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Special Feature

Dengue fever: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine☆

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ABSTRACT

Dengue is an arbovirus affecting humans and spread by mosquitoes. Severe dengue follows a secondary infection with a different virus serotype. The problem is truly global as it is endemic in over 100 countries. Severe dengue can be a life-threatening because of increased vascular permeability, resulting in leakage of fluid from the intravascular compartment to the extravascular space. When major bleeding does occur, it is almost invariably combined with profound shock since this, in combination with thrombocytopenia, hypoxia, and acidosis, can lead to multiple organ failure and disseminated intravascular coagulation. Dengue hemorrhagic fever and dengue shock syndrome are among the leading causes of morbidity and mortality in patients suffering from Dengue. Commercial rapid tests and ELISA kits are freely available, ensuring early diagnosis. The basis of management of severe dengue is effective fluid replacement. Future directions in management will involve vector control and development of effective vaccination.

Contents

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1. Introduction

Dengue is a self-limiting viral infection transmitted mainly by the *Aedes aegypti* species of mosquito and to a lesser extent the Aedes albopicto, which is found in tropical and subtropical regions The virus belongs to the family Flaviviridae and has four serologically distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) [1]. Following infection with one strain, lifelong immunity to that serotype occurs and may also produce limited cross-immunity to the other serotypes. The WHO has stated that the global incidence of dengue has grown dramatically in recent decades with an estimated 390 million (95% credible interval 284–528) infections occurring per year. Of these, 96 million (67–136) of varying severity are actually diagnosed [2]. It is estimated that 3.9 billion people in 128 countries are at risk of infection [3] representing approximately one half of the world's population. Dengue is endemic in regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. Of the possible 400,000 cases of dengue haemorrhagic fever, occurring annually the case fatality is approximately 5% if untreated, but with appropriate therapy it can reduce to <1% [4]. Admission APACHE II and SOFA scores, arterial lactate and serum albumin may predict mortality and outcome of high risk patients [5,6].

2. Pathogenesis

Following a bite from an infected mosquito the virus spreads via the lymphatics to the lymph nodes where it replicates prior to the development of viremia. Infection with any of the four serotypes DEN-1, DEN-2, DEN-3, and DEN-4, is associated with a variety of clinical manifestations ranging from mild fever to severe fatal hemorrhage and shock. Recovery from infection by one strain and a subsequent infection with another serotype can potentially lead to dengue hemorrhagic fever and dengue shock syndrome [7]. Cross-reactive, non-neutralizing anti-dengue antibodies from the prior infection combine with those of the new infecting serotype. These heterologous antibodies form infectious complexes which activate dendritic reticulum cells, monocytes and macrophages [8] which release vasoactive mediators, resulting in increased vascular permeability and the hemorrhagic manifestations characteristic of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). The antibody/virus complex results in cytokine and complement activation, leading to endothelial dysfunction, platelet destruction and consumptive coagulopathy all of which cause hemorrhagic manifestations and plasma leak [7,9]. Dengue NS1, a soluble viral protein, has also been shown to disrupt the endothelial glycocalyx and thus contribute to vascular leak. In addition, many inflammatory lipid mediators such as platelet activating factor (PAF), the leukotrienes, vascular endothelial growth factor and angiopoietin-2 have been shown to be elevated in patients with dengue haemorrhagic fever [10].

2.1. Classification of dengue

Clinical dengue is categorized as dengue fever (DF) and dengue hemorrhagic fever (DHF) (Table 1). The Diagnosis requires the presence of fever and at least 2 of the typical clinical features or any warning signs. Epidemiological or laboratory evidence is required to make the diagnosis. Severe dengue is defined as dengue with any of the following [11]:

[1] severe plasma leakage leading to shock or respiratory distress
[2] severe hemorrhage
[3] any organ failure

2.2. Risk factors for developing DHF and DSS

DHF/DSS are more likely to occur at the extremes of age namely in infants and the elderly [12]. Chronic diseases like asthma, diabetes mellitus and sickle cell anaemia are additional risk factors that contribute significantly to the development of DHF/DSS [13]. The DEN-1 and thereafter DEN-2 serotypes, have been reported to be associated with worse outcome [14]. Host factors such as variations at the HLA-A locus appear to significantly increase susceptibility to DHF, and specific HLA-A susceptibility and resistance alleles have also been identified [15].

Table 1
Dengue classification according to the World Health Organization.

Criteria for dengue ± warning signs		Criteria for severe dengue
Probable dengue	Warning signs*	Severe plasma leakage
Live in/travel to dengue endemic area. Fever and 2 of the following criteria: •Nausea, vomiting •Rash •Aches & pain •Tourniquet test positive •Leukopenia •Any warning signs	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy & restlessness • Liver enlargement >2cms • Laboratory increase in HCT concurrent with rapid decrease in platelet count	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
Laboratory-confirmed dengue (important when no sign of plasma leakage)	*(requiring strict observation and medical intervention)	

3. Clinical features

The incubation period is 4–10 days after the bite of an infected mosquito. Dengue virus can produce various clinical presentations with an unpredictable evolution and outcome [16]. Most patients recover after a self-limiting disease, while a small proportion progress to severe Dengue. Clinical features include fever, nausea, vomiting, rash, headache, retroorbital pain, myalgia, arthralgia, petechiae, positive tourniquet test, and leukopenia [17]. Two other arboviral diseases, Chikungunya and Zika can produce very similar symptoms and complicate timely diagnosis and management of Dengue fever. The WHO/PAHO (Pan American Health Organization) introduced a tool in 2017 to improve the differential diagnosis of these arboviruses [18].

The illness begins abruptly after the incubation period and is followed by three phases: 1) Febrile, 2) Critical and 3) Recovery (Figs. 1 and 2).

1. The febrile phase is characterised by a sudden high grade fever and dehydration that can last two to seven days. During this phase facial flushing, skin erythema, myalgia, arthralgia, retro-orbital eye pain, headache and vomiting may be present. Conjunctival injection with associated sore throat may be seen. The liver may be palable and tender [19] and the presence of a positive tourniquet test at this stage may be confirmatory of the diagnosis of Dengue [20]. Trivial haemorrhagic symptoms such as petechiae and bleeding from mucosal membranes may be seen but excessive bleeding from venepuncture sites can also occur. Laboratory data reveals mild-to-moderate thrombocytopenia and leukopenia, often with a moderate elevation of hepatic enzymes.
2. The critical phase is usually seen in young adults and children, is characterised by capillary leak, bleeding, shock, and organ impairment and lasts for about 24 to 48 h. A large proportion of patients who have dengue fever alone become afebrile after the febrile phase, do not exhibit increased capillary permeability (a warning sign of impending critical disease) and recover without progressing

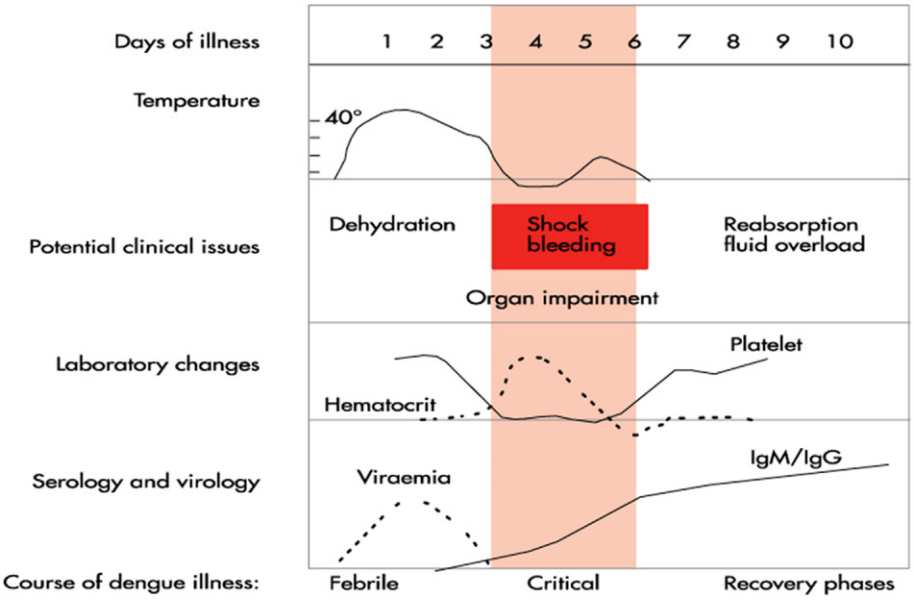

Fig. 1. Reproduced from WHO/TDR (2012). "Handbook for clinical management of dengue". http://www.who.int/tdr/publications/handbook_dengue/en/.

to the critical phase [16]. The latter usually starts around the time that recovery would occur, typically days 3 to 7 of the infection (Table 1). The critical phase starts at the time when the defervescence sets in, this is when the temperature drops to normal or even below normal, followed by increasing hemoconcentration and hypoproteinemia with pleural effusions and ascites. The onset of Dengue shock syndrome is heralded by narrowing of the pulse pressure and hemodynamic collapse with metabolic acidosis and organ dysfunction (such as hepatitis, encephalitis, myocarditis), and disseminated intravascular coagulation [21,22]. Hemorrhagic manifestations may also be seen during this period. These patients need advanced hemodynamic monitoring and resuscitation to maintain organ function.

3. In the recovery phase after the vital 24–48 h of the critical phase, a gradual redistribution of extravascular fluid takes place over the subsequent 48–72 h. During this phase the altered vascular permeability improves, however patients may encounter breathlessness from pleural effusions and pulmonary edema from prior fluid resuscitation. A new maculopapular rash due to leukocytoclastic vasculitis may be seen. Patient may demonstrate ECG changes and bradyarrhythmia.

4. Laboratory diagnosis

Early and accurate diagnosis allows effective medical care, identification of severe cases, and differentiation of dengue from other tropical illnesses. The laboratory diagnosis is made by detecting the virus and its components or by serology (Fig. 3). Detection of the non-structural protein 1 (NS1 antigen) using an enzyme linked immunosorbent assay (ELISA) or rapid kits is useful in early diagnosis and can be positive within days 1–5 of illness. The diagnostic sensitivity of NS1 in the febrile phase is over 90%, and the antigen may be detected for several days after the patient becomes afebrile [23]. Viral nucleic acid detection using reverse-transcriptase–polymerase-chain-reaction (RT-PCR) is the most sensitive and specific test and can be ordered in the first 5 days of fever onset [24]. Serological tests are less specific but more accessible. The IgM and IgG ELISAs are the tests of choice after the first five days of illness with a positive result in a single serum sample highly suggestive of dengue infection [25]. The presence of IgG in the first few days

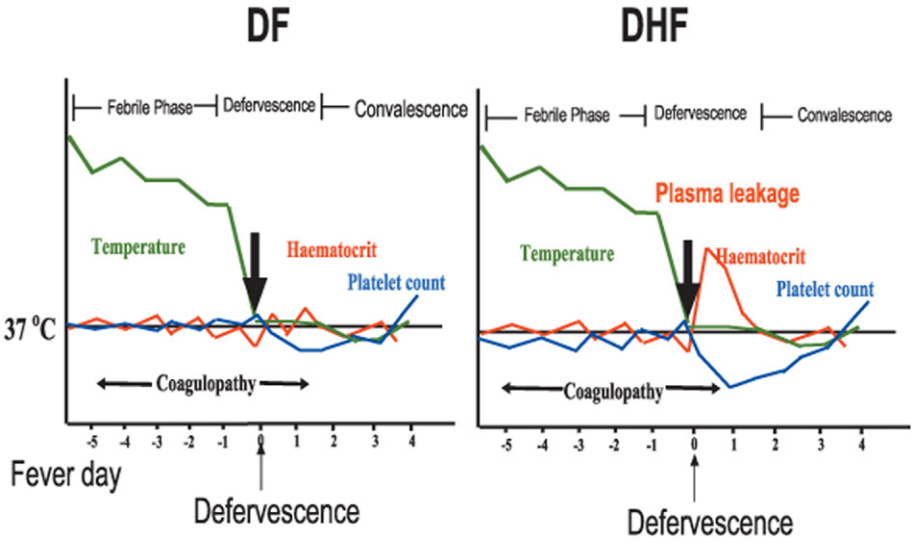

Fig. 2. Reproduced from Srikiatkhachorn A, Thromb Haemost 2009; 102: 1042–1049.

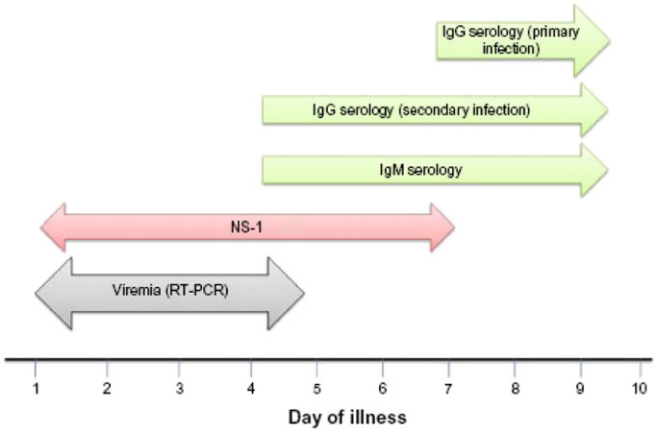

Fig. 3. Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection. Detection of viral nucleic acid, nonstructural protein 1 (NS1), or IgM sero conversion is a confirmatory finding in patients in whom dengue is a possible diagnosis. Day 0 is the first day when the patient noted any symptom during this illness. ELISA denotes enzyme-linked immunosorbent assay, and RT-PCR reverse-transcriptase polymerase chain reaction.
(Taken from Cameron P. Simmons, et al., N Engl J Med 2012;366:1423-32.)

indicate a probable secondary infection. Cross-reactivity has been reported between antibodies of Dengue and Zika virus [26].

Laboratory criteria for confirmed dengue cases include one of the following: positive RT-PCR, positive viral culture, IgM antibody seroconversion in paired sera, IgG antibody seroconversion or fourfold increase of IgG titer in paired sera [16]. Monitoring of serum procalcitonin (PCT) and peripheral venous lactate (PVL) as biomarkers of dengue shock and/or organ failure should be considered as they have prognostic value. A PCT ≥0.7 ng/mL and PVL ≥2.5 mmol/L are independently associated with dengue shock and/or organ failure [27].

5. Management

Management is based on the severity of infection. Patients who have no complications and are able to take fluids orally can be monitored in the community with instructions to return in the event of bleeding or the appearance of warning signs suggestive of vascular leak (group A), Those with warning signs require admission and parenteral hydration if oral intake is inadequate (group B). Patients in the critical phase of the disease (group C) with severe capillary leak, hemorrhage and organ dysfunction require to be managed in the ICU.

Whereas there is no specific treatment for dengue, intensive monitoring and good supportive care can lower mortality rates below 1%. Those with DSS require fluid resuscitation as per PAHO and WHO guidelines [28] [16],. Response to therapy should be monitored clinically and if necessary by invasive hemodynamic monitoring (Fig. 4) [16]. Whereas there is some controversy as to the whether colloids or crystalloids are best, it appears that both can be effective [29-35].

In patients with DHF/DSS, adjuvant therapy, including vasopressor and inotropic therapies, renal-replacement therapy, transfusion of blood and components as necessary and additional support of organ failure is essential. The most reviewed and practised management of sepsis and septic shock are based on the guidelines of the surviving sepsis campaign(SSC) [36]. However these have not been validated and are often not possible to use in practice in low and middle- income countries (LMICs), where the burden of sepsis is immense, and outcomes are often poor [37]. Blood transfusion can be lifesaving for patients with severe bleeding. Component therapy such as platelet concentrates, fresh-frozen plasma, and cryoprecipitate is determined by the coagulation profile. Prophylactic platelet transfusion does not yield substantial and sustainable benefits and hence is not advocated in the absence of significant bleeding [38]. Similarly recombinant factor VIIa is not of benefit [39]. Despite some earlier studies showing benefit of corticosteroids [40,41], more recent studies have not confirmed this [42-44]. This is also the case with IV immunoglobulins (IVIG) where small case series showed benefit, but the only randomized, controlled study had no benefit [45,46].

Alternatively numerous drugs have been tried and many more are under investigation. Carbazochrome, which has previously been shown to reduce the vascular hyperpermeability showed no benefit in outcomes in DSS [47]. In vitro, Chloroquine inhibits Dengue by interfering with pH-dependent steps of viral replication but in vivo did not reduce the duration of viral infection, and demonstrated several adverse effects [48]. Statins display anti-inflammatory effects on the endothelium and some possible antiviral properties against the dengue virus though recently lovastatin showed no evidence of a beneficial effect on any of the clinical manifestations or on dengue viremia [49]. Balapiravir, Celgosivir two antivirals studied did not show benefit [50, 51]. Other antivirals namely, MTase inhibitors, Nucleoside analogs, Helicase inhibitors, Protease inhibitors and NS4B inhibitor are currently being studied in Dengue [52]. Therapeutic and monoclonal antibodies and human serum polyclonal antibodies (IgG), against all serotypes of dengue are exciting new treatment options currently being investigated [52].

6. Vaccines

Live attenuated and inactivated viruses, recombinant proteins, and DNA vaccines are being developed. One dengue vaccine has been registered in several countries (CYD-TDV, or Dengvaxia®); this is a live attenuated (recombinant) tetravalent vaccine. CYD-TDV has been evaluated in two Phase 3 clinical trials [53,54].

7. Conclusion

Vector control of *Aedes aegypti* which is predominantly found in urban areas in the tropics is an important means of reducing the global burden of Dengue. DHF and DSS is a precarious illness that can rapidly progress to death. Diagnosis though previously primarily clinical, has improved with the current laboratory tools. No specific therapy has yet been proven to be of value, and the mainstay of management continues to be careful fluid resuscitation. Thrombocytopenia is not uncommon in dengue during the febrile phase and during defervescence, but overt bleeding is uncommon. Blood component therapy is indicated in patients with major hemorrhage. There are no approved drugs nor any efficient vaccines available currently.

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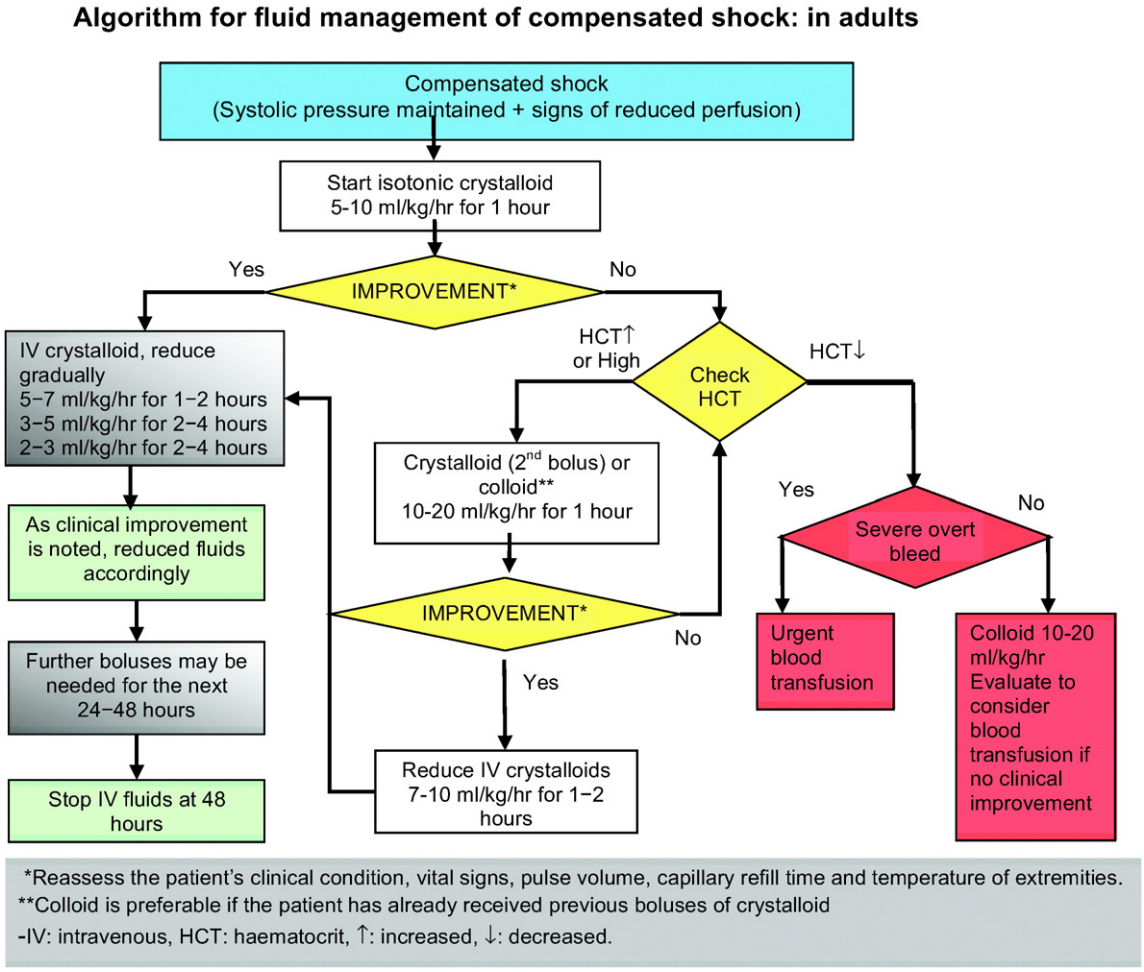

Fig. 4. Algorithm for fluid management of compensated shock: in adults. WHO/TDR (2012). "Handbook for clinical management of dengue".

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