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Guidelines for the management of patients with severe forms of dengue

Recomendações para o manejo de pacientes com formas graves de dengue

ABSTRACT

Dengue is the most common vector-borne viral infection worldwide. In Brazil, the incidence has increased with successive epidemics, and an increasing proportion of patients present with severe forms of the disease. The prognosis for these patients is directly influenced by the quality of

medical care. These guidelines present the management of the severe forms of dengue, including the recognition of warning signs, the treatment for prompt re-establishment of euvolemia and the evaluation and appropriate care of potential complications, thus reducing morbidity and mortality of infected children and adults.

INTRODUCTION

Dengue is caused by four different serotype viruses that belong to the genus *Flavivirus* and are part of the *flaviridae* family (DENV I to IV). Dengue is transmitted by the bite of *Aedes* genus mosquitoes, mostly *Aedes aegypti*. The World Health Organization (WHO) considers dengue to be the world’s most quickly spreading arthropod-borne viral infection. It is endemically transmitted in more than 100 countries, and 50 to 100 million cases are reported yearly. At least twenty four thousand deaths can be attributed to dengue every year. In South America, between 2001 and 2007, 64% of the dengue cases were diagnosed in the Southern Cone countries (Argentina, Brazil, Paraguay and Uruguay). Approximately 98% of these cases were in Brazil, which also has the highest lethality.⁽¹⁻³⁾

The spectrum of the dengue virus infection encompasses asymptomatic forms to severe cases with shock, organ dysfunction and relevant bleeding. The guidelines proposed in this paper focus on severe dengue cases.

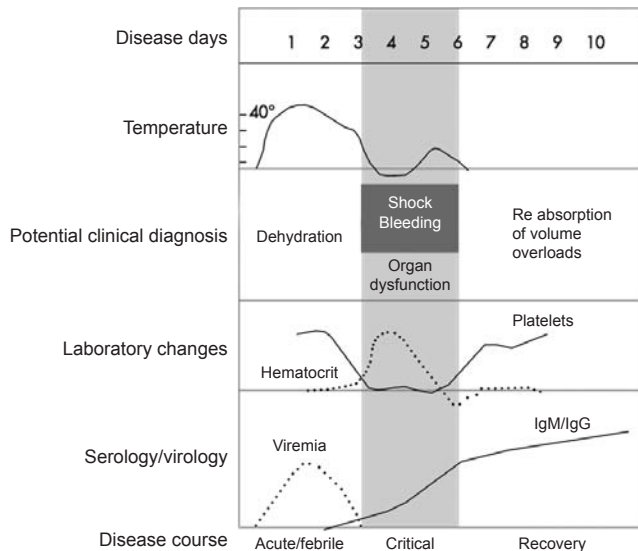
OBJECTIVE

This document is aimed at providing intensive care doctors with a practical approach to treating severe dengue cases. This approach should give better qualifications to the doctors in the frontline of care of dengue patients who are at increased risk of death.

OVERALL CHARACTERISTICS

Disease course

In patients presenting with clinical features of dengue virus infection, three distinct phases can be identified during the course of the disease: febrile, critical and recovery (Figure 1).^(1,2)



Adapted from: World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control [Internet]. New edition. Geneva: WHO; 2009.[cited 2011 Mar 1]. Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

Figure 1 – Dengue disease phases: febrile, critical and recovery.

- **Febrile phase:** The symptoms include fever, myalgia, headache, arthralgia and exanthema, and it is frequently indistinguishable from other acute febrile diseases. Mild bleeding manifestations can occur as bleeding of the gums and epistaxis. The recognition of progression to severe forms may be difficult during this phase. To determine whether progression to more severe forms of the disease has occurred, the warning signs should be observed (Figure 2). Duration of this phase is generally 2-7 days.

- **Critical or defervescence:** This phase is characterized by clinical and laboratorial evidence of endothelial cell dysfunction caused by the viral infection, resulting in increased capillary permeability and plasma leakage to the extravascular space. This phase is marked by sudden defervescence, circulatory and perfusion changes (hypotension and hypovolemic shock), serosal effusions (pleural and ascites) and organ dysfunctions, such as liver failure, encephalitis, myocarditis and clotting disorders. Progressive leukopenia and sudden platelet count drop precedes plasma leakage, and the progressive hematocrit increase mirrors the magnitude of the volume lost to the extravascular compartment. However,

it should be noted that severe organ dysfunctions might be present, including hepatitis, encephalitis, myocarditis and clinically significant bleedings, in the absence of clinical signs of plasma leakage. The critical phase, which is evident in 10-15% of dengue cases, discloses the progression to severe disease. The duration of this phase is 1-3 days.

- **Recovery phase:** This phase is characterized by progressive improvement of endothelial function with gradual fluid resorption from the extravascular space, hematocrit stabilization and progressive platelet recovery. A rash may present as “white islands in a red sea”, along with pruritus and bradycardia. During this phase, due to the progressive recovery of the endothelial function, fluid administration (and eventually diuretics) should be prescribed with caution to prevent volume overload, congestive heart failure and perpetuation of respiratory failure and serous effusions. The duration of this phase is 1-3 days.

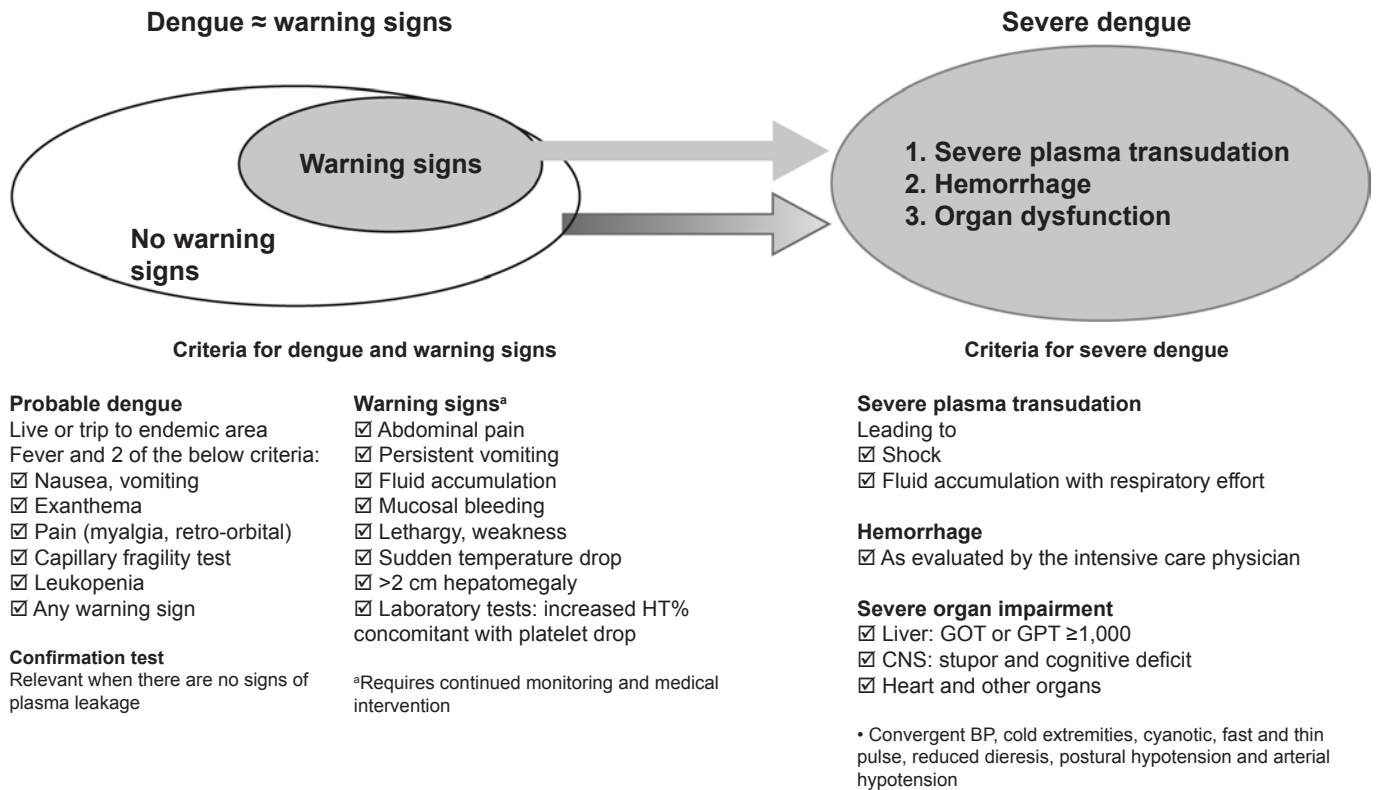
New dengue classifications

Dengue is classically classified in three categories: dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁽³⁻⁶⁾ Based on the DENCO (DENGUE COntrol) multicenter trial,⁽⁷⁾ the WHO proposed a simpler categorization that is more suitable for clinical practice. This categorization is based on medical evaluation and widely available laboratory tests. This new system categorizes dengue cases into two severity categories: 1) dengue (with or without warning signs) and 2) severe dengue (Figure 2).

- **Dengue without warning signs:** In this category, the symptoms correspond to the above-described acute febrile phase. The disease is characterized by myalgia, headache, arthralgia and rash of variable intensities. It should be noted that these clinical findings will not be able to determine whether the patients will progress to a more severe form of the disease or not.

- **Dengue with warning signs:** The warning signs include a sudden temperature drop, severe and continued abdominal pain, persistent nausea and vomiting, hepatomegaly, depressed level of consciousness, spontaneous bleeding, clinical signals of fluid accumulation (pleural effusion, ascites, pericardial effusion) and increased hematocrit with reduced platelets. These warning signs result from increased capillary permeability and plasma leakage to the extravascular compartment, which determines the beginning of the critical phase. Attention to the warning signs during the course of dengue is fundamental because these signs indicate the likelihood of progression to severe dengue.

- **Severe dengue:** Severe dengue is defined as the form of the disease that present with the most severe intensity



Adapted from: World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control [Internet]. New edition. Geneva: WHO; 2009.[cited 2011 Mar 1]. Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

Figure 2 – New dengue classifications and warning signs.

of the critical phase. In this evolutionary form, there is significant plasma leakage, which leads to shock and/or respiratory failure. Additionally, there can be clinically significant bleeding as considered by the attending physician, and/or progression to organ dysfunction.

RECOMMENDATIONS

Dengue diagnosis

Ethiological confirmation is not required for all cases of suspected dengue during epidemics. Confirmation tests should be required for patients with severe forms of the disease, pregnant women, children, during inter-epidemic periods and for those patients with atypical forms.⁽⁸⁾

The election of the laboratory method will depend on the time from the beginning of the disease symptoms. From the first to the fifth day, before serologic conversion, the infection may be diagnosed by virus isolation from cell culture, RNA virus detection using amplification techniques (RT-PCR) or viral antigen identification, such as NS-1. After the fifth day, viremia and antigenemia disappear, coinciding with the possibility of detecting specific antibodies. From the sixth day on, IgM ELISA is the method of choice for

diagnosis of dengue, with more than 70% positivity on the seventh day from the beginning of symptoms, and 100% positivity from the tenth day on.^(1,9)

Indication for hospital admission

The indications for hospital admission include the following conditions:⁽¹⁰⁾

1. Patients with dengue symptoms and warning signs should be admitted to either an observation facility, emergency room or step down units for appropriate monitoring, treatment and eventual reference to an intensive care unit (ICU) in case of medical/laboratory worsening.

2. Due to the potential worsening of preexisting conditions, people under 15 or above 60 years old, pregnant women and patients with underlying conditions, such as obesity, diabetes mellitus, severe cardiovascular disease, asthma and chronic obstructive pulmonary disease (COPD), blood diseases (especially sickle cell anemia and chronic thrombocytopenia), chronic renal failure, active peptic disease, autoimmune diseases or patients on medication such as antiplatelets, anticoagulants, non-steroidal anti-inflammatory and immunosuppressive drugs, deserve special attention.

3. Patients with medical/laboratory features compatible with severe dengue should be considered for intensive care unit admission.

Treatment

Dengue is a dynamic condition, in which a patient may change quickly from one phase to another. The appropriate management of this disease therefore depends on early

recognition of waning signs, continuous monitoring of the patients and re-categorization of cases. Additionally, physicians must act promptly to ensure hemodynamic and respiratory stability and to offer appropriate supportive measures for eventual organ dysfunction.

The treatment of adults^(1,2,8-10) (Figure 3) and children^(8,11-13) (Figure 4) will be discussed in separate flow charts, due to age-related specificities.

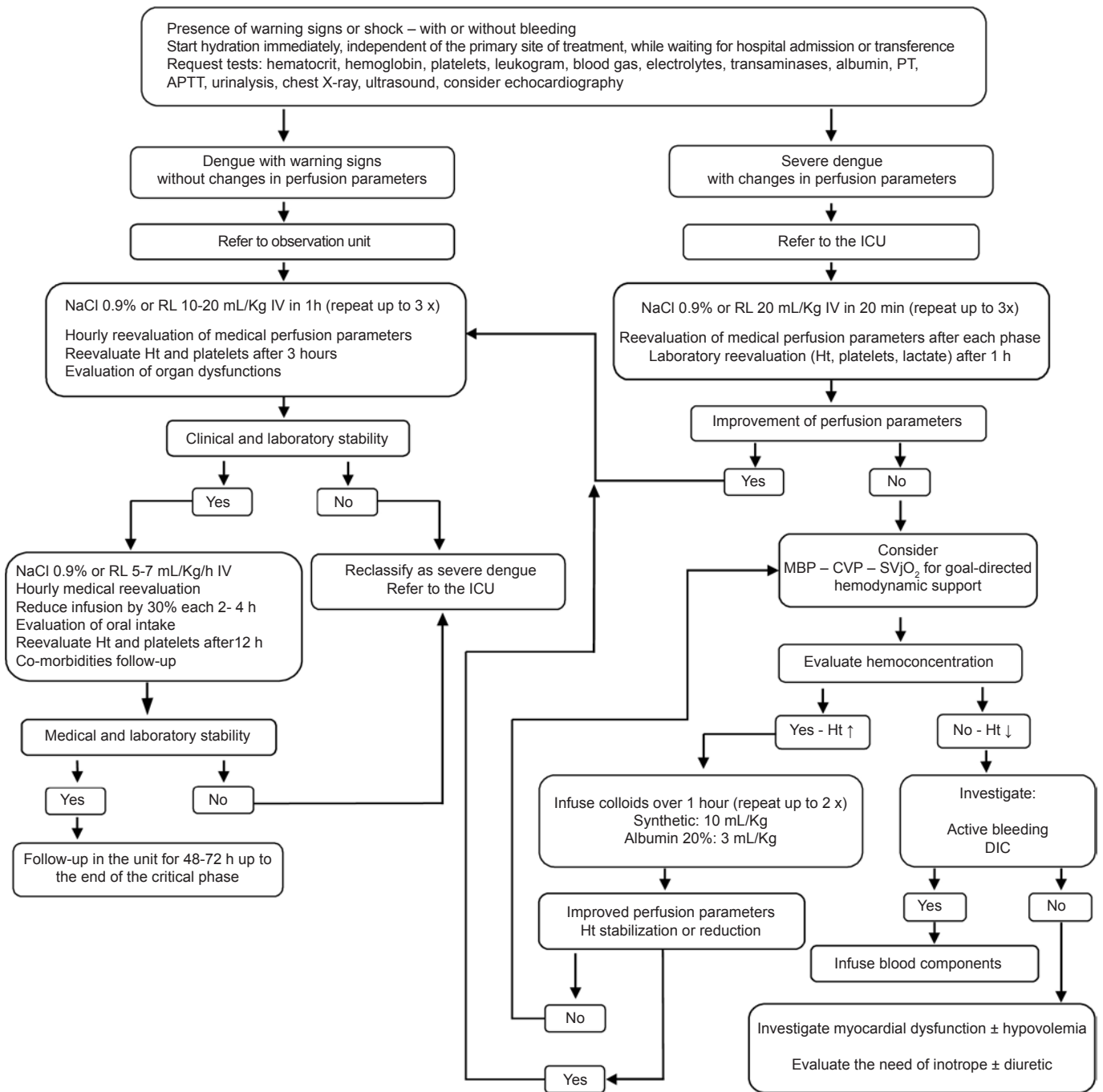


Figure 3 – Care of adult patients with dengue with warning signs and severe dengue.

Severe dengue in children and adolescents

Suspected: acute febrile disease lasting for up to 7 days, plus at least 2 of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, prostration, exanthema. In children below 5 years old, also consider: irritability, frequent crying, drowsiness, prostration, diarrhea, vomiting and refusing food.

Critical phase: 2 to 3 days after the fever is gone. Keep the patient under surveillance, instructing to come back for evaluation if warning signs.

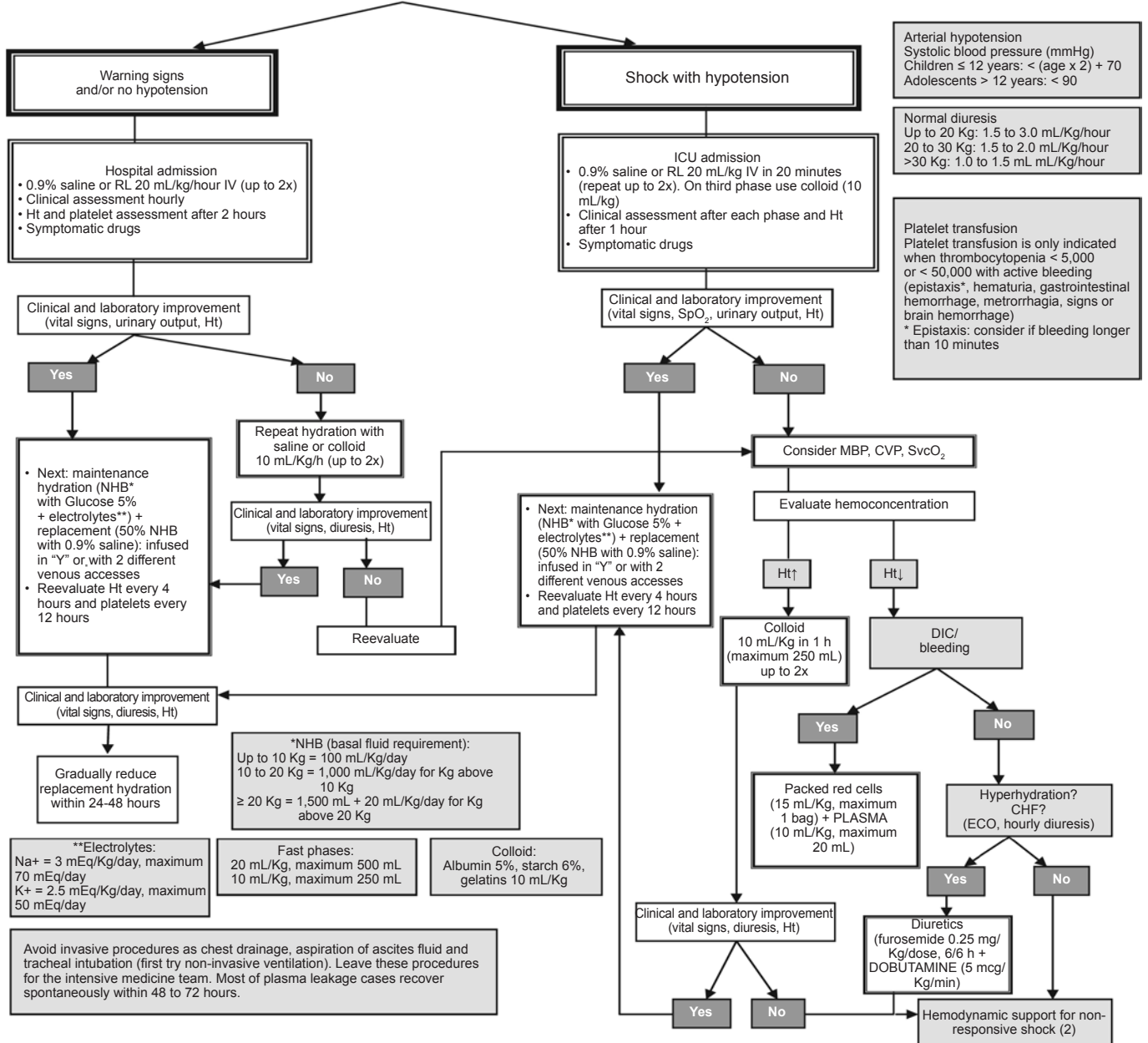
Warning signs: severe abdominal pain, persistent vomiting, drowsiness, irritability, bleeding, reduced urinary output, lipotimia, respiratory distress, hypothermia, postural hypotension, painful hepatomegalia, more than 20% hematocrit increase, sudden platelet count drops

Severe dengue

Symptoms: alarm sign and/or shock. With or without bleeding.

Start hydration right away, independent of the site, while waiting for admission or transference!

Tests: hematocrit, hemoglobin, platelets, white blood cell count, blood gas, electrolytes, transaminases, albumin, PT, APTT, chest X-ray, EAS, ultrasound, consider echocardiography.



1. Adapted from: the Flowchart for dengue therapy in children issued by Secretaria Municipal de Saúde e Defesa Civil do Rio de Janeiro in cooperation with the Sociedade Pediátrica do Estado do Rio de Janeiro [Rio de Janeiro Pediatrics Association] (SOPERJ).

2. Briery J, Carcillo JA, Choong K, et al. Crit Care Med. 2009;37:666-88. [cited 2011 May 30]. Available from: <http://www.learnicu.org/Docs/Guidelines/HemodynamicSupportPediatric.pdf>

Figure 4 – Treatment flowchart for cases of suspected severe dengue in children and adolescents.

SPECIFIC RECOMMENDATIONS

Adult patients

1. Initial medical care should not be postponed while waiting for transfer to specific units but should instead be started immediately on site, according to the severity of dengue.

2. Rapid recovery of the effective volemia is the cornerstone of severe dengue therapy. In order to achieve this goal, crystalloid solutions are recommended because they are universally available and effective for initial resuscitation.⁽¹⁴⁾

3. The persistence of medical and laboratory signs of hypoperfusion (hypotension or convergent pulse pressure, oliguria and hyperlactatemia) after infusion of crystalloid solutions, in association with hemoconcentration, is an indication of persistent fluid loss to interstitial tissue. In this situation, colloids may be used. Ideally, this treatment option should be guided by perfusion targets (mean blood pressure [MBP], urinary output, central venous pressure [CVP], SvO₂ and lactate) in accordance to the local medical expertise and the available resources on site (observation ward, emergency room, step-down units or ICU). When choosing which colloid to use on a particular patient, the potential adverse effects of the different products should be accounted for (allergic reactions and induced coagulation disorders).

4. The insertion of central vein catheter for infusion and assessment of CVP and SvcO₂ should be limited. The preference is to use compressible sites thus avoiding the subclavian vein. Whenever possible, the procedure should be guided by ultrasound. Although there is no consensus on the minimal platelet count for a safe central puncture, platelet transfusion aimed at a 50,000/mm³ level is suggested for ICU procedures and urgent surgery in patients with dengue. Platelet counts using electric impedance methods (as in automated counters) may provide false results because of the presence of fragments of erythrocytes and giant platelets.⁽¹⁵⁾ Therefore, especially when platelet counts are below 30,000/mm³, it is recommended that the results be confirmed by manual counting using a Neubauer chamber.⁽¹⁶⁾

5. During the hemodynamic instability phase, hematocrit and platelet count monitoring should be frequent. The intensive care physician should suspect bleeding complications when hypoperfusion signs persist after volume infusion, in association with a hematocrit (Ht) drop. Ht level should be reassessed following the first phase of volume resuscitation. With shock, an Ht below 40% in children and adult women and below 45% in adult men may be indicative of active bleeding. In these cases, the patients require that isotyped blood for transfusion as soon as possible. In this setting, the

threshold of Ht < 30% for transfusion as recommended in the early goal-directed therapy in the “Surviving Sepsis Campaign” is not applicable, because the concomitant plasma leakage masks the extension and therefore underestimates the actual blood loss.

6. Basic coagulation parameters should be evaluated, including prothrombin time (PT), activated thromboplastin partial time (APTT) and fibrinogen. If fibrinogen levels are below 100 mg/dL, cryoprecipitate should be preferred at a dose of 10 u/Kg. If fibrinogen levels are above 100 mg/dL and PT and/or APTT are more than 1.5 times greater than the control, fresh frozen plasma transfusion at 10-15 mL/Kg should be considered.^(2,8)

7. The transfusion of platelet concentrate is indicated for patients with lower than 50,000/mm³ thrombocytopenia who are also suspected to have severe bleeding (e.g., in the central nervous system). The platelet concentrate should be given in a dose of 1 unit of platelet concentrate for every 7 Kg, every 8 to 12 hours until the bleeding is under control (Figure 5).⁽¹⁷⁾ Ideally, filtered isotype-controlled platelets less than 72 hours old or platelets obtained by apheresis (single donor) should be transfused. Bleeding manifestations in dengue result from increased capillary fragility thrombocytopenia and fibrinogen consumption. The patient samples should undergo medical and laboratory analysis for characterization of disseminated intravascular coagulation (DIC). Thrombocytopenia per se is not a predictor of bleeding and, therefore, prophylactic platelet transfusion is not indicated.⁽¹⁸⁾

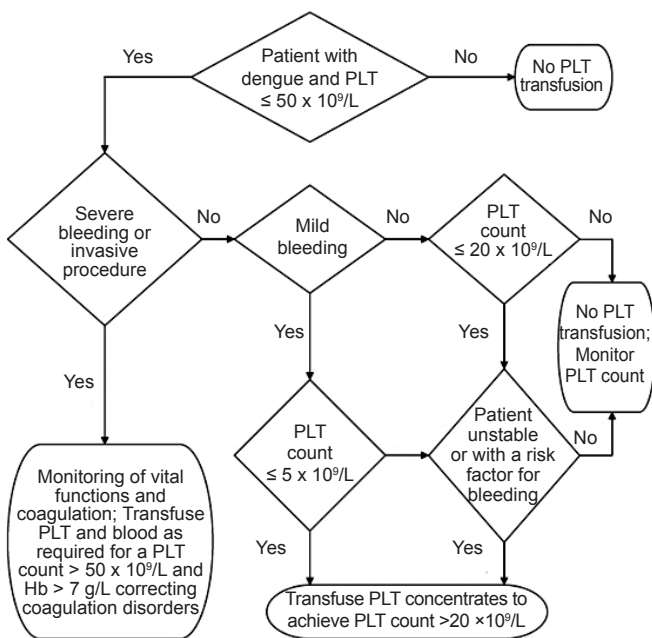
8. Previous use of non-steroidal anti-inflammatory, oral anticoagulant, antiplatelet drugs or a history of peptic ulceration increase the risk of hemorrhage during the course of dengue. Prolonged hypohydration and arterial hypotension/shock and hypothermia are determinant for triggering and perpetuating the coagulation disorder and therefore should be corrected. There is no information supporting the use of glucocorticoids, immunoglobulins or recombinant activated factor VII for the treatment of coagulopathy in dengue.

9. Acute reversible myocardial dysfunction is the most commonly documented heart disorder in dengue, and myocardial depression is fairly common in cases with shock.⁽¹⁹⁾ Although dengue-related shock syndrome is primarily due to increased capillary permeability and the consequent hypovolemia, persistent hemodynamic instability after appropriate volume expansion requires evaluation and treatment of the associated ventricular dysfunction in a similar way as currently recommended for the treatment of sepsis.

10. Varying degrees of liver dysfunction are frequently found in patients with dengue.⁽²⁰⁾ Most trials show increased transaminase levels occurring in more than 60% of the

dengue cases. All serotypes are involved, but serotypes 3 and 4 are associated with increased morbidity. Severe hepatitis (alanine aminotransferase, ALT > 300 IU) is associated with prolonged length of stay in the hospital, increased frequency of severe bleeding and development of acute renal failure, progression to encephalopathy and increased mortality. Fulminant hepatitis should be classified as hyper-acute when encephalopathy and coagulopathy occur before the seventh day post-infection and as acute when it occurs between 7 and 28 days. Hepatic encephalopathy, which is classified according to severity (grade I: mood and sleep disorders; grade II: mental confusion; grade III: stupor; grade IV: coma), is the best criterion for indicating admission to an ICU, preferably one linked to a transplantation program.

11. Other additional causes of encephalopathy should be considered and appropriately investigated and treated in patients with dengue. These causes include hydroelectrolytic disorders (especially hyponatremia), cerebral edema and hemorrhage, anoxia and primary viral encephalitis.



PLT - platelets

Adapted from: Thomas L, Kaidomar S, Kerob-Bauchet B, Moravie V, Brouste Y, King JP, et al. Prospective observational study of low thresholds for platelet transfusion in adult dengue patients. *Transfusion*. 2009;49(7):1400-11.⁽¹⁷⁾

Figure 5 – Criteria for platelet transfusion.

Patients with pre-existing conditions

Patients with pre-existing medical conditions, such as heart disease, diabetes, chronic pulmonary disease and pregnancy, should be carefully followed up during all phases of dengue. Dengue therapy should be tailored to the particular needs of each condition.

- **Obese patients:** Ideal body weight should be used to calculate volume infusion in overweight or obese patients.⁽²⁾

- **Pregnant women:** Dengue during pregnancy is associated with increased maternal and fetal mortality, prematurity, low birth weight and fetal malformations.⁽²¹⁾ Due to the physiologically increased blood volume, pregnant women may mask the clinical signs of volume loss, which are then only detected after reaching critical levels. Obstetric assessment and evaluation of the fetal welfare should be conducted for each maternal condition change, with careful attention to possible hypoperfusion-related maternal and fetal complications, premature placental detachment and other obstetrical bleedings. The resuscitation protocol should be the same as for non-pregnant patients. For cardiorespiratory arrest (CRA) in women who are more than 20 weeks pregnant, cardio-pulmonary resuscitation (CPR) maneuvers should consider the impact of hypovolemia on the CRA mechanics. The uterus should be displaced to the left, releasing the inferior vena cava during CPR, and urgent cesarean section should be considered when the measures are ineffective after 5 minutes of CPR attempt.

- **Antithrombotic therapy users:** As a general rule, patients with dengue should avoid using acetylsalicylic acid (ASA) due to the increased risks of Reye's syndrome and worsening of complications from severe thrombocytopenia.⁽¹⁹⁾

a. Certain patients with dengue have a high short-term risk of thrombosis, such as 1) patients with recent coronary angioplasty with stent placement (one month for non-pharmacological stents and three to six months for pharmacological stents); 2) patients with mechanical valve prostheses, particularly in the mitral or tricuspid positions, or with associated chronic atrial fibrillation (CAF), previous history of thromboembolism or with more than one mechanical valve; 3) CAF patients with multiple risks for thrombosis (ventricular dysfunction, increased age, hypertension, diabetes, valvopathy, previous stroke, or intracavitary thrombus). If these patients at high risk for thrombosis are already using clopidogrel and ASA, these drugs should be maintained. For people using warfarin, the current recommendation is to withhold it and replace it with heparin as soon as the INR is below the therapeutic range and then perform serial platelet and coagulation monitoring. The drugs should be withheld if platelet counts are below 50,000/mm³, if there is clinical or laboratory evidence of bleeding, or if the patient is in shock.

b. For patients with dengue and low short-term risk of thrombosis, such as 1) stable coronary artery disease patients; 2) patients receiving coronary angioplasty with

a stent placed more than six months previously; 3) CAF patients without thrombosis risk factors (or with only one risk factor); 4) patients with biological valve prosthesis, the current recommendations are to withhold ASA and consider withholding clopidogrel and warfarin for one week.

DIFFERENTIAL DIAGNOSIS

For severe dengue, the following differential diagnosis should be considered: acute abdomen (severe gastroenteritis, appendicitis, cholecystitis, pancreatitis, intestinal perforation), bacterial or fungal sepsis, meningococcemia, malaria, leptospirosis, typhoid fever, severe acute viral hepatitis, yellow fever, influenza, spotted fever, hantaviriosis, acute retroviral syndrome, severe acute hematological diseases (leukemia, thrombocytopenic purpuras) and Kawasaki's disease.

CRITERIA FOR DISCHARGE FROM ICU

Patients hemodynamically compensated for more than 24 hours with no vasopressors, with a stable

hematocrit and platelets increasing above 20,000/mm³, ventilatory stability with minimal support (O₂ supplementation or short periods of noninvasive ventilation) and metabolically stable from eventual organ dysfunctions (even if artificially, e.g., with hemodialysis) may be considered for referral to step-down units.

RESUMO

A dengue é a infecção viral transmitida por mosquito mais frequente no planeta. No Brasil a incidência vem aumentando em sucessivas epidemias, com uma proporção crescente de casos graves. A qualidade da assistência prestada influencia diretamente o prognóstico da doença. Estas recomendações apresentam o manejo das formas graves de dengue, incluindo o reconhecimento de sinais de alerta, o tratamento visando o pronto re-estabelecimento da euvolemia e a avaliação e cuidado das potenciais complicações, no intuito de reduzir a morbi-mortalidade de crianças e adultos infectados.

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