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UPDATE MANAGEMENT OF DENGUE COMPLICATION IN PEDIATRIC

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ABSTRACT

Dengue virus infection is one of the important health problems in Indonesia, although the mortality rate has been decreased but many dengue shock syndrome cases is very difficult to be solving handled. It might be due to nature course of dengue virus infection is very difficult to predict of the earlier time of severity occur. THE AIM *To get idea to make update management of dengue complication in pediatric.* MATERIAL AND METHOD *Data were compiled from Dr. Soetomo Hospital Surabaya in 2009. The diagnosis of all cases was based on criteria WHO 1997 and PCR examination in Institute Tropical Disease for identified serotype of dengue virus infection. The unusual cases of dengue virus infection were treated following the new WHO protocol in 2009. RESULT There were only 3 cases with serotype DEN 1, consisted 2 cases had age 1–4 years and 1 had age 5–14 years. 2 cases showed a severe clinical performance as dengue shock syndrome and 1 case showed as unusual case of dengue virus infection. Three report cases of: a. Dengue hemorrhagic fever grade III which liver involvement and had bilateral pleural effusion; b. Dengue hemorrhagic grade III with liver involvement and encephalopathy; c. Dengue hemorrhagic grade III with liver involvement acute kidney injury, myocardial involvement and encephalopathy. All the patients were treated according to new edition WHO protocol and all of the involving organ recovered along with the improvement of the disease.* CONCLUSION *Update management of dengue complication pediatric should be learned carefully used for helping unusual cases of dengue virus infection.*

Key words: *Dengue, update management, revises criteria diagnosis & treatment*

INTRODUCTION

Dengue virus infection is one of the important health problems in Indonesia, although the mortality rate has been decreased but many dengue shock syndrome cases is very difficult to be solving handled. It might be due to nature course of dengue virus infection is very difficult to predict of the earlier time of severity occur.

Some factor influence this situation such as global warming, increasing sub urban area which have many people don't aware with a bad environment sanitation and have highly dynamic people for getting some money for their life. Beside it many unusually cases were found and need new procedure for making diagnosis and use update management.

Dengue control group of WHO want to revise the criteria WHO 1997 for minimize false diagnostic dengue virus infection and to decrease the mortality rate.

Based on the reason, update management dengue virus infection should be made based on many experiences and followed the protocol WHO in 2009.

This paper will reviewed some unusual cases dengue virus infection that had been found in Dr. Soetomo Hospital Surabaya and promoting update management.

MATERIALS AND METHODS

Data were compiled from Dr. Soetomo Hospital Surabaya in 2009. The diagnoses of all cases were based on criteria WHO 1997 and PCR examination in Institute Tropical Disease for identified serotype of dengue virus infection.

The unusual cases of dengue virus infection were treated based on the new protocol WHO for diagnosis and treatment in 2009.

RESULTS

In 2009 the study Dengue virus infection in patient at Dr. Soetomo hospital found that there were only 3 cases with serotype DEN 1, consisted 2 cases had age 1–4 years and 1 had age 5–14 years. 2 cases showed a severe clinical performance as dengue shock syndrome and 1 case showed as unusual case of dengue virus infection. (See table 1)

Table 1. Distribution of Serotype and Clinical Performance of Dengue Virus Infection in 2009

	Clinical Performance & Diagnostic				
Serotype	**DF**	**DHF**	**DSS**	**UNUSUAL**	**Total**
DEN 1	0	0	**2***	**1**	**3**
DEN 2	30	26	7	2	65
DEN 3	1	0	1	0	2
DEN 4	0	0	0	0	0
Total	31	26	10	3	70

Kruskal-Wallis: p = 0,03*
* = significant (p < 0,05)

Serotype DEN 1 was usually mild case but in this study 1 case showed a severe clinical performance as dengue shock syndrome and identified as primary infection (see table 2).

Table 2. Distribution of Clinical Performance of Dengue Virus Infection in 2009

	Clinical Performance & Diagnostic				
Type of Infection	**DF**	**DHF**	**DSS**	**UNUSUAL**	**Total**
Primary	16	7	1*	2	26
Secondary	15	19	9	1	44
Total	31	26	10	3	70

Mann-Whitney; p = 0,035*
* = significant (p < 0,05)

THREE REPORT CASES IN 2009

1. A seven years old boy was brought by his parent on June 2nd, 2009 to Dr. Soetomo Hospital Emergency Department with the main complaint of fever, shortness of breath, nausea, poor appetite and delirium. Supine chest x-ray showed right pleural effusion. The diagnosis was dengue hemorrhagic fever grade III with encephalopathy and liver involvement.
2. A nine years old boy was brought by his parent on June 25, 2009 to Dr. Soetomo Hospital Emergency Department; the patient was looked dyspnea, abdomen was slight distended, the liver was palpable 3cc below the coastal arc. The supine chest x-ray showed bilateral pleural effusion. The working diagnosis was dengue hemorrhagic fever grade III with liver involvement and had bilateral pleural effusion.
3. a three years old boy was referred from Mojokerto hospital with suspicion of hepatic coma on December 2, 2009 to Dr. Soetomo Hospital Emergency Department he looked as a lethargic boy and extremities were clammy with capillary refill time more than two second, the liver was palpable 4cc below the costal arc with dullness merging laboratory examination revealed hemoglobin level 10,3 g/dl. Leukocyte count 14.600/mm^3, platelet count 15.000/mm^3 hematocrite 31,9% blood glucose 79 mg/dl BUN 48 mg/dl creatinine serum 1,8 mg/dl AST 3154 µ/l ALT. 1274 µ/l; nine hours on admission, the patient had generalized seizure for three minutes. The working diagnosis was dengue hemorrhagic fever grade III with liver involvement Acute Kidney Injury (AKI) and encephalopathy.

Update management is:
The new protocol WHO for diagnosis and treatment in 2009, especially to treat some severe cases which unusual manifestation of dengue virus infection.

DISCUSSION

In 2009 the study dengue virus infection in patient at Dr. Soetomo hospital found that stereotype DEN 1 showed clinical performance of Dengue Shock Syndrome 2 cases and unusual case 1 case and totally 3 cases; DEN 2 were found which had clinical performance of Dengue Fever 30 cases and 26 cases of Dengue Hemorrhagic Fever which had a 7 cases of Dengue Shock Syndrome and 2 unusual cases totally 65 cases; DEN 3 were found clinical performance of Dengue Fever 1 case Dengue Shock Syndrome 1 case and totally 2 cases; Finally DEN 4 virus was not found.

Virus isolation from mosquito bites showed DEN V1 has been isolated and identified on DEN 1 Genotype IV, it was new variant virus that correlated with phylogenetic Dengue Virus came from China which had severe clinical performance of Dengue Virus Infection.

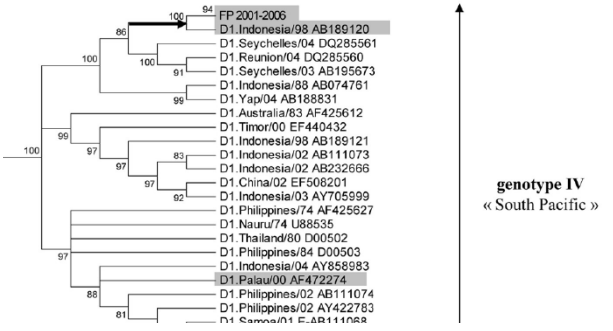

Figure 1. Phylogenetic Dengue Virus in The World

In 2009 we have many experiences to care severe performance of Dengue Virus Infection with unusual

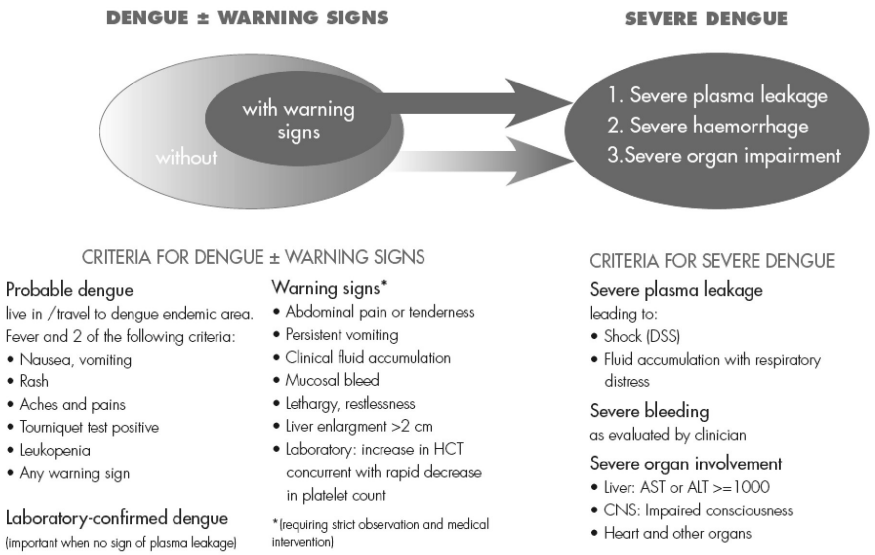

Figure 2. Classification of Dengue Virus Infection cases
(Source: WHO, 2009. Dengue: guidelines of diagnosis,treatment, prevention and control – new edition. Genewa: WHO, p. 23)[3]

manifestation that could not followed WHO criteria 1997. More cases showed criteria for severe dengue virus infection, as followed: 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 organ). Therefore for managing the unusual dengue virus infection we should followed new WHO criteria diagnosis and classification of cases as followed:

In 2009, the study found that DEN V1 genotype IV showed a severe clinical performance and also as a primary dengue virus infection. This study support to the Gubler hypothesis which gave information that a new virulent variant DEN V1 can cause a severe clinical performance of dengue virus infection.

During three decades, the World Helath Organization (WHO) has recommended the classification of dengue virus infection in: dengue fever (DF) and dengue hemorrhagic fever (DHF) with or without dengue shock syndrome (DSS). In order to be regarded as a DF (or classical dengue) case, the patient must present fever and two symptoms out of the following: headache, retroocular pain, osteomyoarticular pains, rash, leucopenia, and some kind of bleeding.[6] The DHF requires the presence of the four following criterias: a) acute sudden onset of high fever for 2 to 7 days; b) some kind of spontaneous bleeding, usually petechiaes, or at least having a positive tourniquette test; c) thrombocytopenia lower than 100,000/mm^3; and d) plasma leakage, evidenced by a 20% elevation of the hematocrite, or by a 20% decrease of the hematocrite after the critical stage, or by the verification of pleural leakage, ascites or pericardial leakage by means of image studies.[6] The course of the dengue disease goes through 3 clinical stages: the febrile stage, the critical stage, and the recovery stage (Figure 3).[1,3]

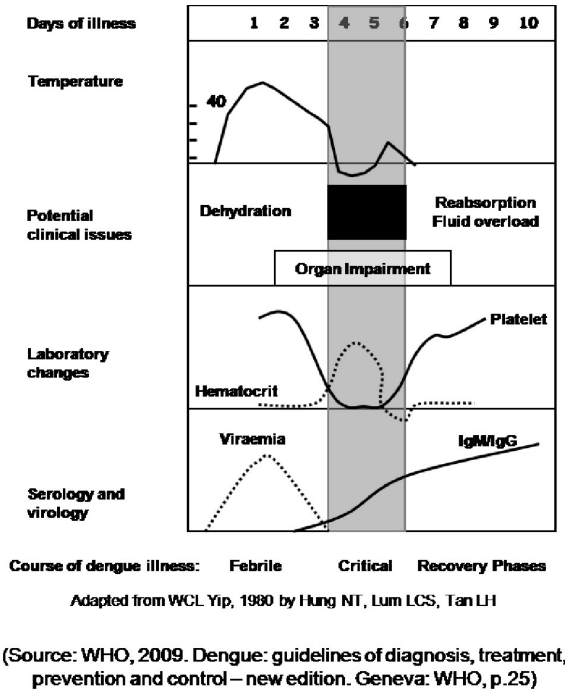

Figure 3. The Course of Dengue Disease

In our cases, all the patients had fever for four to five days on admission, with classic symptoms like aches and pains, nausea and vomiting, and abdominal pain.

They come with clammy extremities, 2 of them with unmeasured blood pressure (case 1 and 2), and 2 with decrease of consciousnesses (case 1 and 3, in case 2 decrease of consciousnesses happened later). They had liver enlargement more than 2 cm and ascites. The signs of bleeding on admission were only present in case 2 as petechiae. In case 1 there was severe gastrointestinal bleeding later (as hematemesis and melena). From the laboratory examination all of them had thrombocytopenia lower than 100,000/mm^3. Two of them had hemoconcentration as shown by the increased hematocrite. The blood coagulation profile tests were performed in case 2 and 3 that revealed abnormal results. From the radiologic examinations all of them had pleural effusions, especially on the right lungs. In all cases there were signs of profound shock that improved after the fluid resuscitation and only in case 2 there was recurrent shock.

The dengue infection may be clinically unapparent and cause an illness with varied intensity, including from febrile forms with body pains to severe pictures of shock and large hemorrhages. The main difference between the classical dengue or dengue fever (DF) and the dengue hemorrhagic fever (DHF) is the leaking of plasma, causing a significant elevation in the hematocrit and an accumulation of fluid in serous cavities.[1] There are also rarer clinical forms that known as "atypical", and result from the especially intense damage to an organ or system: encephalopathy, myocardiopathy or hepatopathy by dengue, as well as kidney dysfunction with acute kidney insufficiency and other that are also associated to mortality.[1,5] To improve the leaking of plasma new finding colloid could be used. For example: HES, gelofusin, hemacel, etc.

Severe organ impairment in dengue infection usually are complications resulting from a prolonged or recurrent shock. However some dengue patients may manifest a special damage to an organ on system, reason why these occurrances have been named "clinical forms of dengue with visceral predominance" in occasions associated to an extreme severity and death. Dengue patients frequently present some kind of liver involvement, that usually recoverable.[1] Clinical finding of liver involvement in dengue infections includes the presence of hepatomegaly and increased serum liver enzymes. Hepatomegaly is frequent and is commoner in patients with DHF than in those with DF. Transaminase levels are also higher in DHF/DSS than in DF and tend to return to normal 14 to 21 days after infection.

In dengue infections, elevations in serum AST appear to be greater, and return to normal more rapidly than ALT levels. If we found dengue virus infection cases with elevated serum AST & ALT please used crystalloid ringer acetate or physiologic salt. It was to prevent the complication using ringer lactate in patient with liver damage. Usually in a case with healthy liver organ can metabolizes the ringer lactate crystalloid. But if this case have liver damage the ringer lactate crystalloid cannot be metabolized and the result; could promote the severe liver dysfunction and the complication such as DIC and bleeding can occur. In a subgroup of predominantly DHF/DSS patients, severe liver dysfunction occurs and is a marker of poor prognosis.[8]

In a Malaysian study of DF and DHF patients with liver invonvements resulted that ALT and ALP (alkaline phosphatase) levels were significantly higher in DHF patients with spontaneous bleeding than those without bleeding.[9] Dengue viral antigens have been found within hepatocytes, and the virus appears to be able to replicate in both hepatocytes and Kupffer calls, a nd dysregulated host immune responses may play an important causative role in liver damage. Liver damage may also be potentiated by the intake of drugs (such as acetaminophen and anti-emetics) during the early phase of the illness.[8] Hepatic failure is a rare, severe and potentially fatal complication of dengue hemorrhagic fever.[10-12]

In our cases, all of them had liver involvements, as seen on the liver enlargements (more than 2 cm) and the elevation of serum liver enzymes. In case 2 and 3 direct hyperbilirubinemias were found, consistent with the presence of jaundice. In case 2 the liver involvement brought the patient into a fulminant hepatic failure condition, that might be correlated with his severe bleeding manifestation after using ringer lactate.Therefore that crystalloid should be changes by ringer acetate solutions; The result all cases with had liver involvement were improved along their disease's improvements.

In some unusual cases, dengue infections may also present signs and symptoms involving the central nervous system (CNS), such as headache, seizures, neck stiffness, depressed sensorium, behavioural disorders, delirium, paralysis and cranial nerve palsies. Such neurological conditions were attributed to plasma leakage into serous spaces, hemorrhage, shock, and metabolic disturbances in severe dengue infections. Acute liver failure is considered to be another factor causing CNS manifestation. The detection of dengue IgM and the isolation of dengue viruses from the cerebrospinal fluid of patients with neurologic disorders indicate the neurovirulance of dengue viruses and their capability of causing encephalitis.[13]

In all of our cases the patients had encephalopathy that might be correlated to the elevated liver enzymes; it might be due to using ringer lactate in the first resuscitation of dengue shock syndrome cases which had liver damage due to dengue virus infection. Based on these experiences please choose other crystalloid such as ringers acetate and physiology-saltz to change the ringer lactate that usually used in the first resuscitations. In case 1 and 3 the patients had electrolyte imbalance (hyponatremia and hypocalcemia) that could play a role in these neurological disturbance. In case 3 the patient had seizure might be caused by the electrolyte imbalance. All of those CNS manifestations were recovered along with their disease's improvement, and no sequela was observed.

Dengue viral infection may also present some myocardial damage – particularly in adults, with little

electrocardiographic expression. Myocardial dysfunction can be seen patients with DHF, approximately 20% of those who developed DHF have a LV ejection fraction of less than 50%, and are likely to return to normal within a few weeks. The pathogenic mechanisms of cardiac dysfunction are not well established; alternation of autonomic tone and prolonged hypotension may play a role. Electrocardiographic abnormalities have been reported in 44-75% of patients with viral hemorrhagic fever, and prolongation of the PR interval or sinus bradycardia commonly occurs, and some have reported atrioventricular block in variable degrees.[14,15] The underlying mechanisms were postulated to be immune in origin, although myocarditis may be a contributory factor.[16] In an Indian study of children with dengue haemorrhagic fever, there was no correlation between myocardial involvement and clinical severity.[17] Myocardial involvement of dengue infections run a benign course without long-term complication. Dengue myocarditis is exclusively asymptomatic with no long term sequelae.[18]

In case 3 bradyarrhytmia was found on the early recovery phase, that might be caused by myocardial injury. There was no symptom of unstable hemodynamic on the patient, and the ECG was return to normal the day after.

Dengue infection usually has transient renal function abnormalities and urinalysis may help the physicians to look for dengue infection. Proteinuria and abnormal urine sediment are the most common renal manifestation observed in patient with dengue infection[19], although according to a Thailand study, abnormal urinalysis (proteinuria, hematuria and pyuria) are not correlated with the severity of disease.[20] Acute kidney injury with acute tubular necrosis due to shock and multiorgan failure, resulting in rhabdomyolysis, haemolysis with haemoglobinuria, proteinuria, and thrombotic microangiopathy, have been described in patients with dengue infection.[21] Acute renal failure can be happened because of extensive capillary leak, hypotension, and severe disseminated intravascular coagulation, which lead to hypoxia/ischemia and multiple organ dysfunction, although this complications can occur without bleeding manifestations or shock.[19]

In case 3 the patient had abnormal renal function test on the critical phase that returned to normal on the recovery phase. The acute kidney injury was improved along with the disease's improvement.

A primary or secondary antibody response can be observed in patients with dengue virus infection. In primary dengue virus infection, IgM antibodies develop rapidly and are detectable on days 3–5 of illness, reach its peak at about 2 weeks post infection and then decline to undetectable levels over 2–3 months. Anti-dengue virus IgG appears shortly afterwards. Secondary infection with dengue virus result in the earlier appearance of high titers of IgG before or simultaneously with the IgM responses.[22-24] The late presenting IgM can be due to variable rapidity which IgM develops among patients: 80% of patients had detectable IgM antibody by day 5 of illness, 93% by day 6-10, and 99% of patient by day 10–20.[23,24] Secondary infections are more likely to result in DHF/DSS, although not all DHF/DSS cases are secondary infections.[25,26]

In our cases, all of them had positive results for immunoglobulin M and G antidengue. In case 1, the initial dengue serologic examination on the 6th day of illness resulted negative, and the repeated examination on the 11th day of illness had initial positive results on the 5th and 7th day of illness, strongly suggested secondary dengue virus infections.

In recent years, articles have been published that bring into question the accuracy of WHO 1997 dengue classification for regarding it as too stern, much too dependent on laboratory result, and for not including dengue patients with other severe forms of the illness, such as the particular damage to the Central Nervous System (encephalitis), to the heart (myocarditis) or to the liver (severe hepatitis).[27–29] For this reason, the TDR/WHO (Program of Training and Research on Transmissible Diseases of The World Health Organization) has sponsored an international study, named DENCO (Dengue Control), of which one of the components was of clinic, and which main purpose was to obtain information from a high number of patients with confirmed dengue and find out a better way to classify them, as well as to identify those signs of alarm that could be useful to improve the protocol of management of dengue cases. The study had a consistent result in the proposal of a binary classification of the disease: dengue and severe dengue.[1,7]

The criteria of severe dengue include: a) severe plasma leakage, expressed in hypovolemic shock, and / or breathing difficulty due to excess accumulation of fluid in the lungs; b) severe bleeding according to the criteria used by doctors; and/or c) severe organ involvements, include severe hepatitis due to dengue (transaminase >1000 units), encephalitis due to dengue, or serious damage to other organs such as dengue myocarditis (Figure 7).[1,3,7] This severity criterium has 95% sensitivity and 97% specificity.[1,7] DENCO criteria could also identify some signs and symptoms that occurred in patients 1 day before the deterioration of conditions. These warning signs allowed early identification of dengue patients who were heading toward a severe dengue and doctors had a chance to start early treatment by replacing fluid intravenously and improve patient's prognosis. Abdominal pain or painful abdominal palpation was a significant risk factor in adults and children, as well as mucosal bleeding, and thrombocytopenia with a platelet counts less than 10,000/mm^3. In adults, the other danger sign was the presence of lethargy, which sometimes turned to irritability, hypoalbuminemia, and increased hematocrite.[1,7]

In all of our cases, there were organ involvements that made the disease's manifestation more severe. According to the WHO criteria, one of 3 cases didn't fulfill the DHF criterias by WHO (case 3). By applying the revised dengue classification, all of them were classified as severe dengue. In case 2 there was evidence of severe plasma leakage, severe bleeding (gastrointestinal bleeding), and severe

organ involvement (encephalopathy, liver involvement). In case 1 there were severe plasma leakage and severe organ involvement, but there was no severe bleeding manifestation (only petechiae). In case 3 there was severe plasma leakage, no sign of bleeding, and there was severe multiorgan involvement (encephalopathy, acute kidney injury, liver and cardiac involvement). Moreover, from the clinical history all of them had several warning signs before their condition deteriorated. If the patients had come before their critical phase, those identifiable warning signs might be helpful to alarm the clinician to give fluid therapy in sufficient amount to replace the losses caused by the plasma leakage.

Management of dengue virus infection 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. In the febrile phase, when the clinical features are indistinguishable between severe and non-severe dengue cases, monitoring for warning signs and other clinical parameters is crucial to recognizing progression to the critical phase. In the critical phase, shock can occur when a critical volume of plasma is lost through leakage. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation, and this in turn leads to severe haemorrhage causing the haematocrit to decrease in severe shock. Those who improve after defervescence are said to have non-severe dengue. Those who deteriorate will manifest with warning signs. Cases of dengue with warning signs will probably recover with early intravenous rehydration, but some cases will deteriorate to severe dengue. If the patient survives the 24–28 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48-72 hours. Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered.[3]

In our cases, all of the patients were observed intensively in pediatric intensive care unit and treated according to WHO protocol. In case number 2 and 3 transfusions of fresh frozen plasma were indicated considering the abnormal coagulation profiles. In case 2 packed red cells transfusions were given individually according to the patient's conditions. No complication or sequelae was found. All the involved organs recovered along with the improvement of the disease.

To make sure us for the future helping to dengue virus infection cases in 2011 "update management of dengue complication in pediatric" should be learned carefully and applied it in the community hospital.

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 a patient with severe dengue should be admitted to a 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 circulating during the period of plasma leakage. Plasma looses should be replaced immediately and rapidly with isotonic crystalloid solution or, in the case of hypotensive shock, colloid solutions (Texbox M). If possible, obtain haematocrit levels before and after fluid resuscitation.

There should be continued replacement of further plasma losses to maintain effective circulation for 24–28 hours. For overweight or obese patients, the ideal body weight should be used for circulating fluid infusion rates (texboxes J and K). 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 second) and improving end-organ perfusion – i.e. stable conscious level (more alert or less restless), urine output š 0.5 ml/kg/hour, decreasing metabolic acidosis.

Treatment of Shock

The action plan for treating patients with compensated shock is as follow (Textboxes D and N, Figure 2.2):

- 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.
- 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 2–3 ml/kg/hr, and then further depending on haemodynamic status, which can be maintained for up to 24–28 hours. (See textboxes H and J for a more appropriate estimate of the normal maintenance requirement based on ideal body weight).

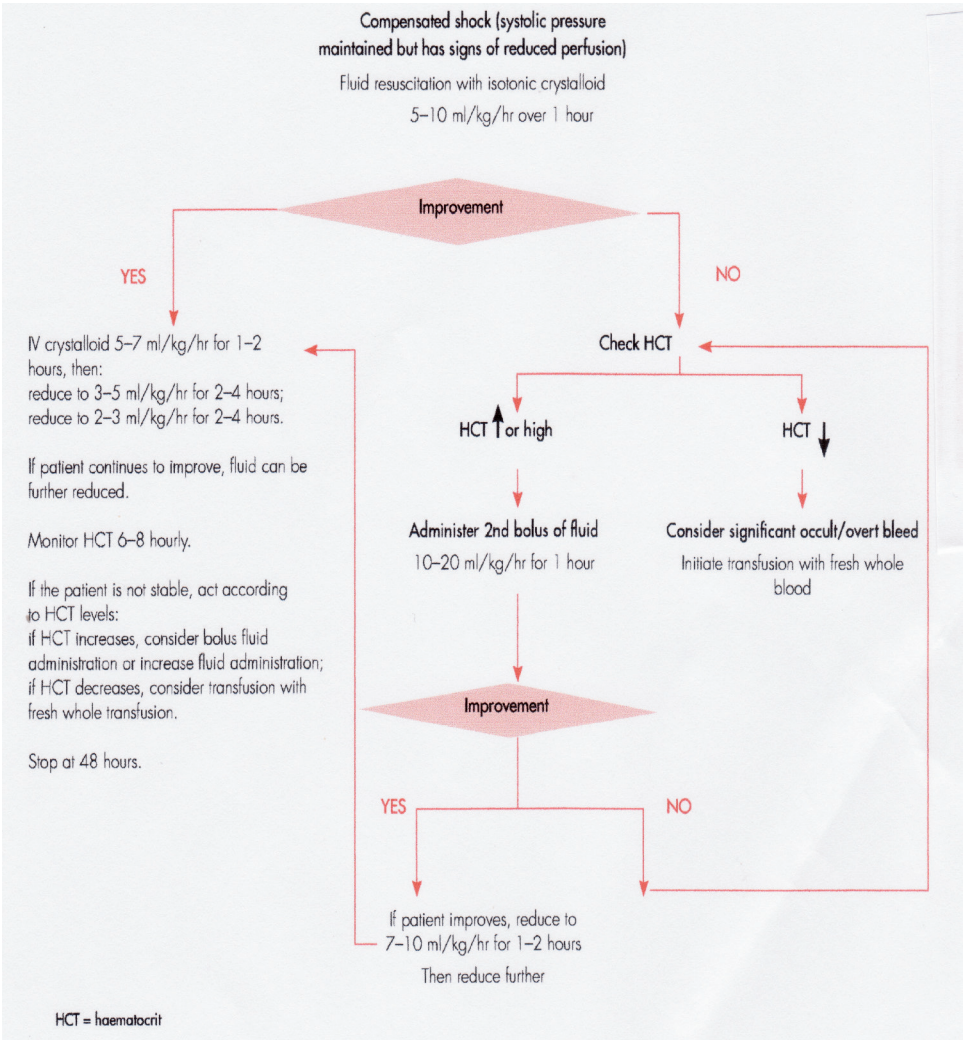

Figure 4. Algorithm for fluid management in compensated shock

- If vital signs are still unstable (i.e. shock persist), check the haematocrit after the first bolus. If the haematocrit increases or 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, reduced the rate to 7–10 ml/kg/hr for 1–2 hours, and then continue to reduce as above. If haematocrit decreases 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).
- Further boluses of crystalloid or colloidal solutions may need to be given during the next 24–28 hours.

Patients with hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is as follows (Textboxes D and N, figure 2.3):

- 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.
- 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 (textbox H).
- If vital signs are still unstable (i.e. shock persist), 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 complication).
- 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.

- If the haematocrit decreased 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 maemorrhagic complication). 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.
- 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 case 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 enables close monitoring of urine output. An acceptable urine output would be about 0.5 ml/kg/hr. 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, changed 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

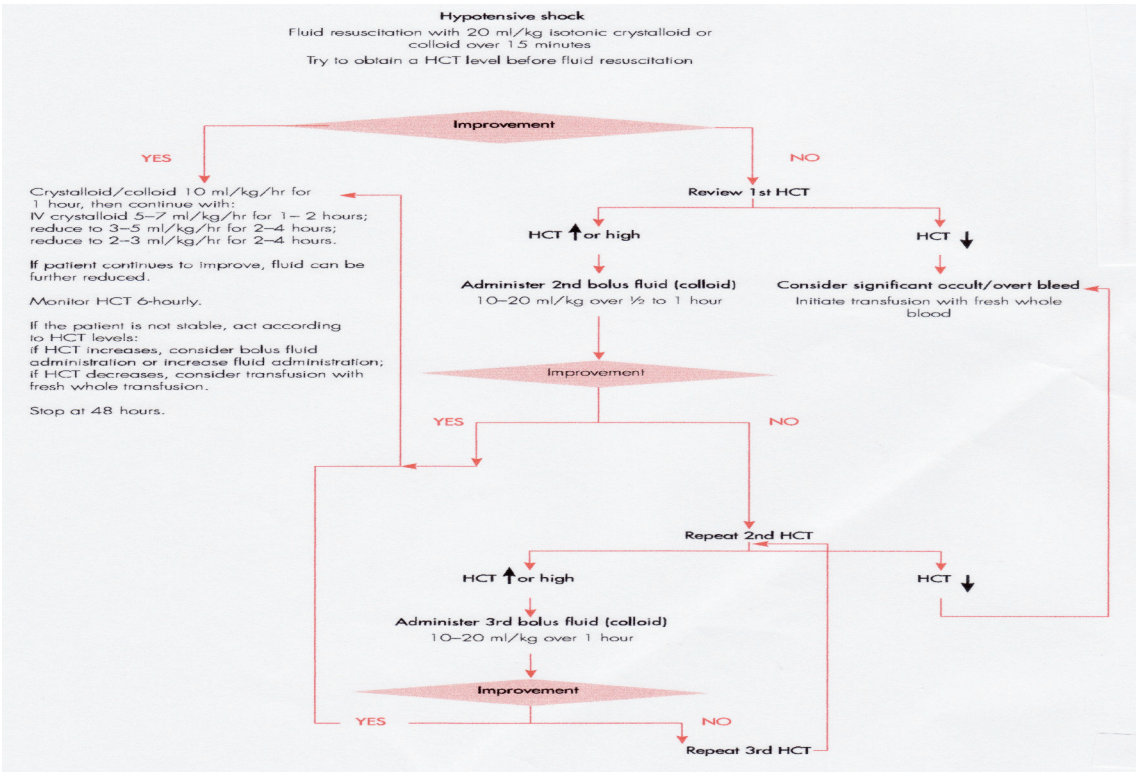

Figure 5. Algorithm for fluid management in hypotensive shock

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 discontinues immediately avoiding 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 thrombocytopaenia, 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 transfusion for severe thrombocytopaenia in otherwise haemodynamically stable patients have not been shown to be effective and are not necessary (14).

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

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

Severe bleeding can be recognized by:
- persistent and/or severe overt bleeding in the presence of unstable haemodynamic status, regardless of the haematocrit level;
- a decrease in haematocrit after fluid resuscitation together with unstable haemodynamic status;
- refractory shock that fails to respond to consecutive fluid resuscitation of 40–60 ml/kg;
- hypotensive shock with low/normal haematocrit before fluid resuscitation;
- persistent or worsening metabolic acidosis ± a well-maintained systolic blood pressure, especially in those with severe abdominal tenderness and distention.

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 (15), 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 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 loos 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 practiced when massive bleeding can not be managed with just fresh whole blood/fresh-packed cells, but it may exacerbate the fluid overload.
- Great care should be taken when inserting a naso-gastric tube which may cause severe haemorrhage and may block the airway. A lubricated oro-gastric tube may minimize the trauma during insertion. Insertion of central venous catheters should be done with ultra-sound guidance or by a very experienced person.

Treatment of complications and other areas of treatment

Fluid overload

Fluid overload with large pleural effusions and acites 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 texbook of clinical care for futhure guidance on management).

Causes of fluid overload are:
- Exessive and/or too rapid intraveneous fluids;
- Incorrect use of hypotonic rether than isotonic crystalloid solutions;
- Inappropriate use of large volumes of intravenous fluids in patiens with unrecognize severe bleeding;
- Inappropriate transfusion of fresh-frozen plasma, platelat concetrates and cryoprecipates;
- Continous of intravenous fluids after plasma leakage has resolved (24–48 hours from defervescence);
- Co-morbid conditions such as contingental or ishaemic heart disease, chronic lug and renal disease.

Early clinical features of fluid overload are:
- Respiratory distress, difficulty in breathing;
- Rapid breathing;
- Chest wall in drawing;
- Wheezing (rather than crepitations);
- Large pleural effisions;
- Tense ascites;
- Increased jugular venous pressure (JVP)

Late clinical features are:
- Pulmonary oedema (caugh with pink or frothy sputum ± crepitations, cyanosis);
- Irreversible shock (heart failure, often in combination with ongoing hypovolaemis)

Additional investigations are:
- The chest x-ray which shows cardionegaly, pleural effusion, upward displacement of the diagphragm by the ascites and varying degress of : bat's wigs" appearance ± Kerley B lines suggestive of fluid overload and pulmonary oedema;
- ECG to exclude ischaemic changes and arrhythmia;
- Arterial blood gases;
- Echocardiogram for assessment of left ventricular function, dimensions and tegional wall dyskenia that may suggest underlying ishaemic heart disease;
- Cardiac enzym.

The actions plan for the treatment of fluid
- Oxygen therapy should be given immediately.
- Stopping intravenous fluid therapy during the recovery phase will allow fluid in 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:
- Sign 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.

- 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 continous infusion of furosemide 0,1 mg/kg/ hour. Monitor serum potassium and correct the ensuing hypokalaemia.
- If the patient has stable haemodynamic status but is still within the critical phase, redusce the intraveonous fluid accordingly. Avoid diuretics during the plasma leakage phase because they may lead to intravascular volum depletation.
- Patients who remain in shock with low or normal haemotocrit levels but show signs of fluid overload may have occult haemorrhage. Futher infusion of large volumes of intravenous fluids wil lead omly to a poor outcome. Careful fresh whole blood transfussion should be initiated as soon as posible. If the patient remains in shock and th haemocrit 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 melitus and/or hypoglycaemic agents. Electrolyte and acid-base imbalance 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 pHš 7.15) can occur. One should also be alert for co-infections and nosocomial infections.

Supportive care and adjuvant therapy

Supportive care and adjuvant therapy may be necessary in severe dengue. This may include:
- Renal replacement therapy, with a peference to continous veno-venous haemodialyis (CWH), since peritoneal dialysis has arisk of bleeding;
- Vasopressor and therapies as temporary measure to prevent life-thrething hypotension in dengue shock ang during induction for intubation, while correction of intravascular volume is being vigorously carried out;

- Futher treatment of organ impairmant, such as severe hepatic involvement or encephalopathy or enchepalitis;
- Futher 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 antravenous immunoglobulins, or of recombinant Activated factor VII.

Refer to standard textbook of clinical care for more detailed information regarding the treatment of compilations and other areas of treatment.

SUMMARY

In 2009, the study Dengue Virus Infection in Patient at Dr. Soetomo hospital found a new serotype variant, it was subtype DEN I and phylo genetic study showed as DEN I genotype IV that correlated with phylo genetic dengue virus came from China which had severe clinical performance of Dengue Virus Infection. Three cases of dengue with unusual manifestations have been reported.

Two classification systems have been applied to address clinical assessment of our patients. Based on the WHO classification, one of our cases did not fulfill the DHF criteria (WHO 1997). By applying the new revised dengue classification all the cases were classified as severe dengue. Several warning signs were present in all patients before their conditions deteriorated. The new revised dengue classification could have helped in detecting severe dengue cases earlier and thus provide the clinicians time to manage severe dengue cases better. All the patients were treated according to WHO protocols and all of the involved organs recovered along with the improvement of the disease.

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