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Research Report

## UPDATE MANAGEMENT DENGUE SHOCK SYNDROME IN PEDIATRIC CASES

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### ABSTRACT

*Background:* Since 1968 Dengue Virus Infection has been found in Indonesia, especially at Surabaya and Jakarta city. Firstly management of dengue virus infection very difficult to improve, therefore the higher mortality nearly 41,4 % had been found but on the following years in five decades the mortality rates was becoming to decrease until 1,27 % on 2011. *Aim:* To find the new management of Dengue Shock Syndrome to reach the lower fatality rate below 1%. *Method:* Until now to manage Dengue Shock Syndrome is very difficult, some cases can be improved but the other lost due to the late coming in the hospital and not involved in criteria diagnosis base on WHO 1997. To solve this problem WHO 2009 had made new criteria diagnosis Dengue Virus Infection focusing on early detection of severe Dengue Virus Infection especially Dengue Shock Syndrome. *Result:* On 2011 WHO had made an integrated criteria diagnosis base on WHO 2009 and WHO 1997. These criteria was focusing in Update Management of Dengue Shock Syndrome in Pediatric Cases. Based on this action, this paper will improve clinical management to reach the lower mortality of Dengue Shock Syndrome in Community until CFR < 1%. *Conclusion:* By using integrated criteria of WHO 2009 and 1997, update management of Dengue Shock Syndrome in Pediatric cases, can improve clinical management to reach the lower mortality in community until CFR < 1%.

**Key words:** Dengue Virus Infection; Criteria diagnosis WHO; Update Management, Shock, Pediatric cases

### ABSTRAK

*Latar belakang:* Sejak tahun 1968, virus infeksi demam berdarah telah ditemukan di Indonesia, khususnya di kota Surabaya dan Jakarta. Pada awalnya, manajemen virus infeksi demam berdarah ini sangat sulit untuk dikembangkan, maka dari itu, ditemukan tingkat kematian hampir sebesar 41,4%; namun dalam beberapa tahun di 5 abad terakhir, tingkat kematian telah menurun sampai 1,27% di tahun 2011. *Tujuan:* Untuk menemukan manajemen baru dari sindrom shock demam berdarah untuk mencapai tingkat kematian yang lebih rendah yaitu dibawah 1%. *Metode:* Sampai saat ini pengendalian sindrom shock demam berdarah masih sangat sulit untuk dilakukan, beberapa kasus dapat dikembangkan namun lainnya tidak tertata akibat keterlambatan penanganan di rumah sakit dan tidak masuk dalam kriteria diagnosis berdasarkan pada WHO 1997. Untuk memecahkan masalah ini, WHO 2009 teolog membuat kriteria diagnosis infeksi virus demam berdarah baru yang berfokus pada deteksi awal pada beberapa infeksi virus demam berdarah khususnya sindrom shock karena demam berdarah. *Hasil:* Pada tahun 2011, WHO telah membuat kriteria diagnosis yang terintegrasi berdasarkan pada WHO 2009 dan WHO 1997; Kriteria ini berfokus pada manajemen terbaru di sindrom shock karena demam berdarah pada ilmu kedokteran anak. Berdasarkan pada tindakan tersebut, penelitian ini akan memotivasi kita untuk mencapai tingkat kematian untuk menurunkan kurs dari 1% menjadi 0%. *Kesimpulan:* Dengan menggunakan kriteria dari WHO 2009 yang telah terintegrasi, pembaharuan manajemen dari sindrom shock akibat demam berdarah diharapkan dapat memotivasi kita untuk mencapai tingkat kematian di masyarakat lebih rendah kurang dari 1%.

**Kata kunci:** Infeksi virus demam berdarah, kriteria diagnosis WHO, pembaharuan manajemen, syok, kasus anak-anak

## INTRODUCTION

Dengue is the most rapidly spreading mosquito borne disease in the world. In last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. In Indonesia, where more than 35% of the country's population lives in urban areas, 150,000 cases were reported in 2007 (the highest on record) with over 25,000 cases reported from both Jakarta and West Java. The case-fatality rate was approximately 1%. Reported case in fatality rates for the region approximately 1%, but in India, Indonesia and Myanmar, focal outbreaks away from the urban areas have reported case-fatality rate of 3–5%.

The mechanisms leading to the severe manifestations of Dengue virus (DENV) infections are still not completely understood but are likely to be multifactorial. The genetic background of the host influences the way that the immune response reacts to DENV infection. Upon inoculation of DENV into the dermis, Langerhans cell and keratinocytes will primarily be infected. The virus subsequently spreads via the blood (primary viremia) and infects tissue macrophages in several organs, especially the macrophages in the spleen. The replication efficiency of DENV in dendritic cells (DC), monocytes and macrophage, as well as its tropism for and replication efficiency in endothelial cells (EC), bone marrow, stromal cells and liver cells, collectively determine the viral load measured in blood. This viral load represents an important risk factor for development of severe disease. Essentially, infection of macrophages, hepatocytes and EC influence the hemostatic and the immune responses to DENV. Infected cells die predominantly through apoptosis and to a lesser extent through necrosis. Necrosis results in release of toxic products, which activate the coagulation and fibrinolytic systems, depending on the extent of infection of bone marrow stromal cells and the levels of IL-6, IL-8, IL-10 and IL-18, hemopoiesis is suppressed, resulting in decrease blood thrombogenicity. Platelets interact closely with EC and a normal number of functioning platelets is necessary to maintain vascular stability.

A high viral load in blood and possibly viral tropism for EC, severe thrombocytopenia and platelet dysfunction may result in increased vascular permeability and coagulopathy is amplified. In addition, enhancing IgG antibodies bind heterologous virus during secondary infection and enhance infection of APCs, thereby contributing to the increased viral load that is in during secondary viremia in some patients. Furthermore, a high viral load overstimulates both low and high-avidity cross reactive T cells. In the context of certain HLA haplotypes, cross-reactive T cells delay virus clearance, while producing high levels of proinflammatory cytokines and other mediators. Ultimately, these high levels of soluble factors, many of which still remain to be identified, induces changes in EC leading to the coagulopathy and plasma leakage characteristic of DSS.

Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and is followed by the three phases, febrile, critical and recovery. Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies or a combination of these techniques. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis.

Until now to manage Dengue Shock Syndrome is very difficult, some cases can be improved but the other lost due to the late coming in the hospital and not involved in criteria diagnosis base on WHO 1997. To solve this problem, WHO 2009 had made new criteria diagnosis Dengue Virus Infection focusing on early detection of severe Dengue Virus Infection especially Dengue Shock Syndrome. On 2011 WHO had made an integrated criteria diagnosis base on WHO 2009 and WHO 1997. These criteria was focusing in Update Management of Dengue Shock Syndrome in Pediatric Cases. Based on this action, this paper will motivate us to reach the lower mortality of Dengue Shock Syndrome in Community until CFR < 1%.

## EPIDEMIOLOGY

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings (Figure 1).

The countries of the region have been divided into four distinct climatic zones with different dengue transmission potential. Epidemic dengue is a major public health problem in Indonesia, Myanmar, Sri Lanka, Thailand and Timor-Leste which are in the tropical monsoon and equatorial zone where *Aedes aegypti* is widespread in both urban and rural areas, where multiple virus serotypes are circulating, and where dengue is a leading cause of hospitalization and death in children. Cyclic epidemics are increasing in frequency and in-country geographic expansion is occurring in Bangladesh, India and Maldives – countries in the deciduous dry and wet climatic zone with multiple virus serotypes circulating. Over the past four years, epidemic dengue activity has spread to Bhutan and Nepal in the sub-Himalayan foothills.

Reported case fatality rates for the region are approximately 1%, but in India, Indonesia and Myanmar, focal outbreaks away from the urban areas have reported case-fatality rates of 3–5%.



**Figure 1.** Countries/areas at risk of dengue transmission (WHO, 2008)

In Indonesia, where more than 35% of the country’s population lives in urban areas, 50,000 cases were reported in 2007 (the highest on record) with over 25,000 cases reported from both Jakarta and West Java. The case-fatality rate was approximately 1%.

Criteria for diagnosing dengue (with or without warning signs) and severe dengue are presented in Figure 2. It must

be kept in mind that even dengue patients without warning signs may develop severe dengue.

Expert consensus groups in Latin America (Havana, Cuba, 2007), South-East Asia (Kuala Lumpur, Malaysia, 2007), and at WHO headquarters in Geneva, Switzerland in 2008 agreed that: “dengue is one disease entity with different clinical presentations and often with unpredictable

**DENGUE ± WARNING SIGNS**



**SEVERE DENGUE**

- 1 Severe plasma leakage
- 2 Severe haemorrhage
- 3 Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

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

**CRITERIA FOR SEVERE DENGUE**

- Severe plasma leakage 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

**Figure 2.** Suggested dengue case classification and levels of severity (WHO, 2009)

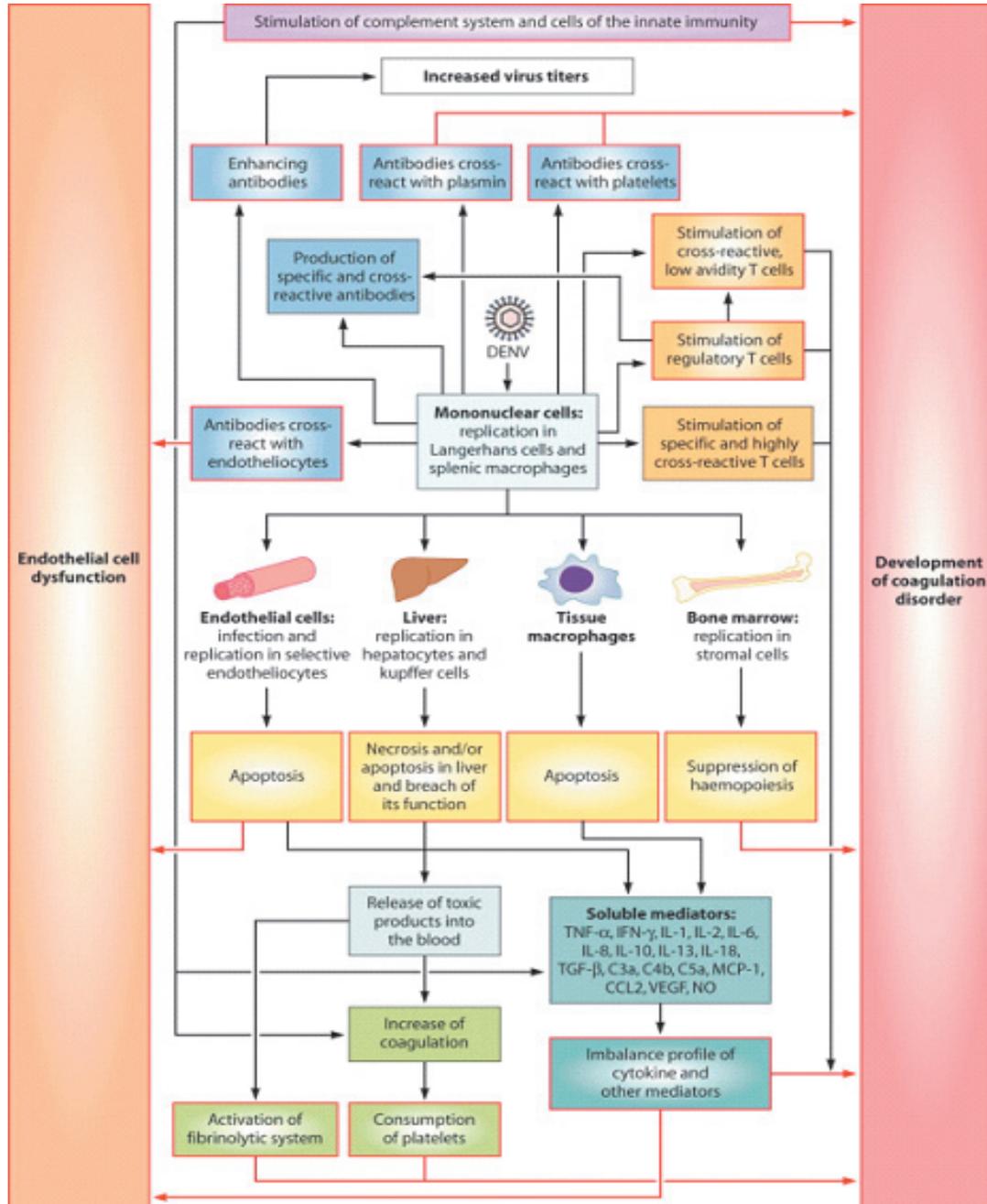
clinical evolution and outcome”, the classification into levels of severity has a high potential for being of practical use in the clinicians decision as to where and how intensively the patient should be observed and treated (i.e. triage, which is particularly useful in outbreaks), in more consistent reporting in the national and international surveillance system, and as an end-point measure in dengue vaccine and drug trials.

This model for classifying dengue has been suggested by an expert group (Geneva, Switzerland, 2008) and is currently being tested in 18 countries by comparing its

performance in practical settings to the existing WHO case classification. The process will be finalized in 2010. For practical reasons this guide adapts the distinction between dengue and severe dengue.

Dengue inflicts a significant health, economic and social burden on the populations of endemic areas. Globally the estimated number of disability-adjusted life years (DALYs) lost to dengue in 2001 was 528.<sup>1</sup>

The number of cases reported annually to WHO ranged from 0.4 to 1.3 million in the decade 1996–2005. As an infectious disease, the number of cases varies substantially



**Figure 3.** Proposed Model for the pathogenesis of DF, DHF and DSS based on an integrated view of the data presented (see section The Integrated View in the text). Black arrows, processes leading to the indicated event, colored boxes with white centers, pathological events. Each event will ultimately affect the EC or the haemostatic system (purple arrows). (WHO, 2009)

from year to year. Underreporting and misdiagnoses are major obstacles to understanding the full burden of dengue.<sup>2</sup>

On average, a hospitalized case of dengue cost three times what an ambulatory case costs. Combining the ambulatory and hospitalized patients and factoring in the risk of death, the overall cost of a dengue case is US\$ 828. Merging this number with the average annual number of officially reported dengue cases from the eight countries studied in the period 2001–2005 (532,000 cases) gives a cost of officially reported dengue of US\$ 440 million.

Children are at a higher risk of severe dengue.<sup>3</sup> Intensive care is required for severely ill patients, including intravenous fluids, blood or plasma transfusion and medicines.

Dengue afflicts all levels of society but the burden may be higher among the poorest who grow up in communities with inadequate water supply and solid waste infrastructure, and where conditions are most favourable for multiplication of the main vector, *Ae. aegypti*.

Travellers play an essential role in the global epidemiology of dengue infections, as viraemic travellers carry various dengue serotypes and strains into areas with mosquitoes that can transmit infection.<sup>4</sup>

## PATHOGENESIS

The mechanisms leading to the severe manifestations of DENV infections are still not completely understood but are likely to be multifactorial (Figure 3). The genetic background of the host influences the way that the immune response reacts to DENV infection. Upon inoculation of DENV into the dermis, Langerhans cells and keratinocytes will primarily be infected. The virus subsequently spreads via the blood (primary viremia) and infects tissue macrophages in several organs, especially the macrophages in the spleen. The replication efficiency of DENV in DC, monocytes, and macrophages, as well as its tropism for and replication efficiency in EC, bone marrow stromal cells, and liver cells, collectively determine the viral load measured in blood. This viral load represents an important risk factor for development of severe disease. Essentially, infection of macrophages, hepatocytes, and EC influences the hemostatic and the immune responses to DENV. Infected cells die predominantly through apoptosis and to a lesser extent through necrosis. Necrosis results in release of toxic products, which activate the coagulation and fibrinolytic systems. Depending on the extent of infection of bone marrow stromal cells and the levels of IL-6, IL-8, IL-10, and IL-18, hemopoiesis is suppressed, resulting in decreased blood thrombogenicity. Platelets interact closely with EC, and a normal number of functioning platelets is necessary to maintain vascular stability. A high viral load in blood and possibly viral tropism for EC, severe thrombocytopenia, and platelet dysfunction may result in increased capillary fragility, clinically manifested as

petechiae, easy bruising, and gastrointestinal mucosal bleeding, which is characteristic of DHF. At the same time, infection stimulates development of specific antibody and cellular immune responses to DENV. When IgM antibodies that cross-react with EC, platelets, and plasmin are produced, the loop that results in increased vascular permeability and coagulopathy is amplified. In addition, enhancing IgG antibodies bind heterologous virus during secondary infection and enhance infection of APCs, thereby contributing to the increased viral load that is seen during secondary viremia in some patients. Furthermore, a high viral load overstimulates both low- and high-avidity cross-reactive T cells. In the context of certain HLA haplotypes, cross-reactive T cells delay virus clearance, while producing high levels of proinflammatory cytokines and other mediators. Ultimately, these high levels of soluble factors, many of which still remain to be identified, induce changes in EC leading to the coagulopathy and plasma leakage characteristic of DSS.<sup>5</sup>

## CLINICAL MANAGEMENT AND DELIVERY OF CLINICAL SERVICES

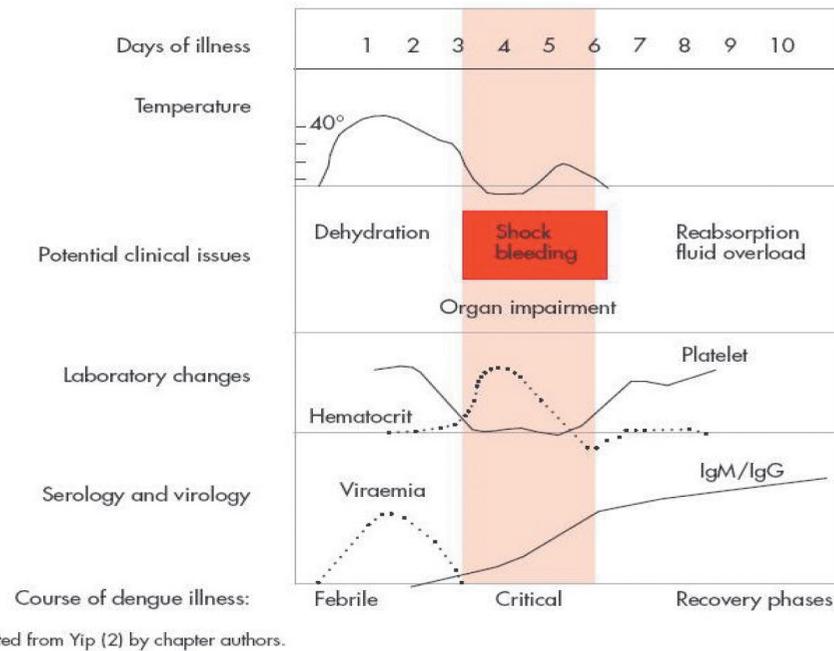
Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations.<sup>6</sup> After the incubation period, the illness begins abruptly and is followed by the three phases – febrile, critical and recovery (Figure 4).

For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives so long as correct and timely interventions are instituted. The key is early recognition and understanding of the clinical problems during the different phases of the disease, leading to a rational approach to case management and a good clinical outcome.

Activities (triage and management decisions) at the primary and secondary care levels (where patients are first seen and evaluated) are critical in determining the clinical outcome of dengue. A well-managed front-line response not only reduces the number of unnecessary hospital admissions but also saves the lives of dengue patients. Early notification of dengue cases seen in primary and secondary care is crucial for identifying outbreaks and initiating an early response. Differential diagnosis needs to be considered.

### Febrile Phase

Patients typically develop high-grade fever suddenly. This acute febrile phase usually lasts 2–7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache.<sup>6</sup> Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early febrile phase. A positive tourniquet test in this phase increases the probability of dengue.<sup>7,8</sup> In addition, these clinical



**Figure 4.** The course of dengue illness (WHO, 2009)

features are indistinguishable between severe and non-severe dengue cases. Therefore monitoring for warning signs and other clinical parameters is crucial to recognizing progression to the critical phase.

Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums) may be seen.<sup>7,9</sup> Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase but is not common.<sup>9</sup> The liver is often enlarged and tender after a few days of fever.<sup>7</sup> The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue.

#### Critical Phase

Around the time of defervescence, when the temperature drops to 37.5–38°C or less and remains below this level, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing haematocrit levels may occur.<sup>10,11</sup> This marks the beginning of the critical phase. The period of clinically significant plasma leakage usually lasts 24–48 hours.

Progressive leukopenia<sup>7</sup> followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. The degree of plasma leakage varies. Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Hence chest x-ray and abdominal ultrasound can be useful tools for diagnosis. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage.

Shock occurs when a critical volume of plasma is lost through leakage. It is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe haemorrhage causing the haematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase in patients with severe bleeding. In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.<sup>12</sup>

Those who improve after defervescence are said to have non-severe dengue. Some patients progress to the critical phase of plasma leakage without defervescence and, in these patients, changes in the full blood count should be used to guide the onset of the critical phase and plasma leakage.

Those who deteriorate will manifest with warning signs. This is called dengue with warning signs. Cases of dengue with warning signs will probably recover with early intravenous rehydration. Some cases will deteriorate to severe dengue.

#### Recovery Phase

If the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of “isles of white in the sea of red”.<sup>13</sup> Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.

**Table 1.** The various clinical problems during the different phases of dengue

1. Febrile phase	Dehydration; high fever may cause neurological disturbances and febrile seizures in young children
2. Critical phase	Shock from plasma leakage; severe haemorrhage; organ impairment
3. Recovery phase	Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period)

The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count.

### Severe Dengue

Severe dengue is defined by one or more of the following: (i) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment.

As dengue vascular permeability progresses, hypovolaemia worsens and results in shock. It usually takes place around defervescence, usually on day 4 or 5 (range days 3–7) of illness, preceded by the warning signs. During the initial stage of shock, the compensatory mechanism which maintains a normal systolic blood pressure also produces tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. Uniquely, the diastolic pressure rises towards the systolic pressure and the pulse pressure narrows as the peripheral vascular resistance increases. Patients in dengue shock often remain conscious and lucid. The inexperienced physician may measure a normal systolic pressure and misjudge the critical state of the patient. Finally, there is decompensation and both pressures disappear abruptly. Prolonged hypotensive shock and hypoxia may lead to multi-organ failure and an extremely difficult clinical course.

The patient is considered to have shock if the pulse pressure (i.e. the difference between the systolic and diastolic pressures) is  $\leq$  20 mm Hg in children or he/she has signs of poor capillary perfusion (cold extremities, delayed capillary refill, or rapid pulse rate). In adults, the pulse pressure of  $\leq$  20 mm Hg may indicate a more severe shock. Hypotension is usually associated with prolonged shock which is often complicated by major bleeding.

Patients with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when

acetylsalicylic acid (aspirin), ibuprofen or corticosteroids have been taken.

Unusual manifestations, including acute liver failure and encephalopathy, may be present, even in the absence of severe plasma leakage or shock. Cardiomyopathy and encephalitis are also reported in a few dengue cases. However, most deaths from dengue occur in patients with profound shock, particularly if the situation is complicated by fluid overload.

Severe dengue should be considered if the patient is from an area of dengue risk presenting with fever of 2–7 days plus any of the following features:

1. There is evidence of plasma leakage, such as:
  - high or progressively rising haematocrit;
  - pleural effusions or ascites;
  - circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than three seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure).
2. There is significant bleeding.
3. There is an altered level of consciousness (lethargy or restlessness, coma, convulsions).
4. There is severe gastrointestinal involvement (persistent vomiting, increasing or intense abdominal pain, jaundice).
5. There is severe organ impairment (acute liver failure, acute renal failure, encephalopathy or encephalitis, or other unusual manifestations, cardiomyopathy) or other unusual manifestations.

### LABORATORY DIAGNOSIS AND DIAGNOSTIC TESTS

Dengue virus infection produces a broad spectrum of symptoms, many of which are non-specific. Thus, a diagnosis based only on clinical symptoms is unreliable. Early laboratory confirmation of clinical diagnosis may be valuable because some patients progress over a short period from mild to severe disease and sometimes to death. Early intervention may be life-saving.

Before day 5 of illness, during the febrile period, dengue infections may be diagnosed by virus isolation in cell culture, by detection of viral RNA by nucleic acid amplification tests (NAAT), or by detection of viral antigens by ELISA or rapid tests. Virus isolation in cell culture is usually performed only in laboratories with the necessary infrastructure and technical expertise. For virus culture, it is important to keep blood samples cooled or frozen to preserve the viability of the virus during transport from the patient to the laboratory. The isolation and identification of dengue viruses in cell cultures usually takes several days. Nucleic acid detection assays with excellent performance characteristics may identify dengue viral RNA within 24–48 hours. However, these tests require expensive equipment and reagents and, in order to avoid contamination, tests must

**Table 2.** Summary of operating characteristics and comparative costs of dengue diagnostic methods<sup>9</sup>

Diagnostic methods	Diagnostic of acute infection	Time to results	Specimen	Time of collection after onset of symptoms	Facilities	Cost
Viral Isolation and serotype identification	Confirmed	1–2 weeks	Whole blood, serum, tissues	1–5 days	Mosquito or cell culture facilities, BSL-2/BSL-3 <sup>o</sup> laboratory fluorescence microscope or molecular biology equipment	\$\$\$
Nucleic acid detection	Confirmed	1 or 2 days	Tissues, whole blood, serum, plasma	1–5 days	BSL-2 laboratory, equipment for molecular biology	\$\$\$
Antigen detection	Not yet determined	1 day	Serum	1–6 days	ELISA facilities	\$\$
	Confirmed	> 1 day	Tissue for immuno-chemistry	NA	Facilities for histology	\$\$\$
IgMELISA	Probable	1–2 days	Serum, plasma, whole blood	After 5 days	Elisa facilities	\$
IgM rapid test		30 minutes			No additional supplies	
IgG (paired sera) by ELISA, HI or neutralization test	Confirmed	7 days or more	Serum, plasma, whole blood	Acute sera, 1– days, convalescent after 15 days	ELISA facilities BSL-2 laboratory for neutralization assay	\$

observe quality control procedures and must be performed by experienced technicians. NS1 antigen detection kits now becoming commercially available can be used in laboratories with limited equipment and yield results within a few hours. Rapid dengue antigen detection tests can be used in field settings and provide results in less than an hour. Currently, these assays are not type-specific, are expensive and are under evaluation for diagnostic accuracy and cost-effectiveness in multiple settings. Table 2 summarizes various dengue diagnostic methods and their costs.

After day 5, dengue viruses and antigens disappear from the blood coincident with the appearance of specific antibodies. NS1 antigen may be detected in some patients for a few days after defervescence. Dengue serologic tests are more available in dengue- endemic countries than are virological tests. Specimen transport is not a problem as immunoglobulins are stable at tropical room temperatures.

For serology, the time of specimen collection is more flexible than that for virus isolation or RNA detection because an antibody response can be measured by comparing a sample collected during the acute stage of illness with samples collected weeks or months later. Low levels of a detectable dengue IgM response – or the absence of it – in some secondary infections reduces the diagnostic accuracy of IgM ELISA tests. Results of rapid tests may be available within less than one hour. Reliance on rapid tests to diagnose dengue infections should be approached with caution, however, since the performance of all commercial tests has not yet been evaluated by reference laboratories.<sup>16</sup>

A four-fold or greater increase in antibody levels measured by IgG ELISA or by haemagglutination inhibition (HI) test in paired sera indicates an acute or recent flavivirus infection. However, waiting for the convalescent serum collected at the time of patient discharge is not very useful

for diagnosis and clinical management and provides only a retrospective result.

#### Differential Diagnosis

Dengue fever can easily be confused with non-dengue illnesses, particularly in non- epidemic situations. Depending on the geographical origin of the patient, other etiologies – including non-dengue flavivirus infections – should be ruled out. These include yellow fever, Japanese encephalitis, St Louis encephalitis, Zika, and West Nile, alphaviruses (such as Sinbis and chikungunya), and other causes of fever such as malaria, leptospirosis, typhoid, Rickettsial diseases (*Rickettsia prowazeki*, *R. mooseri*, *R. conori*, *R. rickettsi*, *Orientia tsutsugamushi*, *Coxiella burneti*, etc.), measles, enteroviruses, influenza and influenza-like illnesses, haemorrhagic fevers (Arenaviridae: Junin, etc.; Filoviridae: Marburg, Ebola; Bunyaviridae: hantaviruses, Crimean-Congo haemorrhagic fever, etc.).

Both the identification of virus/viral RNA/viral antigen and the detection of an antibody response are preferable for dengue diagnosis to either approach alone (see Table 3).

Unfortunately, an ideal diagnostic test that permits early and rapid diagnosis, is affordable for different health

**Table 3.** Interpretation of dengue diagnostic tests adapted from Dengue and Control (DENCO) study

Highly suggestive	Confirmed
one of the following	one of the following:
1. IgM + in a single serum sample	1. PCR +
2. IgG + in a single serum sample with a HI titre of 1280 or greater	2. Virus culture +
	3. IgM seroconversion in paired sera
	4. IgG seroconversion in paired sera or fourfold IgG titer increase in paired sera

systems, is easy to perform, and has a robust performance, is not yet available.

**RECOMMENDATIONS FOR TREATMENT**

Patients who require emergency treatment and urgent referral when they have severe dengue Patients require emergency treatment and urgent referral when they are in the critical phase of disease, i.e. when they have:

- severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress;
- severe haemorrhages;
- severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

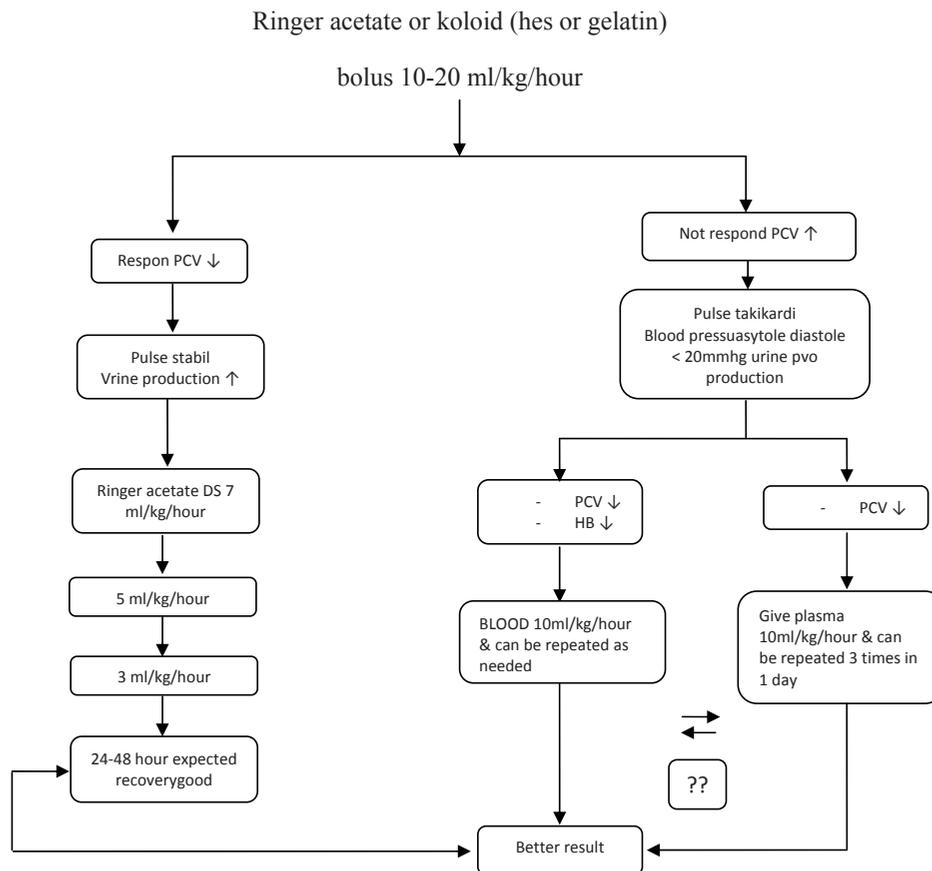
All patients with severe dengue should be admitted to the hospital with access to intensive care facilities and blood transfusion. Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. The crystalloid solution should be isotonic and the volume just sufficient to maintain an effective circulation during the period of plasma leakage. Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution or, in the case of hypotensive shock, colloid solutions. If

possible, obtain haematocrit levels before and after fluid resuscitation.

There should be continued replacement of further plasma losses to maintain effective circulation for 24–48 hours. For overweight or obese patients, the ideal body weight should be used for calculating fluid infusion rates. A group and cross-match should be done for all shock patients. Blood transfusion should be given only in cases with suspected/severe bleeding.

Fluid resuscitation must be clearly separated from simple fluid administration. This is a strategy in which larger volumes of fluids (e.g. 10–20 ml boluses) are administered for a limited period of time under close monitoring to evaluate the patient’s response and to avoid the development of pulmonary oedema. The degree of intravascular volume deficit in dengue shock varies. Input is typically much greater than output, and the input/output ratio is of no utility for judging fluid resuscitation needs during this period.

The goals of fluid resuscitation include improving central and peripheral circulation (decreasing tachycardia, improving blood pressure, pulse volume, warm and pink extremities, and capillary refill time < 2 seconds) and improving end-organ perfusion i.e. stable conscious level (more alert or less restless), urine output ≥ 0.5 ml/kg/hour, decreasing metabolic acidosis.



**Figure 5** Algorithm for fluid management in compensated shock (WHO, 2009 with modified)

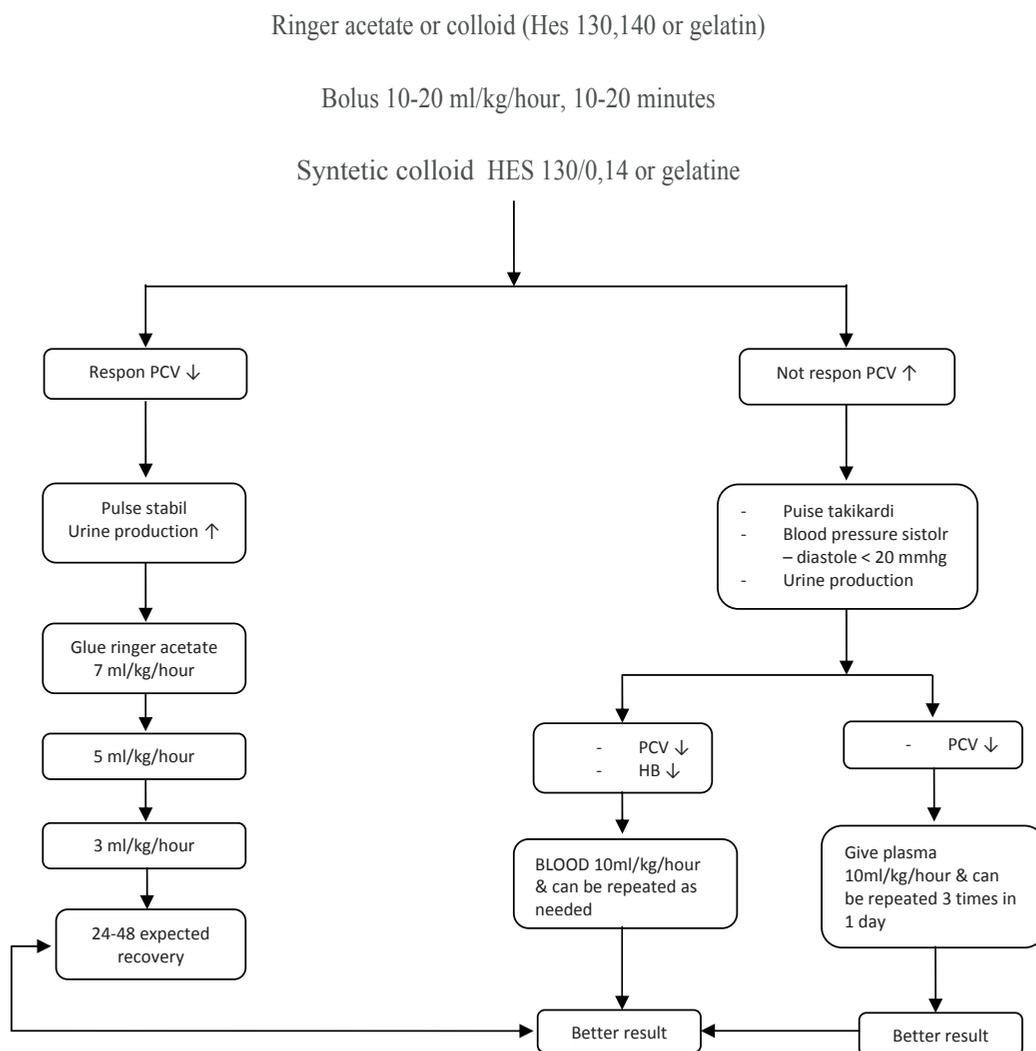
**Treatment of Shock**

The action plan for treating patients with compensated shock is as follows (Figure 5)

1. Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour. Then reassess the patient’s condition (vital signs, capillary refill time, haematocrit, urine output). The next steps depend on the situation.
2. If the patient’s condition improves, intravenous fluids should be gradually reduced 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, and then further depending on haemodynamic status, which can be maintained for up to 24–48 hours.
3. If vital signs are still unstable (i.e. shock persists), check the haematocrit the first bolus. If the haematocrit increases or is still high (> 50%), repeat a second bolus of crystalloid solution at 10–20 ml/kg/hr for one hour. After this second bolus, if there is improvement, reduce the rate to 7–10 ml/ kg/hr for 1–2 hours, and then continue to reduce as above. If haematocrit decreases

4. compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible (see treatment for haemorrhagic complications).
5. Further boluses of crystalloid or colloidal solutions may need to be given during the next 24–48 hours.
6. Awareness of using Ringer Lactat solution in Dengue Virus Infection cases can induce severity.
7. One of indicator not using Ringer Lactat is an increasing liver enzyme, AST and ALT with level more than 100-200 U/L it is marker of Liver damage.
8. Therefore we should choose other solution such as Ringer Acetat or Physiology Salt.
9. Using Ringer Acetat as fluid therapy in Dengue Virus Infection is better to prevent liver damage than using Ringer Lactate.

Patients with hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is as follows (Figure 6).



**Figure 6.** Algorithm for fluid management in hypotensive shock (WHO, 2009 with modification)

1. Initiate intravenous fluid resuscitation with crystalloid or colloid solution (if available) at 20 ml/kg as a bolus given over 15 minutes to bring the patient out of shock as quickly as possible.
2. If the patient's condition improves, give a crystalloid/colloid infusion of 10 ml/kg/hr for one hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, and then to 2–3 ml/kg/hr or less, which can be maintained for up to 24–48 hours.
3. If vital signs are still unstable (i.e. shock persists), review the haematocrit obtained before the first bolus. If the haematocrit was low (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible (see treatment for haemorrhagic complications).
4. If the haematocrit was high compared to the baseline value (if not available, use population baseline), change intravenous fluids to colloid solutions at 10–20 ml/kg as a second bolus over 30 minutes to one hour. After the second bolus, reassess the patient. If the condition improves, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above. If the condition is still unstable, repeat the haematocrit after the second bolus.
5. If the haematocrit decreases compared to the previous value (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible (see treatment for haemorrhagic complications). If the haematocrit increases compared to the previous value or remains very high (>50%), continue colloid solutions at 10–20 ml/kg as a third bolus over one hour. After this dose, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above when the patient's condition improves.
6. Further boluses of fluids may need to be given during the next 24 hours. The rate and volume of each bolus infusion should be titrated to the clinical response. Patients with severe dengue should be admitted to the high-dependency or intensive care area.

Patients with dengue shock should be frequently monitored until the danger period is over. A detailed fluid balance of all input and output should be maintained.

Parameters that should be monitored include vital signs and peripheral perfusion (every 15–30 minutes until the patient is out of shock, then 1–2 hourly). In general, the higher the fluid infusion rate, the more frequently the patient should be monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement.

If resources are available, a patient with severe dengue should have an arterial line placed as soon as practical. The reason for this is that in shock states, estimation of blood

pressure using a cuff is commonly inaccurate. The use of an indwelling arterial catheter allows for continuous and reproducible blood pressure measurements and frequent blood sampling on which decisions regarding therapy can be based. Monitoring of ECG and pulse oximetry should be available in the intensive care unit.

Urine output should be checked regularly (hourly till the patient is out of shock, then 1–2 hourly). A continuous bladder catheter enables close monitoring of urine output. An acceptable urine output would be about 0.5 ml/kg/hour. Haematocrit should be monitored (before and after fluid boluses until stable, then 4–6 hourly). In addition, there should be monitoring of arterial or venous blood gases, lactate, total carbon dioxide/bicarbonate (every 30 minutes to one hour until stable, then as indicated), blood glucose (before fluid resuscitation and repeat as indicated), and other organ functions (such as renal profile, liver profile, coagulation profile, before resuscitation and as indicated).

Changes in the haematocrit are a useful guide to treatment. However, changes must be interpreted in parallel with the haemodynamic status, the clinical response to fluid therapy and the acid-base balance. For instance, a rising or persistently high haematocrit together with unstable vital signs (particularly narrowing of the pulse pressure) indicates active plasma leakage and the need for a further bolus of fluid replacement. However, a rising or persistently high haematocrit together with stable haemodynamic status and adequate urine output does not require extra intravenous fluid. In the latter case, continue to monitor closely and it is likely that the haematocrit will start to fall within the next 24 hours as the plasma leakage stops.

A decrease in haematocrit together with unstable vital signs (particularly narrowing of the pulse pressure, tachycardia, metabolic acidosis, poor urine output) indicates major haemorrhage and the need for urgent blood transfusion. Yet a decrease in haematocrit together with stable haemodynamic status and adequate urine output indicates haemodilution and/or reabsorption of extravasated fluids, so in this case intravenous fluids must be discontinued immediately to avoid pulmonary oedema.

#### Treatment of Haemorrhagic Complications

Mucosal bleeding may occur in any patient with dengue but, if the patient remains stable with fluid resuscitation/replacement, it should be considered as minor. The bleeding usually improves rapidly during the recovery phase. In patients with profound thrombocytopenia, ensure strict bed rest and protect from trauma to reduce the risk of bleeding. Do not give intramuscular injections to avoid haematoma. It should be noted that prophylactic platelet transfusions for severe thrombocytopenia in otherwise haemodynamically stable patients have not been shown to be effective and are not necessary.<sup>14</sup> If major bleeding occurs it is usually from the gastrointestinal tract, and/or vagina in adult females. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of major bleeding are those who:

1. have prolonged/refractory shock;
2. have hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis;
3. are given non-steroidal anti-inflammatory agents;
4. have pre-existing peptic ulcer disease;
5. are on anticoagulant therapy;
6. have any form of trauma, including intramuscular injection.

Patients with haemolytic conditions are at risk of acute haemolysis with haemoglobinuria and will require blood transfusion.

Severe bleeding can be recognized by:

1. persistent and/or severe overt bleeding in the presence of unstable haemodynamic status, regardless of the haematocrit level;
2. a decrease in haematocrit after fluid resuscitation together with unstable haemodynamic status;
3. refractory shock that fails to respond to consecutive fluid resuscitation 40–60 ml/kg;
4. hypotensive shock with low/normal haematocrit before fluid resuscitation;
5. persistent or worsening metabolic acidosis  $\pm$  a well-maintained systolic blood pressure, especially in those with severe abdominal tenderness and distension.

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Do not wait for the haematocrit to drop too low before deciding on blood transfusion. Note that haematocrit of  $< 30\%$  as a trigger for blood transfusion, as recommended in the Surviving Sepsis Campaign Guideline,<sup>15</sup> is not applicable to severe dengue. The reason for this is that, in dengue, bleeding usually occurs after a period of prolonged shock that is preceded by plasma leakage. During the plasma leakage the haematocrit increases to relatively high values before the onset of severe bleeding. When bleeding occurs, haematocrit will then drop from this high level. As a result, haematocrit levels may not be as low as in the absence of plasma leakage.

The action plan for the treatment of haemorrhagic complications is as follows:

- Give 5–10 ml/kg of fresh-packed red cells or 10–20 ml/kg of fresh whole blood at an appropriate rate and observe the clinical response. It is important that fresh whole blood or fresh red cells are given. Oxygen delivery at tissue level is optimal with high levels of 2,3 di-phosphoglycerate (2,3 DPG). Stored blood loses 2,3 DPG, low levels of which impede the oxygen-releasing capacity of haemoglobin, resulting in functional tissue hypoxia. A good clinical response includes improving haemodynamic status and acid-base balance.
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in haematocrit after blood transfusion. There is little evidence to support the practice of transfusing platelet concentrates

and/or fresh-frozen plasma for severe bleeding. It is being practised when massive bleeding can not be managed with just fresh whole blood/fresh-packed cells, but it may exacerbate the fluid overload.

### Treatment of complications and other areas of treatment

#### Fluid overload

Fluid overload with large pleural effusions and ascites is a common cause of acute respiratory distress and failure in severe dengue. Other causes of respiratory distress include acute pulmonary oedema, severe metabolic acidosis from severe shock, and Acute Respiratory Distress Syndrome (ARDS) (refer to standard textbook of clinical care for further guidance on management).

Causes of fluid overload are:

1. excessive and/or too rapid intravenous fluids;
2. incorrect use of hypotonic rather than isotonic crystalloid solutions;
3. inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding;
4. inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates;
5. continuation of intravenous fluids after plasma leakage has resolved (24–48 hours from defervescence);
6. co-morbid conditions such as congenital or ischaemic heart disease, chronic lung and renal diseases.

Early clinical features of fluid overload are :

1. respiratory distress, difficulty in breathing;
2. rapid breathing;
3. chest wall in-drawing;
4. wheezing (rather than crepitations);
5. large pleural effusions;
6. tense ascites;
7. increased jugular venous pressure (JVP).

Late clinical features are:

1. pulmonary oedema (cough with pink or frothy sputum  $\pm$  crepitations, cyanosis);
2. irreversible shock (heart failure, often in combination with ongoing hypovolaemia).

Additional investigations are:

1. the chest x-ray which shows cardiomegaly, pleural effusion, upward displacement of the diaphragm by the ascites and varying degrees of “bat’s wings” appearance  $\pm$  Kerley B lines suggestive of fluid overload and pulmonary oedema;
2. ECG to exclude ischaemic changes and arrhythmia;
3. cardiac enzymes.

The action plan for the treatment of fluid overload is as follows:

1. Oxygen therapy should be given immediately.
2. Stopping intravenous fluid therapy during the recovery phase will allow fluid in
3. the pleural and peritoneal cavities to return to the

intravascular compartment. This results in diuresis and resolution of pleural effusion and ascites. Recognizing when to decrease or stop intravenous fluids is key to preventing fluid overload. When the following signs are present, intravenous fluids should be discontinued or reduced to the minimum rate necessary to maintain euglycaemia:

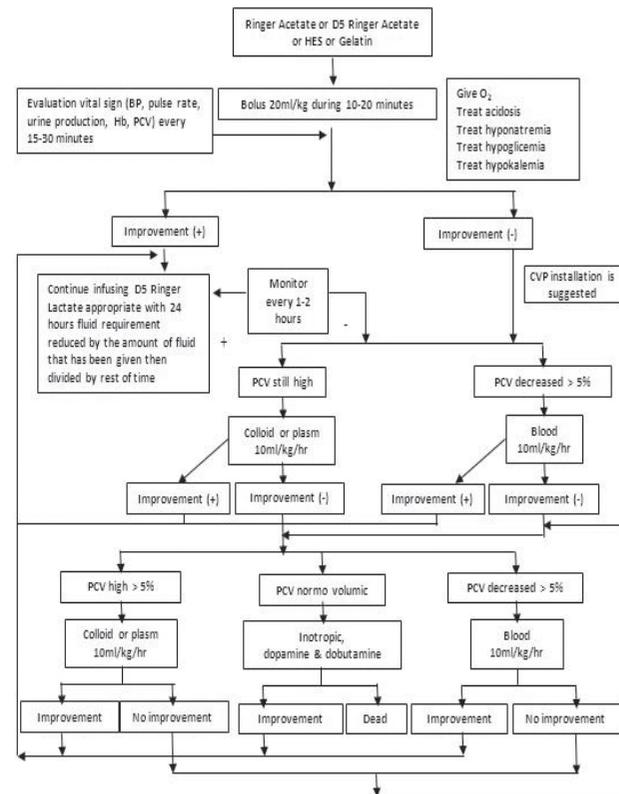
- » signs of cessation of plasma leakage;
- » stable blood pressure, pulse and peripheral perfusion;
- » haematocrit decreases in the presence of a good pulse volume;
- » afebrile for more than 24–48 days (without the use of antipyretics);
- » resolving bowel/abdominal symptoms;
- » improving urine output.

4. The management of fluid overload varies according to the phase of the disease and the patient's haemodynamic status. If the patient has stable haemodynamic status and is out of the critical phase (more than 24–48 hours of defervescence), stop intravenous fluids but continue close monitoring. If necessary, give oral or intravenous furosemide 0.1–0.5 mg/kg/dose once or twice daily, or a continuous infusion of furosemide 0.1 mg/kg/hour. Monitor serum potassium and correct the ensuing hypokalaemia.
5. If the patient has stable haemodynamic status but is still within the critical phase, reduce the intravenous fluid accordingly. Avoid diuretics during the plasma leakage phase because they may lead to intravascular volume depletion.
6. Patients who remain in shock with low or normal haematocrit levels but show signs of fluid overload may have occult haemorrhage. Further infusion of large volumes of intravenous fluids will lead only to a poor outcome. Careful fresh whole blood transfusion should be initiated as soon as possible. If the patient remains in shock and the haematocrit is elevated, repeated small boluses of a colloid solution may help.

#### Other Complications of Dengue

Both hyperglycaemia and hypoglycaemia may occur, even in the absence of diabetes mellitus and/or hypoglycaemic agents. Electrolyte and acid-base imbalances are also common observations in severe dengue and are probably related to gastrointestinal losses through vomiting and diarrhoea or to the use of hypotonic solutions for resuscitation and correction of dehydration. Hyponatraemia, hypokalaemia, hyperkalaemia, serum calcium imbalances and metabolic acidosis (sodium bicarbonate for metabolic acidosis is not recommended for pH  $\leq$  7.15) can occur. One should also be alert for co-infections and nosocomial infections. If found cases with Dengue Shock Syndrome with hypotonic heart muscle complication at figure 7.

#### TO PREVENT LIFE THREATENING HYPOTENSION IN DSS AS FOLLOW



**Figure 7.** Flow Chart of Dengue Shock Syndrome with hypotonic heart muscle complication (WHO, 2009)

#### Supportive Care and Adjuvant Therapy

Supportive care and adjuvant therapy may be necessary in severe dengue. This may include:

renal replacement therapy, with a preference to continuous veno-venous haemodialysis (CVVH), since peritoneal dialysis has a risk of bleeding;

vasopressor and inotropic therapies as temporary measures to prevent life-threatening hypotension in dengue shock and during induction for intubation, while correction of intravascular volume is being vigorously carried out;

further treatment of organ impairment, such as severe hepatic involvement or encephalopathy or encephalitis;

further treatment of cardiac abnormalities, such as conduction abnormalities, may occur (the latter usually not requiring interventions). In this context there is little or no evidence in favour of the use of steroids and intravenous immunoglobulins, or of recombinant Activated Factor VII.

#### CONCLUSION

By using integrated criteria of WHO 2009 and 1997, update management of Dengue Shock Syndrome in

Pediatric cases, can improve clinical management to reach the lower mortality in community until CFR < 1%.

Using Ringer Acetat as fluid therapy in Dengue Virus Infection is better to prevent liver damage than using Ringer Lactate.

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