NATIONAL WORKING GROUP ON CONSENSUS GUIDELINE ON
DENGUE CASE MANAGEMENT

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The 2001 Revised National Consensus on the Case Management of DF and DHF

(The Center for Infectious Diseases of the Department of Health, San Lazaro Hospital, Research Institute for Tropical Medicine, Philippine Pediatrics Society, Pediatric Infectious Disease Society of the Philippines, Philippine College of Physicians, Philippine Society for Microbiology and Infectious Diseases, Philippines Society of Hematology and Blood Transfusion, Philippine Academy of Family Physicians, UP College of Medicine, Biotechnology and Research Division of St. Luke's Hospital and the World Health Organization).

Summary

This document is intended to provide general guidelines to health care providers on the treatment of dengue fever (DF) and dengue hemorrhagic fever (DHF) in the out-patient and in-patient settings. The cornerstone of treatment in dengue illness is fluid management and judicious use of blood or blood products. The aim is to reduce mortality rates, prevent complications, minimize cost and limit untoward reactions from these treatment options.

Background

Dengue is endemic in the Philippines and is one of the leading causes of hospitalizations. During peak months, hospitals become overcrowded because of over-diagnosis and unnecessary confinements. Heightened awareness among the public aggravates the situation wherein hospitalization is considered life saving if not, the only option available. Health care providers likewise respond differently, sometimes worried of legal entanglements especially when the illness or its complications are not immediately recognized and there are preventable consequences.

Because dengue infections have a wide array of manifestations ranging from asymptomatic to fatal shock syndromes, not too many agree on a single course of action when a particular patient is seen for the first time. The pathologic mechanisms underlying the DHF (increased vascular permeability and abnormal hemostasis) are likewise not always consistent to explain every abnormality found on patients. Nevertheless, there is general agreement that effective fluid management remains to be the cornerstone of the treatment, aided by judicious use of blood and blood products. The WHO has recently provided general treatment guidelines for DHF using algorithms to facilitate decision-making.

The Department of Health through San Lazaro Hospital convened a Working Group of experts to establish and finalize a new set of guidelines in September 1998. Treatment recommendations have been formulated and adapted by both public and private sectors in previous years. With sufficient data and experiences, the group deemed it necessary to review and update existing guidelines to come up with a modified and perhaps unified consensus guideline to prevent unnecessary hospitalizations and deaths. Thus, on April 5-6, 2001 a workshop was conducted for this activity. These will make all existing treatment recommendation provided in this document are based on published and unpublished data on dengue infection and treatment and, when no definitive data were available, the consensus of the Working Group that the guidelines be regarded as flexible and not supplant the clinical judgement of experienced health care providers. It is recognized that these guidelines will need to be modified as new information and experience become available.

Important Concepts in the Formulation of Guidelines

The Working Group identifies a number of important concepts that need to be taken into consideration in the formulation of the current treatment guidelines for DF and DHF. They are:

1. Identification of clinical and laboratory parameters that will warrant hospital confinement and predict outcome.
3. Indications for use of blood and blood products.
4. Evaluation of other treatment options.
5. Simple, practical treatment matrix.
6. Ability of health-care providers to conform to these guidelines.

Points of Reference for the treatment guidelines:

- A consensus is needed to be able to come up with a standard protocol for assessment and management of dengue fever and dengue hemorrhagic fever that will be used in hospitals and community-settings so that case fatality rates may be reduced to less than 1%.
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
- Hemoconcentration - a rise in the hematocrit of ≥20% above average of age, sex, and population or greater than 20% drop in hematocrit following treatment with fluids as compared to baseline;
- Clinical (edema, pleural effusion, ascites);
- Hemorrhagic manifestation include:
  - A positive tourniquet test
  - Petechiae, echymoses or purpuric rashes;
  - Bleeding like epistaxis, gum bleeding, hemenmesis or melena or from other sites.

Case definition for dengue shock syndrome (DSS)

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 (≤20 mmHg) or manifested by:
  - Hypotension for age (< 80 mmHg systolic pressure for <5 years of age and <90 mmHg systolic pressure for ≥5 years of age), and
- Cold, clammy skin and restlessness

Grading severity of DHF

DHF is classified into four grades of severity, where grades III and IV are considered to be Dengue Shock Syndrome (DSS).

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.

- Probable

A case compatible with the suspected case classification with one or more of the following:
- Supportive serology (a reciprocal hemagglutination-inhibition antibody titer ≥1280, a comparable IgG enzyme-linked immunosorbent assay (ELISA) titer 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 compatible with the clinical description, laboratory-confirmed (see below)

Laboratory criteria for confirmation of dengue fever are:

A. Serological confirmation
- Demonstration of a fourfold or greater change in IgG antibody titres to one or more dengue virus antigens in paired serum samples.
- Anti-dengue IgM ELISA positive (P/N ≥2)

B. Virological confirmation
- Isolation of the dengue virus from serum or autopsy samples
- Demonstration of the Dengue Virus Antigen by Immunofluorescence (IFAT) or Immunoperoxidase test.
- Demonstration of Dengue Virus Genome by RT-PCR using Dengue Consensus and Serotype specific primers

Case definition for dengue hemorrhagic fever (DHF)

The following must all be present:
- Fever, or history of acute fever lasting 2-7 days;
- Thrombocytopenia (<100,000 cells per mm³ or less) or 1-2 platelets/oil immersion field;
- The consensus defined two categories of patients: those that can be treated at home and those who will require hospitalization.
- Hospitalization will be required if danger sign(s) is/are present; these danger signs anticipate bleeding or occurrence of shock.
- Those requiring hospitalization are further subdivided into those with no evidence of shock and those with significant blood loss with or without
shock.

- Platelet count, hematocrit, bleeding time, partial thromboplastin time (PTT) must be monitored when available; vital signs, urine output are also included.

- IV fluids (crystalloids) such as D$_5$LRS, plain LRS and D$_5$NSS are used to prevent or in early treatment of shock; estimates are based on existing WHO protocol.

- Aside from replacement of fluids, fluid maintenance shall be given.

- Colloids (albumin, plasma or plasma substitutes) may be given if IV fluids are inadequate.

- Whole blood or blood components may be required when there is significant blood loss or when DIC is suspected.

- Patients are sent home if they become clinically stable and remain afebrile for 72 hours and have a platelet count of at least 100,000/cu mm.

**Recommendations**

1. **Who has dengue fever (DF) and dengue hemorrhagic fever (DHF)?**

   The WHO deems it not appropriate to adopt a detailed clinical definition of dengue fever because of the variability in the clinical illness associated with dengue infection. There is a need for laboratory confirmation if technology exists. Otherwise it has proposed the following classification:

   **Case definition for dengue fever (DF)**

   - Suspected
     
     An acute febrile illness of 2-7 days duration with 2 or more of the following:

     - Headache
     - Retro-orbital pain
     - Myalgia
     - Arthralgia
     - Rash
     - Hemorrhagic manifestations (petechiae, TT +, etc.)
     - Leukopenia

   **Comments:** A provisional diagnosis of DHF can be made based upon the presence of high fever of acute onset, hemorrhagic manifestation (at least a positive tourniquet test), plus either thrombocytopenia or hemocoagulation (or at least a rising hematocrit). In monitoring hematocrit, one should strongly consider the effects of pre-existing anemia, severe hemorrhage or early volume-replacement therapy. The grading system should not be used to predict the evolution of more severe manifestations but rather to use it to describe existing manifestations as each grade carries a different prognosis and outcome.

2. **How is the tourniquet test done?**

   Place the cuff of a sphygmomanometer around the arm in the usual manner and inflate to a pressure halfway between systolic and diastolic levels. Maintain compression for five minutes and wait two minutes or more before observation. Describe an area 1-sq. inch on the volar surface of the forearm 1 1/2 inch distal from the antecubital fossa. Count the petechiae within this prescribed area. A positive tourniquet test is ≥20 petechiae.

   **Comments:** The tourniquet test should be done only with the use of a sphygmomanometer, with the corresponding cuff appropriate for age. Healthy individuals may also present with a positive tourniquet test. Patients presenting with shock may have a negative tourniquet test. Thus, tourniquet test should be done only in individuals highly suspected to have DF or DHF, and early in the disease. The presence of petechiae or Herman's rash exempts the patient from such test.

3. **Who will need hospitalization?**

   It is not necessary to hospitalize all patients with suspected DHF, since shock develops in less than one-third of cases. The finding of a continuing drop in the platelet count concurrent with a rise in the hematocrit is an important indicator of the onset of shock. Repeated platelet and hematocrit determinations are needed. The critical period is usually on the day of defervescence, typically after the third day of illness. All patients presenting with DSS should be hospitalized. Those who will require treatment at home should be monitored for danger signs. The presence of any danger sign requires hospitalization.

   **Danger Signs**

   - Spontaneous bleeding (epistaxis, gum bleeding, hematemesis, coffee-ground material per nasogastric tube, bleeding from venepuncture sites, hematuria, melena, hematochezia, menorrhagia)
   - Persistent abdominal pain
   - Persistent vomiting
   - Listlessness
   - Changes in mental status
   - Restlessness
   - Weak and rapid pulse
• Cold, clammy skin
• Circumoral cyanosis
• Difficulty of breathing
• Seizures
• Hypotension or narrowing of pulse pressure (<20 mmHg)
• Platelet count <100,000 cells per mm$^3$ or 1-2 platelet per oil immersion field
• Hemoconcentration
• Prolonged bleeding time (>5 minutes by Ivy method)

Comments: There are no specific manifestations or laboratory tests that accurately identify patients who will require hospitalization. The decision to hospitalize patients may be influenced by the availability and efficiency of health care services. It should be closely monitored after the third day of illness or during defervescence. The appearance of Herman's rash or the absence of fever for at least three days without apparent deterioration usually heralds recovery.

4. How do you give fluids in DHF?

Fluids must be given for replacement and maintenance purposes. In the febrile stage of DHF, fluid loss should be replaced with oral rehydrating salt solution. As much as 75 mL/KBW can be given in 4 hours.

Intravenous fluid (IVF) therapy is recommended when danger signs are present, especially during defervescence. Crystalloids ($D_5$LRS or $D_3$ 0.9 NaCl or Plain LRS or Plain 0.9 NSS) can be given at 5 mL - 15 mL/KBW/hour, with periodic adjustment according to patient's subsequent response. The vital signs and urine output are important parameters to monitor response to IVF therapy. It is suggested that you start at a rate of 5 mL/KBW/hour and gradually increase this to 15mL/KBW/hour by 3-5 mL/hour increments until you achieve the desired response.

When the patient is in shock, IVF must be given at a faster rate and bigger volume, the 20/20 rule, that is, 20 mL/KBW in 20-30 minutes. The patient usually responds after this dose. If you do not improve the situation, colloids at 20 mL/KBW in 20 minutes may be given. Meanwhile, look for other causes of shock such as bleeding, which may or may not be obvious.

After adequately replacing the fluid losses, maintenance IVF therapy should be instituted. $D_5$LRS or $D_5$IMB if <2 yrs. old may be used and should be given at 3 mL/KBW/hour up to 2-3 liters per day in adults. Patients usually require IVF therapy for 24-48 hours.

Comments: IVF therapy is the cornerstone of treatment in DHF. Where facilities exist to institute this therapy it is recommended that adequate supply of fluids (ORESOL and IVFs) including IV sets/needles should always be available. The Philippine Pediatric Society strongly recommends its own guidelines on proper fluids and electrolytes replacement and maintenance. These guidelines are not that different from what has been presented except for its familiarity of use by pediatricians.

Colloids (dextran, haemmacel, haes) are used to improve hemodynamics when IVF alone are not able to reverse shock or as immediate blood substitutes. Excessive use of dextran may have deleterious effects on platelets.

Monitoring of hemodynamic response is emphasized to ensure adequate IVF therapy and to remove the risk of overhydration. Overhydration with its possibly fatal consequence, usually occurs during the recovery phase when fluid volume is not properly adjusted and sequestered fluid goes back to the vasculature.

5. When do you give blood/blood products in DHF?

Whole blood is indicated to correct anemia and shock, if fluids are not able to provide adequate fluid resuscitation. When disseminated intravascular coagulation (DIC) is suspected, fresh, frozen plasma or cryoprecipitate is given. A prolonged PTT is also an indication to give these blood products.

Platelet concentrates are not routinely administered. They are useful in the presence of significant bleeding with platelet counts <50,000/cu mm or as prophylaxis against spontaneous bleeding when platelet counts are below 20,000/cu mm. See Table 1.

Comments: Less than 5% of hospitalized patients will require blood or other blood products. It is important that these are readily available and are appropriately administered. Multiple transfusions may be necessary. Platelet apheresis allows transfusion of platelets that come from one donor.

<table>
<thead>
<tr>
<th>Blood Components</th>
<th>Volume/Amount</th>
<th>Cross-Matching</th>
<th>Transfusion Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma</td>
<td>200 mL</td>
<td>No</td>
<td>Fast-drip</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>20 mL</td>
<td>No</td>
<td>Fast-drip</td>
</tr>
<tr>
<td>Platelet concentrate</td>
<td>50 mL</td>
<td>No</td>
<td>Fast-drip</td>
</tr>
<tr>
<td>Packed RBC</td>
<td>250 mL</td>
<td>Yes</td>
<td>Fast-drip</td>
</tr>
</tbody>
</table>
6. How often should we monitor platelet counts and hematocrit in DHF?

Baseline platelet count and hematocrit should be available at any stage of DHF. Serial determinations may be required during the defervescence stage to anticipate the onset of shock or to detect occult bleeding. After recovery with fluid replacement, platelet count and hematocrit may be repeated just before discharge. See Table 2.

<table>
<thead>
<tr>
<th>Severity Grading</th>
<th>Hematocrit</th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I and II</td>
<td>Once a day</td>
<td>1-3 X a day</td>
</tr>
<tr>
<td>Grade III and IV</td>
<td>As necessary - more frequent for serious cases until normal for age.</td>
<td>50,000 or more - once a day until an increasing trend is established; less than 50,000 - more frequent until more than 50,000.</td>
</tr>
</tbody>
</table>

**Comments:** Thrombocytopenia and plasma leakage are the hallmarks of DHF and are commonly observed just before fever lysis. Low platelet counts do not correlate well with severity except when thrombocytopenia is accompanied by significant bleeding. Hematocrit levels may be affected by aggressive fluid resuscitation so that hemoconcentration may be inapparent. Plasma leakage, though heralded by hemoconcentration also manifests as extravasation of fluid that results in pleural effusion, ascites or even anasarca.

7. When do you send home patients?

The absence of danger signs allows the treatment of DHF at home. Hospitalized patients may be sent home if they have remained afebrile for at least 72 hours or if the danger signs have resolved.

**Comments:** It may not be necessary to wait for the platelet count and hematocrit to completely improve as long as the appropriate IVFs were administered and that the patient has become afebrile and clinically stable and without any obvious evidence of bleeding from any site. Patients should be instructed that they may have repeated infections despite recovery from the current illness.
**Consensus Guideline on Dengue Case Management**

### WHAT TO GIVE

**Out-Patient:**
- **History or presence of fever 2-7 days duration, skin flushing or rash, and/or positive tourniquet test,** with no danger signs (see below).

**In-Patient:**
- **Presence of one or more DANGER SIGNS (especially during defervescence):**
  - Spontaneous bleeding
  - Persistent abdominal pain
  - Persistent vomiting
  - Listlessness
  - Changes in mental status
  - Restlessness
  - Weak, rapid pulse
  - Cold, clammy skin
  - Circumoral cyanosis
  - Difficulty of breathing
  - Seizures
  - Hypotension or narrowing of pulse pressure (<20 mmHg)
  - Platelet count <100,000 cells/cu. mm or 1-2 platelets/oil immersion field
  - Hemoconcentration (rise in >20% above average or 20% drop following treatment with fluids as compared to baseline)
  - Prolonged bleeding time (>5 min by Ivy method)

**What to Monitor**

**Where Patient Must Go**

### PATIENT CATEGORY

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 4 mos</td>
<td>&lt;6 kg</td>
<td>200-400 mL</td>
</tr>
<tr>
<td>4-12 yrs</td>
<td>6-10 kg</td>
<td>400-700 mL</td>
</tr>
<tr>
<td>&gt;1-2 yrs</td>
<td>10-12 kg</td>
<td>700-900 mL</td>
</tr>
<tr>
<td>2-5 yrs</td>
<td>12-19 kg</td>
<td>900-1400 mL</td>
</tr>
</tbody>
</table>

### WHAT TO GIVE

**Out-Patient:**
- Give ORESOL to replace fluids as in moderate dehydration at 75 mL/KBW in 4-6 hours or up to 2-3 liters in adults.
- Give PARACETAMOL for fever. Do not use ASPIRIN if platelet count is <50,000 in a patient with signs of DIC.

**In-Patient:**

#### When PATIENT IS NOT IN SHOCK:
- Give IVF: crystalloids - Start IVF, preferably D$_3$LRS or D$_3$0.9 NaCl or plain LRS) at 5-7 mL/KBW/hr.
- If there is improvement, reduce IVF at 3 mL/KBW/hr (up to 2-3 L/day in adults) and maintain at same rate for 24-48 hrs. using D$_3$LRS alternating with D$_3$IMB (<2 y.o.) or D$_3$NM or D$_3$0.3 NaCl (>2 y.o.);
- If there is NO improvement, increase IVF rate by 3-5 mL/KBW/hr. increments up to 15 mL/KBW/hr then adjust accordingly as above.

#### When PATIENT IS IN SHOCK:
- Give IVF: crystalloids - Plain LRS or Plain 0.9 NSS at 20 mL/KBW IV bolus in <20 minutes (20/20 rule);
- If there is NO improvement, follow-up with colloids (Dextran, Haemacel, Haes) at 10-30 mL/KBW in <20 minutes.
- Give whole blood (20 mL/KBW) when there is gross bleeding or significant blood loss; when blood loss is 25% or more of the blood volume and when Hct falls by 20% (>10% blood loss in adults or >25% blood loss in pediatrics of total blood volume at 80 mL/kg.);
- Give packed red cells (10 mL/KBW) when blood loss is <25% of the blood volume;
- Give fresh frozen plasma (15 mL/kg) in patients with prolonged PT (2 times the control) or patients in impending shock despite crystalloid infusion in the absence of colloids;
- Give cryoprecipitate (1 unit/5/kg) if with prolonged aPTT (>50 sec.) if no reference value; 10 sec. more than the upper limit of normal; or 20 sec. more than the control; or with signs of DIC.
- May give platelet concentrate (1 unit/7 kg) if platelet count is <50,000 in a patient with significant bleeding or platelet count <20,000 in a patient with no bleeding.
- Give oxygen. Correct metabolic acidosis.

**Request for initial CBC, platelet count, bleeding time, blood typing, PT, aPTT**
- Take hematocrit as frequent as necessary for serious cases until normal for age;
- Take platelet count:
  - <50,000: once a day until an increasing trend is established;
  - >50,000: more frequent until recovery from shock;
- Monitor vital signs every 2 hours.
- Monitor urine output and level of consciousness.
- Insert NGT gently to detect the presence of GI bleeding, especially if there is persistent vomiting or sudden onset of abdominal pain.
- Optional:
  - CXR, ECG, ABG, ultrasound
  - TPAG, SGPT
  - Urinalysis, creatinine - for patients in shock that require assessment for renal function

- Assign patient home.
- Ask patient to come back daily until 72 hrs. afebrile or immediately if there is any danger sign.
- Transfer/admit to hospital.
- Discharge/send patient home if:
  - 2-3 days after complete recovery from critical stage (shock)
  - Symptom-free or absence of danger signs
  - Good appetite
  - Good urine output
  - (-) signs of bleeding
  - Rising platelet count (at least on 2 occasions)
  - Normal aPTT (if done)
  - No evidence of cardiac or CNS involvement or other complications
  - Complete recovery from shock

**Address:** National Working Group on Dengue Case Management
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Drugs Mentioned in the Treatment Guideline

This index lists drugs/drug classifications mentioned in the treatment guideline. Prescribing information of these drugs can be found in PPD reference systems.

**Oral Rehydrating Solutions**
- Cholyte-50
- Dehydrosol
- Glucost
- Hydrite
- Orhydrate Concentrate Syrup
- Pedialyte 45/Pedialyte 90

**Non-Opioid Analgesics**

**Paracetamol**
- Aeknil
- Afebrin
- Aldep
- Aminofebrin
- Baropyrine
- Biogenereics Paracetamol
- Biogesic
- Calpol/ Calpol Six Plus
- Carpacet
- Crocin
- Defebrol
- Delgin
- DLI-Paracetamol
- Dolexpel
- Drugmaker’s Biotech
- Paracetamol
- Europharma Paracetamol
- Franciphen
- Gendol Susp/Tab
- Genpyra
- Gifaril-P
- Lenor
- Medgenol
- Medicol-A
- Metagesic
- Myremol
- Naprex
- Naprinol
- Neo-Aspillets
- Nopain Forte
- Octagesic/ Octagesic Forte
- Opigesic
- Pacigesic
- Pharex Paracetamol
- Pynal
- Rexidol
- Reximed
- RiteMED Paracetamol
- Rufenal
- Saridon
- Tempain Syr/Forte Tab/
  Forte Syr/Drops
- Temporal
- Tempra/ Tempra Forte
- Tylenol

**Colloids**
- Albuman Berna
- Albuminar-25
- Albutein
- Gelafundin
- Haes-Steril 6% & 10%
- Onkovertin 70 in Dextrose 5%

**Crystalloids**
- **D\_LRS**
  - Braun 5% Dextrose in
    Lactated Ringer's Soln
  - LVP D\_LR
- **D\_0.3NaCl**
  - Braun Dextrose 5%
    in 0.33% NaCl
  - LVP D\_S\_3
- **D\_NSS**
  - LVP D\_S\_9
- **D\_NM**
- **D\_IMB**
  - Maintesol

**Parenteral Electrolytes**

**Plain LRS**
- Braun Lactated Ringer's Soln

**Plain NSS**
- Braun NaCl 0.9% Soln
- Hizon 0.9% Sodium Chloride
- LVP S\_9