Issues in Management of Dengue

Ampaiwan Chuansumrit, M.D.

Department of Pediatrics, Faculty of Medicine,
Ramathibodi Hospital, Mahidol University,
Bangkok, Thailand
Manifestation of Dengue Virus Infection

Dengue virus infection

Asymptomatic

Symptomatic

Undifferentiated fever (viral syndrome)

Dengue fever syndrome

Without hemorrhage

With unusual hemorrhage

Dengue hemorrhagic fever (plasma leakage)

No shock

Dengue shock syndrome

Dengue fever

Dengue Hemorrhagic fever
### Days of Illness

#### Febrile Stage
- Acute onset of fever
- Headache
- Nausea
- Vomiting

#### Toxic Stage
- Restless
- Shock
- Hemorrhage

#### Convalescent Stage
- Flush face
- Enlarged liver
- Tourniquet test positive
- Skin rash, petechiae, ecchymosis
### Clinical Manifestations in Patients with DHF Compared to DF and other Febrile Illnesses (OFI)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DHF (n=257)</th>
<th>DF (n=71)</th>
<th>OFI (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>97.7</td>
<td>95.8</td>
<td>38 (100.0)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>82.9</td>
<td>81.7</td>
<td>26 (68.4)</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>80.9</td>
<td>83.1</td>
<td>28 (73.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>57.2</td>
<td>43.7</td>
<td>16 (42.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>39.7</td>
<td>43.7</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>40.9</td>
<td>33.8</td>
<td>13 (34.2)</td>
</tr>
<tr>
<td>URI symptom</td>
<td>30.4</td>
<td>31.0</td>
<td>15 (39.5)</td>
</tr>
</tbody>
</table>
### Bleeding Manifestations in Patients with DHF Compared to DF and other Febrile Illnesses (OFI)

<table>
<thead>
<tr>
<th></th>
<th>DHF  (n=438)</th>
<th>DF  (n=174)</th>
<th>OFI  (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>34.7</td>
<td>27.5</td>
<td>32.7</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>21.9</td>
<td>16.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>1.8</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>GI</td>
<td>14.2</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>10.3</td>
<td>2.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Gum &amp; teeth</td>
<td>4.8</td>
<td>4.6</td>
<td>-</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Patients Suspected with DHF Requiring Hospitalization

- Severe abdominal pain
- Severe vomiting
- Unable to eat and drink, dehydration, oliguria
- Irritable, restless, sleepiness, behavior change
- Cold clammy skin
- Clinical deterioration
- Bleeding manifestations except for petechiae or ecchymosis
Plasma Volume in Dengue Hemorrhagic Fever

Dengue Hemorrhagic Fever

- **Clinical manifestations**
  - Sustained high fever 2-7 days
  - Hemorrhagic diathesis
  - Hepatomegaly
  - Circulatory disturbances

- **Laboratory findings**
  - Thrombocytopenia $\leq 100,000/\mu L$
  - Evidence of plasma leakage: hemoconcentration, pleural effusion, ascites
Problem of Laboratory Finding of DHF

• Hemoconcentration (increased of Hct > 20%)
  - Baselined Hct
  - Bleeding manifestation
  - Excessive intravenous fluid

• Low platelet counts ≤ 100,000 /µL
  Requiring daily CBC especially one day before defervescence, day of defervescence and one day after defervescence

• Pleural effusion
  - Physical examination especially during toxic stage
  - CXR in right lateral decubitus view at 12-24 h after defervescence
Severity of DHF

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 forms 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
Laboratory Finding of DHF

- Rising Hct
- Low WBC
- ↑ lymphocyte, ↑ atypical lymphocyte
- ↓ platelet counts
- Virus isolation
- Positive dengue NS1 antigen
- Dengue specific IgM and IgG or hemagglutination inhibition test
Platelet Counts

![Graph showing platelet counts over days and days of illness for different conditions: DF, DHF I, DHF II, DSS, OFIs. The x-axis represents Day of Illness, ranging from Day -3 to 1 Month. The y-axis represents Platelet count (uL) ranging from 0 to 400. The graph shows a significant increase in platelet counts for the OFIs condition starting from Day 1.](image-url)
Dengue NS1 Antigen by ELISA and Ig M Antibody in Patients with Dengue Infection

Febrile

Positive rate (%)

Day of illness

Day-4  Day-3  Day-2  Day-1  Day0  Day+1  Day+2  Day+3

0  20  40  60  80  100  120

NS1

Ig M

NS1 & Ig M
Dengue NS1 Antigen by Strip Method

• Interpretation
  
  - Positive: Blue line at Test (T) and Control (C)

  - Negative: Blue line at Control (C)

  - Doubtful: Faint color at Test (T)
Prominent Features of DHF

• Shock is caused by plasma leakage, which results from increased vascular permeability

• Bleeding is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy
Activated Partial Thromboplastin Time

Day of illness

APTT (sec)

Apoptosis
Prothrombin Time

Day of illness

PT (sec)
Thrombin Time

Day of illness

TT (sec)

Day -3
Day -2
Day -1
Day 0
Day 1
Day 2
FU

DF
DHF I
DHF II
DSS
OFIs

Day of illness
Predictor of Dengue Shock Syndrome during Febrile Stage

- Rising hematocrit > 25%
- Uncontrolled massive bleeding
- Soluble thrombomodulin > 10 ng/ml
Elevated Levels of Soluble Thrombomodulin in the Febrile Stage among Patients at Risk for Dengue Shock Syndrome

Management of Patients with DHF

- No specific treatment
- Intensive supportive care
- Early recognition of the disease and circulatory disturbance
- Adequate & appropriate fluid replacement
- Effective control of bleeding
High Risk Patients with DHF

- Grade IV
- Infant less than 1 year old
- Obesity
- Encephalopathy / encephalitis
- Underlying diseases: G6PD deficiency, thalassemia disease
Fluid Therapy in DHF Grade III

Impending shock (pulse pressure ≤ 20 mmHg)

Hypotension

• Isotonic fluid resuscitation (NSS or 5% D in NSS)
  10-20 ml/kg in 1 h x 1-2 doses

• If vital signs improve:
  Pulse pressure > 20 mmHg
  Urine output 2-4 ml/kg/4h or urine sp gr 1.010-1.020

Monitor Hct: decreased

• Decrease rate of IV fluid: 7 ml/kg/h x 1-2 h
  5 ml/kg/h x 1-2 h

• Gradually decrease rate of IV fluid according to clinical monitoring for 24-48 h
Impending shock (pulse pressure ≤ 20 mmHg)

Hypotension

- Isotonic fluid resuscitation (NSS or 5% D in NSS)
  - 10-20 ml/kg in 1 h x 1-2 doses
- If vital signs NOT improve and Hct increases
  - Colloid 10 ml/kg/h for 1-2 h
  - Decrease rate of IV fluid: 7 ml/kg/h x 1-2 h
  - 5 ml/kg/h x 1-2 h
- Gradually decrease rate of IV fluid according to clinical monitoring for 24-48 h
Fluid Therapy in DHF Grade III

Impending shock (pulse pressure $\leq 20$ mmHg)

hypotension

- Isotonic fluid resuscitation (NSS or 5% D in NSS)
  
  10-20 ml/kg in 1 h x 1-2 doses

- If vital signs NOT improve and Hct decreases
  
  ......BLEEDING is considered

- Effective bleeding control is essential

- Colloid 10 ml/kg for 1-2 h while waiting for PRC
  and other blood components
Fluid Therapy in DHF Grade IV

Profound shock

• Isotonic fluid resuscitation (NSS)
  10-20 ml/kg in 10-15 min x 2-3 doses

• Check BS, ABG, electrolytes, Ca, LFT, BUN, Cr,
  coagulogram, crossmatch for blood components

IMPROVED: BP increases, Hct decreases, urine output

• 5% D in NSS 10 ml/kg/h 1-2 h

• Decrease rate of IV fluid: 7 ml/kg/h x 1-2 h
  5 ml/kg/h x 1-2 h

• Gradually decrease rate of IV fluid according to
  clinical monitoring for 24-48 h
Fluid Therapy in DHF Grade IV

Profound shock

- Isotonic fluid resuscitation (NSS)
  10-20 ml/kg in 10-15 min x 2-3 doses
- Check BS, ABG, electrolytes, Ca, LFT, BUN, Cr, coagulogram, crossmatch for blood components
- If vital signs **NOT improve** and Hct increases, oliguria
- Monitoring in ICU with intensive supportive care
- Change to colloid 10-20 ml/kg/h for 1-2 h
  
  ............IMPROVED

- Change to 5% D in NSS and decrease rate of IV fluid according to clinical monitoring
Fluid Therapy in DHF Grade IV

Profound shock

- Isotonic fluid resuscitation (NSS)
  10-20 ml/kg in 10-15 min x 2-3 doses
- Check BS, ABG, electrolytes, Ca, LFT, BUN, Cr, coagulogram, crossmatch for blood components
- If vital signs NOT improve and Hct decreases, oliguria

……BLEEDING is considered

Effective bleeding control is essential

Monitoring in ICU with intensive supportive care

- Colloid 10-20 ml/kg for 1-2 h while waiting for PRC and other blood components
DHF with Massive Leakage

- Massive pleural effusion: high intra-thoracic pressure
- Massive ascites: high intra-abdominal pressure
  high intra-thoracic pressure

↓

Respiratory system compromises
Acute renal failure frequently occurs

- Multidisciplinary approach of hemodynamic, pulmonary and renal support of peritoneal dialysis, hemodialysis and continuous veno-venous hemodialysis (CVVH)
Very Essential Issue

• Complications of invasive procedures
  – Bleeding
  – Opportunistic infections

• Invasive procedure must be performed with sterile technique by skilful personnel

• Early recognition and effective treatment of opportunistic infections
Management of Massive Bleeding in DHF

- Identify patients at risk
- Recognize the bleeding sites
- Stop the bleeding properly
- An alternative for patients unresponsive to conventional blood component therapy
Identify the Patient at Risk

- DHF grades III and IV
- GI bleeding: hematemesis, melena, hematochezia
- Aspirin, NSAIDS e.g. ibuprofen
- Excessive amount of dextran administration >30 ml/kg
- Prolonged shock or recurrent shock
- Underlying bleeding disorder: von Willebrand disease, hemophilia
**Pictorial Blood Assessment Chart (PBAC)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Score ≥ 40 is suggested excessive vaginal bleeding, hormonal therapy is required</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Small clot 1</td>
<td></td>
</tr>
<tr>
<td>Large clot 5</td>
<td></td>
</tr>
</tbody>
</table>
Concealed Bleeding

After the adequate volume replacement, internal bleeding is suspected in the following conditions:

- Refractory shock with hematocrit < 40%
- Systolic and diastolic BP is elevated or normalized, but the pulse rate is rapid (> 130/min in children, > 150/min in infant)
- A drop in hematocrit of > 10% within 10 h of fluid replacement
Life-Threatening Bleeding

• Bleeding in vital organs e.g. CNS, heart, lungs

• Continuous bleeding in hollow organ e.g. GI

• Massive blood loss
Blood Component Therapy

- RBC: replacement of massive blood loss
- Platelet concentrate: massive bleeding in patients with thrombocytopenia
- FFP: bleeding in patients with coagulopathy
- Cryoprecipitate: fibrinogen replacement in patients with massive bleeding
Early Diagnosis of Massive Bleeding

- Rate and volume of blood loss
- Bleeding of 1.5 ml/kg/min in ≥ 20 min or 150 ml/min
- Replacement with 50% blood volume in < 3 h
Suggested Dose of Recombinant Activated Factor VII in Controlling Bleeding in Patients with DHF

- Failure to conventional blood component therapy
  
  FFP 10-20 ml/kg
  
  Platelet 0.2-0.4 unit/kg (10 units)
  
  Cryoprecipitate 0.2 unit/kg
  
- rFVIIa 100 µg/kg at 15-30 min interval until the bleeding is significant reduced (1-2 doses are usually used) followed by 100 µg/kg at 1-4 h interval (1-2 doses are usually used)
  
- 17/694 patients (2.4%) required rFVIIa to stop massive bleeding
rVIIa - Directly Activates FX on the Surface of Activated Platelets
### Efficacy of Recombinant Activated Factor VII in Bleeding Control in Children with DHF

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>Effective</th>
<th>Partially-effective</th>
<th>Infective</th>
<th>Cases-fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>19</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>26 (68.4%)</td>
<td>1 (2.6%)</td>
<td>11 (29.0%)</td>
<td>9 (23.7%)</td>
</tr>
</tbody>
</table>
Case-Fatality Rate

- Case-fatality rate 13.9% in 1958 decreased to 0.12% in the past five decades
- Of all fatal cases in 2007 were found in patients with DHF (38%) and DSS (62%)
- None of patients with DF died
- Almost all patients with DHF with uncontrolled massive bleeding died
Favorable Outcome for Dengue Hemorrhagic Fever Patients with Bleeding

- Outpatient clinic & inpatient service
- Early recognition of the disease and circulatory failure
- Identify high risk patients
- Prompt treatment of adequate fluid replacement
- Effective control of bleeding
Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

- Wandee Varavithya, M.D.
- Somsak Lolekha, M.D.
- Subharee Suwanjutha, M.D.
- Teerachai Chantarojanasiri, M.D.
- Pongsak Khowsathit, M.D.
- Kanchana Tangnararatchakit, M.D.
- Pimpan Kitpoka, M.D.
- ICU, Ward Pediatric 2 & 5
- Wathanee Chaiyaratana, M.Sc.
- Pakawan Wongwerawattanakoon, B.Sc.
Thank you