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REVIEW ARTICLE

Dengue and dengue hemorrhagic fever: management issues in an intensive care unit

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Abstract

Objectives: To describe the epidemiology, clinical features and treatment of dengue fever and dengue shock syndrome.

Sources: To prepare this review, a literature search was made on Pubmed and on the World Health Organization (WHO) and PAHO websites using the terms dengue and dengue shock syndrome. This information was complemented with personal practice.

Summary of the findings: Dengue is the most important arthropod-borne viral disease of humans. Its presentation is protean and varies from an undifferentiated viral syndrome to hemorrhagic fever and severe shock. Dengue fever is a self-limiting, nonspecific illness characterized by fever, headache, myalgia, and constitutional symptoms. Its severe forms (hemorrhagic fever and shock syndrome) may lead to multisystem involvement and death. Early diagnosis, close monitoring for deterioration and response to treatment are necessary in all cases. WHO has provided a stepwise approach to management that is useful for milder forms and early shock. In the more severe forms aggressive fluid resuscitation and support for failing organs is necessary for the critically ill patient. Research addressing pathophysiological differences between dengue shock and septic shock, choice of fluids, inotropes and techniques of organ support are likely to yield benefits for the critically ill.

Conclusions: There is no specific therapy for dengue infections. Good supportive care may be lifesaving, but ultimately initiatives aimed at vector control and prevention of mosquito bites may provide the greatest benefits.

J Pediatr (Rio J). 2007;83(2 Suppl):S22-35: Dengue fever, sepsis, shock, hemorrhagic shock, fluid infusion.

Introduction

Dengue is a mosquito-borne disease caused by one of the four serotypes of dengue viruses. It is characterized by fever and mild constitutional symptoms to hemorrhagic manifestations and shock, or dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Dengue fever is classically a self-limiting, nonspecific illness characterized by fever, headache, myalgia, and constitutional symptoms. DHF is a more serious clinical entity. It emerged among children in Southeast Asia during the 1950s and has since become a major public health problem worldwide and a significant cause of pediatric morbidity and mortality. The affected children need very careful monitoring. The fluid therapy is challenging and needs modification frequently. Respiratory distress due to extensive pleural effusions, myocardial dysfunction, extensive bleeding and multiple organ failure, including acute respiratory distress syndrome, acute liver failure, and acute renal failure are other potentially life-threatening complications that may need attention in the pediatric intensive care unit (PICU).

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Global burden

The global prevalence of dengue has grown dramatically in recent decades. The disease is now endemic in 112 countries of Africa, the Americas, the Eastern Mediterranean, Southeast Asia and the Western Pacific. WHO estimates that 40% of the world's population, about 2.5 billion people living in tropical and subtropical areas are at risk.

Every year about 50-100 million cases of dengue infection, 500,000 cases of DHF and at least 12,000 deaths occur worldwide; ninety percent of these deaths occur in children less than 15 years of age.[1,2] More than 160,000 cases of dengue and dengue hemorrhagic fever have been reported in the Western Pacific region. In 2005, there were about 320,000 cases of dengue in the Americas, of which 15,253 cases were DHF; there were 80 deaths reported (http://www.paho.org/English/AD/DPC/CD/dengue-cases-2005.htm). Brazil alone accounted for about two thirds of the cases and half of the deaths. These figures are higher than those for the year 2004: 267,050 cases of classic dengue fever and 9,810 cases of DHF, and 71 deaths (http://www.paho.org/English/AD/DPC/CD/dengue-cases-2004.htm). In 2001, Brazil reported over 390,000 cases, including more than 670 cases of DHF.

During dengue epidemics, attack rates among susceptible individuals are often 40-50%, but may reach 80-90%. An estimated 500,000 cases of DHF require hospitalization each year, of which a very large proportion are children. At least 2.5% of cases die, although case fatality could be twice as high. Without proper treatment, DHF case fatality rates can exceed 20%. With modern intensive supportive therapy, such rates can be reduced to less than 1%.

Dengue viruses

Dengue is caused by 40- to 50-mm single-stranded RNA viruses belonging to the Flavivirus group. They are spherical and have a lipid envelope derived from host cell membranes. Four species, known as serotypes, have been described,: DEN-1, DEN-2, DEN-3, and DEN-4. The viral genome encodes three structural proteins (capsid, C, membrane protein, M, and envelope glycoprotein, E) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). The main biological properties of the viruses are located in the E protein. Of the nonstructural proteins, some are involved in viral replication.[3]

Infection with one dengue virus serotype results in specific immunity to that serotype only; theoretically, individuals can be infected with all four serotypes. DEN-2 was the predominant serotype in the 1980s and in the early 1990s, but in recent years, DEN-3 has been more predominant.[4]

Transmission

Dengue is transmitted by the bite of an infected Aedes mosquito. The female Aedes mosquito gets infected with the dengue virus after sucking blood from an infected person during acute febrile illness (viremic phase). After an extrinsic incubation period of 8-10 days, the infected mosquito transmits infection by biting and injecting infected salivary fluid into the wound of another person. An infected female mosquito is capable of vertical transmission of the dengue virus to its next generation, which is important for virus maintenance, but not for the epidemiology of the disease. Vertical transmission from mother to child has been reported.

Aedes aegypti is the most important epidemic vector. *A. albopictus* and *A. polynesiensis* may act as vectors in some geographic locations. *Aedes aegypti* is seen in abundance in at-risk areas. It is found between latitudes 30º north and 20º south and at over 2,200 meters above the sea level. Transmission occurs in geographically diverse areas, including subtropical and tropical cities at various altitudes. The Aedes mosquito rests indoors, mainly in living rooms and bedrooms, and in small collections of water, such as flowerpots or coconut shells.[5,6] This maximizes man-vector contact and minimizes contact with insecticides sprayed outdoors, hence hindering the control of this vector.[7] Eggs can survive for long periods. Improper disposal of garbage or inadequate wastewater drainage may be responsible for high mosquito densities in endemic areas. Significant increases in the mosquito larval populations are seen during the rainy season. This may be a reason why the epidemics of dengue tend to coincide with the rainy season.[5]

Pathogenesis

After the bite of an infected mosquito, the average incubation period lasts 4 to 7 days (range of 3-14 days), during which the patient may or may not experience symptoms, depending on the virus strain, age, immune status, and other factors. This is followed by viremia, which is associated with sudden onset of fever and constitutional symptoms lasting for 5-6 days (range of 2 to 12 days).

The dengue virus replicates within cells of the mononuclear phagocyte lineage (macrophages, monocytes, and B cells). Additionally, infection of mast cells, dendritic cells, and endothelial cells is known to occur.[8] The virus may infect peripheral blood leukocytes, liver, spleen, lymph node, bone marrow, thymus, heart, kidney, stomach, lung, and possibly the brain, suggesting blood-brain barrier disruption.[9]

Following the febrile (viremic) phase, the patient may either recover or progress to the leakage phase, leading to DHF and/or dengue shock syndrome. Peak plasma viremia and circulating levels of the dengue virus nonstructural protein NS1 correlate with the severity of dengue infections.[10] The increased number of infected cells results in increased production of cytokines, including TNF-α and IFN-α, and other chemical mediators. TNF-α and IFN-α also lead to activation of other dendritic cells, virally infected or non-infected.[11,12] The release of various cytokines and mediators is responsible for increased vascular permeability, abnormal leakage of plasma, hypovolemia, shock, and hemostatic abnormalities. In addition, there is evidence to show that endothelial cells also undergo apoptosis, which causes disruption of the endothelial cell barrier, leading to the generalized vascular leak syndrome.[13]

More severe infection occurs when a person is infected for a second time with a different serotype in 2-4% of individuals. How a second dengue infection causes a severe disease and why only some patients get severe disease remains unclear. It is suggested that residual antibodies produced during the first infection are unable to neutralize a second infection with another serotype, and the second infection, under the influence of enhancing antibodies, results in severe infection and disease. This phenomenon is referred to as antibody-dependent enhancement. The pre-existing non-neutralizing antibodies generated from previous primary infection cross-react with viral serotypes involved in secondary infections and bind to the virions, but do not neutralize them. Such antibody-coated virions are taken up more rapidly than uncoated virus particles by tissues, dendritic cells, monocytes and macrophages. This leads to a higher viral load and enhanced antigen presentation by the infected dendritic cells to the T cells, resulting in extensive T-cell activation and proliferation of memory T-cells. This extensive T-cell activation supposedly causes the T-cells to become "stunned", whereby their IFN-γ expression remains low.[14]

Common gross pathologic findings in dengue infection include petechial hemorrhages and ecchymoses, serous pleural and peritoneal effusions, and pulmonary edema. Vasculitis of small vessels in visceral and soft tissues is found on microscopy, and so are focal midzonal hepatic necrosis, subendocardial left ventricle hemorrhage, and gastric mucosal hemorrhage.

Clinical classification

Dengue virus infections may be asymptomatic or may have three main clinical manifestations.[15,16]

1) Undifferentiated febrile illness (UF) or viral syndrome
2) Dengue fever (DF)
3) Dengue hemorrhagic fever (DHF)
   - DHF without shock;
   - Dengue shock syndrome (DSS).

Dengue fever

WHO defines dengue fever as an acute onset febrile illness that lasts 2-7 days, with two or more of the following symptoms: headache, retro-orbital pain, myalgia/arthralgia, maculopapular rash,, petechiae, and positive tourniquet test.[15] Hemorrhagic manifestations are uncommon.

Infants and young children, especially those younger than 15 years, may have an undifferentiated febrile disease that may be accompanied by a maculopapular rash. In Brazil, when children present with exanthema, it is possible that dengue is the primary causative disease, depending on the epidemiological profile of the region. Of 71 children presenting with exanthema at an emergency department in Campo Grande, Brazil, 77.5% had a positive dengue IgM antibody assay.[17] The most common clinical manifestations among these dengue patients were: fever, itching, prostration, myalgia and a positive tourniquet test.[17]

Flushing, which is a characteristic feature of the disease, is commonly observed on the face, neck, and chest. Younger children tend to present with coryza, diarrhea, rash and seizure, and less commonly with vomiting, headache, and abdominal pain. Most dengue infections in young children are mild and indistinguishable from other common causes of febrile illnesses. DF with bleeding complications such as epistaxis, gingival bleeding, gastrointestinal bleeding, and hematuria can be observed during some epidemics. Thrombocytopenia has been also reported in some cases.[15] DF is a very incapacitating disease; however, its prognosis is favorable.

Dengue hemorrhagic fever (DHF)

DHF usually follows secondary dengue infections, but may sometimes follow primary infections, especially in infants. These patients have a significantly higher viral load and a slower rate of clearance of viral load and virus-containing immune complexes than patients with dengue fever.[18] DHF and DSS are the most severe manifestations of dengue infections. In Southeast Asia, these are predominantly seen in children, whereas in the Americas, these are seen in all age groups.

DHF usually begins with a sudden rise in temperature and other symptoms identical to those of dengue fever. The temperature remains high for 2 to 7 days. Hepatomegaly and splenomegaly are occasionally seen, especially in infants. Hemorrhagic tendency may manifest in many ways: positive

tourniquet test; petechiae, ecchymoses or purpura; mucosal bleeding; and, hematemesis or melena. The most common hemorrhagic features are petechiae, easy bruising, and bleeding at venipuncture sites. Epistaxis and gingival bleeding are uncommon, and gastrointestinal bleeding may be observed in severe cases. Occasionally, the bleeding may be occult; intracranial bleeding is rare. In DHF, bleeding may not correlate with the platelet counts and usually occurs once the fever has settled.

According to the current WHO[15] and Pan American Health Organization[19] guidelines, a case of DHF should meet all of the following clinical criteria: acute onset fever, any hemorrhagic manifestation, thrombocytopenia (≤ 100,000 platelets per µL), and objective evidence of increased capillary permeability and plasma leakage manifested by an increase in hematocrit levels equal to or greater than 20%, a drop in hematocrit levels greater than 20% following fluid therapy, signs of plasma leakage (pleural effusion, ascites, hypoalbuminemia or hypoproteinemia). When the only hemorrhagic manifestation is a positive tourniquet test, the case is categorized as grade I DHF, but a spontaneous hemorrhage, even if mild, indicates grade II illness and grades III and IV represent the dengue shock syndrome (DSS).[15] There are, however, difficulties in using these definitions as they may underestimate disease severity. The use of a higher cutoff point for platelet count (< 150,000 per µL) and higher hematocrit levels for plasma leakage (either hematocrit level of 50% or over or hemoconcentration of 10% or over) has been suggested. Caution is needed as new case definition may affect estimation of dengue severity.

In mild to moderate cases, fever subsides with profuse sweating. Mild changes in pulse rate and blood pressure may be noticed with cold extremities and skin congestion. Patients recover spontaneously or after fluid and electrolyte therapy. In severe cases, sudden deterioration may occur after a few days, with progression to DSS.

Hematological changes that are consistently found in DHF include bone marrow suppression, leukopenia and thrombocytopenia. Bleeding mechanisms are multiple: vasculopathy, thrombocytopathy and disseminated intravascular coagulation (DIC). Thrombocytopathy consisting of thrombocytopenia and platelet dysfunction is caused by bone marrow suppression immune injury, and infection of platelets by the dengue virus. DIC and prolonged bleeding are more common in patients with shock, and cause death.

Some patients with dengue infection have varying degrees of mucosal and cutaneous bleeding with some degree of thrombocytopenia. These patients may not demonstrate other criteria for diagnosis of DHF/DSS, i.e., hemoconcentration or objective evidence of fluid leak, e.g. ascites, pleural effusion. These patients are classified as having *dengue fever with unusual bleeding*. Patients falling into this category may be seen in significant numbers in epidemics.[20] Since hypovolemia and hypotension do not occur in this group of children, fluid requirement is lesser than in DHF.[21] It is therefore important to distinguish these children from those with classical DHF.

Convalescence in DHF is usually short and uneventful. The return of appetite is a good indicator of recovery from shock. Bradycardia is also seen in this period. If present, a confluent petechial rash with erythema and islands of pallor (usually known as a recovery rash) are characteristic of dengue infections. During the convalescent stage, many patients also complain of severe itching, especially on the palms and soles.

Dengue shock syndrome (DSS)

WHO defines DSS as DHF plus signs of circulatory failure manifested by rapid and weak pulse, narrow pulse pressure (≤ 20 mmHg) or hypotension for age, prolonged capillary refill, cold and clammy skin and restlessness. Onset of shock is acute and occurs at the time of defervescence, usually after 2-5 days of fever. The temperature is often subnormal, skin is cold and clammy, and pulse rapid and feeble.

Pleural effusion and ascites predict the development of DSS. Intense abdominal pain is a frequent complaint that appears shortly before the onset of shock. Consciousness is usually intact. The duration of the shock is short. The patient usually dies within the first 24 hours of shock or recovers rapidly after appropriate fluid replacement. Uncorrected shock will result in metabolic acidosis, severe bleeding from the gastrointestinal tract and other organs, and a poor prognosis. Recovery from adequately treated DSS is short and uneventful, survivors recover within 2 to 5 days, although pleural effusions and ascites may be detected for a little longer. During the convalescent stage, bradycardia or arrhythmia may be noted. The course of DHF/DSS is approximately 7 to 10 days.

Unusual manifestations: complications

Unusual manifestations of DHF/DSS include hepatitis, encephalitis and glomerulonephritis.[22] Myocardial dysfunction has also been reported.[23]

Central nervous system involvement

CNS involvement usually occurs as a result of an encephalopathy. It manifests with irritability, lethargy, confusion and depression and sometimes seizures, impaired consciousness/coma, and paresis. It is frequently associated

with prolonged shock with metabolic acidosis, metabolic disorders e.g. hypoglycemia and electrolyte imbalances (hyponatremia, hypocalcemia). Encephalopathy could also result from cerebral anoxia, cerebral edema, intracranial hemorrhage, and vascular occlusion. It may be due to acute liver failure or to Reye's syndrome and edema associated with leakage through the cerebral vasculature. However, in DF, the pathogenesis of encephalopathy is less clear.[24]

Nuchal rigidity, mononeural palsies and even encephalitis with seizures may be seen. Occurrence of true encephalitis because of direct invasion of the brain is rare. In a study of 378 Vietnamese patients with suspected central nervous system infections, 4.2% were infected with dengue viruses.[25] In another study of 13 dengue patients with neurologic findings, the cerebrospinal fluid (CSF) was studied. Seven patients had encephalitis, two had myelitis and four showed Guillain-Barre syndrome.[26] Acute flaccid paralysis caused by dengue myositis has been reported.[27]

Acute liver failure

Acute liver failure is of concern. Hepatocellular damage may be caused directly by the dengue virus. It presents with rapid change in the consciousness with rising, high level of liver enzyme. A study in Thai children showed that dengue infection was a major cause of acute liver failure in Thailand.[28] The case fatality rate was 68.6%. Eight of 24 (33.3%) deaths were caused by dengue infection.[28] Rapid recovery in those who survive is more suggestive of Reye's syndrome than viral hepatitis

Acute renal failure

Kidneys are rarely affected in DSS. Most reported cases are associated with late acute liver failure. Other risk factors for acute renal failure are the use of nephrotoxic drugs, intravascular hemolysis (e.g. G-6-PD deficiency), and abnormal hemoglobinopathy.

Diagnosis and differential diagnosis

DF should be considered in any acute febrile illness. During the early febrile phase it may mimic a spectrum of febrile illnesses including the following: infectious mononucleosis, chickengunya, cocksackie and other enteroviral infections, parvovirus B19 infections, rubella, measles, malaria, rickettsia and leptospirosis and bacterial sepsis. In addition, DHF can also mimic Kawasaki disease, yellow fever, hantavirus infections, meningococcemia and other viral hemorrhagic fevers. Acute onset of high fever for 1-2 days, flushed face without coryza or any other respiratory symptom suggest the possibility of dengue infection. A positive tourniquet test (inflate blood pressure cuff to a point midway between systolic and diastolic pressure for a few minutes. Positive test: > 10 petechiae per 2.5 cm^2) increases probability. In an epidemic situation, the test is positive in 50% on the 1st day, and in 80% by the end of the febrile phase. In endemic areas the specificity of WHO criteria may be very low.

Two clinical observations plus one laboratory finding or at least a rising hematocrit level are sufficient to establish a provisional diagnosis of DHF. These include thrombocytopenia (less than 100,000 cells/mm^3) and hemoconcentration. A rise in hematocrit levels greater than 20% of the baseline values can be documented if hematocrit level is monitored regularly from the early stages of illness. Since patients are likely to present with symptoms suggestive of DHF, a drop in hemoglobin or hematocrit of more than 20% following volume replacement therapy can be taken as an indication of previous hemoconcentration.

For individual patients, clinical diagnosis is adequate for starting treatment. A laboratory diagnosis of dengue infections can be accomplished by detecting either the virus or antidengue antibodies. The circulating virus remains detectable in the blood during the febrile (viremic) period (on average 5 days after the onset of symptoms) and is rapidly cleared with the appearance of neutralizing antibodies.[29] Serum is the specimen of choice for both virologic and serologic studies. The available tests for laboratory diagnosis are as follows: 1) for viral isolation (mosquito cell lines, mosquito inoculation technique, and vertebral cell culture), 2) serologic diagnosis (hemagglutination inhibition test, ELISA, complement fixation test, neutralization test, antigen capture enzyme immunosorbent assay) and 3) molecular diagnostic methods (RT-PCR).

The virus isolation by cell culture and fluorescent antibody test is not needed for routine diagnosis, but it is needed to determine the serotype of the infecting virus for research and epidemiological studies. The IgM ELISA test for serologic diagnosis has a sensitivity of 83.9 to 98.4% and a specificity of 100%. On the hemagglutination inhibition test, a fourfold or greater rise in antibody titers is suggestive of a flavivirus infection (and not diagnostic of dengue infections). However, a single antibody titer > 1/2,560 is accepted as indicator of secondary dengue infection if supported by a clinical history suggestive of dengue.

RT-PCR is useful for the early detection of dengue infection when antibodies are not yet detectable. It is less sensitive than viral isolation during early days of fever, but after 5 days of fever it is more sensitive than virus isolation, allows for rapid detection within 24 hours and is able to detect the virus up to 7-8 days of fever. It is useful for

epidemiological studies as dengue serotypes could be identified without cross reactivity with other flaviviruses.[30]

WHO defines a confirmed case as one who has positive viral identification and/or a positive serological test for HI antibody ≥ 1,280 or positive IgM/IgG ELISA test in the convalescent period.

Management

WHO has issued a document focusing on the guidelines for treatment of dengue fever and DHF/DSS.[31] These guidelines are easy to follow and can be used in any hospital until the patient is admitted to an intensive care unit (ICU). Indications for admission to hospital are shown in Table 1 and the steps to the management of a patient in febrile phase are shown in Table 2.

The treatment of dengue fever in the febrile phase is symptomatic (Table 2). Fever is treated with paracetamol. Salicylates and other nonsteroidal anti-inflammatory drugs should be avoided as these may predispose a child to mucosal bleeding. In an epidemic setting, all patients with dengue fever need regular monitoring by a primary care physician for early detection of DHF. The health care provider should monitor the patient for clinical features of DHF/DSS along with hematocrit and platelet counts, if possible. Any patient

Table 1 - High-risk dengue patients and indication for admission to hospital/ICU

High-risk dengue patients that need special attention
Infants under 1 year of age
Overweight/obese patients
Massive bleeding
Change of consciousness, especially restlessness and irritability or coma
Presence of underlying diseases e.g. thalassemia, G-6-PD deficiency, heart disease
Indication for admission
Excessive family concern or cannot be followed up
Very weak, cannot eat or drink, not drinking/feeding poorly
Spontaneous bleeding
Platelet counts ≤ 100,000 cells/mm^3 and/or rising Hct 10-20%
Clinical deterioration in defervescence
Severe abdominal pain/vomiting
Significant dehydration requiring intravenous fluids
Admit immediately if there are signs of shock. These signs are as follows:
Rapid pulse with no fever
Prolonged capillary refill time
Cold clammy skin, mottling
Narrowing of pulse pressure ≤ 20 mmHg, e.g. 100/80
Hypotension
Oliguria, no urine for 4-6 hours
Change of consciousness: drowsiness to stupor, restlessness, irritability (encephalopathy)

Adapted from World Health Organization's *Prevention and Control of Dengue and Dengue Hemorrhagic Fever*.[16]
ICU = intensive care unit.

who develops cold extremities, restlessness, acute abdominal pain, decreased urine output, bleeding and hemoconcentration should be admitted to a hospital. Children with rising hematocrit levels and thrombocytopenia without clinical symptoms should also be hospitalized. Children should be encouraged to improve their oral fluid intake. As there are no specific antiviral medications for dengue infections, supportive and aggressive fluid therapy are the cornerstone of management. Early recognition of these conditions is crucial for the reduction of case fatality rates.

The most important element of treatment in a critically ill patient or in a patient with DSS is providing intensive care with close monitoring of blood pressure, hematocrit levels, platelet count, urinary output, hemorrhagic manifestations, and level of consciousness (Table 3). With adequate and appropriate fluid replacement, DSS is rapidly reversible. In a retrospective study of 858 patients with dengue fever/DHF admitted to a hospital in India, 109 cases with severe forms of the disease required PICU admission, The commonest indication for PICU admission was persistent shock (39 patients) followed by requirement for positive pressure

Table 2 - Steps to the management of the febrile phase

Resting, oral fluids
Reduction of fever: Tepid sponge after a dose of paracetamol 10-15 mg/kg/day for high fever ≥ 39° C, every 4 to 6 hours
Nutritional support: Soft, balanced, nutritious diet, juice and electrolyte solution - plain water is not adequate. Avoid black- or red-colored food or drinks (may be mistaken for bleeding)
Other supportive and symptomatic treatment
Domperidone -1 mg/kg/day in three divided doses in case of severe vomiting for 1-2 days. One single dose may be adequate
H2-blockers (ranitidine) - recommended in case of gastrointestinal bleeding
Antibiotic - not necessary; it may lead to complications
Steroid is ineffective in preventing shock DHF. It may cause harm
Intravenous fluids: In case of doubt, provide intravenous fluids, guided by serial hematocrit, blood pressure, and urine output levels. The volume of fluid should be targeted at treating mild to moderate isotonic dehydration (5-8% deficit); just correct dehydration, and discontinue it as soon as possible
If sent home- Advise about warning signs and symptoms of shock and ask to report immediately if any of the following symptoms occur
Clinical deterioration in defervescence (no fever or low-grade fever)
Any type of bleeding
Severe vomiting/abdominal pain
Intense thirst
Drowsiness, desire for sleeping all the time
Refusal to eat or drink
Cold, clammy skin and extremities, restlessness, irritability, decreased urine output or no urine for 4-6 hours
Behavioral changes e.g. confusion, use of foul language
Follow up preferably everyday - from the 3rd day until afebrile for 24-48 hours. Important points to evaluate are
History of bleeding, abdominal pain, vomiting, appetite, fluid intake, and urine output
Physical examination: vital signs, liver size and tenderness
Blood counts: WBC ≤ 5,000 cells/mm^3 with lymphocytosis and increase in atypical lymphocytes – and platelet counts ≤ 100,000 cells/cumm – indicates progression to critical phase. Rising Hct of 10-20% - indicates that the patient has progressed to the critical phase
Liver function tests in every patient who shows a change in consciousness, restlessness, confusion and irritability

DHF = dengue hemorrhagic fever; WBC = white blood cells.

Table 3 - Steps to the management of the critical phase/DHF and dengue shock syndrome

General measures
Give oxygen via face mask/nasal cannula in case of shock/impending shock. NCPAP should be preferred if there is acute respiratory failure associated with DSS
Frequent monitoring
Stop bleeding with proper techniques e.g. anterior nasal packing for massive epistaxis
Avoid blind invasive procedures e.g. no nasogastric tube insertion, no gastric lavage
Essential nursing care
Sedation is needed in some cases to restrain an agitated child. Chloral hydrate(12.5-50 mg/kg), orally or rectally, is recommended. Long-acting sedatives should be avoided
Monitoring of children with DHF/DSS
Vital signs should be checked every 15-30 minutes until the patient is stable, and every 1-2 hours thereafter
Hematocrit levels must be checked every 2 hours for 6 hours, then every 4 hours until the patient is stable. Monitoring at every 12 hours during recovery
Fluid balance sheet: type of fluid, amount, rate etc
Accurate measurement of urine output
Serum electrolytes and blood gases should be checked every 12 hours
DIC profile and liver function tests as and when indicated
Weight should be measured every 12 hours
Obtain laboratory tests
In uncomplicated DHF cases, Hematocrit and platelet counts are the only necessary tests
In those at high risk of complicated DHF
Blood grouping/cross matching
Blood glucose
Blood electrolyte (Na, Ca, K, CO2)
Liver function test
Renal function test (BUN, creatinine, uric acid)
Blood gas
Coagulogram (PTT, PT, TT)
IV fluid
IV fluids should be given only when the patient enters the critical phase: thrombocytopenia ≤ 100,000, rising Hct of 10-20%. IV fluid before critical phase cannot prevent shock, but may cause fluid overload
Type of IV fluid used: isotonic salt solution (normal saline or Ringer 's lactate)
In young infants without shock-N/2 saline in 5% dextrose; colloid solutions in patients who already have volume overload, i.e., massive pleural effusion
Fluid replacement rate – minimum necessary to maintain effective circulatory volume, excess amount will leak into the pleural and peritoneal spaces
Initial rate of administration
DSS grade III – 10 mL/kg/hour for 1-2 hours
Grade IV – Free flow or 20 mL/kg/dose IV bolus until BP can be measured (usually within 5-15 minutes), then reduce the rate to 10 mL/kg/hour for 1-2 hours
Non-shock patients: normal maintenance or + 5% deficit and then reduce the rate to minimum after 2-4 hours, if possible. Body weight < 15 kg: 4-7 mL/kg/hour. Body weight 15-40 kg: 3-5 mL/kg/hour
Colloids: The initial rate is 10 mL/kg/hour; this will reduce Hct by about 10 percentage points e.g. from 53 to 43%. After that, reduce to 5, then to 3 mL/kg/hour
Increase or decrease the rate of IV fluid depending on: clinical signs of shock, hematocrit level, urine output
In case of no response to IV fluids: consider and correct
Massive plasma leakage
Concealed internal bleeding – decrease in Hct
Hypoglycemia – Blood sugar < 60 mg%
Hyponatremia, hypocalcemia – electrolytes
Acidosis – indicates metabolic acidosis in blood gas analysis
Duration of IV fluid infusion: between 24-48 hours as plasma loss may continue for 24-48 hours. It should be discontinued when the hematocrit level falls to approximately 40%, with stable vital signs. A good urine flow indicates sufficient circulating volume. Reabsorption of extravasated plasma occurs 48 hours after the termination of shock (manifested by a further drop in hematocrit levels after intravenous fluid administration has been stopped), and hypervolemia, pulmonary edema or heart failure may occur if more fluid is given**.** *It is extremely important that a drop in hematocrit levels at this later stage is not interpreted as a sign of internal bleeding.*Strong pulse and blood pressure and adequate diuresis are good signs at this stage. The return of the patient's appetite is also a sign of recovery.

(cont.)

Table 3 - Steps to the management of the critical phase/DHF and dengue shock syndrome ***(cont.)***

Blood and platelet transfusion
The indications for fresh whole blood or packed red cell transfusion are significant blood loss > 10% (6-8 mL/kg), hemolysis, concealed internal bleeding
Dose: Fresh whole blood 10 mL/kg/dose, packed red cells 5 mL/kg/dose
Indication for platelet transfusion: significant bleeding with thrombocytopenia or if platelet count is less than 10,000/mm^3 (10-20 mL/kg of platelets). Mild reductions in platelet counts are usually not associated with significant bleeding. Platelets return to normal within 7-9 days. Only 0.4% of DHF patients need platelet transfusion
Criteria for the discharge of patients
Absence of fever for at least 24 hours without the use of antifever therapy
Minimum of 3 days after recovery from shock: stable pulse, blood pressure and breathing rate
No respiratory distress from pleural effusion and no ascites
No evidence of external or internal bleeding
Good urinary output and stable haematocrit levels
Platelet count > 100,000/mm^3
Convalescent confluent petechial rash

BUN = blood urea nitrogen; DHF = dengue hemorrhagic fever; DIC = disseminated intravascular coagulation; DSS = dengue shock syndrome; IV = intravenous; NCPAP = nasal continuous airway pressure; PT = prothrombin time; TPTT = partial tromboplastin time.

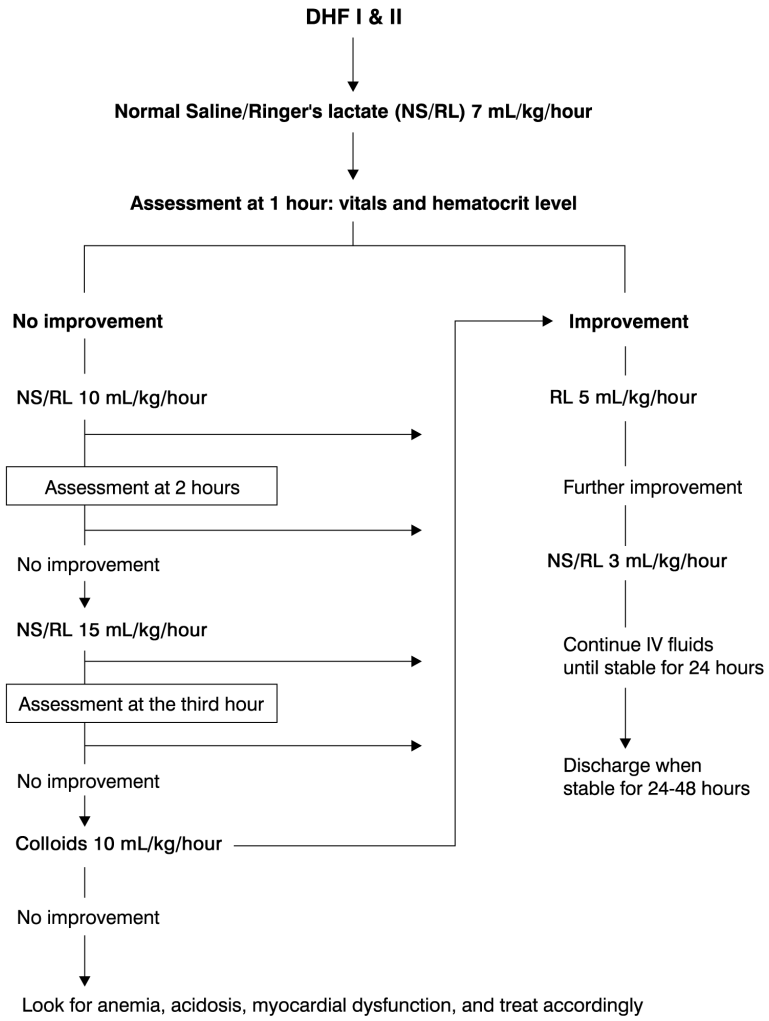
ventilation in 29 patients (10 of whom had acute respiratory distress syndrome [ARDS]) and neurological symptoms in 24 patients. All patients had thrombocytopenia.[32]

In the hospital, all children without hypotension (DHF grades I and II) should be given oxygen and fluids. In a small randomized study of DSS patients complicated by respiratory failure, oxygen administration by nasal continuous airway pressure (NCPAP) was a better option than oxygen by face mask.[32] NCPAP reduced the need for intubation and ventilation.[33]

Ringer's lactate is infused at a rate of 7 mL/kg over 1 hour. After 1 hour, if hematocrit level decreases and vital parameters improve, the fluid infusion rate should be decreased to 5 mL/kg over the next hour and to 3 mL/kg/hour for 24-48 hours. When the patient is stable, as indicated by normal blood pressure, satisfactory oral intake and urine output, the child can be discharged (Figure 1). If at 1 hour the hematocrit level rises and vital parameters do not show improvement, the fluid infusion rate should be increased to 10 mL/kg over the next hour. In case of no improvement, the fluid infusion rate should be further increased to 15 mL/kg over the third hour. If no improvement is observed in vital parameters and hematocrit level at the end of 3 hours, colloids or plasma infusion (10 mL/kg) should be administered (Figure 1). Once the hematocrit level and vital parameters are stable the infusion rate should be gradually reduced and discontinued over 24-48 hours.

In children with hypotension (DSS grade III), Ringer's lactate solution, 10-20 mL/kg, should be infused over 1 hour or given as bolus 20 mL/kg if blood pressure is unrecordable (DSS grade IV) (Figure 2). The bolus may be repeated twice if there is no improvement. If there is no improvement in vital parameters and hematocrit level rises, colloids 10 mL/kg should be rapidly infused. If the hematocrit level is falling without improvement in vital parameters, blood transfusion is necessary, presuming that lack of improvement is due to occult blood loss (Figure 2). Once improvement starts, the fluid infusion rate should be gradually decreased.

A randomized controlled trial of four different types of fluid (dextran, gelatin, Ringer's lactate solution and normal saline) in 230 children with DSS (excluding those with severe bleeding manifestations) in Vietnam did not suggest any clear advantage of the use of any specific fluid type.[34] Allergic reactions occurred in five of the 56 children given 3% gelatin. All children survived, although 51 children had a pulse pressure of ≤ 10 mmHg at the time of presentation. Recently, Wills et al. reported on a double-blind, randomized comparison of three fluids for initial resuscitation of Vietnamese children with dengue shock syndrome.[35] 383 children with moderately severe shock were randomized to receive Ringer's lactate, dextran 70, or 6 percent hydroxyethyl starch. 129 children with severe shock were assigned to receive one of the colloids. The primary outcome measure was a requirement for rescue colloid at any time after administration of the fluid. The case fatality rate was less than 0.2 percent. The primary outcome measure – requirement for rescue colloid – was similar for the different fluids in the two severity groups.[35] Treatment with Ringer's lactate resulted in less rapid improvement in the hematocrit level and a marginally longer time for initial recovery than did the treatment with either of the colloid solutions; however,



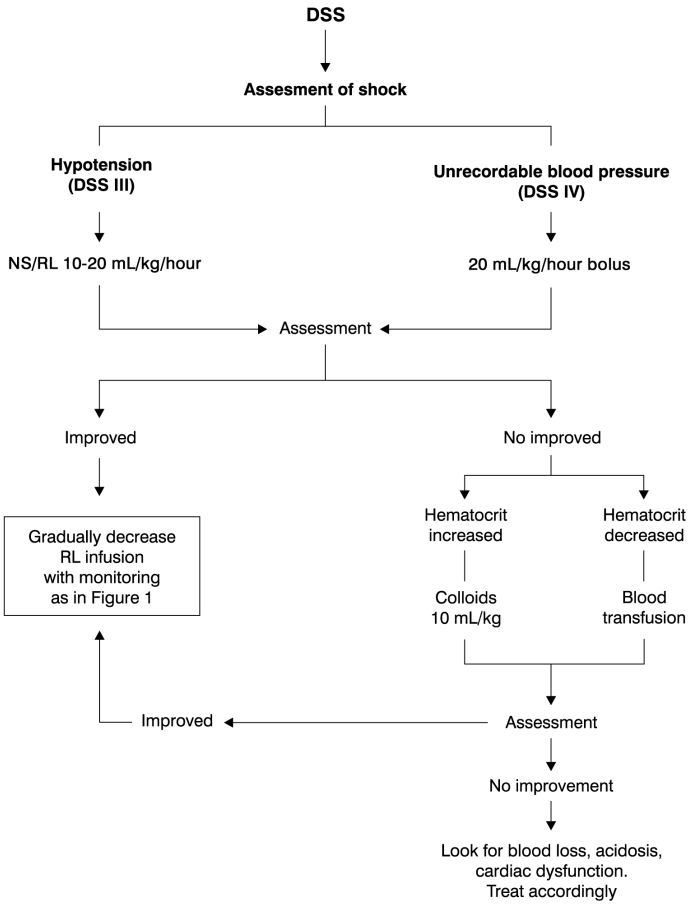
DHF = dengue hemorrhagic fever; IV = intravenous; NS = normal saline solution; RL = Ringer's lactate solution.

Figure 1 - Intravenous fluid infusion algorithm in DHF

there were no differences in treatment response in all other measures.[35] Significantly more recipients of dextran than of starch had adverse reactions. Bleeding manifestations, coagulation derangements, and severity of fluid overload were similar for all fluid-treatment groups. In this study, the authors concluded that initial resuscitation with Ringer's lactate is acceptable for children with moderately severe dengue shock syndrome.[35] Hydroxyethyl starch at 6% may be preferred in children with severe shock; the use of dextran is associated with various adverse reactions.

WHO guidelines are useful in that they offer an algorithmic approach to fluid resuscitation in DHF and DSS. However, the usefulness of these guidelines is limited beyond the immediate resuscitation because they do not address the treatment of complicated forms of the disease, including fluid overload and multiple organ failure, which could cause disability or death. Ranjit et al. evaluated their experience with a new protocol in patients with DHF and DSS. This protocol was intended to prompt earlier recognition of the disease, aggressive management of shock, and early aggressive fluid removal by controlled diuresis or dialysis in the event of extensive edema.[36]

Patients who are unresponsive to fluids may have myocardial dysfunction and decreased left ventricular performance, which may be easily detected by echocardiography.[23,37] Low platelet count may not be predictive of bleeding.[38,39] Platelets or blood should not be transfused based upon platelet count alone.[36] In children with severe thrombocytopenia in absence of significant bleeding, platelet infusion does not alter the outcome.[40] Infusion of fresh frozen plasma and platelet concentrates may be beneficial in patients with disseminated intravascular coagulation. Treatment with methylprednisolone did not show any benefit



DSS = dengue shock syndrome; NS = normal saline solution; RL = Ringer's lactate solution.

Figure 2 - Intravenous fluid infusion algorithm in DSS

in a double blind placebo-controlled trial in patients with DSS.[41] The treatment of complications is outlined in Table 4.

Prognosis

Significant morbidity and mortality can result if early recognition and monitoring of severe forms are not done. If left untreated, the mortality of DHF or DSS patients may be as high as 40-50%. Early recognition of illness, careful monitoring and appropriate fluid therapy alone have decreased mortality to 1%. If shock is identified when pulse pressure starts to drop and intravenous fluids are administered, the outcome will be excellent. Recovery is fast and most patients recover in 24-48 hours without any sequelae. The outcome may not be so good if the patient develops cold extremities. Most deaths from DHF/DSS are caused by prolonged shock, massive bleeding, fluid overload and acute liver failure with encephalopathy. Severe refractory shock, DIC, ARDS, liver failure and neurological manifestations singly or in combination were the commonest causes of death in a recent series.[32] The case fatality rate is high with shortage of experienced medical teams.

Prevention and control

At present, no specific drug or vaccine is available against the dengue virus. The control is primarily dependent on vector control.

1) Environmental changes: improved water supply, mosquito proofing of overhead tanks, cisterns and underground reservoirs.

2) Personal protection: protective clothing, mats, aerosol coils (pyrethrum), repellents e.g., DEET, permethrin impregnated in cloth, insecticide-treated mosquito nets and curtains.

3) Biological control: by larvivorous fish: *Gambria affinis* and *Peorilia reticulate*. Bacteria – *Bacillus thuringiensis* H-14, *Bacillus sphaericus* – in polluted water.

4) Chemical control:

   1% temephos sand granules.

   Space sprays – malathion, fenitrothion, pirimiphos (only in major DHF epidemics).

Insect growth regulators – interfere with development of the immature stages of the mosquito in larvae or disruption of pupal stage.

Vaccines

A tetravalent live attenuated DEN vaccine trial has been done in Thailand. After the third dose, 89% of subjects seroconverted. The trial suggested that this vaccine has moderate, but improvable reactogenicity and high seroconversion rates against four serotypes of DEN virus. It produces 80-90% seroconversion rates to all four serotypes after the administration of two doses in young children.[42] The second vaccine, produced by the Walter Reed Army Institute of Research in the United States and licensed by GlaxoSmithKline, produced similar seroconversion rates in adult volunteers. But the molecular basis of attenuation by these vaccines is not understood and it is believed that interference in replication between the serotypes and/or interference in immune stimulation may lead to imbalanced immune responses resulting in incomplete protection and enhanced disease severity. In addition, reversion to virulence through mutation or recombination between the vaccine components or with wild virus, are causes for concern.

Future issues

Dengue is an important public health problem that causes great expenses because of temporary absenteeism from work, and undermines regional and national economic development.[43] A better assessment of the economic cost of the disease is needed. Data on DHF and DSS in infants are very limited. Better understanding of immunopathogenesis in this immunologically distinct group is needed. Clinical studies defining the role of myocardial dysfunction and inotropes and vasoactive support in fluid refractory DSS, and evaluation of specific immunoglobulins to treat thrombocytopenia are needed.

Table 4 - Treatment of complications

Electrolyte imbalance
Hyponatremia
Hypocalcemia – 10% Ca gluconate 1 mL/kg/dose, IV push slowly every 6 hours
Fluid overload: avoid the common causes of fluid overload, which are
Early IV fluid therapy- in the febrile phase
Excessive use of hypotonic solutions
Non-reduction in the rate of IV fluid after initial resuscitation
Blood loss replaced with fluids in cases with occult bleeding
Judicious fluid removal using colloids with controlled diuresis (furosemide 1 mg/kg infusion over 4 hours) or dialysis
Large pleural effusions, ascites
Careful titration of intravenous fluids
Large pleural effusions during the recovery phase after 48 hours - small doses of furosemide (0.25-0.5 mg/kg at 6 hours' interval for 1 to 2 doses). Avoid insertion of intercostal drains and tracheal intubation
Disseminated intravascular coagulation
Some seriously sick patients with bleeding and DIC have benefited from heparin therapy and cryoprecipitate (1 unit per 5 kg body weight) followed by platelets (4 units/m^2 or 10-20 mL/kg) within 1 hour and fresh frozen plasma (FFP – 10-20 mL/kg). Frequent clinical assessment and regular coagulation profile (PT, aPTT, fibrinogen, platelet and FDP) are mandatory, as indicated

aPTT = activated partial tromboplastin time; DIC = disseminated intravascular coagulation; FDP = fibrin degradation products; FFP = fresh frozen plasma; IV = intravenous, PT = prothrombin time.

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