Dengue Infections

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ABSTRACT

Background: Dengue fever is one of the most common mosquito-borne viral illnesses in the world. It is usually transmitted to humans through the bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito. Dengue infections are caused by four antigenically distinct but closely related viruses (DEN 1–4). Infection with any one of the viruses is thought to provide lifetime immunity to future infections from the same virus but only short-term cross-immunity to the other types, leading to the possibility of secondary infections. Dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), more severe types of dengue infections, sometimes result when an individual is subsequently infected with a second virus serotype during their lifetime. The most commonly accepted theory for the development of these more severe dengue infections is that of antibody-dependent enhancement, although other factors likely play a role. Infections complicated by DHF/DSS in areas where dengue is endemic are most often seen in the later half of the first year of life, when waning maternal antibodies may enhance the development of a more severe infection, and in young school-age children experiencing secondary infections. Widespread infections are most commonly seen during the rainy season of endemic areas when the breeding habitat of the *Aedes* mosquito is most favorable.

KEYWORDS: *dengue hemorrhagic fever, dengue shock syndrome, mosquito-borne viral illness*

Clinical

Dengue infections with any one of the four serotypes can cause a wide range of illness. Those infected will usually be asymptomatic or have a nonspecific febrile illness. Less than half of those infected will manifest as classic dengue fever or severe dengue infections (dengue hemorrhagic fever/dengue shock syndrome [DHF/DSS]).

In recent years, some changes were made in the nomenclature regarding dengue infections, but the clinical manifestations of the disease remains the same. Symptomatic dengue infections are characterized by fever, lasting between 2–7 days, accompanied by retro-orbital pain and intense muscle and joint discomfort. (Dengue is also known as *breakbone* fever.)

Petechiae can present early in the course of the illness or may be seen following a tourniquet test. This test is conducted by inflating a blood pressure cuff to a middle point between the patient's systolic and diastolic blood pressures for 5 minutes and then counting the number of petechiae present in a 1-inch^2 area—more than 20 is typically called a "positive" test. Recent studies have not shown this to be a particularly sensitive test, meaning that the lack of a "positive" test does not rule out a dengue infection.

Thrombocytopenia and leukopenia are often seen as well as an elevation of hepatic enzymes. Toward the end of the febrile period of the illness, a confluent rash may develop, which has been described as a "sea of red" sparing "islands" of the patient's normal skin tone. Following resolution of the fever, adult patients often take weeks to recover physically and psychologically with profound fatigue and not uncommonly depressive symptoms while recovering from the illness.

A small percentage of adults and children go on to develop a more severe form of dengue, with signs and symptoms appearing at the time of defervescene. These *severe dengue* illnesses—DHF/DSS—are characterized by plasma leakage into the extravascular space. If not recognized early in the course of the illness, shock and death can result. It is impossible to predict which patients recovering from classic dengue fever will go on to develop more severe forms of the disease. Physicians experienced in endemic areas often report that patients who go on to more severe disease report abdominal pain out of proportion to their illness and feelings of "impending doom." Secondary infections, with differing serotypes of dengue infections, have a higher risk

of worsening to more severe types of dengue infections. These types of dengue infections should be managed with judicious boluses of isotonic crystalloid fluids to prevent irreversible shock.

Editor's Note: **The WHO Guide can be downloaded from http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf.**

The most recent Centers for Disease Control and Prevention clinical descriptions for case definitions are as follows:

Dengue fever is most commonly an acute febrile illness defined 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 dengue fever.

Dengue hemorrhagic fever is characterized by all of the following:

- Fever lasting 2–7 days
- Evidence of hemorrhagic manifestation or a positive tourniquet test
- Thrombocytopenia (≤ 100, 000 cells/mm3)

Evidence of plasma leakage 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.

Dengue shock syndrome 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

Diagnosis

Dengue can be diagnosed within the first several days of the onset of fever by detection of a nonstructural component (NS-1) of the virus particle by reverse transcription–polymerase chain reaction or later by serologic testing for antidengue immunoglobulin M or G (IgM/IgG) by enzyme-linked immunosorbent assay (ELISA). The differential of dengue in the initial phase of the illness, before a definitive diagnosis can be made, should be broad and must include, among others, malaria, rickettsial infections, typhoid, and leptospirosis, as well as sepsis.

Treatment

The case management guide on pages 66-67 is from *Dengue Guidelines for Diagnosis, Treatment, Prevention, and Control* (Geneva: World Health Organization; 2009:52–53).

Vaccination

No vaccination currently exists, although the U.S. Army and Navy are both actively involved in research in conjunction with laboratories around the world to develop one. Among the complexities in creating a dengue vaccine is that it must adequately cover all four dengue serotypes (DEN 1–4) to avoid severe infections in recipients who may be subsequently infected by serotypes not well protected by a combination vaccine.

Importance in a Deployed Setting

With no vaccine or chemoprophylaxis available, prevention of dengue infections through the use of bednets, mosquito control of billeting areas, the use of *N,N*-diethyl-meta-toluamide (DEET)-containing mosquito repellent, and permethrin pretreatment of uniforms is critically important while operating in the tropical areas of the world where dengue is endemic. Also important to understand is that the *Aedes* mosquito is a day biting mosquito, which thrives in urban environments where the risk of infection is greatest.

Disclaimer

The views expressed in this publication are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the Government.

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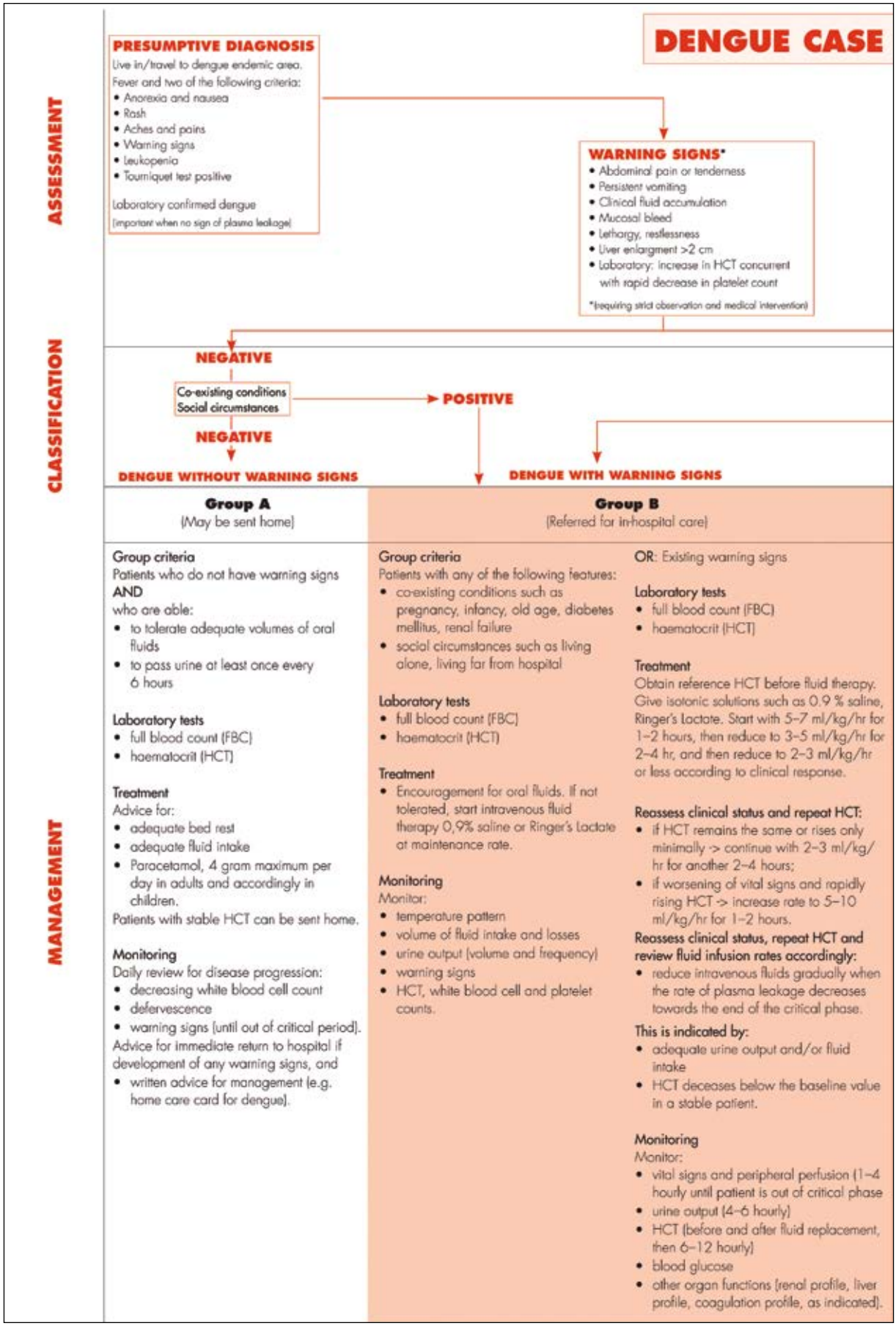
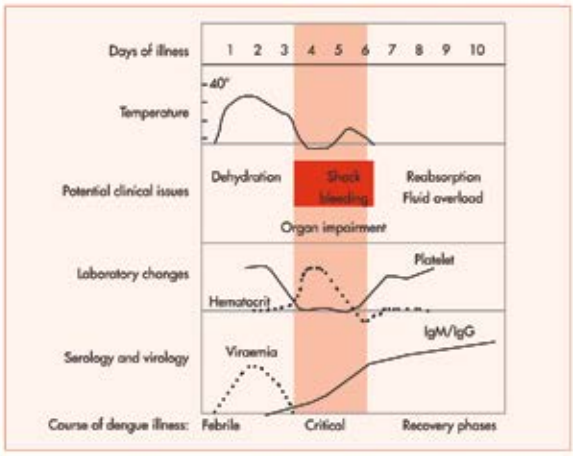
(article continues on page 68)


DENGUE CASE
ASSESSMENT
PRESUMPTIVE DIAGNOSIS
Live in/travel to dengue endemic area.
Fever and two of the following criteria:
• Anorexia and nausea
• Rash
• Aches and pains
• Warning signs
• Leukopenia
• Tourniquet test positive
Laboratory confirmed dengue
(important when no sign of plasma leakage)
WARNING SIGNS*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy, restlessness
• Liver enlargment >2 cm
• Laboratory: increase in HCT concurrent with rapid decrease in platelet count
*(requiring strict observation and medical intervention)
CLASSIFICATION
NEGATIVE
Co-existing conditions
Social circumstances
POSITIVE
NEGATIVE
DENGUE WITHOUT WARNING SIGNS
DENGUE WITH WARNING SIGNS
MANAGEMENT
Group A
(May be sent home)
Group criteria
Patients who do not have warning signs
AND
who are able:
• to tolerate adequate volumes of oral fluids
• to pass urine at least once every 6 hours
Laboratory tests
• full blood count (FBC)
• haematocrit (HCT)
Treatment
Advice for:
• adequate bed rest
• adequate fluid intake
• Paracetamol, 4 gram maximum per day in adults and accordingly in children.
Patients with stable HCT can be sent home.
Monitoring
Daily review for disease progression:
• decreasing white blood cell count
• defervescence
• warning signs (until out of critical period).
Advice for immediate return to hospital if development of any warning signs, and
• written advice for management (e.g. home care card for dengue).
Group B
(Referred for in-hospital care)
Group criteria
Patients with any of the following features:
• co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
• social circumstances such as living alone, living far from hospital
Laboratory tests
• full blood count (FBC)
• haematocrit (HCT)
Treatment
• Encouragement for oral fluids. If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer's Lactate at maintenance rate.
Monitoring
Monitor:
• temperature pattern
• volume of fluid intake and losses
• urine output (volume and frequency)
• warning signs
• HCT, white blood cell and platelet counts.
OR: Existing warning signs
Laboratory tests
• full blood count (FBC)
• haematocrit (HCT)
Treatment
Obtain reference HCT before fluid therapy. Give isotonic solutions such as 0.9 % saline, Ringer's Lactate. Start with 5–7 ml/kg/hr for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hr, and then reduce to 2–3 ml/kg/hr or less according to clinical response.
Reassess clinical status and repeat HCT:
• if HCT remains the same or rises only minimally -> continue with 2–3 ml/kg/hr for another 2–4 hours;
• if worsening of vital signs and rapidly rising HCT -> increase rate to 5–10 ml/kg/hr for 1–2 hours.
Reassess clinical status, repeat HCT and review fluid infusion rates accordingly:
• reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase.
This is indicated by:
• adequate urine output and/or fluid intake
• HCT deceases below the baseline value in a stable patient.
Monitoring
Monitor:
• vital signs and peripheral perfusion (1–4 hourly until patient is out of critical phase
• urine output (4–6 hourly)
• HCT (before and after fluid replacement, then 6–12 hourly)
• blood glucose
• other organ functions (renal profile, liver profile, coagulation profile, as indicated).

MANAGEMENT



POSITIVE

SEVERE DENGUE

Group C

(Require emergency treatment)

Group criteria

Patients with any of the following features:

- severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- severe bleeding
- severe organ impairment

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)
- other organ function tests as indicated

Treatment of compensated shock

Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hr over 1 hour. Reassess patients' condition.

If patient improves:

- IV fluids should be reduced gradually to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, then to 2-3 ml/kg/hr for 2–4 hours and then reduced further depending on haemodynamic status;
- IV fluids can be maintained for up to 24–48 hours.

If patient is still unstable:

- check HCT after first bolus;
- **if HCT increases**/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 ml/kg/hr for 1 hour;
- if there is improvement after second bolus, reduce rate to 7–10 ml/kg/hr for 1–2 hours and continue to reduce as above;
- **if HCT decreases**, this indicates bleeding and need to cross-match and transfuse blood as soon as possible.

Treatment of hypotensive shock

Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus for 15 minutes.

If patient improves:

- give a crystalloid/colloid solution of 10 ml/kg/hr for 1 hour, then reduce gradually as above.

If patient is still unstable:

- review the HCT taken before the first bolus;
- **if HCT was low** (<40% in children and adult females, <45% in adult males) this indicates bleeding, the need to cross-match and transfuse (see above);
- **if HCT was high** compared to baseline value, change to IV colloids at 10–20 ml/kg as a second bolus over 30 minutes to 1 hour; reassess after second bolus.
- **If patient is improving** reduce the rate to 7–10ml/kg/hr for 1–2 hours, then back to IV cystalloids and reduce rates as above;
- **if patient's condition is still unstable**, repeat HCT after second bolus.
- **If HCT decreases**, this indicates bleeding (see above);
- **if HCT increases**/remains high (>50%), continue colloid infusion at 10–20 ml/kg as a third bolus over 1 hour, then reduce to 7–10 ml/kg/h 1–2 hours, then change back to crystalloid solution and reduce rate as above.

Treatment of haemorrhagic complications

Give 5–10 ml/kg of fresh packed red cells or 10–20 ml/kg of fresh whole blood.

Recommended Internet Links

http://www.cdc.gov/Dengue/
http://www.who.int/topics/dengue/en/

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Disclosure

The author has nothing to disclose.

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