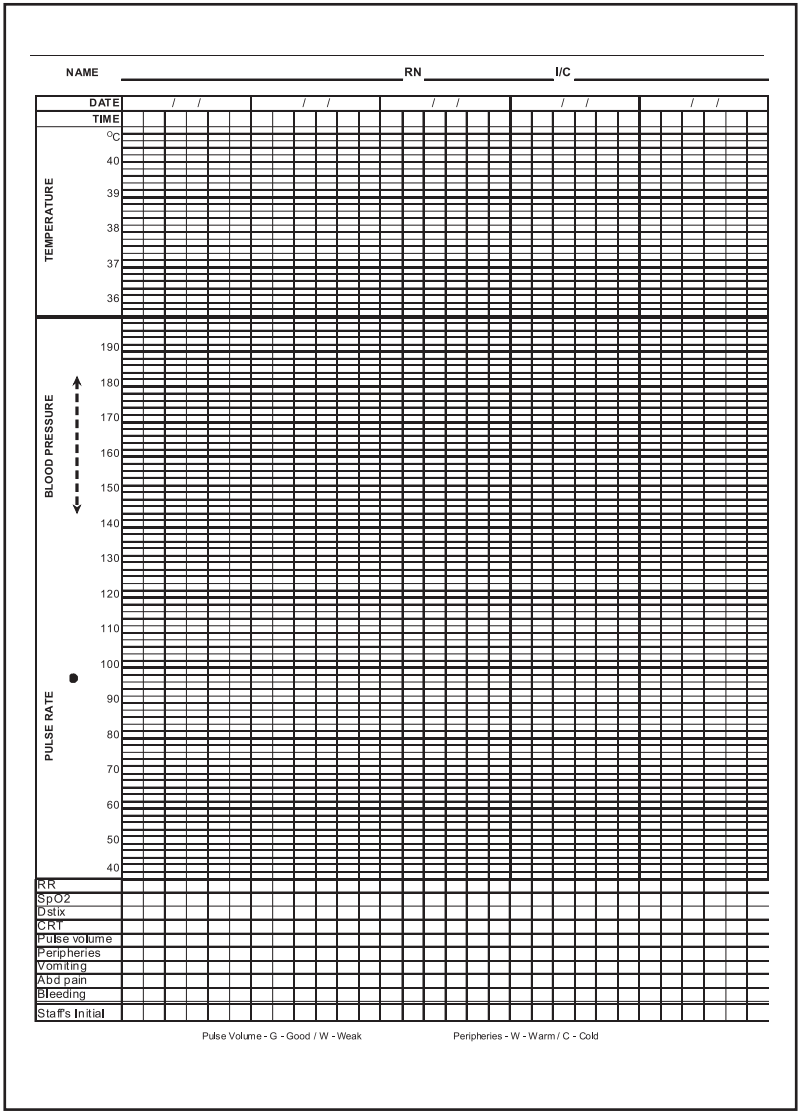
Address : .....

..... Date of Onset of Fever : .....

Date	Temp (°C)	BP (mm Hg)	PR (min)	HCT (%)	WCC ($x10^3/\mu l$)	Platelet ($x10^3/\mu l$)	Attending Clinic/Tel No.	Next Appointment

DENGUE MONITORING CHART

REVISED
JULY 2010



CLINICAL QUESTIONS

1. **What is the epidemiological data and notification system for dengue?**

2. **How to diagnose dengue?**
   a. Clinical
      i. latest definition of DF, DHF, DSS
      ii. ICD 10 Classification
      iii. stages of disease and pitfalls of WHO Classification
      iv. differential diagnosis
      v. unusual presentation (hepatitis, liver failure, acute abdomen, encephalitis, myocarditis)
      vi. co-infection-typhus, bacteraemia, malaria

   b. Laboratory diagnosis and its pitfalls
      i. When should IgM and IgG be taken? Role of rapid test kit
      ii. Is there a role of routine virology – culture, antigen assay
      iii. What is the role of PCR/ molecular in diagnosis?

3. **How to manage the patients with dengue infection as outpatients and in the emergency facility?**
      i. OPD and A/E triaging-fast tracking during outbreak
      ii. Who can be treated at home? Clinical and laboratory criteria - risk stratification at first contact
      iii. When should the GP refer the suspected dengue case to OPD or hospital?
      iv. What should be the home care advice (Appendix/ Card)
      v. Specific out patient management and follow-up

4. **Who requires hospitalisation?**
      i. Clinical and laboratory criteria including social assessment
      ii. Co-morbidities and pregnancy
      iii. Communication on disease severity (inter-departmental/ inter-hospital and inter healthcare facilities)
      iv. Role of bed netting and/or mosquito repellent in the hospital setting-place under general issues

5. **How to monitor the patient in the ward?**
      i. What to monitor - parameter (clinical and lab)
      ii. Pitfalls
      iii. Alarm triggers - Aid chart /alert card /refer algorithm

6. **When to refer patient from district hospital without specialist to general hospital?**
    i. Clinical and laboratory criteria
    ii. Early risk stratification, obtain early specialist advice for those at higher risk

7. **When to refer the patient for intensive care management? How to manage the critically ill dengue patient?**
    i. What are the clinical criteria for referral to intensive care team
    ii. Respiratory support, haemodynamic and renal support
    iii. Guide on safety and risk of invasive procedures

8. **What should be the fluid management in DF/ DHF /DSS?**

9. **DHF/DSS**
    i. Definition based on WHO classification
    ii. Clinical features- compensated & decompensated
    iii. Management of shock (refer algorithm)

10. **How do we manage haematological and haemostatic abnormalities?**
    i. Interpreting laboratory results
    ii. Is there a role of prophylactic transfusion?

11. **How to management bleeding in dengue patient?**
    i. What is considered significant bleeding
    ii. GIT Bleed -role of OGDS/ PPI and other treatment
    iii. Use of blood and blood products
    iv. Role of hormone treatment- oestrogen
    v. Role of vitamin K and tranexamic acid
    vi. Recognizing occult bleed

12. **Is there a role of drug therapy in DHF/DSS?**
    i. Role of recombinant Factor VII
    ii. Role of IVIG
    iii. Role of steroid

13. **What are the discharge criteria?**

14. **Guidance for follow-up after discharge whose readings have not normalised – serologically negative, developed complications and lab abnormality**

SEARCH STRATEGY

The following free text terms or MeSH terms were used either singly or in combination: Dengue Hemorrhagic Fever"[MeSH] OR "Dengue"[MeSH] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]) AND English[lang] AND "humans"[MeSH Terms] ("Dengue Hemorrhagic Fever/classification"[MeSH] OR "Dengue Hemorrhagic Fever/diagnosis"[MeSH]) OR "Dengue/classification"[MeSH] OR "Dengue/diagnosis"[MeSH]) AND English[lang] AND "humans"[MeSH Terms]; Dengue AND "viral Isolation"; Dengue AND "Laboratory test" ; Dengue AND "Laboratory diagnosis" Dengue AND "serology diagnosis"; IgM AND IgG; Dengue AND "molecular test"; (Dengue AND "Dengue Hemorrhagic Fever") AND "Fluid Management"; "Dengue Shock Syndrome "[MeSH] OR "Dengue Hemorrhagic Fever"[MeSH]; (Dengue Hemorrhagic Fever) AND (Fluid Management) AND Shock; dengue AND admission criteria AND laboratory AND clinical; dengue AND admission criteria AND laboratory ; dengue AND hospitalization; dengue AND hospitalization criteria; dengue AND admission; Dengue AND viral load AND day; dengue & defervescence ; dengue AND viraemia AND duration; dengue AND viral load AND duration; dengue AND "net screen"; dengue AND net AND hospital; dengue and triage; dengue AND triage AND "emergency department"; dengue AND ICU; Dengue AND ventilation; dengue AND "invasive procedures"; "dengue infection in ICU"; [MESH] dengue or dengue hemorrhagic fever or dengue shock syndrome-therapy and mortality.

LIST OF ABBREVIATIONS

BP	Blood Pressure
BUSEC	Blood Urea Serum Electrolyte Creatinine
CRT	Capillary Refill Time
CVC	Central Venous Catheter
DBP	Diastolic Blood Pressure
DF	Dengue Fever
DHF	Dengue Haemorrhagic Fever
DSS	Dengue Shock Syndrome
FBC	Full Blood Count
GCS	Glasgow Coma Scale
GXM	Group Cross Match
HCT	Haemotocrit
HCO_3	Bicarbonate
HELLP	Haemolysis, Elevated Liver Enzymes, Low Platelets
HI	Haemagglutination Inhibition
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LFT	Liver Function Test
NSI Ag	Non-Structural Protein-1 Antigen
PCR	Polymerase Chain Reaction
PP	Pulse Pressure
PR	Pulse Rate
RR	Respiratory Rate
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SBP	Systolic Blood Pressure
TCO_2	Total CO_2
WCC	White Cell Count

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LEVELS OF EVIDENCE SCALE

LEVEL	STRENGTH OF EVIDENCE	STUDY DESIGN
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)