AN OBESE GIRL WITH COMPLEX SEVERE DENGUE: UNCOMPENSATED DENGUE SHOCK SYNDROME, DIC, MASSIVE BLEEDING, SEVERE LIVER INVOLVEMENT, AND RESPIRATORY FAILURE

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ESPID Annual Meeting, Madrid

2017

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INTRODUCTION

Dengue infection is one of international health problem which a half of the world's population is now at risk and severe dengue is a leading cause by serious illness and death among children.[1] Patients with prolonged or uncorrected shock may develop a more complicated course with metabolic acidosis and electrolyte imbalance, multiple organ failure, and severe bleeding from various organs.[2] Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection have been increasingly reported in DHF and also in dengue patients who do not have evidence of plasma leakage. These unusual manifestations may be associated with coinfections, comorbidities or complications of prolonged shock.[3]

Each year, more than 250,000 cases of DHF/DSS are reported from an estimated 50 million dengue infections.[4] In 20-30% of DHF cases, the patient develops shock. Mortality rates from 1% to 5% are usually quoted for DHF/DSS from centers experienced in fluid resuscitation, but rates up to 44% have occasionally been reported with regard to established shock.[5] In 2004-2005 study of malavige in Srilanka, 15 patients with dengue infections developed encephalopathy. Eight (60%) had grade III and seven (40%) had grade IV DHF. Eleven (73%) patients had evidence of acute liver failure, Eight patients developed severe respiratory distress due to pulmonary oedema. Electrolyte abnormalities were seen in 80%, and shock 40%. 5 cases (33.3%) seizure. Five patients developed disseminated intravascular coagulation (DIC). There children had mortality rate 47%.[6] Data from hospitalized children in the six Indonesia teaching hospitals. During a period of 2008 – 2013, 13.940 children treated with dengue infection include 2165 patients with dengue shock syndrome.[7]

Blood vessels and platelets are the two main end organs involved in dengue, intravascular volume gets contracted and leads to shock in severe cases. Increased vascular permeability is the hallmark pathophysiology. Thrombocytopenia and hemoconcentration are constant findings in DHF.[8] In a small proportion of cases the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation (DIC).[9] Massive bleeding due to DIC and hepatic failure after prolonged shock is another characteristic of severe and complicated DHF patients before death.[10] In the pathogenesis of DHF, the participation of DIC which is more frequent in severe established shock, has been suggested by concomitant thrombocytopenia, increased fibrinogen degradation products (FDP), decreased fibrinogen levels, and prolonged partial thromboplastine time (PTT).[11]

Obese children have a higher risk of contracting dengue with more unusual presentations; encephalopathy, associated infections and complications of fluid overload.[12] Some studies found that patients with excessive body weight were at increased risk for more severe DHF.[13]

Intensive supportive care is the most important aspect of management. Early recognition of the disease and careful monitoring for circulatory disturbance are essential. Optimal fluid therapy to maintain the functions of the vital organs during the critical period and effective control of bleeding episodes will lead to favorable outcomes.[14] Children referred late were harder to resuscitate. The bleeding usually improves rapidly during the recovery phase.[10] 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.[15]

The purpose of this case report is to present a case of recurrent shock and massive bleeding in an obese child where proper management ended up to full recovery.

CASE REPORT

A 10 year-old girl, was admitted on May 24th 2016, with the chief complaint of high fever since 4 days before admission. Patient developed a suddenly high temperature between 39-41°C which responded to antipyretic. Fever was associated with headache, myalgia, arthralgia, retro-orbita pain, nausea and vomiting, decreased appetite, weakness and clammy extremities. On the third day of illness, she had diffuse abdominal pain, repeated vomiting, decrease in temperature and headache. She was still awake but appeared weak. No cough and runny nose, no rash, no diarrhea, no bleeding, no history of drugs consumptions except antipyretic were reported. The patient already went to emergency room on the second day of illness and suspected for dengue fever; however she was treated ambulatory with instruction for serial laboratory examination.

This patient experienced proven dengue infection in 2013 at the age of 7 years, with chief complaint of fever, nausea, and trombocytopenia, was therefore hospitalized for 5 days.

From the family history there was no disease noted. No one had the same symptoms like her in the family. In her school there were two students suffered for dengue fever. The school environment have a lot of plant and mosquitoes breed in the area. She has 2 sisters who had normal nutritional state. But her parents were obesity.

She was delivered spontaneously, from healthy mother. Helped by doctor. The gestation age was 32 weeks and her birth weight was 1700 gram. She was exclusively breastfed until 22 months old. The immunization was completed. The growth and development were normal. She was able to stand at age 10 months old and to walk by herself at age 14 months old, talk fluently at age 18 months old. She was studying at junior high school. She doesn't like outdoor activity and prefer stay at home and library.

Physical examination presented an alert girl, with body weight 49 kg and height 141 cm, with percentage of ideal body weight was 150%. Body mass index was 24.74. The blood pressure was 90/60 mmHg, the pulse was 140 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 37.4°C. The girl looked weak. No anemia, cyanosis or dyspnea was observed. The chest was symmetric, no retraction was observed. The heart and lungs were normal. The abdominal examination, there was liver enlargement 4x4x3 cm, sharp edge, normal consistency, tenderness. The extremities were clammy, wet and capillary refill time was three seconds. Rumple leede test was positive. Less urine production in the last 24 hours (urine production ~0.8cc/kgbw/hr).

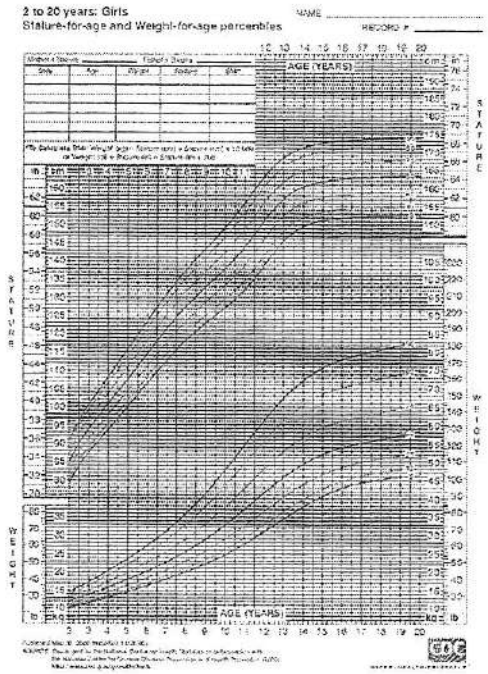


Figure 2.1 CDC Growth Chart of 10 year-old girl. IBW 35 kg, % IBW 140%

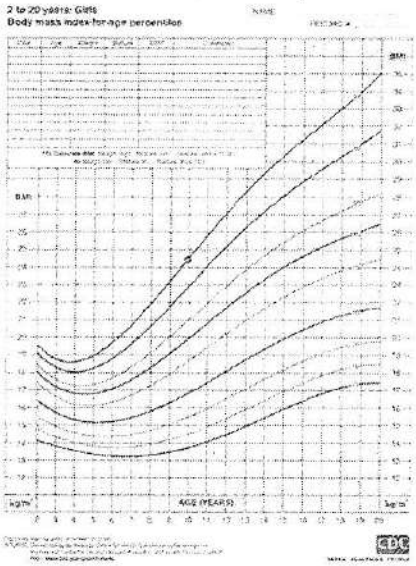


Figure2.2 Body Mass Index of a 10 year-old girl. BMI was 24,74 ($P_{>95}$); Obesity

Based on the history taking and physical examination we suspected this patient with dengue hemorrhagic fever grade III, we planned a laboratory examination and chest xray. The result were Hb 15.5 g/dl, hematocrite 47.3 %, leucocyte 1830 cells/mm^3 and platelet was 17.000 cells/mm^3. BUN 11 mg/dl, creatinine serum 0.92 U/L, alanine aminotransferase 91 U/L, aspartate aminotransferase 593 U/L, APTT 48.6 seconds, PPT 12 seconds, electrolite serum sodium 135 mmol/L, pottasium 3.9 mmol/L, chlorida 106 mmol/L and Calsium 7.6 mmol/L. Chest radiography result right pleural efusion.

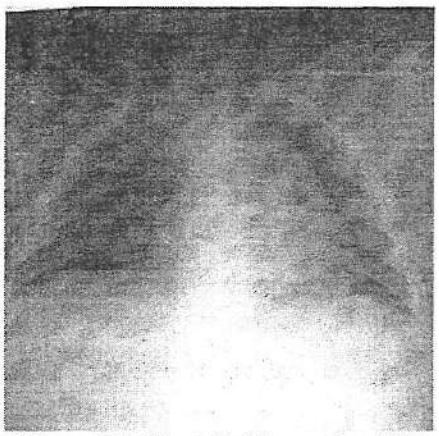


Figure 2.5 Chest Radiography AP

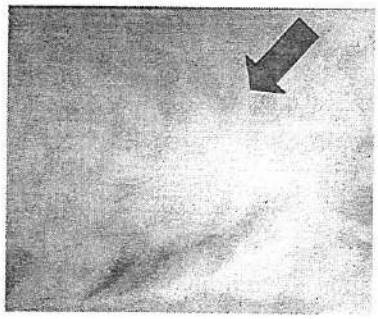


Figure 2.4 The chest roentgenogram (right lateral decubitus) showed pleural effusion on the right hemithorax

This patient diagnosed as DHF grade III and obesity. The patient was hospitalized and submitted to a management protocol for DHF grade III. She was given O_2 nasal 2 lpm and intravenous saline solution. Which was RL 350 cc/hr gived twice then RLD5% 245cc/hr (7cc/kg/hr) evaluation for the vital sign, then continued with RLD5% 175cc/hr (5cc/kg/hr) for two hours then followed RLD5% 5 105cc/1hr (3cc/kg/hr) until stable vital sign.

During the first 24 hours of hospitalization the patient had episodes of epistaxis, right upper abdominal pain and vomiting, and once period of hypovolemic shock. The Fluid Balance was excess 1540 cc/24hr.

May 25th 2016 (5th DOI)

In the morning the patient got abdominal pain at right uppper region, nausea but no fever. She was concious. Epistaxis about 30 cc from the right nose. Physical examination presented an alert girl, with blood pressure was 90/60, the pulse was 120 times per minute, the respiratory rate was 28 times per minute and the axillary temperature was 36.7 $^{\circ}$C. Bleeding from the right nose. The extremities red, warm and capillary refill time was 2 seconds. Serial laboratory examination was planned. The lab examination result (10.05 AM) were Hb 14.6 g/dl, hematocrite 45%, leucocyte 9730 cells/mm^3 and platelet was 14.660 cells/mm^3. Urine production 1400 cc for 24 hours equal to 1.2cc/Kgbw/hr. Patient got Asering 5 equal to 3cc/kg/hr and FFP tranfusion about 350 cc

At (17.20 PM), the patient got dyspnea, no fever, abdominal pain, 50 cc of hematemesis. Physical examination presented an alert girl, with blood pressure was 90/70 mmHg, the pulse was 168 times per minute, the respiratory rate was 32 times per minute and the axillary temperature was 36.7°C. Capillary refill was 4 seconds. The result of laboratory test were Hb 13.84 g/dl, hematocrite 42.3%, leucocyte 13520 cells/mm^3 and platelet was 14.600 cells/mm^3. Partial protrombine time 14.30 seconds (9-12 sec), Activated partial protrombine time 63.10 seconds (21-31 sec). Urine production 300 cc for 6 hours equal to 1cc/Kgbw/hr.

The patient got coloid (Gelofucin) 350 cc/hr continued to Asering 5 7cc/hr then 5cc/kgbw/hr and 3cc/kgbw/hr. Patient gived trombocyte tranfusion 7 unit and dobutamine equal to 5 mcg/kg/minute was given to the patient.

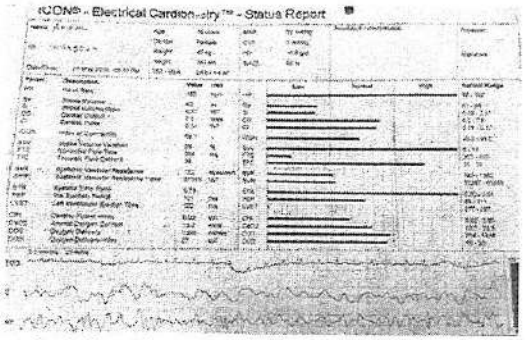


Figure 2.5 Electrical Cardiometry of 10 year-old girl with DHF grade III

At (01.00 AM), an actived bleeding from left and right nose was occured about 50 cc an still on going when the otolaryngologist came about 30 cc, it took 30 minutes. It stopped with anterior tamponade. There was also 200 cc of hematuria. Physical examination presented an alert girl, with blood pressure was 110/85, the pulse was 144 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 37°C. Clammy extremities and capillary refill time was 3 seconds. Whole blood tranfussion 350 cc was given. The fluid balance for 24 hours was excess 1785 cc/24 hours.

May 26th, 2016 (6th DOI)

The patient with hematemesis 30cc, abdominal pain, no fever, bleeding from nose 30cc, and melena 50 cc.

Physical examination presented an alert girl, with blood pressure was 100/50, the pulse was 140 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 37.5°C. Bleeding from the right nose. The chest was symmetric, no retraction was observed. The heart and lung were normal. The abdominal examination, hepatomegaly. Size was 4x4x3 cm, sharp edge, normal consistency, tenderness. The extremities still in good perfusion. Urine production was 250 cc/5hr equal to 1 cc/kgbw/hr.

Serial laboratory examination was planned. The result (08.45 AM) were Hb 10.6 g/dl, hematocryte 31.9%, leucocyte 16690 cells/mm^3 and platelet was 53000 cells/mm^3, BUN 25 mg/dl, creatinine serum 1.33 U/L, aspartate aminotransferase 3251 U/L, alanine aminotransferase 1255 U/L, albumin 3.6 mg/dL, Protrombine time 15.7 seconds (9-12 sec) Antiprotrombine time seconds 48.30 (21-31 sec), IgM Dengue (-), IgG Dengue (+). Laboratory result at 01.20 pm were Hb 9.2 g/dl, hematocrite 26.4 %, leucocyte 16950 cells/mm^3 and platelet was 68000 cells/mm^3, partial protrombine time 13.8 sec (9-12 sec), activated partial thromboplastin time 49.3 sec (21-31 sec), electrolite serum sodium 133 mmol/L, pottasium 4 mmol/L clorida 99 mmol/L and Calsium 7.6 mmol/L.

She got O_2 mask reservoar 6 lpm, Asering-5 solution 105cc/hr (3cc/kg/hr), thrombocyte transfusion 7 unit, ranitidin 2x40 mg iv, dobutamin equal to 5 mcg/kg/min, termoregulation with paracetamol iv, cefotaxime 3 x 1 gr and vitamin K inj for 3 days. The patient was fasting until evaluation of the hematemesis. Patient was moved to icu.

At 06.30 PM the patient looked pale, weak, a long with blood pressure was 115/50, the pulse was 130 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 37°C. Capillary refill time was 2 seconds. Laboratory result were Hb 6.4 g/dl, hematocrite 18.2%, leucocyte 10.500 cells/mm^3 and platelet was 194.000 cells/mm^3. We planned to give PRC transfusion.

At 07.00 PM the patient got dypsnea, decreased of consiousness, hematemesis about 250 cc. Physical examination presented delirium, GCS E3V4M5 with hemodinamyc blood pressure 82/25mmHg, pulse 166 times per minute, the respiratory rate was 48 times per minute and the axillary temperature was 37.5°C. The girl looked weak, anemic, tachypneic associated with nasal

flaring. The chest was symmetric, retraction on suprasternal and intercostal was observed. The heart was normal and lung we found rhales in bilateral hemithorax. The abdominal was distended, abdominal sound was decreased, shifting dullness was positive. The capillary refill times was 3 seconds. From chest xray founded lung edema. At 08.00 PM, lab test result Hb 6.8 g/dl, hematocrtite 21, lactate 3.6 and Blood gas analysis pH 7.503/$pCO_2$35.1/$pO_2$45.9/ HCO_3 27.8/BE 4.4/SaO_2 84.8%. Fluid balance for 24 hours was excess 976 cc/24 hours.

This patient got intubated with ETT no 6.5 with cuff and was give dobutamin equal to 8 mcg/kg/min, vasopressin NE 50 nanogram/min and furosemide 3 x 15 mg iv, and 350 cc of whole blood tranfusion. We established this patient with expanded dengue syndrome with liver involvement, acute kidney injury stage injury and obesity.

May 27th 2016 (7th DOI)

Patient with oxygen ventilator support, bleeding from the orogastric tube about ± 100 cc, last bloody stool was the day before. Physical examination presented patient was on sedasion, with blood pressure was 107/50, the pulse was 138 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 38°C. The girl looked weak and pale. Bleeding from the orogastric tube. The chest was symmetric, no retraction was observed. The heart and lung were normal. The abdominal examination, distended, abdominal sound was normal, shifting dulness (+), organomegaly was hard to evaluation. The extremities still in good perfusion with capillary refill time was 2 seconds. Urine production for 24 hours 1850cc ~ 2.2 cc/kgbw/hr.

Serial laboratory examination was planned. The result (09.46 am) were Hb 5.81 g/dl, hematocrite 17.3 %, leucocyte 12.400 cells/mm^3 and platelet was 141.000 cells/mm^3, fibrinogen 185.4 (150-450). Electrolite serum sodium 137 mmol/L, pottasium 3.2 mmol/L, clorida 97 mmol/L and Calsium 7.4 mmol/L, Mg 1.9 mmol/L, albumin 3.2 mg/dL. Partial protrombine time 12.6 (9-12 sec), Activated partial protrombine time 61.6 (21-31 sec). The result (06.26 pm) were Hb 6.4 g/dl, hematocrite 17.3 %, leucocyte 10500 cells/mm^3 and platelet was 194.000 cells/mm^3, D-dimer 3812.68 (500 ng/ml), fibrinogen 184.5 (200-400), lactat 2.3. From laboratory result Blood gas analysis pH 7.561/pCO_2 30.6/pO_2 295.5/HCO_3 27.7/BE 5.8. At 21.00 pm ; Hb 7.1 g/dl, hematocrite 21 %, electrolite serum sodium 132 mmol/L, pottasium 3.1 mmol/L, clorida 102 mmol/L and Calsium 6.8 mmol/L, lactat 3.6. Fluid balance 24 hours was deficit 208cc/ 24 hours.

This patient with ventilator support ASV. She also got D12.5% 1.5cc/kgbw/hr, FFP and PRC transfusion, ranitidin 2x40 mg iv, vit K 1 x 10 mg im for 3 days, cefotaxime 3x1 gram, adrenalin syr pump, and dobutamin ~ 8 mcg/kg/min, furosemide syr pump 100 mg/24hr.

Figure 2.6 An Obese 10-year-old girl with Expanded Dengue Syndrome

May 28th 2016 (8th DOI)

Patient with oxygen ventilator support, melena once time anout 50 cc, no more bleeding from orogastrictube. She was conscious these day.

Physical examination presented patient alert girl, with blood pressure was 107/50, the pulse was 126 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 38.5°C. The girl looked anemic. The chest was symmetric, no retraction was

observed. The heart and lung were normal. The abdominal examination, slight distended, abdominal sound was normal, organomegaly was hard to evaluation. The extremities still in good perfusion, with capillary refill time was 2 seconds.

Laboratory test result (09.02 am) were Hb 8.0 g/dl, hematocrite 23.5 %, leucocyte 8720 cells/mm3 and platelet was 223.000 cells/mm3, aspartate aminotransferase 1642 U/L, alanine aminotransferase 340 U/L, APTT 39.8 sec (25.2 sec), PPT 11.7 sec (10.3 sec), electrolite serum sodium 145 mmol/L, pottasium 2.9 mmol/L clorida 105 mmol/L and Calsium 7.8 mmol/L and blood gas analysis pH 7.49/pCO_2 38/pO_2 97/HCO_3 29 /BE 5.7/SaO_2 98.

Ventilator setting was ASV mode. This patient got D12.5% ~1.5cc/kg/hr, ranitidin 2x40 mg iv, vit K 1 x 10 mg im, cefotaxime 3x1 gram, adrenalin syr pump, and dobutamin ~ 5 mcg/kg/min, furosemide syr pump 5 mg/hr, Calcium gluconas 10% 35cc iv. Fluid balance for 24 hours was deficit 560 cc/24 hours.

May 29th 2016 (9th DOI)

Patient with oxygen ventilator support, no melena, no bleeding from orogastrictube. She was concious and able to communication with her mother.

Physical examination presented patient alert girl, with blood pressure was 108/50, the pulse was 108 times per minute, the respiratory rate was 28 times per minute and the axillary temperature was 37°C. The girl looked anemic.The chest was symmetric, no retraction was observed. The heart and lung were normal. The abdominal examination, supel, abdominal sound was normal, liver was palpable 3x3x2 cm, sharp edge, normal consistency. The extremities still in good perfusion. Urine production for 24 hours was 1540 cc ~ 1.8 cc/kgbw/hr.

Figure 2.7 Ninth day of illness of patient with expanded dengue syndrome

Laboratory examination was planned. The result (09.23 AM) were Hb 8.1 g/dl, hematocrite 24.5 %, leucocyte 6680 cells/mm^3 and platelet was 213000 cells/mm^3, APTT 35.5 sec (25.2), PPT 12.1sec (10.3), electrolite serum sodium 147 mmol/L, pottasium 3.2mmol/L, clorida 117 mmol/L and Calsium 7.8 mmol/L. Blood culture result was sterile. Laboratory test result at 07.08 PM Hb 12.3g r/dL, hematocrite 37 %.

This patient got ranitidin 2x40 mg iv, vit K 1 x 10 mg im, cefotaxime 3x1 gram, adrenalin syr pump, and dobutamin equal to 5 mcg/kg/min, furosemide syr pump 5 mg/hr, Calcium gluconas 10% 35 cc iv.

These day the patient got improved, no dyspnea, stable hemodinamic, good result of blood gas analysis so we decided to extubated the endotracheal tube. She got O_2 nasal 2-3 lpm, antibiotic stop, ranitidin 2 x 40 mg iv, metamizole 3x750 mg iv, Dobutamin decreased equal to 3 mcg/kg/min, furosemid 2 x 15 mg iv. Fluid balance was deficit 250 cc/24 hours.

May 30th 2016 (10th DOI)

The patient already improved, no dyspnea, no fever, consious, no bleeding, had good appetite. These day the patient moved to PICU.

Physical examination presented patient alert girl, with O_2 support nasal canule 2-3 lpm. Blood pressure was 100/60 mmHg, the pulse was 90 times per minute, the respiratory rate was 30 times per minute and the axillary temperature was 36.8°C, oxygen saturation 98%. The chest was

symmetric, no retraction was observed. The heart and lung were normal. The abdominal examination, abdominal sound was normal, no organomegaly was found. The extremities still in good perfusion. Urine production for 24 hours was 1230 cc equal to 1.4 cc/kgbw/hr.

Laboratory examination was planned. The result (08.40 AM) were Hb 12.0 g/dl, hematocrite 36.7 %, leucocyte 7660 cells/mm^3 and platelet was 233000 cells/mm^3, APTT 35.5 sec (25.5 second), PPT 12.1 sec (10.20 second), electrolite serum sodium 143 mmol/L, pottasium 3.2 mmol/L, chlorida 117 mmol/L and Calsium 8.1 mmol/L, aspartate aminotransferase 433, alanine aminotransferase 182.

This patient got ranitidin 2x40 mg iv, cefotaxime 3x1 gram stopped,, dobutamin equal to 3 mcg/kg/min (tapp off), furosemide syr pump 5 mg/hr changed to 3x15 mg iv. Fluid balance for 24 hours was deficit 285 cc/ 24 hours.

During hospitalized this patient got special nutritional therapy for her nutrition. In the 8^{th} day of illness this patient had total parenteral nutrition. Which was D12,5% 2000 cc Aminofusin 10% 32 gram equal to 320 cc equal to 128 kkal, ivelip 20% equal to 32 gram equal to 60cc (288 kkal). Maintenance Nacl 15% 35cc/24hr, Kcl 7.4% 32 cc/24hr, Cagluconas 10% 32 cc/24 hr. Then in the 9^{th} day of ilness she got parsial parenteral nutrition with tropic feeding with pepti junior 8x25cc (increased gradually), D12,5% 1000cc Aminofusin 10% 32 gram equal to 320 cc equal to 128 kkal, ivelip 20% equal to 32 gram equal to 60cc (288 kkal). Maintenance Nacl 15% 35cc/24hr, Kcl 7.4% 32 cc/24hr, Cagluconas 10% 32 cc/24 hr.

This patient got improved, no damage symptom presented. No dyspnea, no bleeding, alert and good appetite with the convalescence rash. After 24 hours got PICU observation this patient delivered to the ward. In 12^{th} day of illnes (3/5/2016) this patient planned to discharged and became tropic and infection out patient clinic. With the stable and good condition.

Physical examination presented patient alert girl. Blood pressure was 110/60 mmHg, the pulse was 98 times per minute, the respiratory rate was 26 times per minute and the axillary temperature was 37°C, with oxygen saturation 99%. The chest was symmetric, no retraction was observed. The heart and lung were normal. The abdominal examination, abdominal sound was normal, no organomegaly. The extremities was warm, with capillary refill time less than 2 seconds.

Last laboratory test were Hb 10.8 g/dl, hematocrite 33, leucocyte 7800 cells/mm^3 and platelet was 243000 cells/mm^3, APTT 25 sec (13-33), PPT 11.2 sec (9-12), aspartate aminotransferase 132, alanine aminotransferase 89,BUN 7 mg/dl, creatinine serum 0.65 U/L

Figure 2.9 An obese 10-year-old girl recovered from Expanded dengue syndrome

DISCUSSION

A 10 year-old girl, admitted with the chief complaint of fever since 4 days before admitted. This patient got developed a suddenly high temperature and improved with antipyretic drug, with other symptom headache, myalgia, arthralgia, retro-orbital pain, nausea and vomiting, decrease of appetite, weakness and clammy extremities. Abdominal pain and repeated vomiting occurred in the third day of illness, before lysis of the temperature. At the same time one of her schoolmate also ssuffered from dengue fever. She also had a history of dengue infection, at the age of 7 years. On physical examination the child was obese found with BMI 24.74, above the 95th percentile according to age and sex. The vital sign showed tachycardia with a pulse rate of 140 times per minute, normal respiratory rate, normal blood pressure, normal axillary temperature. The rumple leed test was positive. We also found hepatomegaly 4x4x3 cm, sharp edge, normal consistency with tenderness. Clammy extremities and bad perfusion with capillary refill time equal to 3 seconds. With insufficient urine production in 24 hours (equal to 0.8 cc/kg/hr).

We performed laboratory and radiology examination to establish the diagnosis. From the laboratory result hemoconcentration and thrombocytopenia. Increased of liver function test, prolonged of blood coagulation, and hypocalcemia. Right pleural effusion showed in the right lateral decubitus chest radiograph.

The patient came to the emergency ward on the fourth day of illness with symptomatic dengue infection. Evidence of plasma leakage were hemoconsentration, right pleural efusion. Rumple leede test was positive, and thrombocytopenia was evident. From the hemodynamic we found compensated dengue shock syndrome. According to WHO definitions of Dengue Hemorrhagic Fever, the criteria in this patient was appropriate as dengue hemorraghic fever grade III.

Expert consensus groups have suggested that dengue is a single entity with different clinical presentations and infected patients present with a range of clinical symptoms that vary according to severity and age.[16] Infection by any of the four dengue serotypes maybe asymptomatic or lead to classic dengue fever (DF) or more severe forms of the disease, haemorrhagic fever (DHF) and expanded dengue syndrome.[3]

The clinical diagnosis of DHF is based on fever and 2 or more clinical manifestations, with evidence of plasma lekeage : (i) sustained high fever lasting 2–7 days; (ii) hemorrhagic tendency such as a positive tourniquet test, petechiae or epistaxis; (iii) thrombocytopenia (platelet count $\leq$ 100.000/mm^3); and (iv) evidence of plasma leakage manifested by hemoconcentration (an increase in hematocrit $\geq$ 20% above average for age, sex and population), pleural effusion and ascites. Pleural effusion can be demonstrated by a chest X-ray in right lateral decubitus view at 12–24 hours after defervescence.[7 14]

In critical phase, the differential diagnoses include thypoid fever, hepatitis, and severe infection like bacterial sepsis, septic shock. Neoplasma or leukemia, acute abdomen, acute appendicitis, trombocitopenia and hemorrhage, renal failure, diabetes ketoasidosis. Haemorrhagic manifestations, e.g. positive tourniquet test and leucopenia ($\leq$ 5000 cells/mm^3) suggest dengue illness. The presence of thrombocytopenia with concurrent haemoconcentration differentiates DHF/DSS from other diseases. In patients with no significant rise in haematocrit as a result of severe bleeding and/or early intravenous fluid therapy, demonstration of pleural effusion/ ascites indicates plasma leakage. Hypoproteinaemia/ albuminaemia supports the presence of plasma leakage. A normal erythrocyte sedimentation rate (ESR) helps differentiate dengue from bacterial infection and septic shock.[17] It should be noted that during the period of shock, the ESR is <10 mm/hour. The hallmark of DHF is the increased vascular permeability resulting in plasma leakage, contracted intravascular volume, and shock in severe cases. The leakage is unique in that there is selective leakage of plasma in the pleural and peritoneal cavities and the period of leakage is short (24–48 hours). Rapid recovery of shock without sequelae and the absence of inflammation in the pleura and peritoneum indicate functional changes in vascular integrity rather than structural

damage of the endothelium as the underlying mechanism. In cases with shock, a high haematocrit and marked thrombocytopenia support the diagnosis of DSS.[18]

The severity of DHF is categorized into four grades. DHF grade III, circulatory failure manifested by a rapid and weak pulse with narrowing pulse pressure (≤ 20 mmHg) or hypotension, with the presence of cold clammy skin and restlessness; and grade IV, profound shock in which pulse and blood pressure are not detectable. It is note worthy that patients who are in threatened shock or shock stage, also known as dengue shock syndrome, usually remain conscious.[14]

In this case. Before the illness started the critical phase, there were warning signs that occurred in this patient, abdominal pain or tenderness and vomiting that occurred one day before the patient got shock (third day of illness). Then followed with declined temperature to 37.4°C, increased of hematocrite, leucopenia and thrombocytopenia, evidence of plasma leakage hemoconcentration and pleural effusion.

Warning signs usually precede the manifestations of shock (clinical evidence of plasma leak) and appear towards the end of the febrile phase, usually between days 3–7 of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. A rapid and progressive decrease in platelet count to about 100 000 cells/mm^3 and a rising haematocrite above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (≤ 5000 cells/mm3).[19] The warning signs mark the beginning of the critical phase. Warning Signs (risk of plasma leak high) : abdominal pain, persistent vomiting, restlessness, altered conscious level, enlarged tender, hepatomegaly, extensive mucosal bleeding.[20]

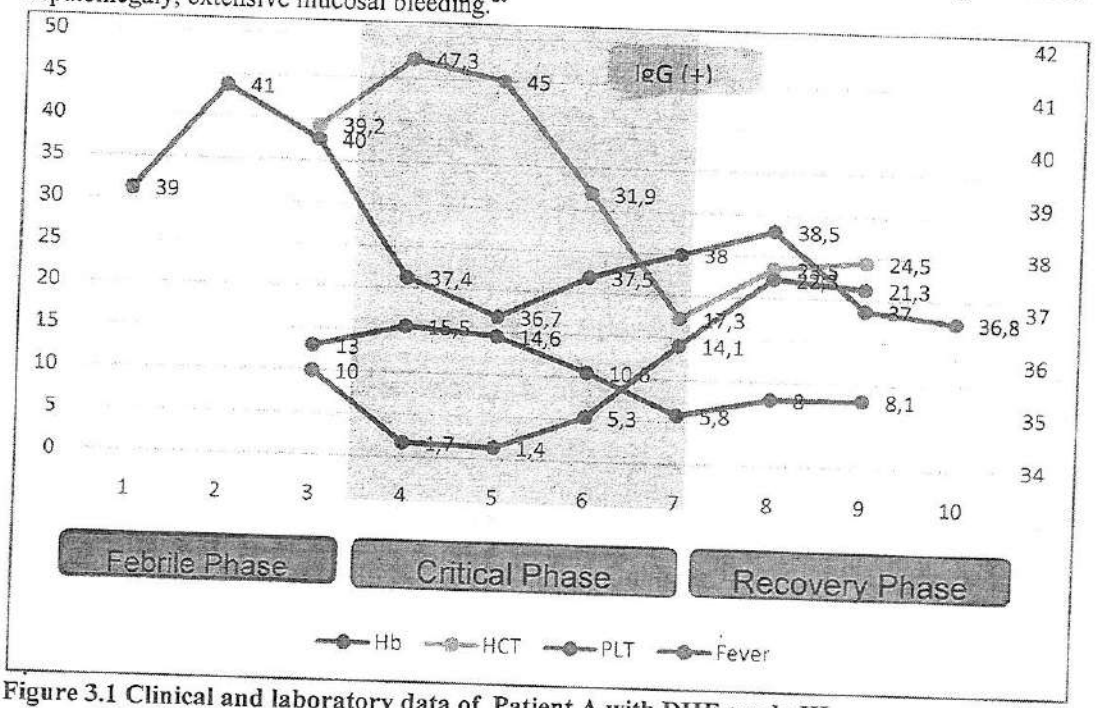


Figure 3.1 Clinical and laboratory data of Patient A with DHF grade III

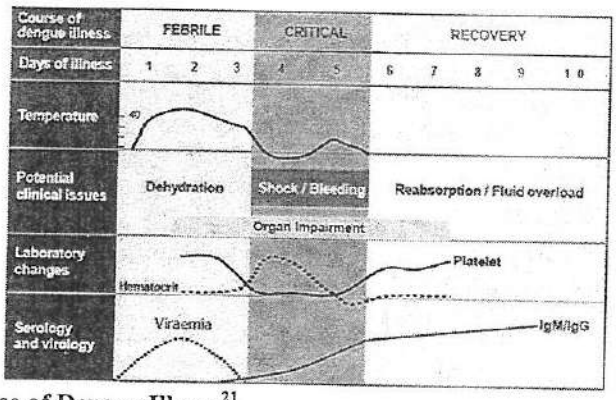
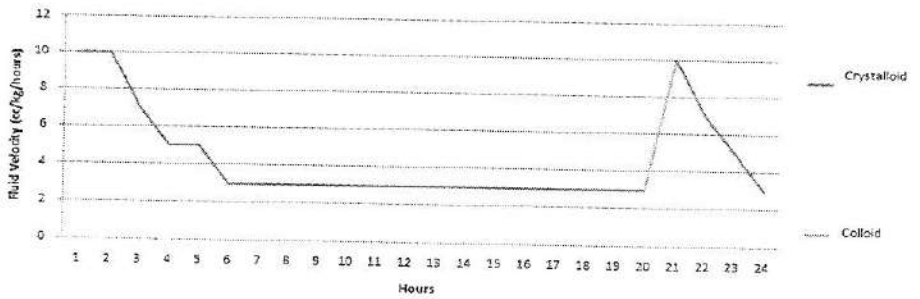


Figure 3.2 The course of Dengue Illness[21]

Lum LCS, Ng CJ, Khoo EM. Managing dengue fever in primary care: A practical approach. Malaysian Family Physician : the Official Journal of the Academy of Family Physicians of Malaysia 2014;9(2):2

According to history taking, physical examination, laboratory and radiology examination we established this patient with DHF grade III, Pleural effusion and obesity. The patient already submitted to a management protocol for Dengue Hemorrhagic Fever Grade III. She got intravenous saline solution from the emergency department. Lactate ringer solution was gived 10cc/kgbw/hr repeated twice for two hours and after hemodinamic stable continued with saline solution RLD5% 7cc/kg/hr then followed with RLD5% 5cc/kg/hr for 2 hours and 3cc/kg/hr.

This patient hospitalized in the critical phase. The important element of treatment this patient is providing intensive observation of blood pressure, hematocrite levels, platelet count, urinary output, hemorrhagic manifestations, and level of consciousness.



Hours	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time	8 am	9 am	10 am	11 am	12 am	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm	12 pm	1 am	2 am	3 am	4 am	5 am	6 am	7 am
HR	140	135	132	127	120	118	120	128	115	100	108	118	110	100	108	118	120	130	153	168	148	130	130	125
BP	90/ 50	90 /60	90 /60	100 /60	100 /60	100 /65	100 /60	100 /70	110 /60	100 /60	98 /60	95 /63	90 /60	100 /70	100 /70	100 /60	90/ 60	90/ 60	90/ 55	80/ 40	90/ 55	90/ 60	90/ 60	100 /60
Ht %	47.3					48							47								47.6			
Urine (ml)	700 /24hr			300			160			150			150			130			210			160		100
CRT	3"	2"	2"	<2"	<2"	<2"	<2"	<2"	2"	<2"	<2"	<2"	<2"	<2"	<2"	2"	2"	2"	2"	3"	2"	<2"	<2"	<2"

Figure 3.3 Fluid resuscitation on 4th day of illness Dengue Hemorraghic Fever grade III. Fluid balance was excess 1540 cc/24hr

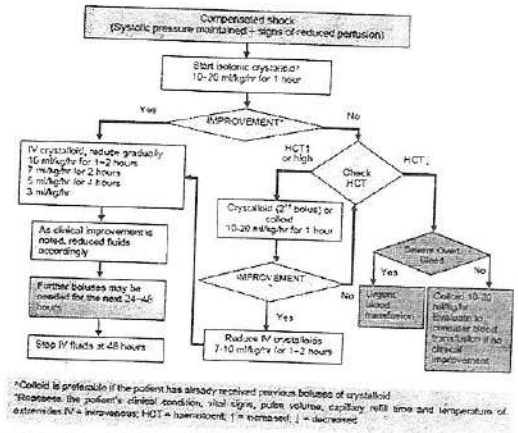
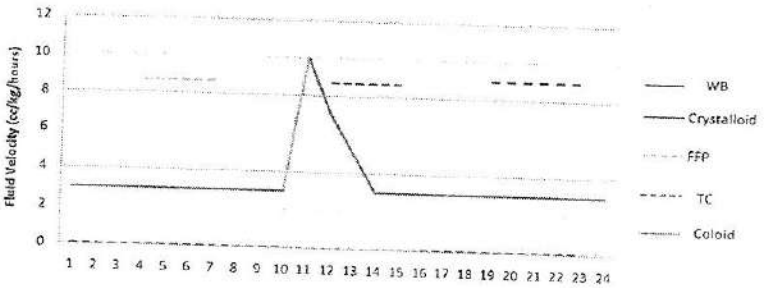


Figure 3.4 Management of compensated DHF
Addapted from : World Health Organization. Handbook for CliniCal Management of dengue.2012

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. 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 severeshock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase in patients with severe bleeding.[22]

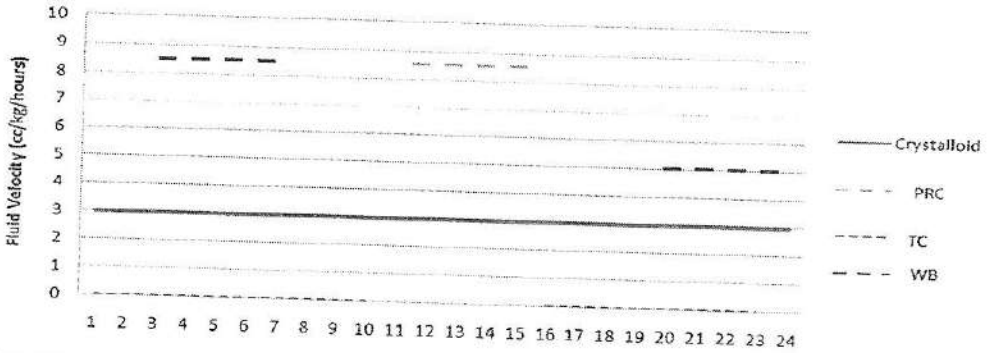
With adequate and appropriate fluid replacement, we expected the patient was stable in good condition. Monitoring this patient after the shock condition was recording of the vital signs and determination of the hematrocrit are important in evaluating the results of treatment. The following measures had taken routinely (pulse, blood pressure, capillary refill time, hemoglobin and hematocrite, fluid balance). Meanwhile under observation, there was repeat compensated shock, with the evidence of bleeding and decreased of hematocrit and hemoglobin levels showed that hypovolemic shock happened according to severe bleeding. From the 5th day until 8th day of illness, there was active bleeding and organs involved due to dengue infection. There were epistaxis, hematemesis, melena and hematuria.

Progression of the disease, there were some complication such as severe bleeding, liver involvement, and renal involvement.



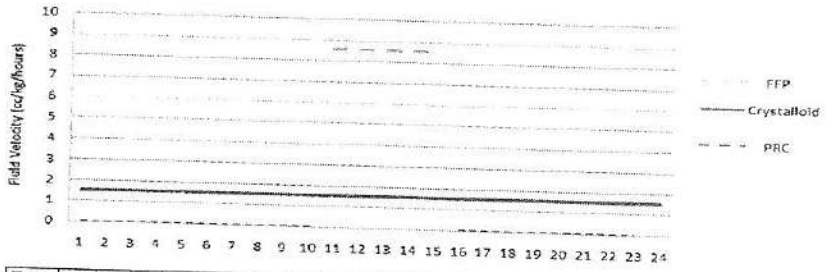
Hours	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time	9 AM	9 am	10 am	11 am	12 am	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm	12 pm	1 am	2 am	3 am	4 am	5 am	6 am	7 am
HR	120	116	120	128	128	128	120	120	130	148	140	133	120	140	136	144	136	130	136	140	136	130	130	128
BP	90 /60	100 /65	110 /68	100 /59	110 /70	100 /55	100 /60	90 /60	98 /60	90 /70	95 /60	98 /65	90 /60	110 /50	100 /70	90 /50	90/ 60	100 /50	90/ 60	100 /70	90/ 60	90/ 60	130 /70	130 /50
Ht %	43					45.2							42.3						23					
Urine (ml)	1400 Cath			100			200			100			100			100			100			100		100
CRT	2	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"	2"

Figure 3.5 Fluid resuscitation on 5th day of illness patient A with DHF grade III and obesity. Fluid balance was excess 1785 cc/24 hr.



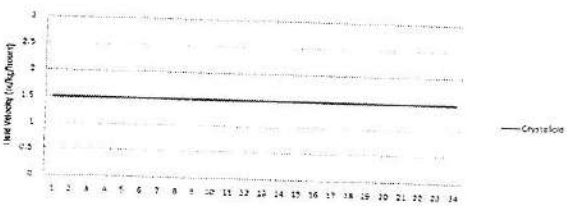
Hours	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time	8 am	9 am	10 am	11 am	12 am	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm	12 pm	1 am	2 am	3 am	4 am	5 am	6 am	7 am
HR	140	140	130	120	128	130	138	120	130	128	144	166	150	138	126	126	135	137	133	140	128	128	130	130
BP	100 /50	90 /60	90 /50	100 /60	126 /75	100 /65	100 /60	90 /60	90 /65	100 /41	115 /50	82 /25	90 /40	100 /50	110 /70	120 /50	110 /50	100 /50	90/ 65	100 /70	90/ 60	90/ 60	100 /50	100 /50
Ht %	31.9										35.2					21								15
Urine (ml)	1116 24hr			200	50				250			150		100		300			250			300		250
CRT	<2"	2"	2"	<2"	2"	<2"	<2"	<2"	2"	2"	2"	3"	2"	2"	2"	2"	<2"	<2"	<2"	<2"	2"	2"	2"	<2"

Figure 3.6 Fluid resuscitation on 6th day of illness patient A with expanded dengue syndrome and obesity. Fluid balance was excess 976 cc/ 24 hr.



Hours	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time	9 am	9 am	10 am	11 am	12 am	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm	12 pm	1 am	2 am	3 am	4 am	5 am	6 am	7 am
HR	139	140	140	130	134	130	138	130	130	126	144	140	120	140	136	130	130	132	135	140	138	128	135	130
BP	107 /50	110 /75	100 /75	100 /50	124 /85	120 /65	90 /60	90 /60	130 /85	121 /65	125 /69	136 /70	120 /90	110 /75	110 /70	110 /60	110 /60	100 /60	90/ 65	100 /70	90/ 60	90/ 60	100 /70	100 /68
Ht %	31			27.3						33			32					33						27.3
Urine (ml)	1815 24hr			270		200			150			300			182			220			260			270
CRT	2"	2"	2	2	<2"	<2"	<2"	<2"	<2"	<2"	<2"	2"	2"	2"	<2"	<2"	2"	<2"	<2"	2"	<2"	<2"	2"	<2"

Figure 3.7 Fluid resuscitation on 7th day of illness patient A with expanded dengue syndrome and obesity. Fluid balance was deficit 208 cc/ 24 hr.



Hours	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time																								
HR																								
BP																								
Ht %																								
Urine (ml)																								
CRT																								

Figure 3.8 Fluid resuscitation on 8th day of illness patient A with expanded dengue syndrome and obesity. Fluid balance was deficit 560 cc/ 24 hr.

The stage of recurrent shock was trigger or accelerate the development of disseminated intravascular coagulation (DIC). Trombocytopenia, decreased fibrinogen levels, prolonged protrombine time and increased D-dimer levels. Supported the diagnosis of disseminated intravascular coagulation (DIC). To assess the presence of disseminated intravascular coagulation in this patient, a DIC scores by International Society of Trombosis and Hemostasis (ISTH) was applied. The score was 8 compatible with overt DIC.

Table 3.1 Diagnostic Algorithm for the Diagnosis of Overt DIC[23]

1. Risk assessment : Does the patient have an underlying disorder known to be associated with overt DIC?	
If Yes : Proceed ; If No : do not use this algorithm	
2. Order global coagulation tests (platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers or fibrin degradation product)	
3. Score global coagulation results	
Platelet count (>100 – 0; < 100 – 1; < 50 – 2)	2
Elevated fibrin-related marker (eg, soluble fibrin monomers/fibrin degradation products) (No increase : 0; moderate increase : 2; strong increase : 3)	3
Prolonged prothrombin time (<3 sec : 0 ; > 3 sec ; <6 sec : 1 ; >6 sec : 2)	2
Fibrinogen level (> 1 gram/l : 0 ; < 1 gram/l : 1)	1
Calculate Score	8
If ≥ 5 : compatible with overt DIC ; repeat scoring daily < 5 : suggestive (not affirmative) for non-overt DIC	

Addopted from : Taylor FB, Jr., Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thrombosis and haemostasis 2001; 86(5):1327-30

DIC is a serious complication of the underlying primary disease. In the pathogenesis of DHF, the participation of disseminated intravascular coagulation (DIC) has been suggested by concomitant thrombocytopenia, increased fibrinogen degradation products (FDP), decreased fibrinogen levels, and prolonged PTT.[15] As a result, successful treatment of DIC is dependent on identifying and treating the underlying cause, thereby removing the triggering factors implicated in the DIC process. In some cases, successful treatment of the underlying cause will lead to resolution of DIC. In others, despite vigorous therapy directed towards the primary disease, coagulation abnormalities persist resulting in significant hemorrhage and/or thrombosis with organ damage. These patients have a high rate of mortality, and as a result, commonly receive DIC supportive therapy. There is no consensus on how supportive therapy should be used due to the paucity of data. In general, supportive care is divided into component replacement and anticoagulation therapy. Treatment is individualized based upon a patient's age, severity of clinical symptoms, underlying primary disorder, and overall clinical status.[24]

As far as replacement therapy is concerned. There have been no randomized controlled trials to study the efficacy of platelet, fresh frozen plasma (FFP), or cryoprecipitate transfusions in children or adults with DIC.[25]

The goal of replacement therapy is to reduce or stop significant bleeding. Although replacement therapy should not be used to normalize laboratory tests (which often is impossible), a reasonable guide for the judicious use of blood components in the setting of significant bleeding

includes maintaining platelet counts > 50,000 per mm^3 and fibrinogen concentration >100 mg/dL (1 mol/L).[24]

Indication for platelet transfusion : significant bleeding with thrombocytopenia or if platelet count is less than 10,000/mm^3 (10-20 mL/kg of platelets). Mild reductions in platelet counts are usually not associated with significant bleeding. Platelets return to normal within 7-9 days.

Fresh frozen plasma (FFP) is helpful in maintaining effective intravascular volume and restoring the coagulation factors. However, transfusion-transmitted disease is a constraint to be considered. Virus-inactivated FFP is not routinely available especially in economically less developed countries. Nevertheless, prompt and adequate fluid replacement to overcome massive plasma leakage is a medical emergency.[26]

Clotting factors can be replaced by either FFP or cryoprecipitate. FFP provides both procoagulant and anticoagulant proteins and is administered every 12 to 24 hours at a dose of 10 to 15 mL/kg per infusion. Cryoprecipitate has higher concentrations of factor VIII and fibrinogen, and can be used to correct hypofibrinogenemia. It is administered every 6 hours as needed at a dose of 10 mL/kg per infusion. Platelet transfusions are administered with a goal of maintaining the platelet counts >50,000 per mm^3. Repeat transfusions may be necessary. The theoretical concern of replacement therapy increasing thrombotic risk by "adding fuel to the fire" has not been demonstrated, and should not dissuade the clinician from administering replacement therapy to control significant bleeding. Clinicians should monitor for volume overload in patients who receive factor replacement. [24]

The progression of the illness showed that the dengue infection involved some organ damage include hepato and renal involvement also DIC. There were unusual manifestations of dengue infection. Liver involvement in dengue can range from asymptomatic elevation of liver enzymes to fulminant hepatic failure. In the 4th day of illness there was elevation of liver enzymes and prolonged of coagulation factor, and it still increased until the 8th day of illness. Renal involvement in this case presented due to a pre-renal acute kidney injury (AKI) and happened related to the dehydration, bleeding and fluid loss. According to the unusual manifestation, in the end diagnosis this patient diagnose as expanded dengue syndrome and obesity.

Expanded dengue syndrome is a terminology developed in the WHO guidelines of year 2012. Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection has been increasingly reported in dengue hemorrhagic fever (DHF) and also in dengue patients who do not have evidence of plasma leakage. These unusual manifestations maybe associated with co-infections, co-morbidities or complications of prolonged shock and can be clubbed under the expanded dengue syndrome. The unusual manifestations may be underreported or unrecognized or not related to dengue.[8]

There were some of risk factors that influenced for DHF infection in this patient. First, ten years old girl, obesity, with secondary infection were individual risk factors. Second, she lived in endemic area, high vector density and high susceptible group of dengue infection. Third, more frequent of dengue infection increased viral strain virulence and possibility of dengue infection with different serotype. It could be the underlined of possibility severe dengue infection in this patient. The severity related to the risk factor that belongs to this patient which is obesity and secondary infection.

Epidemiologic studies have identified young age, female sex, high body-mass index, virus strain or virulence and genetics of the human host as risk factors for severe dengue.

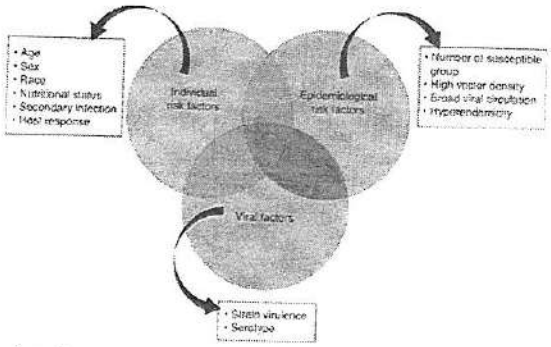


Figure 3.9 Risk factors for dengue haemorrhagic fever
Addapted from : Guzman MG, Kouri G. Dengue: an update. Lancet Infect Dis.2002;2:33–42.

Dengue, an arthropod-borne viral infection of humans, is endemic to tropical and subtropical regions of the world and represents an important public health problem. Dengue viruses are transmitted by the bite of the *Aedes aegypti* mosquito infected by the one of the four dengue virus serotypes: dengue-1, -2, -3, and -4. [27]

From the laboratory serology of dengue infection in 6th day of illness gived positive result for Ig G dengue. The high level of Ig G antibodies increased the possibility of secondary infection of dengue virus. Lower IgM levels in secondary infection could be a false negative. This patient had history of dengue infection that proven by a serology lab in 2013. Ig M and Ig G dengue was positive at that time.

In general, diagnostic of dengue is dependent on the phase of the infection, current dengue diagnostics are based on either detection of viral agent (antigen/genome) or antibodies (IgA/IgM/IgG) produced against it.[28] NS1 circulates in the serum from 1 to 9 days after the onset of clinical signs, with a peak from 3 to 5 days.[29] Understanding the features of host humoral immune response is important for the interpretation of dengue infection. A primary antibody response is observed in individuals who are not immune to dengue and a secondary immune response is observed in patient who have had a previous dengue infection. In primary infection, IgM antibodies develop by 3-10 days after the onset of infection and reach its peak level ~ 2 weeks later. IgM generally decline to undetectable levels over the next 2-3 months.[30] IgM levels are significantly lower in secondary dengue infections and thus some anti-dengue IgM false-negative reactions are observed during secondary infections. After the end of first week of infection, IgG is detectable at low titre and slowly increases, and persists for life. By contrast, during the secondary infection, high level of IgG antibodies is detectable even in the acute phase and rapidly rises over the following 2 weeks.[31]

Generally, the greatest risk for DHF is thought to be with the second virus serotype exposure (although this risk may also be affected by the particular serotype and sequence of infection). There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.

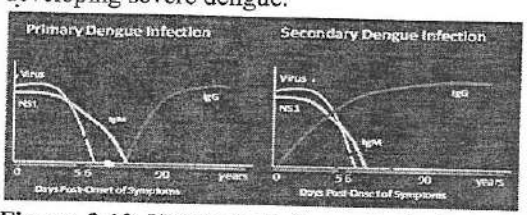


Figure 3.10 Virological & serological markers of dengue infection according to time of illness[32]

Addapted from : Organization WH. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: WHO, 2009

Some studies found that patients with excessive body weight were at increased risk for more severe DHF.[13] Patients with obesity are at risk of undertreatment or over-treatment in terms of intravenous fluid replacement. Also, the venous access is difficult especially during the critical period of the toxic stage. Compared with malnourished patients or patients with normal weight for age, overweight patients are more susceptible to have a severe degree of DHF.[33] Fluid estimation in obese patients is more difficult and IV fluid based on BW may be too much for obese patients and may relate to the higher complication rate for fluid overload seen in obese patients. The thick thoracic wall may add to the observed signs and symptoms of fluid overload in these obese individuals.

Obese children are expected to have a stronger immune response than normal children, so they are at higher risk of developing DF/DHF. Rashes, including petechii, maculopapular and convalescence rashes, were more commonly observed in obese patients. This suggests that obese patients have a stronger immune response, since rashes are usually the result of interactions between host cells and infected viruses. Liver enlargement, which was less often palpated in obese patients, possibly due to the thick abdominal wall.[13]

Obese patients resulted in the larger number of encephalopathy cases observed in obese patients. Most of the encephalopathy cases in DHF had a hepatic cause. Associated infections, pneumonia, diarrhea, UTI, and phlebitis were more commonly observed in obese patients. This may be due to more complications of fluid overload seen among them and the need for more invasive interventions, making them bed-ridden and more prone to nosocomial infections.

This patient survives from her critical phase and had eritematous rash on 9 days of illness. From the examination the patient got improved, appetite returns, hemodynamic stabilizes. Laboratory on last day was normal.

As 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 have a confluent erythematous or petechial rash with small areas of normal skin, described as "isles of white in the sea of red". Some may experience generalized pruritus. The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count.[3]

SUMMARY

A case of massive bleeding in an obese child with dengue shock syndrome has been reported. Patient admitted with dengue hemorrhagic fever grade III and develop to unusual manifestation such as severe organ involvement like liver and kidney. Reccurent hypovolemic shock and massive bleeding of the patient had relation. Stage of recurrent shock was trigger or accelerate the development of disseminated intravascular coagulation (DIC). This unusual manifestation may be associated with co-infections, co-morbidities or complications of prolonged shock and can be clubbed under the expanded dengue syndrome.

The important element to manage the critical phase of DHF/DSS patient is providing intensive observation of blood pressure, hematocrite levels, platelet count, urinary output, hemorrhagic manifestations, and level of consciousness. With adequate and appropriate fluid replacement, we expected the patient pretend stable in good condition. Monitoring patient after the shock condition was recording of the vital signs and determination of the hematrocrit are important

in evaluating the results of treatment. The goal of replacement therapy is to reduce or stop significant bleeding. Although replacement therapy should not be used to normalize laboratory tests.

Prognosis of this patient was good. Early recognition of illness, careful monitoring and appropriate fluid therapy alone have decreased mortality to 1%.. Significant morbidity and mortality can result if early recognition and monitoring of severe forms are not done. If left untreated the mortality of DHF or DSS patients maybe as high as 40-50%. Severe fractory shock, DIC, ARDS, liver failure and neurological manifestations singly or in combination were the commonest causes of death in a recent series. The case fatality rate is high with shortage of experienced medical teams.

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35TH ANNUAL MEETING OF THE
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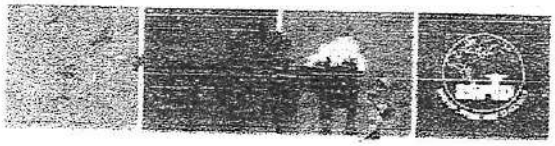

CME/CPD Certificate

This is to certify that

Dominicus Husada MD, PhD

participated in the

35th Annual Meeting of the European Society for Paediatric Infectious Diseases

Madrid, Spain
May 23-27, 2017

and received 21 credits

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Chairs, ESPID 2017 Meeting
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