Dengue GCP Guidelines 2012

Prof. Faisal Masud
Dr. Tayyaba Khawar Butt, Prof. Mohammad Ali
Adapted and modified from Clinical Practice Guidelines: Academy of Medicine, Malaysia
PREFACE

DENGUE GCP GUIDELINES – 2012

These are the first Good Clinical Practice Guidelines published by Dengue Expert Advisory Group (DEAG) for the management of dengue Infection in adults, hence forth going to be referred to as GCP dengue-guidelines-2012.

It must be emphasized that these guidelines are only meant to provide broad recommendations for good clinical practice, based on the best evidence available at the time of development of these recommendations - an overall management strategy in a garden variety of dengue patient. As each patient is unique hence adherences to these guidelines will, by no means, guarantee the best outcome in every case.

*Attending healthcare provider is best suited to make appropriate decisions for his patients, taking ground realities into consideration, regarding implementation / modifications of these “generic” protocols. After all, he is primarily responsible, for the management of his/her “unique patient” based on the clinical picture and the locally available management options.*

Review of the Guidelines

The authors have issued these GCP guidelines in 2012. It would be reviewed in 2014 or sooner if new evidence becomes available.

DEAG Secretariat
Services Institute of Medical Sciences,
Jail Road, Lahore

GUIDELINES DEVELOPMENT AND OBJECTIVE

GUIDELINES DEVELOPMENT

Primary Authors:

Prof. Faisal Masud
Dr. Tayyaba Khawar Butt
Prof. Mohammad Ali
Development and Review Committee:

In addition to the primary authors the development and review committee for these guidelines consisted of:

1. Prof. Javed Raza Gardezi
2. Prof. Mehmood Ayyaz
3. Prof. Aziz ur Rehman
4. Dr Sajid Nisar
5. Dr Saqib Shafi
6. Dr. Tahir Bashir

Special Committees

During the process of development of these guidelines, there was active involvement of the special committees tasked to formulate recommendations for dengue associated with co-morbidities.

Following authors contributed text of the manuscript:

- Prof. Rakhshanda Rehman
  
  *Dengue Fever in Pregnancy*

- Dr. Faisal Sultan and Dr. Syed Hammad Nazeer
  
  *Dengue Fever in Immunocompromised Host*

These guidelines are geared to provide:

1. In-depth description of the clinical course of dengue virus related illnesses to understand the dynamic and systemic nature of disease which has a significant bearing upon the clinical management of the patient.

2. An understanding of the basic pathophysiology of severe dengue (DHF i.e. plasma leakage and hypovolemia/shock) in the clinical context - and provide generic guidelines for the recognition of these changes and subsequent clinical management.

3. A brief discussion on WHO Classification (1997-2011) and its limitations.
4. A list of differential diagnoses that can be confused with dengue fever or vice versa; during different stages of dengue and some generic advice about it.

5. Appropriate documentation and forms for focused monitoring and management of the dengue disease taking into account the dynamic changes during the course of illness.

6. Simple practical action plan to diagnose, monitor and manage the plasma leak – with particular emphasis on its early signs and symptoms and on its relationship with hematocrit (HCT) and hemodynamic status of the patients.

7. Easy to follow algorithms on fluid management in dengue hemorrhagic fever (compensated and decompensated shock).

8. A guideline for early detection of occult bleed – importance of recognizing it and guide for replacing blood or its constituents.

9. A guidelines about recognition the signs of recovery and guide about when to safely discharge a patient.

Reference has also been made to other guidelines

- WHO Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control,
- Guidelines for DHF Case Management, Bangkok, Thailand 2002;
- Clinical Practice Guidelines: Academy of Medicine, Malaysia was used as general framework for these guidelines and was referred to extensively.

Our literature search yielded only a very few studies that were carried out on adult dengue patients and these could not provide us with sufficient breadth of information to draw up evidence-based recommendations. We have had to therefore, draw upon the studies carried out in the pediatric population. Extrapolating the results of these studies to the adult population carries the obvious risk of reaching biased conclusions and the committee is cognizant of this fact.
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 14 times throughout the development of the guidelines.

OBJECTIVES

GENERAL OBJECTIVES

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

SPECIFIC OBJECTIVES

• To improve recognition and diagnosis of dengue fever and provide appropriate advice for the care to these patients

• To identify severe dengue infection where it becomes mandatory to provide 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 provide guidelines for early and accurate notification of dengue cases for prompt public health intervention

CLINICAL QUESTIONS FOR SELF EVALUATION

Please refer to Appendix 15
TARGET POPULATION

Patients with dengue fever, dengue hemorrhagic fever or dengue shock syndrome and other forms of severe dengue fever and dengue fever with pre-existing co-morbidities. Adults are defined, in our GCP guideline, as patients aged 15 or more.

TARGET GROUP/USER

These guidelines are applicable to primary care family physicians, house officers, PGRs, senior registrars, public health personnel, nurses, medical officers & consultant physicians at DHQs, and critical care providers involved in treating patients with dengue fever.

HEALTHCARE SETTINGS

Teaching hospitals, DHQs and private health facilities - Both outpatient and inpatient settings.

ACKNOWLEDGEMENTS

External Reviewers

The following external reviewers provided feedback on the draft. The authors are grateful for their valuable comments

1. Prof. Javed Akram
2. Dr. LakKumar Fernando
3. Prof. Tahir Masood Ahmed
4. Prof. Tariq Salahuddin

Secretarial Staff (in alphabetical order)

The authors are indebted to the following for providing invaluable secretarial assistance in preparation of this manuscript

1. Mr. M Adil Ali
2. Mr. M. Zaheer Ud-Din Babar
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFACE</td>
<td>pI</td>
</tr>
<tr>
<td>GUIDELINES DEVELOPMENT AND OBJECTIVE</td>
<td>pI</td>
</tr>
<tr>
<td>GUIDELINES DEVELOPMENT COMMITTEE</td>
<td>pII</td>
</tr>
<tr>
<td>REVIEW COMMITTEE</td>
<td>pII</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>pIV</td>
</tr>
<tr>
<td>EXTERNAL REVIEWERS</td>
<td>pV</td>
</tr>
<tr>
<td>TABLE OF CONTENT</td>
<td>pVI</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>pIX</td>
</tr>
<tr>
<td>1. EPIDEMIOLOGY</td>
<td>p1</td>
</tr>
<tr>
<td>2. VIROLOGY</td>
<td>p5</td>
</tr>
<tr>
<td>3. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY</td>
<td>p6</td>
</tr>
<tr>
<td>3.1 Spectrum of Dengue Infection</td>
<td>p6</td>
</tr>
<tr>
<td>3.2 Clinical Course of Dengue Infection</td>
<td>p6</td>
</tr>
<tr>
<td>I. Febrile Phase</td>
<td>p6</td>
</tr>
<tr>
<td>II. Critical Phase</td>
<td>p7</td>
</tr>
<tr>
<td>III. Convalescent Phase</td>
<td>p8</td>
</tr>
<tr>
<td>3.3 Pathophysiology of Plasma Leak</td>
<td>p11</td>
</tr>
<tr>
<td>3.4 Tourniquet Test</td>
<td>p16</td>
</tr>
<tr>
<td>3.5 WHO Dengue Classification</td>
<td>p16</td>
</tr>
<tr>
<td>3.5.1 Limitations of WHO Classification</td>
<td>p17</td>
</tr>
<tr>
<td>3.5.2 Suggested WHO Classification 2009</td>
<td>p17</td>
</tr>
<tr>
<td>3.6 Other Important Manifestations</td>
<td>p19</td>
</tr>
<tr>
<td>3.7 Diagnostic Challenges</td>
<td>p20</td>
</tr>
<tr>
<td>4. DISEASE NOTIFICATION</td>
<td>p22</td>
</tr>
</tbody>
</table>
4.1 Epidemiological Classification for Disease Reporting p22

5. LABORATORY INVESTIGATIONS p24
   5.1 Disease Monitoring Laboratory Tests p24
   5.2 Diagnostic Tests p25
      5.2.1 Dengue Serology Tests p25
      5.2.2 Virus Isolation p27
      5.2.3 Polymerase Chain Reaction (PCR) p27
      5.2.4 Non-structural Protein-1 (NS1 Antigen) p28

6. INVESTIGATION OF POST MORTEM CASE p29

7. MANAGEMENT OF DENGUE INFECTION p30
   7.1 Introduction p30
   7.2 Triaging the patient at Emergency and Outpatient Department p34
   7.3 Criteria for Hospital Referral / Admission p34
      7.3.1 Referral from Primary Care Providers to Hospital p34
      7.3.2 Referral from Basic Health Units / Hospitals without Specialist to the Hospitals with Requisite Expertise p35
   7.4 Disease Monitoring p36
      7.4.1 Principles of Disease Monitoring p36
      7.4.2 Outpatient Disease Monitoring p36
      7.4.3 Inpatient Disease Monitoring p36
   7.5 Fluid Management p39
      7.5.1 Dengue with Warning Signs p39
      7.5.2 Patients in Critical Phase without Shock p40
      7.5.3 Dengue Shock Syndrome (DSS) p41
      7.5.4 Principles for Fluid Resuscitation p41
7.5.5 Calculation of Fluid Quota for Adults

ALGORITHM A - FLUID MANAGEMENT IN COMPENSATED SHOCK

ALGORITHM B - FLUID MANAGEMENT IN DECOMPENSATED SHOCK

7.6 Management of Bleeding/Hemostasis

7.6.1 Hemostatic Abnormalities in Dengue Infection

7.6.2 How to Recognize Significant Occult Bleeding?

7.6.3 Management of Bleeding in Dengue

7.6.4 Management of Upper Gastrointestinal Bleeding (UGIT)

7.6.5 The Role of Prophylactic Transfusions in Dengue

7.6.6 The Role of Adjunctive Therapy in Dengue

7.7 High Dependency Management

7.7.1 Indications for Respiratory Support (Non-invasive and Invasive Ventilation)

7.7.2 Indications for Hemodynamic Support

7.7.3 Safety & Risk – A Guideline for Invasive Procedures

8. DISCHARGE CRITERIA

9. PREVENTION OF DENGUE TRANSMISSION IN HOSPITALS

10. VACCINATION

11. DENGUE FEVER IN PAEDIATRIC POPULATION

11.1.1 Calculation of Ideal Body Weight

11.1.2 Choice of Fluid

11.1.3 Rate of Administration of IV Fluids in Critical Phase – without Shock

11.1.4 Rate of Administration of IV Fluids – During Shock
APPENDICES

| APPENDIX 1a – Investigations Summary | APPENDIX 9 – Home Care Advice Leaflet |
| APPENDIX 1b – Radiology Request Form | |
| APPENDIX 2 – Dengue Monitoring Charts | APPENDIX 10 – List of Abbreviations |
| APPENDIX 3a – OPD “Form O” | APPENDIX 11 – Acknowledgements |
| APPENDIX 3b – Inpatients “Form I” | |
| APPENDIX 4a – Reporting “Form R” (Suspected/Probable case) | APPENDIX 12 – Disclosure Statement |
| APPENDIX 4b – Reporting Form (Confirmed Case) | |
| APPENDIX 4c – SOP for Reporting Dengue Patients | |
| APPENDIX 5 – Diagnostic criteria – Non Epidemic Setting | APPENDIX 13 – Source of Funding |
| APPENDIX 6 – Dengue Temporary Regulations (by the Govt. of the Punjab) | APPENDIX 14 – Outcome & management indicators |
| APPENDIX 8 – Methods of Sample Collection | |
1. EPIDEMIOLOGY

Dengue has emerged as one of the most important mosquito-borne viral diseases of the humans. If improperly managed; it can carry a significant morbidity and mortality. It is predominantly a disease of urban and semi urban area in the tropics and sub-tropics. Because of the vector’s sensitivity to the temperature, a January isotherm of 10 °C in the northern hemisphere is considered to be the vector limiting range. Changing weather pattern associated with the global warming, mosquito vector is likely to extend its range from the tropical regions, deeper into the subtropical zones, of which Pakistan is a part. Lately, as a result of Lahore epidemic-2011, dengue has become an important public health issue in Pakistan.

Spread of dengue fever, therefore, illustrates how global trade (allowing the transport of the mosquito vectors in the used tires), increasing travel within and between countries (thereby allowing the movement of viremic people), urban crowding (which is conducive to multiple infections from a single infected mosquito), and ineffective vector-control strategies have supported a pandemic in the modern era. 1
The number of reported dengue fever (DF) and dengue hemorrhagic fever (DHF) are increasing all around the world. For example cases reported in Malaysia show an upward trend from 44.3 cases/100,000 population in 1999 to 181 cases/100,000 population in 2007 (Figure 1). But this increase in reported cases may be biased as all the febrile ailments (without dengue confirmation) are reported and included in the analysis.

Figure 1: Dengue Incidence Rate by Age Group in Malaysia, 1999-2007

Most of the Dengue related morbidity is related to Dengue fever; DHF accounts for less than 5% of all reported cases in S.E. Asia. (Figure 2)

Figure 2: Number of Dengue Cases DF & DHF, 1995-2007

Only 40-50% of the reported cases in the region are serologically confirmed at the time of notification (Figure 2). This relatively low percentage of seropositivity is often due to lack of availability of convalescent samples (second blood specimen) for confirmation. As discussed before, this low threshold for epidemiological reporting of dengue – without serological or viral confirmation - may have resulted in exaggerated number of cases reported from some of the SE Asian countries.

In Cambodia DF is mostly the disease of the younger age group (Figure 3). It might well be speculated that most of the adults, there, have acquired some degree of immunity to the virus because of their earlier exposures.

Figure 3: Age-specific incidence of dengue fever, Cambodia, 2002–2008
In Malaysia, however, the highest incidence of dengue is among the adults and adolescents above the age of 15 (Figure 1). An increase of dengue deaths in the adult population has been observed there since 2002 (Figure 4).

![Figure 4: Dengue Deaths by Age Group in Malaysia, 1999-2007](image)

Seventy to eighty percent of the dengue cases are reported were from the urban areas. Here a high density of population and rapid development activities and poor sanitation favors the vector replication and dengue transmission. Countries of South East Asia in general and Thailand in particular have one the biggest disease burden and have contributed a great deal of knowledge and understanding of the disease.
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 (by another serotype) is a major risk factor for DHF, mainly due to antibody induced enhancement (see section 3.3). Epidemiologic studies have identified young age, female sex, high body-mass index, virus strain or virulence and genetics of the human host e.g. major histocompatibility complex class I related sequence B and phospholipase C epsilon 1 genes as risk factors for severe dengue.⁴, ⁵, ⁶, ⁷

All four serotypes may be circulating in the population at any one time but from the experience in the south-east Asia it appears that the predominant circulating dengue virus will show a sinusoidal pattern – with a peak to peak interval of 6-7 years (Figure5). It is likely that this interval allows a buildup of immuno-naïve population of children.
3. CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

3.1 SPECTRUM OF DENGUE INFECTION

The incubation period (time between the viral invasion and onset of clinical disease) for dengue infection is generally between 4-7 days (range 3-14). The spectrum of clinical manifestations vary from totally asymptomatic disease to the severe disease, with or without plasma leakage and organ impairment.

Clinically significant dengue infection is a systemic disorder where clinical and hematological profiles may change by the hour or even minutes, particularly during the critical phase while the plasma leakage is going on (refer to section 3.3). Understanding the dynamic nature of this disorder is of paramount importance.

Realizing the systemic and dynamic nature of the pathophysiological changes during each phase of the dengue disease, an attempt will be made to provide a rational approach to the management of the disease.

3.2 CLINICAL COURSE OF DENGUE INFECTION

After the incubation period, the illness begins abruptly. Subsequent clinical course of dengue disease can be highly variable but can be, broadly, divided into three phases: febrile, critical and convalescent phase (refer Figure 6).

I. Febrile Phase

Typically, begins with sudden onset of high grade fever. This acute febrile phase generally lasts for 2-7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache.

There is often associated anorexia, nausea and vomiting. Some patients may have sore throat with congested pharynx and conjunctivae. These initial clinical features are common to both the patients who have simple DF and those who would go on to develop DHF subsequently.
On physical examination: Mild hemorrhagic manifestations like mucosal bleeding, petechial hemorrhages and positive tourniquet test are equally common – both in DF and DHF.\textsuperscript{10, 11} Vaginal bleeding is also seen frequently in the young adult females. Uncommonly, however, massive vaginal or gastrointestinal bleeding may occur during this phase.\textsuperscript{12, 11} Hepatomegaly is common but \textbf{tender} hepatomegaly is highly suggestive of DHF.\textsuperscript{10}

Investigations: The earliest hematological abnormality is a progressive decrease in total white cell count. A precipitous drop in platelet count could be a heralding feature of impending critical phase. This nonspecific viral response should alert the physician about the possibility of dengue, particularly during the dengue epidemic. NS1 antigen and PCR is generally positive during this early stage.

\textbf{II. Critical Phase}

Towards the end of febrile phase - around the time of defervescence (usually between 3\textsuperscript{rd} to 5\textsuperscript{th} day of illness but may up to 7\textsuperscript{th} day) a few patients enter the phase of increased capillary permeability. Unlike in other routine viral infections, where patient’s condition tends to improves with defervescence, in DHF at this point, depending upon the capillary leak, patient can go in two different clinical directions. Patients without significant plasma leak would gradually convalesce but those who would develop major plasma leak may actually deteriorate in the face of critical loss of volume.\textsuperscript{8, 9, 11, 14}

The critical phase would typically last for about 24-48 hours. (\textbf{Figure 6}) During this stage varying degree of circulatory disturbances (\textbf{Table 1}) can develop. In less severe cases, these changes are minimal and transient. Many of these patients recover with routine oral fluid and electrolytes or even with non-specific management at home. In more severe forms of plasma leakage, significant volume depletion occurs. A compensatory response in the form of increased sympathetic drive kicks in. Now the patient becomes restless, with cold clammy skin, rapid thready pulse and prolonged capillary refill time. As the diastolic blood pressure rises (increased sympathetic tone) in the face of unchanged systolic pressure (due to vasoconstriction) 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 with increased possibility of rapid progression to shock.\textsuperscript{14, 15, 16} In this stage The patient can rapidly progress to profound and irreversible shock, if fluid resuscitation is not instituted promptly and appropriately.

It is important to note that hemoconcentration (a rising trend of hematocrit from the baseline value) and thrombocytopenia are usually detectable even before the subsidence of fever and the onset of shock. It gives credence to the notion that low
grade plasma leak has started before hemodynamic compromise has become clinically apparent. Refer to 3.5.1 for further details. The HCT level correlates well with the amount of plasma volume loss and disease severity. Hematocrit may not, however, truly represent the volume loss in case of frank hemorrhage, early and excessive fluid replacement or when HCT determination is wrongly timed. Usually observed biochemical abnormalities include leucopenia with relative lymphocytosis, prolonged PT/APTT, elevated transaminases (typically AST > 3 x ALT), hypoproteinemia and hypoalbuminemia.8, 9, 10

The HCT level correlates well with the amount of plasma volume loss and the disease severity.

HCT may not, however, truly represent the volume loss in case of

1. Significant obvious or concealed hemorrhage
2. When HCT determination is wrongly timed

III. Convalescent Phase

Plasma leak stops within 24-48 hours from the time of onset, and is followed by reabsorption of extravascular fluid. Patient’s general wellbeing improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a classical rash of “isles of white in the sea of red”.8 Some patients may experience generalized pruritus. Bradycardia and electrocardiographic changes are not uncommon during this stage. It is important to note that during this phase, HCT level may drop further due to resorption associated hemodilution. The recovery of platelet count is typically preceded by recovery of white cell count (WCC).

Signs of recovery – convalescent phase

- Improved appetite, generalized feeling of wellbeing, diuresis
- Development of rash - “White isles in the sea of red”
- Recovering platelet count followed by reversal of leucopenia
Dengue related rash during convalescence stage. This maculo-papular rash is flat, erythematous and blanch able (disappears upon pressure): typically described as **isles of white in a sea of red**.

The rash in dengue is **usually centripetal**.

This means that the rash starts on the limbs before "moving" or spreading to the trunk! (Differential diagnosis would include coxsackie virus infection, secondary syphilis, and rocky mountain spotted fever). ¹⁷

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**Figure 6: Clinical Course of DHF**¹⁸

Note: Onset of defervescence usually occurs between day 3 to day 5 of illness
- **Critical phase is so named because during this stage, clinical deterioration** (due to the plasma leakage) can occur.
- It is therefore crucial to recognize the onset of this CRITICAL PHASE.
- Onset of critical phase often coincides with defervescence.
- **Warning signs often precede the** clinical evidence of plasma leak.
- **Warning Signs (risk of plasma leak high):**

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Persistent vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>Altered conscious level</td>
</tr>
<tr>
<td>Enlarged tender hepatomegaly</td>
<td>Extensive mucosal bleeding</td>
</tr>
</tbody>
</table>

- Evidence of plasma leakage includes: **raised HCT** (early marker), hemodynamic instability, **and fluid accumulation in extravascular space** (rather late marker) or hypoproteinemia.
3.3 PATHOPHYSIOLOGY OF PLASMA LEAK

The initial, febrile, phase of the Dengue disease mimics the picture of common acute viral illnesses. Only towards the end of febrile illness, in a small subset of the patients, features of increased capillary permeability and plasma leak are witnessed. Although it might well be speculated that increased plasma permeability is present in all the case of dengue disease – plasma leak remains small and clinically compensated in most of the patients. Only in a small percentage of patients does this condition cross the critical threshold of compensatory mechanisms to become clinically significant.

This acute increase in vascular permeability beyond the critical limit of compensatory responses - is the primary pathophysiological event that would differentiate DHF and DSS from uncomplicated DF. This leak is responsible for the loss of plasma into the extravascular compartment, giving rise to the hemoconcentration, hypovolemic state and in extreme condition, to shock.\textsuperscript{8, 9, 19} In common with classical volume depleted state, it leads to reflex tachycardia and generalized vasoconstriction as a result of increased sympathetic activity.\textsuperscript{20, 21}

This compensated stage of shock is characterized by the responses initiated by the patient to overcome the stress of volume depletion. Physiological mechanisms - neural, hormonal and bio-chemical – kick in to compensate for the stress of hypovolemia. The baroreceptors in the arteries detect a drop in BP, and cause the release of adrenaline and noradrenaline. These catecholamines cause vasoconstriction and tachycardia – body’s attempt to increase the blood pressure. Vasoconstriction results in tissue hypoxemia and anaerobic glycolysis which in turn gives rise to acidosis. Acidosis mediated respiratory center stimulation causes hyperventilation (tachypnea). By hyperventilating and washing out CO\textsubscript{2}, the body is, indirectly, trying to correct the acidosis. Vasoconstriction can affect the kidneys, stimulating renin-angiotensin-aldosterone axis to cause further vasoconstriction and conservation of fluid via increased renal reabsorption. Vasoconstriction which started in the splanchnic circulation can spread to kidneys, gastrointestinal tract, and other organs to divert blood preferentially to the heart, lungs and brain. This reduction in renal circulation (GFR) manifests itself in the form of reduced urine production.\textsuperscript{22}

Severity of shock in the face of plasma leak - due to increased vascular permeability - would depend upon:

- State of hydration at the time of the onset of the leak
- Cardiac reserve
- Severity of the vasculopathy (rate of plasma leak)
- Any existing co morbidity
Pathophysiological events that occur during DSS are exactly like those of “classical hypovolemic shock” due to blood loss (or volume loss during gastroenteritis). The only difference is that in DHF the volume lost to the serosal cavities is rich in proteins and is available for reabsorption (through lymphatics) subsequently.

Clinical manifestations of vasoconstriction in various systems are as follows:

- **Skin**—is cold, clammy skin, with pallor and delayed capillary refill time
- **Cardiovascular system**—shows raised diastolic blood pressure and a narrowing of pulse pressure – an effect of increased sympathetic outflow.
- **Renal system**—As a result of reduced GFR, urinary output drops.
- **Gastrointestinal system**—nausea, vomiting and abdominal pain
- **Central nervous system** – As a function of reduced cerebral perfusion there may be lethargy, restlessness, apprehension, impaired consciousness and combative behavior.
- **Respiratory system** – Tachypnea (respiratory rate >20/min in adults) – a feature of shock

In patients where consciousness is not obtunded, **intense thirst** can also be a significant symptom. As mentioned before, inadequate perfusion of the tissues, as a result of intense vasoconstriction and viscous hemoconcentrated blood, leads to increased anaerobic glycolysis and **lactic acidosis**. If the loss of volume is not corrected promptly, the patient will progress into the state of decompensated shock. Once this stage of decompensation is reached, patient can rapidly progress to the stage of refractory shock. In this state, any amount of volume replacement would not restore the normal tissue perfusion or cardiac output and pressures, even if vasopressor agents are used.

Primary reason for the irreversibility of shock at this point is that in the absence of O₂, to act as an electron receptor in the mitochondrial matrix, most of the cellular ATP gets degraded into adenosine. Adenosine is a potent vasodilator. It readily diffuses out of cellular membranes into extracellular fluid, further increasing the capillary vasodilation. Because the cells have a very limited capacity to replenish adenosine (at the rate of about 2% of the cell’s total need per hour), restoring oxygen, at this point, is futile because there is no adenosine to be phosphorylated into ATP.
As mentioned before, lactic acidosis which often accompanies shock, has suppressant effect on myocardium which in turn further worsens the hypotension. Intense vasoconstriction and subsequent ischemic necrosis of the tissues can result in massive bleeding, disseminated intravascular coagulopathy (DIC) and multi-organ failure - a common late complications of prolonged shock.

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

<table>
<thead>
<tr>
<th>Normal Circulation</th>
<th>Compensated Shock</th>
<th>Decompensated / Hypotensive Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear consciousness</td>
<td>Clear consciousness - shock can be missed if you do not touch the patient</td>
<td>Change of mental status - restless, apprehensive, combative or lethargic</td>
</tr>
<tr>
<td>Brisk capillary refill time (&lt;2 sec)</td>
<td>Prolonged capillary refill time (&gt;2 sec)</td>
<td>Mottled skin, very prolonged capillary refill time</td>
</tr>
<tr>
<td>Warm and pink extremities</td>
<td>Cool extremities</td>
<td>Cold, Clammy extremities</td>
</tr>
<tr>
<td>Good volume peripheral pulses</td>
<td>Weak &amp; thready peripheral pulses</td>
<td>Feeble or absent peripheral pulses</td>
</tr>
<tr>
<td>Normal heart rate for age</td>
<td>Tachycardia</td>
<td>Severe tachycardia bradycardia in late shock</td>
</tr>
<tr>
<td>Normal blood pressure for age</td>
<td>Normal systolic pressure with raised diastolic pressure and postural hypotension</td>
<td>Hypotension / un-recordable BP</td>
</tr>
<tr>
<td>Normal pulse pressure for age</td>
<td>Narrowing pulse pressure (≤30 mmHg)</td>
<td>Narrowing of pulse pressure (≤20mmHg) OR Pulse pressure not recordable</td>
</tr>
<tr>
<td>Normal respiratory rate for age</td>
<td>Tachypnea</td>
<td>Metabolic acidosis; hyperpnoea Kussmaul’s breathing</td>
</tr>
<tr>
<td>Normal urine output</td>
<td>Reduced urine output</td>
<td>Oliguria or anuria</td>
</tr>
</tbody>
</table>

**Table 1:** *A continuum of pathophysiological changes from normal circulation to compensated and decompensated/hypotensive shock (Adapted from 21)*

The molecular mechanism responsible for the increased vascular permeability seen during DHF/DSS is still not well understood. This is partly due to the lack of animal models that would accurately replicate the event of plasma leak as seen during DSS. There is no evidence that the virus infects endothelial cells, and only minor nonspecific
changes have been detected in histopathological studies of the microvasculature, although some perivascular edema and loss of integrity of endothelial junctions with endothelial dysfunction are found.

It appears that immune hyper-drive results in massive over production of cytokines (Cytokine Storm), due to aberrant activation of T-lymphocytes and disturbances of homeostatic system involving Tregs. High concentrations of mediators of inflammation including C3a, C5a, tumor necrosis factor-α, interleukin 2, 6 and 10, interferon-γ and histamine have also been noted.

There is still paucity of data to suggest a specific pathway that would link the immunopathological event on one hand with event of increased vascular permeability and disturbed thrombo-regulation on the other. However, there is some preliminary data to suggest a transient dysfunction of the endothelial glyocalyx layer. This layer functions as a molecular sieve, selectively restricting molecules from seeping out of the
vasculature, according to their size, charge, and shape\(^1\). A crucial alteration in the filtration characteristics of the glycocalyx occurs during dengue related plasma leak. It would cause proteins - up to and including the size of albumin - to preferentially leak out of the vascular tree. This may explain hypoalbuminemia and proteinuria - observed during dengue infection.\(^2^9\) Both the virus itself and dengue NS1 are known to adhere to heparin sulfate, a key structural element of the glycocalyx, and increased urinary heparan sulfate excretion has been detected in children with severe dengue infection.\(^3^0, 3^1\)

It seems that increased capillary permeability is a non-specific event that happens in all forms and phases of the Dengue Disease. It is just the extent and rapidity of the fluid loss that defines the clinically crucial “critical phase”. Patients with minimal capillary leak which occurs slowly, fall towards the benign end of the spectrum while those with rapid & severe leak, which overwhelms the compensatory responses, constitute the “critical end” comprising of DSS.

A second infection with a heterotypic dengue virus may impart increased risk of developing DHF. Antibody-dependent enhancement of viral replication is believed to be responsible for this phenomenon.\(^3^2, 3^3, 3^4\) Dengue virus is released from the host cells in two forms. The immature form, unlike mature particles, is **incapable** of entering new host cells. Sub-neutralizing concentration of the cross-reacting antibody from the previous infection may opsonize these immature virus particles and allow the entry and replication of immature virion in the macrophage or mononuclear cells.\(^3^5\) This is mediated through Fc epitope recognizing domains on the macrophages. The 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 enhanced immunopathology found in patients with DHF.\(^9, 2^6\)

- Dengue Disease exhibits a continuous spectrum of illness - from benign DF to DSS - with escalating vascular permeability from minimum to severe.
- Increased vascular permeability - beyond the capacity of compensatory mechanisms - leads to plasma leakage and results in hypovolemia & shock.
- Significant amount of volume is lost in the third space and it constitutes the primary pathophysiological abnormality in DHF/ DSS.
3.4 TOURNIQUET TEST

In mild DHF, a positive tourniquet test may be the only indicator of hemorrhagic tendency. The sensitivity of the test varies widely from low to very low. Depending upon the phase of illness and how frequently the test was repeated it shows positivity in 0% to 57%, of cases. A positive tourniquet test is quite non-specific. About 5-21% of patients with dengue like illness returned a positive tourniquet test but subsequently turned out to have negative dengue serology.\(^{36}\)

A recent study, however, asserts that presence of fever, leucopenia, thrombocytopenia, hemoconcentration and positive tourniquet test had 95.3% positive predictive value for dengue.\(^{37}\)

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 10 or more petechiae per 2.5 cm (1 inch) square are observed.

Recommendation

Although a positive tourniquet test alone has a poor predictive value but in the presence of other supportive evidence may be helpful in differentiating dengue from other febrile illnesses.

3.5 WHO DENGUE CLASSIFICATION

Based on current WHO dengue classification scheme (refer Appendix 7), 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 do overlap and it is often impossible to differentiate DF and DHF.

DHF is further sub-classified as mild (grades I and II) or severe (grades III and IV), the presence of shock, due to volume leakage, being the main difference. Grades III and IV are classified as Dengue Shock Syndrome (refer Appendix 7).

(Note: The existing WHO dengue classification have been reviewed and revised)
3.5.1 Limitations of WHO classification

With ever increasing spread of Dengue fever WHO recommendations were adopted widely. But it has been observed that the existing WHO classification scheme has several limitations and shortcomings. For example:

1. Dengue with shock without fulfilling all the 4 criteria for DHF (Fever, Thrombocytopenia, Hemorrhage, Plasma Leak). There have been many case reports of patients with severe dengue with shock who do not fulfill all the 4 criteria for DHF. These patients would automatically get classified as dengue fever (DF) if the WHO criteria were to be applied strictly.

2. Arguably; one of the major causes of morbidity and mortality in DHF is severe end-organ impairment - hepatic, respiratory, cardiac and brain dysfunction – which is not considered as a criterion for labeling it as DHF, 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 often not available in most of the patients. Diagnosis of a plasma leak can, therefore, be only be made retrospectively, using this criterion.
   b. Dilution due to early fluid administration may affect the level of HCT
   c. Bleeding will have an impact upon patient's HCT and may not rise despite significant leak.

4. The existing WHO classification, sometimes, cannot be used prospectively in the clinical management of the patient because the disease can only be classified retrospectively.

Patients can present with severe dengue without fulfilling ALL the four criteria (refer Appendix 7) for DHF/DSS.

3.5.2 Suggested WHO Classification 2009

Grading the disease according to severity is a very useful tool for clinical management and algorithm driven decision making. It can help decide the course of action for the clinician in a reproducible fashion as to where, when 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

**Figure 1.4 Suggested dengue case classification and levels of severity**

**DENGUE ± WARNING SIGNS**

**With warning signs**
- Probable dengue: Lives in / travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, Vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Thrombocytopenia
  - Any warning sign
- Laboratory - confirmed dengue (Important when sign of plasma leakage)

**SEVERE DENGUE**

1. Severe plasma leakage
2. Severe hemorrhage
3. Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

**Warning Signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count, (requiring strict observation and medical intervention)

**CRITERIA FOR SEVERE DENGUE**

Severe plasma leakage leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress
- Severe bleeding as evaluated by clinician
- Severe organ involvement
- Liver: AST or ALT> =1000
- CNS: Impaired consciousness
- Heart and other organs

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-recognized or misdiagnosed:

1. Acute abdomen:

Acute abdominal pain - a common symptom in dengue infection - and occasionally misdiagnosed as acute appendicitis; can have diverse etiology ranging from flavivirus associated hepatitis, acalculous cholecystitis and shock. When fever precedes abdominal pain, and laboratory findings of leucopenia, thrombocytopenia instead of leukocytosis, prolonged APTT in the face of normal PT help to differentiate acute abdominal pain due to dengue infection from surgical causes of acute abdomen. Again subsidence of abdominal pain with treatment of shock with appropriate fluids would characterize dengue rather than surgical cause.

2. Hepatitis and liver failure:

As in other flavivirides, mild to severe hepatitis is common in patients with DF/DHF irrespective of the degree of plasma leakage. In some cases, liver failure may occur. Patients with liver failure have a high propensity to bleed, especially from gastrointestinal tract.

3. Neurological manifestation:

A few patients (<1%) with dengue infection may develop neurological manifestations, mainly encephalitis, encephalopathy and rarely myelitis and Guillain-Barré Syndrome. Some of these patients, at least, belong to MAS (Macrophage activation syndrome) associated encephalopathy, therefore, dengue fever must be included in the differential diagnosis in any patient diagnosed as viral encephalitis.

4. Hemophagocytic Histiolympocytosis (HLH) syndrome

This is an uncommon syndrome and is often seen as sequel to overactive cytokine productions. It is often associated with dysregulated T cell activation and macrophage function, following dengue virus infection. The “cytokine storm” induced by massive
immense plasma leakage leading to cellular edema, cellular damage, necrosis and the cell death. This syndrome should be looked for in patients with unusually low ESR, progressive cytopenia and multi-organ complications. Serum triglycerides and serum ferritin are often markedly elevated with very low fibrinogen levels. Definitive diagnosis can be made by performing bone marrow biopsy which demonstrates hemophagocytic activity.

### 3.7 DIAGNOSTIC CHALLENGES

It is easy to misdiagnose dengue in non-endemic setting because clinical features of dengue infection are rather non-specific and mimic many other diseases. An early and accurate diagnosis would need an astute physician with high index of suspicion. Situation may get complicated further if a dengue patient carries an additional 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>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like syndrome</td>
<td>Influenza; Measles; Chikungunya, Adenovirus; Infectious mononucleosis</td>
</tr>
<tr>
<td></td>
<td>Acute HIV seroconversion illness</td>
</tr>
<tr>
<td>Rash</td>
<td>Rubella; Measles; Scarlet fever, Meningococcal Infection; Drugs</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Rotavirus, Food poisoning</td>
</tr>
<tr>
<td>Neurological manifestation</td>
<td>Meningo-encephalitis Febrile seizures</td>
</tr>
</tbody>
</table>

Table 2: Differential diagnoses for dengue illness during febrile phase
## Table 3: Differential diagnoses for dengue illness during critical phase

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute abdomen</td>
<td>Acute appendicitis; Acute cholecystitis Perforated viscus; Viral hepatitis Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Shock</td>
<td>Septic shock; Cardiogenic shock</td>
</tr>
<tr>
<td>Respiratory distress (Kussmaul’s breathing)</td>
<td>Diabetic ketoacidosis; Renal failure Lactic acidosis</td>
</tr>
<tr>
<td>Leucopenia &amp; Thrombocytopenia/Bleeding</td>
<td>Acute leukemia; Aplastic anemia; Immune thrombocytopenic purpura; Thrombotic thrombocytopenic purpura; Malaria / Leptospirosis / Typhoid / Typhus Bacterial sepsis; SLE Acute HIV seroconversion illness</td>
</tr>
</tbody>
</table>
4. DISEASE NOTIFICATION

4.1 Case Reporting and Epidemiological categorization

For the purpose of epidemiological disease notification, the prompt diagnosis and reporting of all the dengue cases is essential.

In areas of the world where dengue disease is endemic, all the cases of PUO, presenting with nonspecific features, would have DF included in the list of differential diagnosis. The category of “SUSPECTED DENGUE” as defined by GCP guidelines will be inclusive of all such cases (Appendix 5). The diagnostic yield in non-epidemic situation, within this cohort, is often very small. (All the viral illnesses, malaria, typhoid and PUOs would muddy up the data).

In our clinical practice, all the “suspected cases” have to have a CBC done. If Patient has WBC count of less than 3000 and platelet count of less than 100,000, patient would be categorized as “PROBABLE DENGUE”. Case reporting is then, mandatory. (Section 5.1 & DEAG “Form R”, Appendix 4a)

Confirmatory tests in these patients in the form of viral isolation (PCR), documentation of NS1, or four fold increases in the immunoglobulin titer on paired sample taken 5 days apart would clinch the diagnosis as “CONFIRMED DENGUE” – albeit too late for epidemiological purpose. (Section 5.2 & Appendix 5) Filing of a detailed case report form (Appendix 4b) is mandatory here.

---

Dengue fever diagnosis is divided into three categories for epidemiological purposes (This is not a clinical staging)

- Suspected dengue:
- Probable dengue:
- Confirmed Dengue: (See Appendix 5 for detailed description)

All Probable dengue cases, admitted to the hospital or under the care of a GP, must be notified to the EDO health who in turn will report to DG health within one hour – it is to be followed by written notification within 24 hours using the standard notification format (Ref to DEAG “Form R” on Appendix 4a). Absence of disease notification system or delay, if there was indeed a system, was the major cause of the dengue epidemic in Lahore in 2011.
In the state of epidemic, notification should be done as soon as a clinical diagnosis of dengue is suspected; hematological/serological confirmation is not necessary. The DG health would appoint officers to visit the notifying doctor to get the particulars of the patient for the verification of case and initiation of preventive measures. It is also important to note that re-notification has to be done if the diagnosis is reversed from DHF/DF to other diagnosis.

Failure to notify dengue is liable to be compounded under the Punjab prevention and control of Dengue (temporary) regulations 2011 - NO.S.O. (PH) 9-98/2002 (P-1) (Appendix 6)

This reporting protocol is similar to the one being followed in Malaysia.
5. LABORATORY INVESTIGATIONS

5.1 Disease Monitoring Laboratory Tests

Full Blood Count (FBC)

1. White cell count (WCC):
In the beginning of the febrile phase WCC is usually normal but will decrease rapidly as the disease progresses.\(^{10}\) WCC may show relative lymphocytosis, this non-specific trend of leucopenia should raise the suspicion of possible dengue infection in appropriate settings.

2. Hematocrit (HCT):
Hemoconcentration as depicted by rising HCT is a marker of plasma leakage in dengue infection and helps to differentiate between DF and DHF — A significant blood loss and early fluid replacement may mask this trend.\(^{36}\) It is of paramount importance to get a baseline HCT in the early febrile phase of disease. It will become handy latter on for early recognition of plasma leak – detection of rising HCT level.

3. Thrombocytopenia:
Thrombocytopenia is perhaps the most common (and most maligned) laboratory investigation in dengue infection.\(^{36}\) 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\(^{8, 45}\) but it is not predictive of bleeding.\(^{46, 47, 48, 49, 50}\)

4. Liver Function Test
Abnormal LFTs in the form of elevated transaminases is common and is characterized by greater elevation of the AST as compared to the ALT.\(^{51}\) The frequency and degree of elevation of the liver enzymes are higher with DHF compared to DF.\(^{51, 52}\)
• Leucopenia followed by progressive thrombocytopenia is suggestive of dengue infection.
• A rising HCT accompanying progressive thrombocytopenia 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.

Recommendations

• The baseline HCT and WCC should be established as early as possible in all patients with suspected dengue.
• Serial FBC and HCT must be monitored as the disease progresses.

5.2 Diagnostic Tests

Definitive diagnosis of dengue infection can only be made through laboratory investigations. Interpretation of laboratory diagnostic results, however, should only 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

Hemagglutination Inhibition Test

The hemagglutination Inhibition (HI) test: HI test is considered a gold standard for the serological diagnosis of dengue. It is non-mechanized labor intensive test which requires paired samples for proper interpretation, therefore it is a test that is mainly being used for research - to differentiate between primary and secondary dengue infections.

Dengue IgM test: Dengue-IgM capture enzyme-linked immunosorbent assay (ELISA) is the most widely used serological test, to diagnose dengue. The titer of IgM tends to be significantly higher in primary infections (1^0) as compared to secondary (2^0) infections. Once the IgM becomes detectable by day 5, it rises rapidly and peaks at
about 2 weeks after the onset of symptoms, it wanes slowly in the following months to reach undetectable levels after a variable interval. Some fully recovered healthy people, who had had an exposure to the dengue virus in the recent past, might well test positive to the dengue IgM. Therefore, mere presence of IgM might not be diagnostic of a current illness. A positive IgM result, in endemic situation, therefore, has to be interpreted with care taking the clinical picture in to consideration. If the dengue IgM test is the only available diagnostic test in the hospital, a paired sample - one in early febrile phase and other later, after day 5 of illness - will be essential for proper interpretation of the results.

Specific IgM was detected in all the cases with primary dengue virus infection on disease day 9 or later. Anti-dengue IgM is, a sensitive test for detection of primary dengue after day seven – (IgM was detected in only 55% of patients with primary dengue infections between day 4-7 of the onset of fever) - which became positive in 100% of the patients after day seven to nine.

In secondary dengue infections, IgM was detected in only 78% of patients after day seven. In another study, 28% of secondary dengue infections remained undiagnosed when IgM was the only test performed. It can be assumed, therefore, that IgM is not very reliable test for detection of secondary dengue infection.

Indirect IgG ELISA test: Both in primary and secondary dengue infection, dengue IgG becomes detectable in 100% of patients after day seven of onset of fever. A paired dengue IgG is, therefore, a recommended test to see the seroconversion; if dengue IgM stays negative after day seven, if the disease is still suspected clinically.

**Recommendations**

- Seroconversion for dengue IgM in a paired sample is conclusive evidence of dengue fever. Therefore dengue IgM should be taken as soon as the disease is suspected.
- Dengue IgM is usually becomes positive after day 5-7 of illness. Therefore a negative IgM taken before day 5-7 of illness does not exclude dengue infection.
- If dengue IgM is negative before day seven, a repeat sample must be taken in recovery phase.
- If dengue IgM is still negative after day seven with negative IgG test reported at less than seven days, a four fold rise in reciprocal Ig G antibody titre between acute and convalescent sera is needed for diagnostic confirmation. **Appendix 4b**
Simple rapid tests such as the strip assays (immune-chromatography test) are available for qualitative detection of dengue IgM and IgG. These rapid tests have moderate sensitivity and specificity when the samples are collected in the late convalescent phase. These can be used when ELISA test were not available. But have to be interpreted within the clinical context with clear understanding of significantly reduced sensitivity and specificity. It is recommended that the dengue IgM ELISA test be done after a rapid test.

**Note: False positive dengue serology:**

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

- Other flavivirides – Japanese Encephalitis.
- Non-flavivirus infections – malaria, leptospirosis, toxoplasmosis, syphilis.
- Connective tissue diseases – rheumatoid arthritis.

### 5.2.2 Virus Isolation

The definitive test for dengue infection is the virus isolation. However this test can only be performed in specialized labs equipped with tissue culture and virus isolation facilities. It is useful only at the early viremic phase of the illness. Generally, virus can be detected in the blood until day five 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. This costly test may take up to two weeks to complete.

Note: Virus isolation has a poorer yield as compared to PCR. It is most probably due to poor viability of the virus and the poor quality of the samples.

### 5.2.3 Polymerase Chain Reaction (PCR)

In the early phase (< 5 days of illness), molecular tests such as the reverse transcriptase – polymerase chain reaction (RT-PCR) can be very useful for the diagnosis of dengue infection. It was shown to have a sensitivity of 100% in the first 5 days of disease, but is reduced to about 70% by the day six, as expected with declining
viraemia. An additional advantage of RT-PCR is the ability to determine dengue serotypes

Limitations of RT-PCR are:

a) This test is only available in a few centers with facilities and trained personnel (e.g. NIH Islamabad, AIMC, IPH and Services Institute of Medical Sciences, Lahore).

b) The test is costly.

c) The specimen requires special handling for storage and transport, between the time of collection and extraction (Appendix 8) 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. 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%).

The sensitivity of NS1 antigen detection starts to drop off from the day 4-5 of illness and is usually undetectable in the convalescence phase.

Recommendations

- PCR can be used as a diagnostic tool in early dengue infection. It is not recommended as a routine diagnostic test due to limited availability and cost.

- NS1 Ag is a good diagnostic tool that is very useful in the early phase of dengue infection. It is not useful in the convalescence phase.

Please refer to Appendix 8 for methods of sample collection for diagnostic 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.\textsuperscript{3, 78} However PCR is a more sensitive method.\textsuperscript{78, 79, 80}

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.

**Recommendations**

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

Please refer to Appendix 8 for methods of sample collection.
7. MANAGEMENT OF DENGUE INFECTION

7.1 Introduction

There is no currently available anti viral medication against the dengue virus after the host invasion. The mainstay of dengue infection management stays 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 three phases of the clinical course (section 7.4). It is crucial to recognize plasma leakage & shock at an early stage, to guard against severe organ impairment. This can only be achieved through frequent clinical and laboratory monitoring.

Dengue patients who are managed in the outpatient setting should be provided with an OPD form (DEAG Form O, Appendix 3a) to ensure that all relevant information stays available to all the concerned health care providers.

Primary care providers with no immediate hematocrit facilities should refer patient to the nearest health care facility where hematocrit measurement facility is available for further management.

Table 4:  A Stepwise Approach in Evaluation of Dengue Fever

It is important to evaluate every patient in a stepwise manner - as follows:

**Step 1: Overall assessment**

1. **History**
   - Date of onset of fever/ illness
   - Oral intake of fluids (estimated)
   - Assess for warning signs – Table 5
   - Diarrhea
   - Bleeding
   - Change in mental state/seizure/dizziness
   - Urine output (frequency, volume and time of last voiding)
   - Other important relevant points in history:
     - History of dengue in the family or the neighborhood
     - Jogging/walks in the park and swimming in waterparks
- H/O recent travel to the endemic zones (inside or overseas destinations)
- Recent unprotected sexual or drug use behavior (consider acute HIV seroconversion illness)
- Co-morbidities (consider sepsis particularly in patients with diabetes mellitus)

2. **Physical examination**
   
i. Assess mental state and record Glasgow Coma Scale (GCS) score
   
   ii. Assess hydration status
   
   iii. Assess hemodynamic status
       - Skin color
       - Capillary refill time (normal <2 seconds)
       - Pulse volume
       - Cold/ warm extremities
       - Pulse rate
       - Blood pressure
       - Pulse pressure

   iv. **Resp. Sys:** Look out for tachypnea/ acidotic breathing/ pleural effusion

   v. **G.I Sys:** Check for abdominal tenderness/ hepatomegaly/ ascites

   vi. Examine for manifest bleeding

   vii. Tourniquet test (Repeat at 6 hourly interval – 3 times - if previously negative)

3. **Investigations**

   1: CBC and HCT
   
   2: Dengue serology

OPD form (Appendix 3a) is useful for screening febrile patients with suspected and probable dengue. Elucidating details in history and examination as above will be required in admitted patients (Appendix 3b – Form I)

Once the diagnosis is made it is important to recognize the stage of the disease and the presence of any warning signs. Further management will depend on the preceding information.
Step 2: Diagnosis, disease staging and severity assessment

Based on evaluations from history, physical examination +/- CBC and HCT, the clinicians should be able to determine:

1. Diagnosis of Dengue Fever (suspected, probable or confirmed)
2. The phase of illness (febrile/critical/convalescent or recovery)
3. The hydration and hemodynamic status of patient
4. Whether the patient requires admission

Step 3: Plan of management

1. Notify the EDO health
   - via phone of all the probable cases of dengue - followed by a written notification on DEAG-“Form R” (Appendix 4a)
   - In confirmed cases use disease notification form. (Appendix 4b)

2. If admission is indicated - refer to admission criteria 7.3.1:
   - Stabilize the patient (Algorithm A or B as appropriate - page 45, 46)
   - Communicate with the receiving hospital/ Emergency & Trauma Department/HDU before transfer

3. If admission is not indicated (Table 6 - page 33):
   - 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 (Appendix 9)

Adapted from3, 8, 9
### Table 5: Warning signs \(^{13,14}\)

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain or tenderness</td>
<td>Increasing HCT with falling platelets</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>Free fluid in pleura or peritoneum on ultrasonography</td>
</tr>
<tr>
<td>Pleural effusion, ascites</td>
<td></td>
</tr>
<tr>
<td>Significant manifest bleed</td>
<td></td>
</tr>
<tr>
<td>Restlessness/ lethargy/ Irritability in infants</td>
<td></td>
</tr>
<tr>
<td>Tender enlarged liver</td>
<td></td>
</tr>
<tr>
<td>Decreased urine output</td>
<td></td>
</tr>
</tbody>
</table>

Patients who are not in critical phase and hemodynamically stable can be treated at home with close follow-up as required

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

1. Tolerating orally, adequate urine output
2. Absence of significant manifest bleed
3. Absence of clinical alarm signals (refer Table 5)

**Physical examination defining hemodynamic stability:**

<table>
<thead>
<tr>
<th>Physical Examination</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pink, warm extremities</td>
<td>Normal capillary refill time (normal &lt;2 seconds)</td>
</tr>
<tr>
<td>Good pulse volume</td>
<td>Stable blood pressure</td>
</tr>
<tr>
<td>Normal pulse pressure (&gt; 30mmHg)</td>
<td>Absence of disproportionate tachycardia</td>
</tr>
<tr>
<td>No tachypnea or acidic breathing</td>
<td>Absent hepatomegaly or abdominal tenderness</td>
</tr>
<tr>
<td>No bleeding manifestation</td>
<td>No sign of pleural effusion/ ascites</td>
</tr>
<tr>
<td>No alterations in mental state and full GCS score</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6: Investigation defining hematological stability stable state:

- Stable serial HCT
- In the absence of a baseline HCT level, a HCT value sustained at >40% in female adults and >46% in male adults should be safe enough for the patient to be discharged \(^ {81,82}\)

Adapted from \(^ {83,81,82}\)

#### 7.2 Triaging the Patient at Accident & Emergency / Outpatient Department

As usual the purpose of triaging patients in A&E department is to identify those patients who would require urgent medical attention. This is to avoid critically ill patients being ignored while less critical patients are being attended to. \(^ {84,83,85,86}\)

Triage the patient according to warning signs already given (Table 5)

#### 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 upon the overall assessment of the patient, taking history, physical examination and labs into consideration.

---

**Referral from primary care providers to hospital**

1. **Symptoms**
   - Presence of warning signals (Table 5)
   - Inability to tolerate oral fluids
   - Inadequate urine output (less than 25ml/hour or 0.5ml/kg/hour in children)
   - Seizure
2. **Signs**

- Clinical signs of dehydration
- Shock *(Table 1)*
- End organ failure

3. **Special Situations for early referral to the hospital**

- Patients with co-morbidity e.g. Diabetes, Hypertension, Ischemic Heart Disease, Coagulopathies, Morbid Obesity, Renal Failure, Chronic Liver disease, COPD
- Infants < 1 year of age and elderly > 65 years of age
- 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 basic health units / hospitals without specialist to the hospitals with requisite expertise**

All the doctors are encouraged to talk to the DEAG expert for on-line advice. Early consultation with the nearest expert should be initiated for all DHF patients, irrespective of the complications, end organ dysfunction or bleeding.

**Prerequisites for transfer**

1. All efforts must be made to optimize 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. As discussed previously, dengue is a systemic and dynamic disease. Therefore disease monitoring would vary dynamically in different phases of the disease.

2. During the critical phase (plasma leakage) which 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 convalescent 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, who presents in outpatient or A & E department and is suspected to be suffering from dengue, 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. An outpatient assessment and advice form (Form O; Appendix 3a) is recommended for use for outpatient care (Appendix 3a).

7.4.3 Inpatient Disease Monitoring

Once admitted, every patient with suspected dengue should be reviewed thoroughly in the shortest possible time (Form I, Appendix 3b). In addition to the routine history, physical examination a stepwise approach (Table 4) should be employed to record the relevant data. The plan of management and monitoring cannot be static and should be based on the phase of the disease and the hemodynamic status of the patient. Table 8 summarizes the recommendations regarding the parameters and frequency of monitoring according to the different phases of the illness.
<table>
<thead>
<tr>
<th>Phase of Illness</th>
<th>Key Points</th>
</tr>
</thead>
</table>
| Febrile         | - Differentiation of dengue illness from other febrile illness  
                  - Not possible to differentiate DF from DHF |
| Critical        | - Plasma leakage occurs as patient progress to late febrile phase or as temperature begins to defervesce (T < 38.0 °C)  
                  - Clinical deterioration occurs during this phase due to plasma leakage  
                  - Plasma leakage results in hemoconcentration and hypovolemic / shock.  
                  - Excessive intravenous fluids may increase plasma leakage in pleural space and contribute to 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  
                  - Hemodilution occurs following fluid reabsorption.  
                  - Hypervolemia and pulmonary edema if intravenous fluid therapy is continued |

**Table 7:** Key points in different phases of Dengue Fever
Table 8: Parameters and frequency of monitoring according to different phases of dengue illness.

Adapted from \(^3,^{83}\)

<table>
<thead>
<tr>
<th>Parameters of monitoring</th>
<th>Febrile phase</th>
<th>Critical phase</th>
<th>Convalescent Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitoring charts to use</strong></td>
<td>Use “Monitoring Chart I” - Appendix 2a”</td>
<td>Use “Monitoring Chart II &amp; III” - Appendix 2b &amp; 2c”</td>
<td>Use “Monitoring Chart I” - Appendix 2a”</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General well-being, appetite / oral intake, warning signs &amp; symptoms, neurological / mental state</td>
<td>4 – 6 hourly</td>
<td>hourly</td>
<td>4-6 hourly</td>
</tr>
<tr>
<td>Signs of bleeding, abdominal tenderness, ascites and pleural effusion</td>
<td>Daily or more frequently towards late febrile phase</td>
<td>At least twice a day and more frequently as indicated</td>
<td>Daily or more frequently as indicated</td>
</tr>
<tr>
<td><strong>Hemodynamic status:</strong></td>
<td>4 – 6 hourly depending on clinical status</td>
<td>Hourly</td>
<td>4 – 6 hourly</td>
</tr>
<tr>
<td>• Pink/ cyanosis</td>
<td></td>
<td><strong>During Shock:</strong> Every 15 minutes till stable then 1 – 2 hourly</td>
<td></td>
</tr>
<tr>
<td>• Extremities(cold/warm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Capillary refill time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pulse Rate &amp; volume, BP, Pulse pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory status:</strong></td>
<td>4 – 6 hourly</td>
<td>Hourly</td>
<td>4 – 6 hourly</td>
</tr>
<tr>
<td>• Respiratory Rate</td>
<td></td>
<td><strong>During shock:</strong> Repeated before and after each bolus of fluid during resuscitation and as indicated</td>
<td></td>
</tr>
<tr>
<td>• SpO₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine output</strong></td>
<td>4 – 6 hourly</td>
<td><strong>During shock:</strong> Every 15 minutes</td>
<td>4 – 6 hourly</td>
</tr>
<tr>
<td><strong>FBC + HCT</strong></td>
<td>Daily or more frequently if indicated</td>
<td>4 – 12 hourly depending on clinical status</td>
<td></td>
</tr>
<tr>
<td><strong>BUSE/Creatinine, LFT, RBS, Coagulation profile, HCO₃/TCO₂/Lactate</strong></td>
<td>As indicated</td>
<td>At least daily or more frequently as indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>During shock:</strong> It is crucial to monitor acid-base balance / ABG closely</td>
<td></td>
</tr>
</tbody>
</table>
7.5 FLUID MANAGEMENT

7.5.1 Dengue with Warning Signs (Table 5)

Presence of warning signs usually heralds the onset of plasma leak in critical phase. All such patients should be admitted and monitored in a health care facility.

**Common pitfalls in fluid therapy:**

1. Treating patient with unnecessary fluid bolus basing decision solely on HCT
2. Excessive and prolonged fixed fluid regime in stable patients. Failure to adjust rate of fluid administration in accordance with the rate of plasma leak which can be assessed with appropriate monitoring
3. Continuation of intravenous fluid during the convalescent phase

At least some of patients exhibiting warning signs of dengue would recover with early intravenous rehydration without ever going into shock. However, some cases would deteriorate to severe dengue shock syndrome. If the patient has dengue fever with warning signs, the recommended action plan is depicted in Table 9a.

**Table 9a: Action Plan for Patient who has Dengue Fever with Warning Signs (without shock)**

**Recommendations**

- Admit the patient. If stable may be given fluid quota (7.5.5) orally
- IV fluid is indicated in patients who are vomiting or unable to tolerate oral fluids. 9b: section 7.5.2
- IV fluid is also indicated in patients with increasing HCT (indicating on-going plasma leakage) despite increased oral intake.
- Crystalloid (0.9% Saline) is the fluid of choice
As mentioned above, if patient is unable or is non-tolerant of oral fluids; IV fluids may be started according to table 9b: section 7.5.2

7.5.2 Patients in Critical Phase without Shock

There are no studies that have looked at fluid therapy in non-shock dengue patients. Appropriate (as per quota) oral fluid intake may be sufficient in some patients who are hemodynamically stable and not vomiting. However IV fluid (0.9% saline is recommended) is indicated in patients with serially increasing HCT (indicating on-going plasma leakage) despite appropriate oral intake. Intravenous fluid therapy should also be considered in patients who are vomiting and not tolerating orally.87, 83

The normal maintenance requirement for IV fluid therapy in such patients could be calculated based on the formula (M+5% - 7.5.5). 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. Fluid infusion rate should be reviewed regularly to match the rate of infusion with estimated rate of plasma leak.

A rising HCT AND/ OR hemodynamic instability indicates on-going plasma leakage and will require an increase in the IV fluid infusion rate. If patients deteriorate and progress to shock, a more aggressive fluid resuscitation is indicated (section 7.5.3).87, 83

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

Table 9b - IV Fluid management during critical phase without shock

- Obtain a baseline HCT before fluid therapy
- Use crystalloids solution (such as 0.9% saline).
- Start with 1.5 - 7 ml/kg/hour for 1 hour. Subsequent rate should be adjusted according to the pulse pressure (≥30 mm) and urine output (≥ 0.5 ml/kg/hr or 25ml/hr in adults).
- 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
**7.5.3 Dengue Shock Syndrome (DSS) (Compensated and Decompensated - Refer to Algorithms A and B)**

Dengue shock syndrome is a medical emergency. Recognition of shock in its early (compensated) stage and prompt fluid resuscitation will ensure a good clinical outcome.\(^8\) (Refer to Table 1 for details). Consequences of failure to recognize the compensated shock phase may be drastic. As the compensated phase leads to decompensated phase the disease outcome becomes less certain with increasing chance of a more complicated course. **Pulse pressure of < 20 mmHg and severe oliguria are late signs of shock**

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

In spite of successful initial resuscitation the patient may experience recurrent episodes of shock because of continuing capillary leakage which can last for 24-48 hours.

Intravenous fluid therapy is the mainstay of treatment for dengue shock.\(^3, 8\)\(^8\),\(^8\)\(^9\) To date, only three randomized controlled trials studying different types of fluid regime in DSS in children aged from 5 to 15 years of age are available.\(^8\)\(^8\),\(^8\)\(^9\),\(^9\)\(^0\) Because of this paucity of studies in the adult population, 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 after crystalloid resuscitation. Colloids seem to restore the cardiac index and reduce the level of HCT faster than crystalloids in patients with intractable shock.\(^8\)\(^9\) The choice of colloids includes dextran 40, gelatin solution (e.g. Hemaxel) and hetastarch solution (e.g. Hespan, Hextend).

**Principles for fluid resuscitation**

The volume of initial and subsequent fluid resuscitation depends on the degree of shock. Initial fluid bolus can be 10 or 20 ml/kg ideal body weight in compensated and decompensated shock respectively. 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 indicating adequacy of fluid resuscitation:

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Indication</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in general well-being</td>
<td>Improving pulse pressure</td>
</tr>
<tr>
<td>Good orientation &amp; mental state</td>
<td>Reduction in tachycardia or normalization of heart rate</td>
</tr>
<tr>
<td>Warm peripheries</td>
<td>Increase in urine output</td>
</tr>
<tr>
<td>Capillary refill time ≤ 2 sec</td>
<td>Reducing tachypnea or normalization of respiratory rate</td>
</tr>
<tr>
<td>Stable BP</td>
<td></td>
</tr>
</tbody>
</table>

### Laboratory parameters indicating adequacy of fluid resuscitation:

- Decrease in HCT (in face of hemodynamic stability)
- Improvement in metabolic acidosis

If the initial cycles of fluid resuscitation with crystalloids (30 ml/kg in total - refer to Algorithms A & B) fail to establish a stable hemodynamic state and HCT remains high, colloids should be considered.

If the repeat HCT drops after 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).

#### 7.5.4 Persistent Shock (Refer to Algorithms A and B)

Consider persistent shock in patients who fail to improve with adequate fluid resuscitation.
Following causes of persistent shock must be considered and managed:

**Significant bleeding:** (Often occult).
- Treat with Packed cells (5ml/kg) or whole blood (10ml/kg) may be used. This is expected to increase the HCT by 5%. If HCT is >45% it must be decreased by giving iv fluids before using blood; even if bleeding is likely

**Hypocalcemia:**

Treat with IV (10%) calcium gluconate @ 1 ml/kg (max 10mls diluted in equal volume of saline) as slow bolus over 10 minutes with cardiac monitoring (may be repeated 6 hourly). Empiric treatment with calcium may be given if patient fails to improve or deteriorates despite fluid resuscitation.\(^91\)

**Acidosis:**

If the arterial blood bicarbonate \((HCO_3^-)\) falls below 15 meq/l in the patients with decompensated shock, treat with NaHCO3 (8.4%) with an empiric dose of 1ml/kg, diluted in equal volume of saline in a slow infusion. (A bolus of not more than 10 ml /dose – maximum up to 5 doses). Shift the patient to HDU under expert supervision.\(^91\)

**Hypoglycemia:**

Treat with intravenous dextrose after bed side glucose measurement

If patient’s is still in state of persistent shock despite all the above measures consider sepsis and cardiogenic shock
- Treat with I/V antibiotics: Use intravenous antibiotics as oral administration may worsen vomiting and result in erratic absorption. Choice of antibiotics should be sufficiently broad to provide cover for Gram+, Gram- and anaerobic organisms in keeping with the prevailing culture sensitivity pattern. Choice may later be reviewed in light of blood C/S result of the patient.
- Consider inotropic support

Fluid therapy has to be judiciously controlled to avoid fluid overload which could result in massive pleural effusion, pulmonary edema or ascites.\(^3\,83\)
7.5.5 Calculation of Fluid Quota for Adults

Fluid quota in adults is based on the maximum lean mass of 50kg in adults. Irrespective of the real weight of an adult - (even if he weighs more than 50 kg) - he still would have the same amount of circulatory volume as that in a 50 kg adult. For adults weighing less than 50 kgs, the actual weight may be used for calculating fluid quota (Section 11). The following discussion explains fluid calculation for adults weighing ≥ 50 kgs. The formula is referred to as M+5%. This refers to a sum of maintenance fluids PLUS 5% losses. The entire fluid quota is given over 48 hours (the duration of the critical phase). For patients presenting in shock the quota may be given over 24 hours. Such a patient may have been leaking for a considerable length of time and may well be in the latter half of the critical phase.

Calculation of total fluids during critical phase in adult (50 kg)

<table>
<thead>
<tr>
<th>M (Maintenance)</th>
<th>Maintenance</th>
<th>5% of body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>100ml/kg for 1st 10 kg</td>
<td>1000</td>
<td>50ml x body wt. (kg)</td>
</tr>
<tr>
<td>+50 ml/kg for next 10 kg</td>
<td>+ 500</td>
<td>50 kg x 50 mls = 2500 mls</td>
</tr>
<tr>
<td>+20 ml/kg for balance wt</td>
<td>+ 600</td>
<td></td>
</tr>
<tr>
<td>Total Maintenance</td>
<td>2100</td>
<td></td>
</tr>
</tbody>
</table>

M + 5% = 4600 mls

It is important to note that if the patient is taking oral fluids, this oral intake should also be included in the total fluid quota which also would include any fluid given in the form of boluses.
Algorithm A – Fluid Management in Compensated Shock

**COMPENSATED SHOCK**

Signs of plasma leak signs of reduced perfusion like:
cold clammy skin, tachycardia, restlessness, increased thirst, increased capillary refill time
pulse pressure 20-30 mm, or Urine output 25-30ml/hr - (0.5ml/kg/hr)

Fluid resuscitation with isotonic crystalloid 10 ml/kg over 1hour (500ml in adult of 50kg or above)

- Any Improvement?
  - **Send** CBC, HCT, LFTs, BU, SE, Ca++, Glucose, HCO₃, GXM
  - **Yes**
    - Measure urine output
    - Infuse N/S @ 1.5 – 10 ml/kg/hr – Keeping to the minimum infusion rate, sufficient to maintain a urine output of 0.5 ml/kg/hr- (25ml/hour for adult).
    - Upon improvement, fluid can be further adjusted to stick to the fluid quota.
    - Monitor HCT 4 – 6 hourly
    - If the patient becomes unstable at any time - Go to ⭐️
    - Consider stopping IV fluid at 48 hours of plasma leakage / defervescence or earlier according to clinical judgment.
  - **No**
    - **Check HCT**
      - Increased, Normal or less than 10 points reduction of HCT from the baseline
      - Decrease of HCT by more than 10 points from the baseline
      - Administer another bolus N/S
        - 10 ml/kg/hr over 1 hour i.e, 500 ml in 60 minute in adults.
      - Is there any improvement?
        - **Yes**
          - Consider Ionotropic support plus fluids / blood- Check ABCS
        - **No**
      - **Administer Colloid** infusion 10 - 20 ml/kg over 1 - 2 hrs respectively
      - **Is there any improvement?**
        - **Yes**
          - **Check HCT**
        - **No**
          - **Total Amount of fluid given?**
            - Less than 30 ml/kg
            - More than 30 ml/kg

ABCS: Acidosis, Bleeding, Hypocalcaemia, Sugar.¹ GXM: Ask for Grouping & Cross Match or in case of emergency get an O negative;² fresh blood: Means blood less than 5 days old
Algorithm: B – Fluid Management in Decompensated Shock

DECOMPENSATED SHOCK
Signs of Plasma leak (Pleural / peritoneal fluid)
Pulse pressure <20 mm, Urine output <25ml/hr
Or Profound shock – Pulseless, BP less

Fluid resuscitation with isotonic crystalloid 20 ml/kg as fast as you can (1000ml in adult of 50kg or above)

Any Improvement?

CBC, HCT, LFTs, BU, SE, Ca++, Glucose, HCO₃, GXM² Anyway

Bolus of N/S 10 ml/kg iv rapidly

• IV crystalloid @ 1.5 - 10 ml/kg/hr for the 1ˢᵗ hour: Try to stick to the minimum infusion rate, sufficient to keep the pulse pressure between 20-30mm of Hg.
• Measure urine output
• Subsequently follow the patient up to maintain the urine output of about 0.5 ml/kg/hr – (25 ml/hour for adults).
• Upon improvement, fluid can be further adjusted to stick to the fluid quota.
• Monitor HCT 4 – 6 hourly
• If the patient becomes unstable at any time, Go to ✱
• Consider stopping IV fluid at 48 hours of plasma leakage / defervescence or earlier according to clinical judgment.

Any Improvement?

• Improvement
• Check HCT

Increased, Normal or less than 10 points reduction of HCT
Decrease of HCT by more than 10 points from the baseline

Administer Colloid infusion
10 ml/kg over 60 min, i.e (500 ml) in 60 min

Any Improvement?

• Yes
• Consider significant occult/overt bleed
  Initiate transfusion with fresh blood² (Whole blood / or packed cells)

• No

Calculate the amount of total colloids given

Less than 30 ml/kg
More than 30 ml/kg

No Improvement

Proceed to

Consider Ionotropic support
Plus fluids / blood- check ABCS

ABCs: Acidosis, Bleeding, Hypocalcaemia, Sugar

¹GXM: Ask for Grouping & Cross Match or in case of emergency get an O negative:
²fresh blood: means blood less than 5 days old
7.6 MANAGEMENT OF BLEEDING/HAEMOSTASIS

7.6.1 Hemostatic Abnormalities in Dengue Infection

The hemostatic changes that occur in dengue infection are considered to be the result of endothelial activation.92, 93 This process may aggravate thrombocytopenia in addition to the activation of coagulation pathways which are an inherent part of the disease.92, 93, 94 However, thrombocytopenia and coagulation abnormalities would not reliably predict bleeding in dengue infection.47, 48

Markers of endothelial activation such as elevated levels of thrombomodulin, tissue factor and Von Willebrand factor are more often seen in severe dengue fever.95, 96 Increased levels of these proteins may indicate microvascular thrombosis and end-organ damage.97

7.6.2 How to Recognize Significant Occult Bleeding?

Bleeding is considered significant when it results in hemodynamic instability. Bleeding from the gums or per vagina, epistaxis and petechiae are common but will usually cease spontaneously and are often not significant.3 Significant bleeding can a consequence of disseminated intravascular coagulation which usually occurs following prolonged shock and acidosis.46

Suspect significant occult bleeding in the following situations:

1. Hematocrit not as high as expected, for the degree of shock to be explained by plasma leakage alone. 46

2. A drop in hematocrit, without clinical improvement, despite adequate fluid replacement 46, 81

3. Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement. 46
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. Transfusion of blood and blood components in dengue is indicated when there is evidence of significant bleeding.

Transfusion of blood in patients with significant bleeding

- Transfuse 5 ml/kg of fresh-packed red cells or 10 ml/kg of fresh whole blood at an appropriate rate and observe the clinical response.
- Repeat blood transfusion if there is further blood loss or HCT fails to rise appropriately after blood transfusion.

Recommendations

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

7.6.4 Management of Upper Gastrointestinal Bleeding

There is no study to our knowledge that has looked at the use of proton pump inhibitor in upper GIT bleeding in dengue setting. Endoscopy and endoscopic injection therapy in upper GIT hemorrhage increases the risk of bleeding and must be avoided.

Generally, most of the GIT bleed will improve after 48-72 hours of the defervescence. Any bleed that persists beyond this time will require further investigation.
Recommendations

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

7.6.5 The Role of Prophylactic Transfusions in Dengue

Prophylactic transfusion with platelets and fresh frozen plasma does not produce sustained changes in the coagulation status and platelet count in patients with DHF/DSS.\(^99, 100\) Prophylactic transfusion with platelets and fresh frozen plasma does not change or reduce the bleeding outcome in DHF.\(^50, 99, 100\)

Inappropriate transfusion of blood components increases the risk of pulmonary edema and respiratory embarrassment.\(^99\)

Recommendation

There is no role for prophylactic transfusion with platelets and fresh frozen plasma to prevent bleeding in the dengue patients.

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.\(^101, 102\) The coagulation system seems to be over-activated in dengue and infusion of activated factor concentrates may increase the risk of thrombosis.\(^103\)

There is insufficient evidence to support the use of intravenous immunoglobulin\(^104\) and steroids\(^105\) in the management of dengue patients. Likewise, there appears to be no role for the use of Vitamin K and tranexamic acid. However there are anecdotal reports,\(^106\) that demonstrated a dramatic response when pulse methylprednisolone and high dose immunoglobulin G (IgG) was used in the early phase of haemophagocytic syndrome.
7.7 MANAGEMENT IN HIGH DEPENDENCY UNIT (HDU)

The management DSS in high dependency unit (HDU) follows the general principles of management of any critically ill patient in the HDU. However, there are certain aspects which are of particular relevance to the management of DSS. There are several indications for referring these patients for care in HDU. These are listed in the box below. 15, 107, 108

**Indications for referral to HDU:**

1. Any patient with significant plasma leak – (Patients falling in Algorithm A&B)
   - Pulse Pressure < 30 mm of Hg, Urine output of < 25ml/hour
2. Requirement for respiratory support (non-invasive and invasive ventilation)
3. Significant bleeding
4. Encephalopathy or other complications

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. There is some evidence that respiratory support should be considered early in a patient’s course of illness and should not be delayed unnecessarily.109

In patients with metabolic acidosis, respiratory support may be considered early despite the preservation of relatively normal arterial blood pH. When PaCO2 is higher than what is expected to compensate for the acidosis, the patient should be promptly intubated.

Formula to calculate the expected PaCO2 = 1.5 x [HCO3-] + 8±2 mmHg

In patients with encephalopathy and GCS of < 9, intubation is often required to protect the airway.110, 111
**Indications for mechanical ventilation:**

- Respiratory failure
- Severe metabolic acidosis
- Encephalopathy with GCS < 9

### 7.7.2 Indications for Hemodynamic 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.** ¹¹²

**CAUTION:** While vasopressors increase the blood pressure, tissue hypoxia may be further compromised by the vasoconstriction. Instituting inotropic support **without fluid repletion may be detrimental.**

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

DBP = diastolic blood pressure; SBP = systolic blood pressure

Volume overload, seen towards the end of the critical phase and subsequently, provokes an important patho-physiological consideration.

It can be argued that in the face of normal cardiac & renal function, it is difficult to overhydrate a person to an extent that pulmonary edema results. Kidneys are very efficient in getting rid of extra volume. Volume over load in the recovery phase of dengue theoretically may be explained by the following:

- Renal status in dengue related volume overload is akin to that of post-surgery patient with poor volume handling.
- Extravasated fluid is protein rich and exerts its own colloidal osmotic pressure thereby retaining fluid in the third space, only to be resorbed through lymphatics. Balance between extravasation and reabsorption may be critical in determining the circulatory volume.
7.7.3 Safety and risk – a guideline for invasive procedures

a. Central venous catheter (CVC) insertion

Volume resuscitation alone would not be a justification for CVC if adequate peripheral intravenous access can be obtained (e.g. 14 – or 16-gauge intravenous catheters). Assuming that the diameter stays equal, peripheral intravenous catheter may provide a better flow rate because of a shorter length.\(^{113}\)

There are no studies that would, specifically, address the (bleeding) risks of invasive procedures in dengue patients. In general, thrombocytopenia and other bleeding diathesis are relative contraindications for placement of CVC. A high femoral, low internal jugular and subclavian venous punctures are difficult to compress and thereby, confer an increased risk of uncontrolled bleeding. However, studies have shown that there are significant variations (0 - 15.5\%) in the risk of bleeding in patients with different coagulopathy.\(^{114, 115, 116, 117, 118}\)

When CVC is indicated in dengue patients (e.g. poor peripheral venous access, requirement of vasopressors, monitoring of CVP in critically ill and surgical patients) it should be inserted by an experienced operator and under ultrasound guidance if available.\(^{119, 120}\)

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.\(^{121, 122}\)

**Recommendation**

- Volume resuscitation does not require a central venous catherization (CVC) if sufficient peripheral intravenous access can be obtained.
- When CVC is indicated, it should be inserted by a skilled operator, preferably under ultrasound guidance if available.
- Subclavian vein cannulation should be avoided as far as possible.
b. Arterial catheter insertion

Intra-arterial cannulation provides additional advantage of continuous arterial pressure monitoring and repeated arterial blood gas sampling. It has a very low incidence of bleeding (1.8 – 2.6%)\textsuperscript{123}

**Recommendation**

An arterial catheter should be inserted in DSS patients who require intensive monitoring and frequent blood taking for investigations.

c. Gastric tube

It is hard to imagine a reason for NG tube in dengue; but if a NG 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 hemorrhage and sudden circulatory collapse.\textsuperscript{124}

**Recommendation**

Intercostal drainage for pleural effusion is not indicated to relieve respiratory distress. Mechanical ventilation should be considered.
8. DISCHARGE CRITERIA

The following criteria are to be taken into account while contemplating a discharge of a dengue patient.83, 81

**Discharge criteria:**

- Must be afebrile for 48 hours (without antipyretics)
- Stable general condition
- Recovery of appetite
- Stable hematocrit for at least 24 hours
- Rising trend in platelet count (minimum 40,000)
- No dyspnea or respiratory distress attributable to pleural effusion or ascites
- No or minimal visible bleeding
- Fully recovered organ dysfunction
9. PREVENTION OF DENGUE TRANSMISSION IN HOSPITALS

Patients are viraemic and hence potentially infectious during the febrile phase.\textsuperscript{125, 126}

There are a few small studies that demonstrate higher\textsuperscript{127, 128} levels and prolonged duration of viraemia in patients with DHF. There are no scientific studies that address the efficacy of mosquito repellents or mosquito netting in reducing dengue transmission in hospitalized patients. However several community studies have shown that the use of mosquito netting/screening was efficacious in preventing transmission of dengue in the community.\textsuperscript{129, 130}

Generally, repellent products with higher concentrations of DEET (N,N-diethyl-m-toluamide) were found to have longer repellence times.\textsuperscript{131}

A consensus dengue guideline advised the use of mosquito netting or repellent day and night for hospitalized dengue patients to reduce nosocomial infection.\textsuperscript{81}
10. VACCINATION

There is no effective vaccine available for dengue.\textsuperscript{132, 133} Attempts are being made to make a tetravalent vaccine to provide immune protection against all 4 serotypes of dengue virus in a sustained and predictable manner. Results of trails are still awaited.
11. DENGUE FEVER IN PEDIATRIC POPULATION

The pathogenesis of Dengue Fever and the principles of management apply equally well to children as they do to the adults. In the pediatric population special consideration has to be given to the weight of the patient; because of its wide variation. Fluid quota, therefore, has to be carefully calculated keeping in mind the weight of the patient. In the dehydrated child the measured weight may not be a true representation of the actual weight of the child. Additionally, the ideal body weight of a child may not be the same as the actual weight.

11.1.1 Calculation of Ideal Body Weight

Estimation of the ideal body weight may be made by any of the following ways:

- Weight for height using a growth chart (50th centile) - **Best Method**
- Weight for age using a growth chart (50th centile)
- In an emergency situation use the following formulae may be used

<table>
<thead>
<tr>
<th>Age (in Months)</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>Weight + 9</td>
</tr>
<tr>
<td>&lt; 7 years</td>
<td>((Age x 2) + 8)</td>
</tr>
<tr>
<td>&gt; 7 years</td>
<td>Age x 3</td>
</tr>
<tr>
<td>APLS</td>
<td>((Age + 4) x 2)</td>
</tr>
</tbody>
</table>

The weight chosen for calculation should be the current weight or ideal body weight, whichever is lower.

Following illustrates calculation of fluids for critical period in a child

<table>
<thead>
<tr>
<th>Calculation of total fluids for critical period</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (Maintenance)</td>
</tr>
<tr>
<td>100 ml/kg for 1st 10 kg</td>
</tr>
<tr>
<td>+50 ml/kg for next 10 kg</td>
</tr>
<tr>
<td>+20 ml/kg for balance wt</td>
</tr>
<tr>
<td>5% of body weight = +50 ml x body wt (kg)</td>
</tr>
<tr>
<td>E.g.: Body weight 25 kg (This is ideal or actual body weight, whichever is smaller)</td>
</tr>
<tr>
<td>M = 100 x 10 + 50 x 10 + 20 x 5 = 1600 ml</td>
</tr>
<tr>
<td>5% = 50 x 25 = 1250 ml</td>
</tr>
<tr>
<td>M + 5% = 1600 + 1250 = 2850 ml</td>
</tr>
<tr>
<td>This is the total fluid volume this patient will need over the entire critical period irrespective of its length.</td>
</tr>
</tbody>
</table>

The maximum weight for which fluid is calculated in any patient should not exceed 50 kg. Accordingly M + 5% should not exceed 4600 ml in any patient (adult or pediatric).
11.1.2 Choice of fluids

Use half normal saline (N/2) in 5% dextrose in infants less than 6 months of age because of poor sodium handling by immature kidneys. For children above 6 months of age, when the patient is not taking orally for prolonged periods, it is useful to give normal saline in 5% dextrose to avoid hypoglycemia.

11.1.3 Rate of administration of IV fluids in critical phase – without shock

- Upon entering the critical phase shift to HDU and start IV fluids.
- Initial fluid requirement (oral + IV) is 1.5 ml/kg/hr. Those who can drink well may be given IV fluids at the minimal rate 0.5ml/kg/hr and the balance as oral.
- Calculation of fluid quota (M+ 5%) is for entire critical phase. If the patient has been in the critical phase for some time, calculate the remaining volume of fluid keeping in mind the duration of critical phase elapsed and the amount of fluid already given.
- Rate of infusion depends on the rate of leak judged by pulse, BP, pulse pressure, capillary refill time, HCT and urine output.
- Urine output should be maintained between 0.5 -1 ml/ kg/hour during the critical period.

Hourly urine output is the best guide to decide the rate of infusion. If UOP is above one ml/kg/hour it suggests that infusion rates are too high. If the UOP is <0.5ml/kg/hr it may suggest inadequate fluids. Catheterization may be required for accurate UOP measurement.

* There is wide variation in the rate of leak from patient to patient and within the same patient over period of time.

*(Chart II below may be used as a guide for patients with shock while remembering that there is wide variation in rate of leak from patient to patient)*
11.1.4 Intravenous fluid replacement – during shock (refer to Algorithms A & B)

- Patient who is in significant shock might well be in a stage of plasma leak for considerable length of time, therefore he might stop leaking much earlier than 48 hours.

- Individual patient's fluid rates administered will depend on his/her rate of leak – as judged by the pulse pressure and urine output.

- Remember that total fluid quota (M+5%) would not only include the IV fluids but also the bolus fluids given during resuscitation and any administered orally.

(Char II below may be used as a guide for patients with shock while remembering that there is wide variation in rate of leak from patient to patient)
11.2 Special Considerations for Infants

DHF/DSS is less common in infancy but mortality is higher than in older children. There are very few published studies on fluid management in DHF in infants. Physiologically speaking, fluids account for a greater proportion of body weight in infants than in children and minimum daily requirements are correspondingly higher. Infants have lower intracellular fluid reserves and the capillary beds are intrinsically more permeable than older children and adults. Early cardiovascular compromise and significant fluid overload are more likely to occur if capillary leak occur in this age group. Babies born to mothers who have developed dengue fever close to delivery will have circulating antibodies due to trans-placental passage. In such babies DHF may develop even during first infection due to antibody-dependent enhancement of viral replication mediated by the antibodies of maternal origin.

Like in adults, primary dengue infection in infants often presents as simple fever, indistinguishable from other viral infections. Maculopapular rashes may accompany the fever or may appear during defervescence. Upper respiratory and gastrointestinal symptoms (gastroenteritis) may be seen. Unusually, infants may present with seizures.
Splenomegaly has been observed in young infants (especially under six months) clinically or by radiological examination (USS). Leucopenia may not be present; instead the total white cell count may be high - reaching up to 18-19 x 10^3. Infants are more prone to liver involvement with AST in the range of 200 – 500 (may occasionally rise to > 1000). They are also more prone to electrolyte imbalance due to poor renal handling of Na⁺.

As compared to older age group, infants experience plasma leakage for shorter duration and respond quickly to fluid resuscitation. The volume actually required may be less than the calculated quota of M + 5%. Fluid administration in infants should be evaluated meticulously and oral intake (i.e. breast feeding) taken into account. Intravenous fluids should be stopped as soon as the leaking phase is over – in order to avoid the risk of fluid overload. All infants with dengue fever must be treated as high-risk patients in HDU and they all would require early intervention with colloids, at par with the older children with severe disease.

### Dengue in infants: Difference from the adult presentation

<table>
<thead>
<tr>
<th>Fits are more common</th>
<th>URT, or GI features predominate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytosis rather than leucopenia</td>
<td>More prone to plasma leak</td>
</tr>
<tr>
<td>More prone to electrolyte imbalance (particularly sodium)</td>
<td>Hepatomegaly and deranged LFTs are more common</td>
</tr>
</tbody>
</table>
12. DENGUE FEVER 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.\textsuperscript{137, 138}

However, the signs and symptoms may be confused with other complications of pregnancy such as toxemia, Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) syndrome.\textsuperscript{91} There are some reports of an increased incidence of prematurity, in-utero death and abruptio placenta in these women.\textsuperscript{138, 139} The following physiological changes in pregnancy may make the diagnosis and assessment of plasma leakage challenging:

- Elevation of HCT in dengue is masked by hemodilution 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 labor during critical phase (plasma leakage).\textsuperscript{91} Procedures/maneuvers that may provoke or augment labor 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 labor and its complications.

The baby should be observed for vertical transmission of dengue after delivery.\textsuperscript{91}

**Recommendation**

All pregnant women with suspected dengue infection must be admitted.
13. DENGUE FEVER IN IMMUNOCOMPROMISED PATIENTS

Dengue in immunocompromised persons

A working definition of immunocompromised states would be:

1. Patients on cancer chemotherapy
2. Solid organ transplant patients undergoing anti-rejection therapy
3. Bone marrow transplant patients undergoing anti-rejection therapy
4. Primary/congenital immunodeficiency disorders
5. Chronic steroid therapy
6. Auto-immune diseases undergoing treatment with immunomodulator/immune suppressive medicines
7. HIV/AIDS with CD4 count < 200 (severe immune deficiency), between 200-500 (mild to moderate immune deficiency)
8. Conditions such as short term use of corticosteroids (< 2 weeks), HIV patients having CD4 count > 500, patients with leukemias/lymphomas whose disease is in remission and last chemotherapy was more than 3 months ago, patients on whom steroids have been discontinued more than 1 month ago, patients with bone marrow transplant done > 2 years ago and not taking any immunosuppressive medications plus no graft versus host disease are not considered as significant immunosuppression

Management guidelines

1. Clinical presentation of dengue in immunocompromised patients seems to be similar to that in immunocompetent individuals, except that the disease course could be prolonged.
2. Unusual presentations of dengue infection do occur but does not seem to be as common as in other infections
3. Limited data suggest similar sensitivity and specificity of diagnostic tests as in immunocompetent individuals.
4. Principles of treatment and prevention remains the same as in immunocompetent individuals
5. Individuals with severe neutropenia (absolute neutrophil count below 500) and fever (above 38.3C) may be given empiric antimicrobial cover with an antibiotic, as per standard guidelines for such patients (e.g. IDSA guidelines for febrile neutropenic patients 2010)
**Potential immunocompromised state in dengue fever patients**

1. This may be due to neutropenia as a result of Dengue
   
   i. Management principles of treatment would be as per standard guidelines, PLUS

   ii. Empiric use of antibiotics may be considered, (after blood has been drawn for culture and sensitivity in individuals with severe neutropenia - absolute neutrophil count below 500 – PLUS fever of more than 38.3°C.

   *(As there is no experimental data exists on the use of antibiotics regimen – data from immune-compromised cancer patients is therefore being extrapolated)*
14. ANTIHYPERTENSIVE TREATMENT IN DENGUE FEVER:

1. Patients with uncomplicated hypertension, once diagnosed to have Dengue Fever (irrespective of plasma leak) should stop taking diuretics as soon as the diagnosis is suspected. Patients taking diuretics for other reasons (Chronic heart failure, valvular lesions, etc.) should be evaluated individually.

2. Other antihypertensive agents (beta blockers, Calcium channel blockers, ACE inhibitors) may be continued with frequent monitoring of blood and pulse pressure at home - (at least 6 hourly). For in hospital management refer to Appendix 2

3. A declining trend in blood pressure or pulse pressure on two consecutive occasions should be taken as warning sign for the patient at home or the GP to refer to a better equipped health facility.

4. Dengue related hospital admissions, taking antihypertensive treatment, should be monitored regularly as per monitoring charts. Appendix 2

5. Fall in pulse pressure ≤30 mm Hg indicates that patient may be developing hemodynamic instability. If blood pressure measured on 3 successive occasions at hourly intervals reveal PP to be ≤30 mm Hg; Stop All antihypertensive treatment - patient monitored as per Appendix 2b.

6. Once the pulse pressure starts rising above 30mm Hg, depending upon the clinical judgment, antihypertensive medication may be carefully reintroduced. One may like to choose shortest acting agent, from within the class of antihypertensives, patient was already taking; avoiding diuretics.

7. Once the patient is stable and in convalescent phase regular anti hypertensives may be reintroduced one by one according to the clinical status.

- Diuretics should be stopped as soon as the probable diagnosis of dengue is made.
- Other anti-hypertensive treatment may be continued if the Pulse Pressure stays above 30 mm of Hg.
- In case the Pulse Pressure drops, ≤30 mm Hg, stop all anti-hypertensive treatment and introduce monitoring –Appendix 2b.
15. DENGUE FEVER IN PATIENTS ON ANTITHROMBOTIC THERAPY

A significant number of patients with cardiac ailments would be on long term anti-coagulants/antithrombotic treatment. Management of these patients, in case of dengue virus infection, needs careful considerations. Risk of significant bleed during DF may be compounded by anticoagulation/antithrombotic treatment. While hemoconcentration and rising HCT can be prothrombotic.

From the perspective of clinical management the need of anticoagulation / antithrombotic treatment could be obligatory in high risk group and non-obligatory in the low risk group.

High risk patients - need of anti-coagulation obligatory:

Following group of patients have high risk for thrombotic complications:

1. Patients with recent coronary angioplasty with stent placement (one month for bare-metal stents and three to six months for drug-eluting stents)
2. Patients with mechanical valve prostheses, particularly in the mitral or tricuspid positions,
3. Patients with chronic atrial fibrillation (CAF), previous history of thromboembolism or with more than one mechanical valve.
4. CAF patients with multiple risk factors for thrombo-embolism (ventricular dysfunction, increased age, hypertension, diabetes, valvopathy, previous stroke, or intra-cavity thrombus).

For this high risk group the antiplatelet treatment may be continued.

High Risk patients already taking anti-platelet therapy:
- For patients who are at a high risk of thrombo-embolic event and are already using clopidogrel and aspirin these drugs should be continued.
- Stop in case of significant bleeding.
High Risk patients needing obligatory anti-coagulation:

- In patients using warfarin, the current recommendation is to withhold it and perform serial platelet and coagulation monitoring.
- As soon as the INR is below the therapeutic range introduce heparin to keep INR within the desired range - continue serial platelet and coagulation monitoring.

Even in these High Risk patients – All anti-coagulants should be withheld if:

- Platelet count falls below 50,000/mm³
- There is clinical or laboratory evidence of bleeding
- Patient is in shock.

Low risk patients - need of anti-coagulation non-obligatory:

These patients exhibit minimal short term risk for thrombo-embolic event:

1. Stable coronary artery disease patients
2. Patients with coronary angioplasty with a stent emplacement more than six months previously
3. Chronic Atrial Fibrillation patients without additional risk factors (or with a single risk factor) for thromboembolic event;
4. Patients with biological valve prosthesis

Current recommendation for the low risk group is to withhold aspirin and consider withholding clopidogrel and warfarin for one week.
16. SURGERY IN DENGUE

Algorithm for Surgical Management in Dengue Patients

Defer all elective procedures until platelet count is within normal limits

Emergency surgery

Get urgent CBC, HCT, platelet count, blood glucose, serum calcium, blood for grouping and cross matching, ultrasound chest and abdomen

Dengue Fever (no evidence of leak)

Platelet management

Platelet count more than 50,000

Transfuse 1 bag of single donor platelet

Proceed with surgery (One bag of single donor platelets on standby)

Platelet count less than 50,000

Dengue Fever in critical phase (plasma leak but no shock)

Fluid management

*Start with maintenance fluids Monitor

- **UOP** (keep between 0.5 to 1ml/kg/hr)
- **MAP** >60mmHg
- **HCT** (measure 3 hrly)
- **CVP** (measure ¼ hrly)

Resuscitate the patient (algorithms A and B) to achieve hemodynamic stability. Perform resuscitative surgery if required.

Dengue Shock

Complications: (Consider when no improvement)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A: Acidosis</strong></td>
<td>If the arterial blood bicarbonate (HCO₃⁻) falls below 15 meq/l give NaHCO₃ (8.4%) 1ml/kg, diluted in equal volume of saline as slow bolus (10 ml/dose–maximum upto 5 doses)</td>
</tr>
<tr>
<td><strong>B: Bleeding</strong></td>
<td>Consider Whole blood (10 ml/kg) or packed cell (5 ml/kg)</td>
</tr>
<tr>
<td><strong>C: Hypocalcemia</strong></td>
<td>Check serum calcium and QT intervals Give 10% calcium gluconate. Dose 1ml/kg/min, max 10ml at one time, repeat 6 hourly if needed.</td>
</tr>
<tr>
<td><strong>S: Sugar Levels</strong></td>
<td>Monitor Blood Sugar levels and manage accordingly.</td>
</tr>
</tbody>
</table>

Urine output

- < 0.5 ml/kg/hr - increase rate of maintenance fluids > 1 ml/kg/hr - consider decreasing rate of maintenance fluids

Pulse Pressure ≤ 30 - follow algorithms A or B as appropriate

HCT – Falling HCT consider whole blood transfusion 20ml/kg

- Volume overload with falling HCT 10 ml/kg PCV

CVP (maintain between 10 – 14 cm of water)

- Rising trend – consider decreasing rate of i.v fluids & furosemide 0.5mg/kg if BP is normal
- Falling trend – consider increasing rate of i.v fluids –consider whole blood transfusion if HCT falls ≥ 10 points from base line
REFERENCES


87: WHO Regional Publication SEARO , 29, 1999


91: De Roeck D, Deen J, Clemens JD. Policymakers’ views on dengue fever/dengue hemorrhagic fever and the need for dengue vaccines in four southeast Asian countries. Vaccine. 2003; 22: (1)121–19.


94: Sosothikul D, Seksarn P, Pongsewalak S. Activation of endothelial cells, coagulation and fibrinolysis in children with dengue virus infection. Thromb Haemost, 2007. Apr;97;627-34


USE OF APPENDICES 1 TO 5:

Appendix 1a: Investigation Summary – To be used in admitted patients for summarizing investigations in conjunction with patient case notes

Appendix 1b: Radiology Request Form – To be used for requesting and reporting evidence of plasma leak in patients in critical phase

Appendix 2: Dengue Monitoring Charts – To be used for monitoring admitted patients

  2a: Monitoring Chart to be used in admitted patients during Febrile Phase/Convalescent

  2b: Monitoring Chart to be used in admitted patients during Critical Phase

  2c: Monitoring Chart to be used in admitted patients who present with Shock

Please note that monitoring parameters remain the same as in previous charts but monitoring is required at 15 minutes intervals.

Appendix 3a OPD Form: To be used in patients presenting in the out-patient department. Text boxes may be appropriately ticked to arrive at the diagnosis of suspected, probable or confirmed dengue fever.

Appendix 3b Form I: To be used for history taking, examination and documenting relevant investigations in admitted patients with dengue fever.

Appendix 4: Reporting forms to be used for reporting dengue fever patients to the EDO/office of the Director General Health

  4a: Reporting Form (R) to be used in patients who have suspected or probable disease based on the criteria given on the form but without confirmatory evidence

  4b: Reporting Form to be used in patients who have confirmatory evidence of dengue fever. Criteria for confirmation are as given in the form. For each confirmed case detailed information must be documented as given in the form.

  4c: SOP for Reporting Dengue Patients – Gives steps to be taken from diagnosis of dengue fever to electronic reporting of cases in hospital setting.

Appendix 5: Dengue Diagnostic Criteria – To be used during inter epidemic phase. Please note that diagnostic criteria may need revision from time to time and may be different during an epidemic.
APPENDICES

APPENDIX 1a Investigation Summary

DENGUE INVESTIGATION SUMMARY

Name: ------------ Age: ------------ Hospital: -------------- Ward: --------------

MRID: ------------

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>WBC-Total</th>
<th>N</th>
<th>L</th>
<th>HCT</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>AST</th>
<th>Se. Creative</th>
<th>ALT</th>
<th>Se. Na⁺</th>
<th>Se. K⁺</th>
<th>Se.ca²⁺ (Ionized)</th>
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<table>
<thead>
<tr>
<th>Date / Time</th>
<th>Date / Time</th>
<th>CXR-R.Decubitus</th>
<th>Se. Albumin</th>
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<tbody>
<tr>
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<thead>
<tr>
<th>Date / Time</th>
<th>pH</th>
<th>HCO₃⁻</th>
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Other investigations:

<table>
<thead>
<tr>
<th>Date / Time</th>
<th></th>
</tr>
</thead>
</table>
APPENDIX 1b Radiology Request Form

Radiology Request Form
(For suspected Dengue Hemorrhagic Fever)

Name: ___________________________ W/o, D/o, S/o: ___________________________ Age: ___________________________

Sex: ___________________________ Date: ___________________________ Ward: ___________________________ MRN No: ___________________________

History:


Ultrasound:
Abdomen and pelvis to detect ascites


Chest to detect pleural effusion


X-Ray Chest:
Right lateral decubitus to detect minimal pleural effusion


PA view to assess pleural effusion


Report by Radiologist:


Name & Signature
**APPENDIX 2 Dengue Monitoring Charts**

### Monitoring Chart - 1 for management of Dengue Patients – Febrile Phase / Convalescent Phase (4-6 hourly)

Name of the patient: ..................................  Hospital: ..................................  Ward: .........................  MR#: .......................  Wt.: ..............................

IBW: ..................................  Age: ..............................

<table>
<thead>
<tr>
<th>Date Time</th>
<th>HR/Min</th>
<th>BP mmHg</th>
<th>Pulse Pressure</th>
<th>CRT Sec</th>
<th>Extremity Warm / Cold</th>
<th>RR</th>
<th>HCT</th>
<th>Platelet Count $\times 10^3$</th>
<th>UOP ml</th>
<th>UOP ml/kg/hr</th>
<th>IV Fluid Amount mls</th>
<th>Type</th>
<th>Oral fluid mls</th>
<th>Total fluid mls</th>
<th>Treatment /Remarks</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>


### Monitoring Chart II for Management of DHF Patients during Critical Phase – Page 1

**Name of the patient:** ………………………… **MR#:** …………………………… **Hospital:** …………………………… **Ward:** ……………………………

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Ideal body weight (kg)</th>
<th>M</th>
<th>M+ 5% = ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Critical Phase Commencing [date and time] — ……………………………** **End [date and time] — ……………………………**

<table>
<thead>
<tr>
<th>10</th>
<th>9</th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mL/kg/hr</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

**HCT**

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Used</th>
<th>Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ML/kg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Monitoring Chart II for Management of DHF Patients during Critical Phase – Page 2

**Name of the patient:** ………………………… **Hospital:** …………………………… **Ward:** …………………………… **MR#:** ……………………………

<table>
<thead>
<tr>
<th>10</th>
<th>9</th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mL/kg/hr</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>34</td>
</tr>
</tbody>
</table>

**HCT**

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Used</th>
<th>Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ML/kg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monitoring Chart III to be used during the Peak of leakage and **during Shock**

(Patient to be monitored every 15 mins)

Name of the patient: .................................................. Hospital: .................................. Ward: .................................. MR#: ...........................................

**Fluid Boluses Given**

<table>
<thead>
<tr>
<th>Normal Saline:</th>
<th>Dextran:</th>
<th>Maximum 3 per 24h / 6 per 48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M+ 5% = ................................ ml for 24 hours</td>
</tr>
</tbody>
</table>

Starch: ........................................ Maximum 5 per 24h / 10 per 48h

Other fluid: PRC/WB .................................................................

| Fluid m/kg/hr | 20 | 19 | 18 | 17 | 16 | 15 | 14 | 13 | 12 | 11 | 10 | 9  | 8  | 7  | 6  | 5  | 4  | 3  | 2  | 1  |
|---------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|    |

| time         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| HCT          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Fluids Used  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Remaining    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| HR           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| BP           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Pulse Pressure |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| RR           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| CRFT         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Extremities  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| UOP          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Mi/kg/hr     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

| Platelet count |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
APPENDIX 3a OPD Form

Dengue Expert Advisory Group
March 2012

DEAG FORM - O
For inter epidemic use

Name __________________________ s/o d/o w/o __________________________ Date: __________________________

Age __________________________ Sex: M / F __________________________ Receipt No: __________________________

MR # __________________________

Address & Telephone __________________________

☐ Fever > 2 and < 10 days (essential criterion)
☐ Headache
☐ Retro orbital pain
☐ Myalgia
☐ Arthralgia/ severe backache/ bone pains
☐ Rash
☐ Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis)

☐ Severe abdominal pain
☐ Decreased urinary output despite adequate fluid intake
☐ Irritability infant

Presence of 3 or more Clinical Criteria

Declared Suspected Case

Request CBC

Advised

d #3 of Fever ☐ HCT ☐ WBC ☐ Platelet
d #4 of Fever ☐ HCT ☐ WBC ☐ Platelet
d #5 of Fever ☐ HCT ☐ WBC ☐ Platelet

WBC < 3000, and Platelet <100000 or falling on any occasion

Declared Probable Case

Admit Patient

Warning Signs (one or more)

- No clinical improvement / worsening clinical parameters on Form I
- Persistent vomiting
- Severe abdominal pain
- Lethargy and or restlessness
- Bleeding: severe epistaxis, black stools, hematemesis, extensive menstrual bleeding, hematuria
- Giddiness
- Pale cold clammy extremities
- Less / no urine output for 4 - 6 hours

Name, Signature and Date
After admissions confirm case based on any one of the confirmatory evidence below:

Positive NS1 antigen

OR

Viral detection by PCR

OR

Seroconversion from negative for dengue virus specific IgM antibody in acute phase (<5 days after onset of symptoms) to positive for dengue virus specific IgM antibody in convalescent phase specimen collected ≥ 5 days after onset of symptoms

OR

≥ 4 - fold rise in titre of IgG in paired acute and convalescent serum sample

Declared Confirmed Case

For confirmed cases fill in Dengue Case Report Form

Paracetamol

Ibuprofen, Disprin

CBC with Platelet Count

24
APPENDIX 3b Inpatient Form

DEAG FORM - I (Inpatients)

March 2012
To be used in patients admitted with diagnosis of Probable/Confirmed Dengue Fever

Name: ......................................... s/o d/o w/o: ......................................... Date: .........................................

Age: ......................................... Sex: M / F: ......................................... Receipt No: .........................................

MR #: ......................................... Address & Telephone: .........................................

History

Date of onset of fever/illness: [dd mm yyyy]

Assess for Alarm Symptoms:

- Diarrhea: Yes | No
- Persistent vomiting: Yes | No
- Severe Abdominal Pain: Yes | No
- Manifest Bleeding: Yes | No

Site of bleeding: .........................................

Urine output frequency: Normal | Decreased

Volume: Normal | Decreased

Time of last voiding: .........................................

Estimated oral intake of fluids: [mls] last 24hr

Other important relevant points in history:

- History of dengue in the family or the neighborhood: Yes | No
- Jogging/walks in the park and swimming in waterparks: Yes | No
- H/O recent travel to the endemic zones: Yes | No
  (inside or overseas destinations)
- Co-morbidities: (Encircle as appropriate)
  Diabetes Mellitus, Anticoagulants, Antiplatelets, HTN, CRF, CLD, Immunocompromised
  (Consider sepsis particularly in patients with diabetes mellitus)

Mention co morbidity if present: .........................................

Physical Examination

General:

Glasgow Coma Scale (GCS) score: .........................................

Hydration status: Well hydrated | Dehydrated

Hemodynamic status:

Warning Signs:

- Skin color: Normal | Pale/cyanosed | Flushed
- Cold Extremities: Yes | No
- Restlessness: Yes | No
- Change in mental status: None | Combative/Irritability | Drowsiness | Comatose | Seizure
- Capillary refill time less than 2 sec: Yes | No
- Pulse pressure less than 30 mmHg: Yes | No
Pulse rate/min

Pulse volume: Normal | Feeble | High Volume

Blood pressure mmHg:

Pulse pressure:

**Respiratory System:**

Respiratory Rate:/min

Type breathing: Normal | Acidotic

Evidence of pleural effusion: Yes | No

**G.I System:**

Abdominal tenderness: Yes | No

Hepatomegaly: Yes | No

Evidence of Ascites: Yes | No

Manifest bleeding: Yes | No

Site of bleed:

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 10 or more petechiae per 2.5 cm (1 inch) square are observed)

(Repeat at 6 hourly interval – 3 times - if previously negative)

**Investigation**

<table>
<thead>
<tr>
<th></th>
<th>Date:</th>
<th>Date:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Serology:**

<table>
<thead>
<tr>
<th>Date:</th>
<th>Date:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti Dengue IgM</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti Dengue IgG</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Ns1 Antigen: Positive | Negative

Date of Test: __________

PCR Positive | Negative

Date of Test: __________

(For Patients with positive PCR/NS1 Antigen or serology evidence of confirmed Dengue Fever use Form 4b)
APPENDIX 4a Reporting for Dengue Patients (Suspected & Probable)

Dengue Expert Advisory Group
March 2012

REPORTING FORM - R
For inter epidemic use

Filling of all fields is compulsory

Name ___________________________ s/o d/o w/o ___________________________ Date of Admission ___________________________
Age ___________________________ Sex: M / F ___________________________ Receipt No: ___________________________
MR # ___________________________
Address & Telephone

☐ Fever > 2 and < 10 days (essential criterion)
☐ Headache
☐ Retro orbital pain
☐ Myalgia
☐ Arthralgia/ severe backache/ bone pains
☐ Rash
☐ Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis)
☐ Severe abdominal pain
☐ Decreased urinary output despite adequate fluid intake
☐ Irritability infant

Presence of 3 or more Clinical Criteria

Declared Suspected Case
Request CBC

Advised

- d # 3 of Fever ☐ HCT ☐ WBC ☐ Platelet
- d # 4 of Fever ☐ HCT ☐ WBC ☐ Platelet
- d # 5 of Fever ☐ HCT ☐ WBC ☐ Platelet

WBC < 3000, and Platelet <100000 or falling on any occasion

Declared Probable Case

Warning Signs (one or more)
- No clinical improvement / worsening clinical parameters on Form I
- Persistent vomiting
- Severe abdominal pain
- Lethargy and or restlessness
- Bleeding: severe epistaxis, black stools, hematemesis, extensive menstrual bleeding, hematuria
- Giddiness
- Pale cold clammy extremities
- Less / no urine output for 4 - 6 hours

Name, Signature Registrar
Name, Signature Sr. Registrar
Name, Signature Focal Person

Received by Focal Person

Patient Name ___________________________
MR # ___________________________
## APPENDIX 4b Reporting Form for Dengue Patients (Confirmed)

### PATIENT INFORMATION

<table>
<thead>
<tr>
<th>First Name</th>
<th>Middle Name</th>
<th>Last Name</th>
<th>Primary language</th>
<th>Father’s Name</th>
<th>Husband Name</th>
<th>DOB (dd/mm/yyyy)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ English ☐ Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ Urdu ☐ Punjabi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>House Number</th>
<th>Street</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Locality (like Shadman, Baghbanpura etc.)</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Home Telephone</th>
<th>Cellular phone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E-mail Address</th>
<th>Phone number of relative / attendant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Work Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Locality (like Shadman, Baghbanpura etc.)</th>
<th>City</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>☐ Uneducated ☐ Under matric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Undergraduate ☐ Others:___</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>☐ Male ☐ Female ☐ Other (Please specify): ____________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnant?</th>
<th>If yes, Est. Delivery Date (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Yes ☐ No ☐ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

### CLINICAL INFORMATION

<table>
<thead>
<tr>
<th>Physician Name – Last Name</th>
<th>First Name</th>
<th>Telephone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NIC Number: _______________________

Serial No: _______________________
Government of The Punjab, Health Department, Lahore

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Onset Date (dd/mm/yyyy)</th>
<th>Date First Sought Medical Care (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td>If yes, specify as noted</td>
<td>Purpura / Ecchymosis</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Eye pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sweats</td>
</tr>
<tr>
<td>Muscle pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bleeding gums</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hematuria</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaginal bleeding</td>
</tr>
<tr>
<td>Irritability in infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Petechiae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diastolic BP</td>
</tr>
<tr>
<td>Other symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulse Pressure</td>
</tr>
</tbody>
</table>

**Travel History**

Did patient travel outside of his district in last 10 days?  
- Yes  
- No  
- Unknown

Has the patient traveled outside Pakistan during the last 10 days period?  
- Yes  
- No  
- Unknown

If yes or either of these questions, specify all locations and dates below.

**Travel History – Details**

<table>
<thead>
<tr>
<th>Location (City, county, country)</th>
<th>Date travel started (dd/mm/yyyy)</th>
<th>Date travel ended (dd/mm/yyyy)</th>
</tr>
</thead>
</table>

**Exposures / Risk Factors**

Did patient recall any mosquito bites during the incubation period?  
- Yes  
- No  
- Unknown

Occurrence of confirmed cases of dengue fever in family or neighborhood  
- Yes  
- No  
- Unknown
Government of The Punjab Health Department, Lahore

**PAST MEDICAL HISTORY**

<table>
<thead>
<tr>
<th>Has the patient been previously diagnosed with dengue?</th>
<th>If yes, date of Diagnosis (dd/mm/yyyy)</th>
<th>Serotype (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No □ Unknown</td>
<td></td>
<td>□ 1 □ 2 □ 3 □ 4</td>
</tr>
</tbody>
</table>

**PREVIOUS HOSPITAL VISIT**

<table>
<thead>
<tr>
<th>Did patient visit emergency room for illness?</th>
<th>Was the patient hospitalized?</th>
<th>If yes, how many total hospital nights</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No □ Unknown</td>
<td>□ Yes □ No □ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Was patient placed in isolation ward?</th>
<th>If there were any ER or hospital stays related to this illness, specify details below</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No □ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

**HOSPITALIZATION – DETAILS**

<table>
<thead>
<tr>
<th>Hospital Name 1</th>
<th>Hospital Name 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Address</td>
<td>Hospital Address</td>
</tr>
<tr>
<td>Telephone</td>
<td>Telephone</td>
</tr>
<tr>
<td>Admission Date (dd/mm/yyyy)</td>
<td>Admission Date (dd/mm/yyyy)</td>
</tr>
<tr>
<td>Discharge / Transfer Date (dd/mm/yyyy)</td>
<td>Discharge / Transfer Date (dd/mm/yyyy)</td>
</tr>
<tr>
<td>Discharge Diagnosis</td>
<td>Discharge Diagnosis</td>
</tr>
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</table>

**LABORATORY INFORMATION**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Date Collected (dd/mm/yyyy)</th>
<th>WBC</th>
<th>HCT</th>
<th>Hb</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No □ Unknown</td>
<td>Date Collected (dd/mm/yyyy)</td>
<td>WBC</td>
<td>HCT</td>
<td>Hb</td>
<td>Platelets</td>
</tr>
</tbody>
</table>

**Serology**

<table>
<thead>
<tr>
<th>Specimen Type 1</th>
<th>Type of test</th>
<th>ELISA-IgM</th>
<th>ELISA-IgG</th>
<th>NS 1</th>
<th>PCR</th>
<th>Other (please specify):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection date</td>
<td>Level</td>
<td>Level</td>
<td>Pos</td>
<td>Neg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Pos</td>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Please specify):</td>
<td>level</td>
<td>level</td>
<td>pos</td>
<td>neg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Specimen Type 2</th>
<th>Type of test</th>
<th>ELISA-IgM</th>
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**OUTCOME**

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Government of The Punjab Health Department, Lahore

NOTES / REMARKS


REPORTING AGENCY

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First reported by
☐ Clinician ☐ Laboratory ☐ Other (please specify): __________________________

DISEASE CASE CLASSIFICATION

Case classification (see case definition below)
☐ Confirmed ☐ Probable ☐ Suspected

CASE DEFINITION

DENGUE (2012)
Dengue Fever
Dengue Hemorrhagic Fever
Dengue Shock Syndrome

CLINICAL DESCRIPTION

Dengue Fever
Dengue fever (DF) is characterized by the presence of fever and two or more of the following, retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations (e.g., positive tourniquet test, petechiae; purpura/ecchymosis; epistaxis; gum bleeding; blood in vomitus, urine, or stool; or vaginal bleeding) but not meeting the case definition of dengue hemorrhagic fever. Anorexia, nausea, abdominal pain, and persistent vomiting may also occur but are not case-defining criteria for DF.

Dengue Hemorrhagic Fever
Dengue hemorrhagic fever (DHF) is characterized by evidence of plasma leakage as shown by hemoconcentration (an increase in hematocrit ≥ 20% above average for age or a decrease in hematocrit ≥ 20% of baseline following fluid replacement therapy), OR pleural effusion, OR ascites or hypoproteinemia. Plus one of the following:
• Fever lasting from 2-7 days,
• Evidence of hemorrhagic manifestation or a positive tourniquet test,
• Thrombocytopenia (≤100,000 cells per mm³), AND

Dengue Shock Syndrome
Dengue shock syndrome (DSS) has all of criteria for DHF plus circulatory failure as evidenced by:
• Rapid and weak pulse and narrow pulse pressure (< 20mm Hg), OR
• Age-specific hypotension and cold, clammy skin, and restlessness.
CASE DEFINITION (CONTINUED)

LABORATORY CRITERIA FOR DIAGNOSIS

Confirmatory:
- Isolation of dengue virus from or demonstration of specific carboviral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid by polymerase chain reaction (PCR) test, immunofluorescence or immunohistochemistry, OR
- Seroconversion from negative for dengue virus-specific serum Immunoglobulin M (IgM) antibody in an acute phase (≤ 5 days after symptom onset) specimen to positive for dengue-specific serum IgM antibodies in a convalescent-phase specimen collected ≥ 5 days after symptom onset, OR
- Demonstration of a ≥ 4-fold rise in reciprocal Immunoglobulin G (IgG) antibody titer or Hemagglutination inhibition titer to dengue virus antigens in paired acute and convalescent serum samples, OR
- Demonstration of a ≥ 4-fold rise in PRNT (plaque reduction neutralization test) end point titer (as expressed by the reciprocal of the last serum dilution showing a 90% reduction in plaque counts compared to the virus infected control) between dengue viruses and other flaviviruses tested in a convalescent serum sample, OR
- Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF.

Presumptive/Probable:
- Dengue-specific IgM antibodies present in serum with a P/N ratio ≥ 2

Exposure:
- Travel to a dengue endemic country or presence at location with ongoing outbreak within previous two weeks of dengue-like illness, OR
- Association in time and place with a confirmed or probable dengue case.

Case Classification:
Suspected: A clinically compatible case of DF, DHF, or DSS that is epidemiologically linked to a confirmed case
Probable: A clinically compatible case of DF, DHF, or DSS with laboratory results indicative of presumptive infection
Confirmed: A clinically compatible case of DF, DHF, or DSS with confirmatory laboratory results

Comment:
Asymptomatic Blood or Tissue Donor
Dengue virus - specific viral antigen or genomic sequences demonstrated in donated blood or organs during screening and confirmatory testing in the absence of symptoms in the donor.

Dengue viruses are members of the Flaviviridae and have sufficient antigenic similarity to yellow fever virus, Japanese encephalitis virus, and West Nile virus that previous infection or vaccination may raise cross-reactive serum antibodies. After a primary infection with a heterologous flavivirus, subsequent antibody testing by ELISA may produce false positive results for a different flavivirus. PRNT can often resolve cross-reactive serum antibodies in this situation and identify the infecting virus. However, high-titered cross-reactive antibody levels produced from multiple previous flavivirus infections cannot be resolved by PRNT. This demonstrates the complexity inherent in serological diagnosis and differentiation in populations living in regions where more than one flavivirus co-circulates.

Reference testing is available from DEAG, Services Institute of Medical Sciences, Jail Road, Lahore, Pakistan
Telephone:042-99203401 – 21, Fax:042-99203426. Email: principalsoffice@gmail.com, deag.punjab@gmail.com
APPENDIX 4c

SOP for Reporting of Dengue Patients in Teaching Hospitals

Source:

1. Emergency
2. Indoor

Steps:

1. Resident should fill in the appropriate proforma Reporting Form – R (Appendix 4). All fields are compulsory.
2. Duly filled form will be signed by the concerned Registrar and SR and handed over by the concerned Registrar to focal person designated by MS.
3. Filled, signed forms will be received at The Office of the MS and will be signed by the administrative focal person as designated by the MS.
4. Incomplete forms will be returned by the administrative focal person to the concerned SR for completion.
5. Forms that are complete in all respects (ALL fields filled) bearing signatures of the Registrar, SR, focal person (administrative) will be handed over to the designated focal person from PITB by MS. Record of all forms thus handed will be kept in the office of MS.
6. The process will be completed by 10 am of the next working day.
7. The focal person from PITB will use these forms to fill the appropriate database.
8. This process will capture “suspected and probable cases” as defined by “Revised Diagnostic Criteria” (DEAG March 2012).
9. “Confirmed Cases” as defined by DEAG will need to be filled in on a separate proforma (Appendix 4b).

In view of the above SOP each teaching hospital will need to designate an administrative focal person in order for the above SOP to proceed.
APPENDIX 5 Diagnostic Criteria – Non Epidemic Setting

Revised Criteria for Diagnosis of Dengue Fever (Applicable In Non Epidemic Setting From Feb 2012 Onwards Until Further Revision)

The revised criteria is being introduced by DEAG to supersede the previous diagnostic criteria during dengue epidemic (used in dengue epidemic, 2011). Issuance of revised criteria was considered essential in view of following points.

1. According to unpublished data approximately 30%, population of Lahore was infected with dengue virus during the 2011 epidemic. This population will continue to have raised immunoglobins (IgG, IgM) for variable period of time. Therefore, presence of IgM alone would not indicate ongoing infection; it might be markers of previous infection.

2. The immune response during second dengue infection is significantly different from primary infection. IgM response is much smaller than in primary infection. Therefore rise in IgG titers over time is much more significant.

The diagnostic criteria would be divided into 3 categories;

1. Suspected case of Dengue Fever
2. Probable case of Dengue Fever
3. Confirmed case of Dengue Fever

Following is the revised criteria for each segment.

1. Suspected Case - Presence of 3 or more Clinical Criteria

Clinical Criteria
Fever > 2 and < 10 days (essential criterion)
Headache
Retro orbital pain
Myalgia
Arthralgia/ severe backache/ bone pains
Rash
Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis)
Abdominal pain
Decreased urinary output despite adequate fluid intake
Irritability in infants
2. **Probable Case – Suspected Case with both Supportive Lab Evidence**

**Supportive Lab Evidence**

- Thrombocytopenia
- Leukopenia

3. **Confirmed Case – Probable case with any one of the three Confirmatory Evidence**

**Confirmatory Evidence**

- Positive NS1 antigen
- Viral detection by PCR
- Seroconversion from negative to positive for serum IgM OR ≥ 4- fold rise in titre of IgG

Confirmatory evidence of viral infection would therefore, be based on:

- Detection of viral antigen (NS1 antigen in blood)
  - OR
- Detection of virus by PCR
  - OR
- Seroconversion from negative for dengue virus specific Ig M antibody in acute phase (≤ 5 days after onset of symptoms) to positive for dengue virus specific IgM antibody in convalescent phase specimen collected ≥ 5 days after onset of symptoms
  - OR
- Demonstration of ≥ 4 fold rise in reciprocal Ig G antibody titre in paired acute and convalescent serum sample

*Issued by Dengue Expert Advisory Group (Punjab)*

*25.02.2012*
APPENDIX 6

GOVERNMENT OF THE PUNJAB
HEALTH DEPTMENT

Dated Lahore, the 4th January, 2012

NOTIFICATION

No. S.O. (PH) 9-98 / 2002 (P-I). In exercise of the powers conferred under sub-section (1) of section 2 of the Punjab Epidemic Diseases Act 1958 (XXXVI of 1958), Governor of the Punjab is pleased to prescribe the following temporary regulations:

1. Short title and commencement.—(1) These regulations may be cited as the Punjab Prevention and Control of Dengue (Temporary) Regulations 2011.
   (2) They shall come into force on and from 4th January, 2012.
   (3) These regulations shall remain in force till 30th November, 2012 and shall stand repealed on 1st December, 2012.

2. Definitions.—(1) In these regulations:
   (a) “Act” means the Punjab Epidemic Diseases Act, 1958 (XXXVI of 1958);
   (b) “Government” means the Government of the Punjab;
   (c) “Health Inspector” means an officer appointed or designated by the Government as Health Inspector;
   (d) “occupier” means a person in occupation of any premises or having the charge, management or control thereof, whether on his own account or as an agent of any other, but does not include a lodger;
   (e) “owner” includes a co-owner, a lessee, any person who by whatever right is entitled to the rent or produce of any premises and any individual, association of persons (by whatever name called), institution, body corporate or official who is responsible for the proper maintenance of the premises; and
   (f) “premises” means any land together with any building or part of a building standing thereon and includes a vehicle or a vessel.

3. Responsibilities of owners and occupiers.—For purposes of ensuring the prevention and eradicating of dengue, an owner or occupier of premises shall immediately and not later than within two days from the commencement of these regulations:
   (a) remove, destroy or otherwise effectively dispose of open tins, bottles, boxes, tyres, or any other article or receptacle found in or within such premises, capable of holding water and placed in open air;
   (b) clear all obstructions of gutters, down-pipes and drains so as to allow a smooth flow of water;
(c) maintain in good repair, closed and covered cisterns, tanks, room coolers, air conditioners and other receptacles for water so as to prevent the breeding of mosquitoes;

(d) maintain and keep in good repair any well in the premises or its surroundings so as to make it mosquito-proof and thereby prevent the breeding of mosquitoes;

(e) empty at least once in every week artificial pond or pool in the premises;

(f) regularly drain any casual collection of water within the premises which is conducive to mosquito breeding;

(g) remove shrubs, undergrowth and all other types of vegetation, other than those grown for purposes of food or those which are ornamental, within or outside any building or structure with the premises which has become a breeding place for mosquitoes;

(h) remove any debris which is likely to become a breeding place for mosquitoes;

(i) remove and destroy the water plants and other plants which promote the breeding of mosquitoes; and

(j) eliminate or prevent any other condition favourable to the breeding of mosquitoes in the premises.

4. Spraying of pesticides.– The Health Inspector may, by notice in writing served on any owner or occupier of a premises, require such owner or occupier to spray any pond, cistern, fountain or any other place where water collects and where mosquitoes are found to be breeding, with such type of pesticide as may be specified in such notice and within the time specified therein.

5. Directions to take certain measures.– (1) Where it appears to the Health Inspector that any premises or anything kept or maintained therein has become favourable to the breeding of mosquitoes, the Health Inspector may, by written notice, require the owner or occupier of such premises to adopt or take any one or more of the following measures within the time specified in such notice:

(a) to repair all gutters, down-pipes and drains of any building found in the premises;

(b) to construct or reconstruct any cistern, tank, room cooler or artificial pond found in the premises in such manner so as to make it capable of being emptied periodically;

(c) to temporarily drain and clear any cistern, tank, room cooler, fountain or pond found in the premises and the closing thereof when it is no longer being used by the owner or occupier of the premises;

(d) to maintain any well found in the premises in such condition so as to prevent the breeding of mosquitoes;

(e) to fill-up, drain or treat with larvicide, any excavation, disused well, cesspit, pond or any other place where water is capable of being collected and stagnated;

(f) to fill-up pits and low lying areas found within the premises;
(g) to fill-up or drain or treat once a week with larvicide, swamps and water courses and water logged area as found in the premises;

(h) to remove any debris which is likely to be a breeding place for mosquitoes;

(i) to remove, uproot and destroy or trim water plants and any other plants which promote the breeding of mosquitoes; and

(j) to take such other measures as the Health Inspector may deem necessary for the prevention of spread of mosquitoes.

(2) The written notice, referred to in these regulations, shall further inform that in the event the owner or occupier neglects or fails to comply with such notice within the time specified therein, the Health Inspector shall be forced to carry out the measures specified in the notice and any expenses incurred in carrying out the same shall be recovered from such owner or occupier as arrears of land revenue.

(3) Where the owner or occupier of any premises on whom any written notice has been issued under these regulations, neglects or fails to comply with the requirement of such written notice within the time specified therein, the Health Inspector may authorize any person or persons, as the case may be, to enter such premises at any reasonable hour during the day and carry out the work or measures specified in the notice which the owner or occupier has neglected or failed to do.

(4) Prior to commencing any work or measure under these regulations, such person or persons shall be required to show the owner or occupier, a copy of the document issued by the Health Inspector by which such person or persons were authorized to carry out such work.

(5) Nothing contained in these regulations shall preclude the owner or occupier who failed to comply with a notice so issued from being prosecuted for an offence under section 3 of the Act.

6. Lessening the efficiency of any measures adopted.- (1) An owner or occupier or any other person shall not knowingly or willfully commit any act which is likely to -

(a) cause the deterioration of any anti-mosquito measures carried out or adopted in any premises; or

(b) lessen the efficacy of any anti-mosquito measures carried out or adopted in any premises,

whether such measures were carried out or adopted by the owner or occupier of the premises or by the Health Inspector as the case may be.

7. Co-owners and co-occupants to be liable severally.- Where any premises are in the occupation of more than one person or where any property is co-owned by more than one person, for purposes of enforcement of these regulations or any order under these regulations, each of the occupiers and each of the co-owners shall be severally liable for any neglect or failure to comply with any requirement of any order or these regulations.

8. Body of persons.- Where any premises is owned or occupied or managed by a body of persons, then -

(a) if that body of persons is a body corporate, every director, manager or secretary of that body corporate;
(b) if that body of persons is a partnership, every partner of that partnership; and
(c) if that body of persons is an unincorporated body, every individual who is a member of that body,

for purposes of the enforcement of these regulations or any order, shall be liable for any neglect or failure to comply with any requirement of these regulations or any order under these regulations.

9. Directions issued to local authorities.-(1) Where any drain, canal, water course or swamp found within the administrative limits of a local authority which such authority is required to maintain in proper condition, is found to have become conducive to the breeding of mosquitoes owing to the failure or negligence on the part of such local authority to maintain the same in such proper conditions, the Government, on the report of a Health Inspector or otherwise, shall have the power to issue such directions as it may consider necessary or appropriate, to rectify such situation and prevent the breeding of mosquitoes, and such local authority shall comply with the direction in such manner and within such time as may be mentioned in the direction.

10. Collection of data.- (1) If a doctor, nurse, healthcare service provider, owner or occupier has reason to believe that any person is suffering from dengue fever, he shall immediately inform the Government or the Health Inspector concerned as to the particulars of the patient.

(2) The owners or occupiers of laboratories and hospitals shall provide the information under para (1) within one hour of their knowledge that a person is suffering from dengue fever.

(3) The information under paras (1) and (2) shall be furnished in such manner and through such means as the Government may publish in the media.

11. Directions to patients.-(1) The Health Inspector may require the person who is or is suspected to be suffering from dengue fever to undergo medical examination, to remain quarantined and to get proper medical treatment.

(2) Where the person who is or is suspected to be suffering from dengue fever is a minor, the Health Inspector may require the parent or guardian of the minor to have the minor medically examined, quarantined or treated.

12. Laboratories and hospitals.-(1) The owner or occupier of a laboratory or hospital shall take all necessary measures effectively to deal with the epidemic of dengue fever.

(2) Without prejudice to the generality of para (1), the owner or occupier of a laboratory or hospital shall:

   (a) segregate the patients suffering from dengue fever from the other patients;
   (b) use such protective equipments, such as nets, in order to prevent transmission of dengue fever from one person to another;
   (c) carry out fogging or spray in the premises of the laboratory or the hospital to prevent spread of the epidemic of dengue fever; and
(d) disseminate information to persons coming to the laboratory or hospital the measures which are necessary to prevent spread of dengue fever and breeding of mosquitoes.

13. Educational institutions.—(1) The owner or occupier of an educational institution shall:

(a) carry out larvicidal activity, insecticidal fogging or spray in the educational institution at such intervals as the Government or the Health Inspector may direct;

(b) identify the common breeding habitats of mosquitoes in the educational institution and take immediate measures to remove and eradicate them;

(c) educate students and teachers regarding measures to prevent breeding of mosquitoes and handling of persons suspected to be suffering from dengue fever;

(d) regularly create awareness among students as to common breeding places of the mosquitoes and the ways and means to prevent spread of the epidemic of dengue fever;

(e) adopt in the educational institution such safety measures as may be necessary for the prevention of dengue infection such as full sleeves shirts, socks, and use of mosquito repellants and shall take such other measures as the Government or the Health Inspector may direct; and

(f) follow such other directions about the timings of the educational institution or its closure for such period as the Government may, from time to time, specify through public notice.

14. Power of entry and inspection.—(1) Subject to the provisions of para (2), the Health Inspector or any other person authorized by him, shall have the power to enter any premises at any reasonable time—

(a) to carry out any survey, inspection or search for purposes of determining whether:

i) any duties imposed under these regulations are being complied with by the owner or occupier of such premises; or

ii) any measures are necessary, and if so the extent to which they are necessary, for the elimination or the prevention of the breeding of mosquitoes; or

(b) to execute any work or measure required to be carried out under these regulations.

(2) For purposes of carrying out any survey, inspection or search under para (1), written consent to enter the premises on production of a docket shall be obtained:

(a) where the premises concerned is a place of religious worship or is a place not open to the public, from the person in charge of such premises or any other competent person; or
(b) where the premises concerned is used as a place of private residence, from the owner or occupier of such residence;

(3) Where the consent required to be obtained under para (2) is unfairly refused and the Health Inspector is satisfied that there is reason to suspect that any requirement imposed under these regulations is not being complied with, the Health Inspector may obtain from the court of a Magistrate having jurisdiction in the area a search warrant under the Code of Criminal Procedure for purposes of entering such premises or private residence, as the case may be, and exercise all or any of the powers conferred upon him by such search warrant.

15. **Penalty.**— Every owner or occupier or any other person who contravenes or fails to comply with any duty or requirement or order under these regulations or under the Act shall be guilty of an offence under section 3 of the Act.

[Signature]

SECRETARY
GOVERNMENT OF THE PUNJAB
HEALTH DEPARTMENT
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 emphasized.

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  - hemorrhagic manifestations
    - Leucopenia

  **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 HEMORRHAGIC FEVER

The following must **ALL** be present:

1. **Fever, or history of acute fever, lasting 2–7 days**, occasionally biphasic.
2. **Hemorrhagic tendencies**, evidenced by at least one of the following:
   a. A positive tourniquet test
   b. Petechiae, ecchymoses or purpura
   c. Bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
   d. Hematemesis or melena.
3. **Thrombocytopenia** (100,000 cells per mm³ or less).
4. **Evidence of plasma leakage** due to increased vascular permeability, manifested by at least one of the following:
   a. A rise in the HCT equal to or greater than 20% above average for age, sex and population;
   b. A drop in the HCT following volume-replacement treatment equal to or greater than 20% or baseline;
   c. 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 hemorrhagic 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 hemorrhages.

*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.
**APPENDIX 8**

**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:** Hemolysed or icteric or lipaemic specimens invalidate certain tests. 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 -70°C 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 a 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 °C bath such as dry ice/alcohol as quickly as possible after collection. Once frozen, the tissue specimen can be stored at -70°C 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 plain 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 4°C 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 4°C 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 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 patients) 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.
THE DANGER SIGNS OF DENGUE INFECTION
(If any of these are observed, please go immediately to the nearest hospital)

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<thead>
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<th>Number</th>
<th>Description</th>
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<tbody>
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<td>1.</td>
<td>Bleeding</td>
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<td>for example:</td>
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<td>- Extensive red spots or patches on the skin</td>
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<td>- Excessive bleeding from nose or gums</td>
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<td>- Black tarry stools</td>
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<td>- Heavy menstruation / vaginal bleeding</td>
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<td>2.</td>
<td>Frequent vomiting</td>
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<td>3.</td>
<td>Severe abdominal pain</td>
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<td>4.</td>
<td>Drowsiness or irritability</td>
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<td>5.</td>
<td>Pale, cold and clammy skin</td>
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<td>6.</td>
<td>Difficulty in breathing</td>
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## APPENDIX 10

### List of Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>BU SE C</td>
<td>Blood urea, Serum Electrolytes, Creatinine</td>
</tr>
<tr>
<td>CRT</td>
<td>Capillary Refill Time</td>
</tr>
<tr>
<td>CVC</td>
<td>Central Venous Catheter</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>DF</td>
<td>Dengue Fever</td>
</tr>
<tr>
<td>DSS</td>
<td>Dengue Shock Syndrome</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GXM</td>
<td>Group Cross Match</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>HCO3</td>
<td>Bicarbonate</td>
</tr>
<tr>
<td>HELLP</td>
<td>Hemolysis, Elevated Liver Enzymes, Low Platelets</td>
</tr>
<tr>
<td>HI</td>
<td>Hemagglutination inhibition</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function Test</td>
</tr>
<tr>
<td>NG Tube</td>
<td>Naso-Gastric Tube</td>
</tr>
<tr>
<td>NSI Ag</td>
<td>Non-structural protein – 1 antigen</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PP</td>
<td>Pulse pressure</td>
</tr>
<tr>
<td>PR</td>
<td>Pulse rate</td>
</tr>
<tr>
<td>RBS</td>
<td>Random blood sugar</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase Polymerase chain reaction</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>TCO2</td>
<td>Total CO₂</td>
</tr>
<tr>
<td>WCC</td>
<td>White cell count</td>
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</table>
APPENDIX 11

Acknowledgement

The development group of this guideline would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Technical Advisory Committee for Clinical Practice Guidelines for their valuable input and feedback.

APPENDIX 12

Disclosure Statement

None of the primary authors holds shares in pharmaceutical firms or acts as consultants to such firms.

APPENDIX 13

Sources of Funding

The development of the CPG on Management of Dengue Infection in Adults was supported financially in its entirety by the Government of the Punjab Pakistan and was developed without any involvement of the pharmaceutical industry.
APPENDIX 14

Outcome and Management Indicators

Primary Indicators:

i. Case fatality rate (DF & DHF)
Numerator: No of adult DF & DHF/DSS death
Denominator: No of adult DF & DHF cases (clinically diagnosed)
National target = ? < 0.2%

ii. DHF fatality rate
Numerator: No of adult DHF/DSS death
Denominator: No of adult DHF/DSS cases (clinically diagnosed)
National target = ? <1.0%

SECONDARY INDICATORS (Adults)

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
APPENDIX 15

Self-Evaluation - Review

1. What is the epidemiological data for dengue? (Section 1, P1)

2. How to diagnose dengue? (Section 3.7, P20, Appendix 5)
   a. Clinical
      i. Latest definition of DF, DHF, DSS (Section 3.1, P6)
      ii. Stages of disease and pitfalls of WHO Classification (Section 3.5, P16)
      iii. Differential diagnosis (Section 3.7, P20)
      iv. Unusual presentation (hepatitis, liver failure, acute abdomen, encephalitis, myocarditis) (Section 3.6, P19)
      v. Co-infection – Typhoid, septicemia, malaria (Section 3.7, P20)
   b. Laboratory diagnosis and its pitfalls (Section 5, P 24, Appendix 5)
      i. When should IgM and IgG be taken? Role of rapid test kit. (Section 5.2.1, P25)
      ii. What is the role of PCR / NS1 in the diagnosis? (Section 5.2.2, P27)

3. How to manage the patients with dengue infection as outpatients and in the emergency facility? (Appendix 3a – Form O)
   i. OPD and A/E triaging-fast tracking during outbreak (Section 7.2, P34)
   ii. Who can be treated at home? Clinical and laboratory criteria – risk stratification at first contact (Table 6, P33)
   iii. When should the GP refer the suspected dengue case to OPD or hospital? (Section 7.3.1, P34)
   iv. What should be the home care advice (Appendix 3a, Form O)
   v. Specific out patient management and follow-up (Appendix 3a, Form O)
4. When to hospitalize?

   i. Clinical and laboratory criteria including social assessment (Section 7.3.1, P34)
   
   ii. Co-morbidities (which need hospital admission)? (Section 7.3.1, P34)
   
   iii. Communication and notification protocol (government / inter-departmental/ inter-hospital and inter healthcare facilities) (Appendix 4a, 4b, 4c)
   
   iv. Role of bed netting and/or mosquito repellent in the hospital setting-place under general issues (Section 9, P55)

5. How to monitor the patient in the ward?

   i. What to monitor - parameter (Table 8, P 38, Appendix 2a, 2b, 2c, 3b)
   
   ii. Pitfalls of management (Section 7.5.1, P39)
   
   iii. Alarm triggers - Aid chart /alert card /refer algorithm (Table 5, P33)

6. When to refer patient from district hospital without specialist to general hospital? (Section 7.3.2, P35)

   i. Clinical and laboratory criteria
   
   ii. Risk stratification protocol,
   
   iii. When to obtain early specialist advice for those at higher risk

7. When to refer the patient for high dependency management? How to manage the critically ill dengue patient?

   i. What are the clinical criteria for referral to HDU. (Section 7.7 P50)
   
   ii. Criteria for respiratory and hemodynamic support. (Section 7.7.1, 7.7.2, P 50, 51)
   
   iii. Guide on safety and risk of invasive procedures (Section 7.7.3, P52 )

8. What should be the fluid management in DF/ DHF /DSS? (Section 7.5, P39, Algorithms A & B, P 45, 46)

9. DHF/DSS

   i. Definition based on WHO classification (Section 3.5, P16 )
   
   
10. How do we manage hematological and hemostatic abnormalities?
   i. Interpreting laboratory results (particularly HCT) (Section 5.1, P24)
   ii. Is there a role of prophylactic transfusion? (Section 7.6.5, P49)
   iii. Is there any role of prophylactic platelet transfusion? (Section 7.6.5, P49)

11. How to management bleeding in dengue patient?
   i. What is considered to be significant bleeding? (Section 7.6.2, P47)
   ii. GIT Bleed - role of OGDS/ PPI and other treatment (Section 7.6.4, P48)
   iii. Use of blood and blood products (Section 7.5.4, P42, Algorithms A & B, P45, 46)
   iv. Role of vitamin K and Tranexamic acid (Section 7.6.6, P49)
   v. Recognizing occult bleed (Section 7.6.2, P47)

12. Is there a role of drug therapy in DHF/DSS?
   i. Role of recombinant Factor VII (Section 7.6.6, P49)
   ii. Role of IV- Immunoglobulin G (Section 7.6.6, P49)
   iii. Role of steroid (Section 7.6.6, P49)

13. What are the discharge criteria? (Section 8, P54)

14. What is the guidance for follow-up for those patients where
   i. Dengue serology returns negative (Section 5.2.1, P25)
   ii. Complications develop (patients with complications should remain admitted…common sense!!)
“These guidelines for diagnosis and management of dengue/dengue hemorrhagic fever are very comprehensive and timely. They will serve the medical and public health communities in Pakistan well as dengue hemorrhagic fever continues its geographic expansion in the country”