WEBINAR 2

DECIMATE DENGUE: THE PRE-SUMMIT WEBINARS

MANAGING THE SEVERELY ILL DENGUE PATIENTS

January 20, 2021

INTRODUCTION

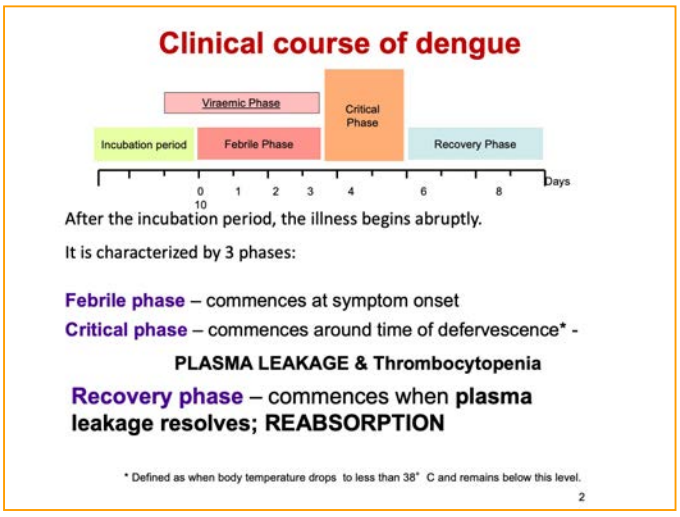
Due to the ongoing COVID-19 pandemic, 5th Asia Dengue Summit has been postponed to January 2022. In the meantime, the Asia Dengue Voice and Action (ADVA) Group, in collaboration with the Global Dengue and Aedes transmitted Diseases Consortium (GDAC), Fondation Merieux (FMx), International Society for Neglected Tropical Diseases (ISNTD) and Southeast Asian Ministers of Education Tropical Medicine and Public Health Network (SEAMEO) bring a series of online meetings titled "Decimate Dengue: The Pre-Summit Webinars." The second webinar in the series titled "Managing the severely ill dengue patients" was held on January 20, 2021. Prof. Zulkifli Ismael, Consultant Pediatrician and Pediatric Cardiologist at KPJ Selangor Specialist Hospital, Malaysia and Prof. Usa Thisyakorn, Professor of Pediatrics and Executive Director of Tropical Medicine Cluster at Chulalongkorn University, Mahidol University, Thailand, chaired the webinar. The webinar featured talks by Prof. Lucy Lum and Prof. Terapong Tantawichien who provided an overview of the clinical features, complications and management of dengue in adults and children. Prof. Bridget Wills focused her talk on clinical evidence on interventions in management of vascular leakage and shock.

MANAGING THE SEVERELY ILL DENGUE PATIENTS IN PEDIATRICS

Prof. Lucy Lum
Professor, Department of Pediatrics,
Faculty of Medicine
University of Malaya, Malaysia

Clinical course of dengue

After an initial incubation period of 5-7 days, the level of viremia is high enough to produce a clinical illness. The febrile phase characterized by high fever, headache, nausea, vomiting, retro-orbital pain, myalgia and arthralgia, lasts for 2-7 days. At the end of the febrile period the viremia is cleared and the next phase of the disease sets in. Some patients who do not have increased capillary permeability feel better at this stage. However, if the disease is going to enter the critical phase, it is around the 3rd- 8th day. Critical phase is characterized by severe plasma leakage and thrombocytopenia. The severity of the plasma leakage is variable and determines the severity of the disease. The plasma leakage lasts for 24-48 hours, after which the patient transitions in the recovery phase where the fluid that is leaked is reabsorbed.[1]



"Whenever we see dengue patients we need to classify them in a timeline to know the phase and severity of the disease and remain vigilant for the complications that can arise during different phases." Prof. Lucy Lum

Vascular leakage in dengue

Treatment of vascular leakage in dengue mainly involves maintenance of fluid balance with intravenous fluid (IV) therapy. However, in patients with vascular leakage, cautious administration of IV fluids with frequent monitoring is essential to avoid fluid accumulation and respiratory distress. A prospective observational study in 1734 dengue patients was performed in 11 hospitals in seven endemic countries across South-East Asia and from Latin America to determine the effect of parenteral fluid therapy. 88% of hospitalized patients did not experience dengue shock syndrome (DSS), while only 12% suffered from DSS. 83% patients with DSS had clinical fluid accumulation, out of which 40% suffered from shock or respiratory distress. This study identified the factors affecting risk of respiratory distress with fluid accumulation.[2]

Risk Factors for respiratory distress with fluid accumulation[2]
1. Age < 15 years
2. Referral from another inpatient facility
3. Longer Duration of IV fluid therapy
4. Greater amount of IV fluid therapy in the preceding 24 hours
5. Female gender
6. Poor nutrition

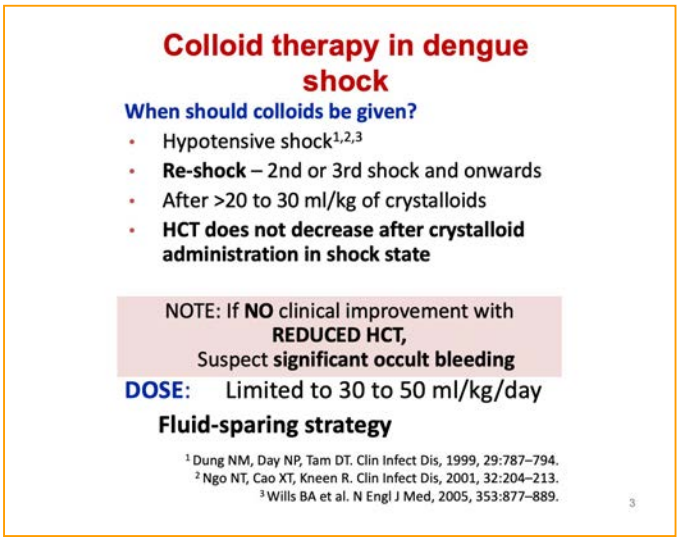
**AHR – adjusted hazard ratio; HR - hazard ratio*

Phases of intravenous fluid therapy

Though intravenous fluid (IV) therapy forms the mainstay of treatment in patients with hospitalized dengue, judicious administration of IV fluid is essential to prevent complications of fluid overload. Individualized fluid therapy is crucial to reduce risk of complications. Four phases of fluid resuscitation have been described, which include rescue, optimization, stabilization,

and de-escalation. Clinical and hemodynamic parameters and blood chemistry should be continuously monitored in patients receiving IV fluid therapy.[3]

Phases of IV fluid resuscitation[3]	
1. Rescue	Use of fluid bolus therapy to resuscitate patients in shock with continuous hemodynamic monitoring
2. Optimization	Cautious and titrated fluid administration to improve cardiac function and tissue perfusion and prevent organ dysfunction
3. Stabilization	Use of maintenance fluid therapy as the patient is more or less stable
4. De-escalation	IV fluids are gradually cut down and eventually stopped

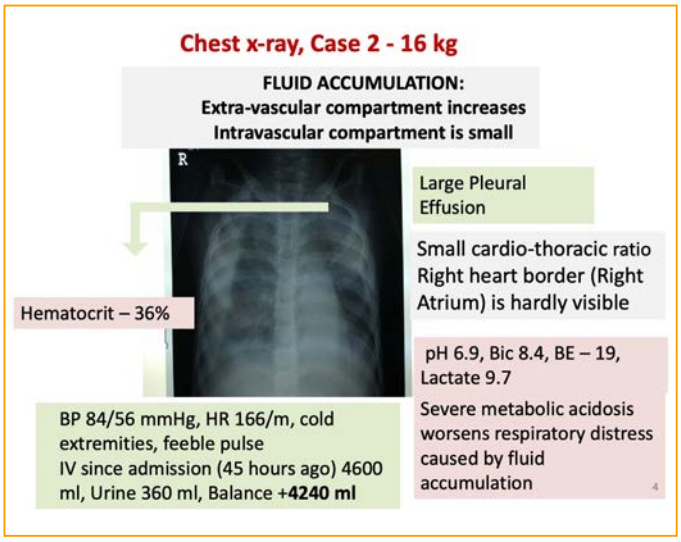


Monitoring of hemodynamic responses to IV fluids

In most pediatric patients, DSS can be treated successfully with isotonic crystalloid solutions. However, when a colloid is deemed necessary, clinicians should use personal experience and familiarity to determine the best option. A medium-molecular-weight colloid that has good intravascular persistence and an acceptable side-effect profile should be considered.[4] A close and on-going assessment of vital signs and serial hematocrit measurements is essential to guide fluid therapy and prevent fluid overload. A systematic review and meta-analysis of 44 studies including 7507 children showed that fluid overload is associated with poor outcomes such as worsening respiratory function, acute kidney injury, longer pediatric intensive care stay, and death in critically ill children.[5] Hypervolemia from fluid overload increases the release of atrial natriuretic peptide (ANP) that has diuretic, natriuretic and vasodilating effects. Hypervolemia also increases shedding of the endothelial glycocalyx, which increases the capillary permeability, which in turn leads to tissue edema.[6] The relationship between fluid balance and outcomes in critically ill children admitted to pediatric intensive care warrants frequent assessment of fluid responsiveness. Caution should be exercised during intravenous fluid therapy to maintain hemodynamic stability and avoid fluid overload.

Non-invasive monitoring of hemodynamic response

Recurrent episodes of shock can occur in approximately 30% of patients with dengue shock syndrome. These patients are at an increased risk of fluid overload, respiratory distress and poor outcomes.[7] Developments in non-invasive monitoring, providing faster assessment of intravascular volume may be useful in reducing over-resuscitation. Non-invasive cardiovascular monitoring such as echocardiography can be used to determine cardiac function and intravascular volume and identify patients at risk.[7] Echo-derived stroke volume index, together with heart rate monitoring and venous lactate levels can be used to identify patients at high risk of recurrent shock and guide fluid resuscitation in these patients.[7] Point-of-care ultrasonography (POCUS) of the inferior vena cava (IVC) is another non-invasive method for intravascular volume assessment.[8]



DENGUE AND SEVERE DENGUE IN ADULTS AND ELDERLY

Prof. Terapong Tantawichien
Chairman, Tropical Medicine Cluster, Chulalongkorn University, Thailand

Dengue in adults with co-morbidities

The incidence of dengue has been increasing in adults and ageing population. High risk of dengue death is reported in patients with underlying comorbidities such as renal, infectious, pulmonary disease and diabetes.[9] In a two-year review on epidemiology and clinical characteristics of dengue deaths in Malaysia, causes of dengue death included DSS (70%), severe organ involvement (69%) and severe bleeding (29.7%).[10]

In a systematic review of maternal dengue and pregnancy outcomes, case reports observed high rates of cesarean deliveries (44.0%) and pre-eclampsia (12.0%). Risk of vertical transmission was observed in 64.0% of women in case reports and 12.6% of women in case series.[11] A retrospective cohort study in Thailand highlighted older patients >60 years of age with comorbid hypertension are at increased risk of DHF. The risk of DHF was higher is in older patients >60 years (40.69%) compared to adults above 18 and younger than 60 years (30.71%).[12]

"Elderly patients and those with underlying comorbid conditions are at increased risk of complications from dengue and therefore require close monitoring."
Prof. Terapong Tantawichien

Clinical and laboratory risk factors of ICU requirement

Several clinical and laboratory parameters can be used to determine the risk of intensive care unit (ICU) admission in adult patients with dengue. [13]

Clinical risk factors at presentation associated with ICU requirement[13]
Hematocrit change ≥20% concurrent with platelet <50 K
Hypoproteinemia
Hypotension
Severe organ involvement
Early laboratory risk factors at presentation[13]
Neutrophil proportion
Serum urea
Alanine aminotransferase level
Early laboratory risk factors at 24 hours prior to ICU[13]
Lmphocyte and monocyte proportions
Pulse rate
Blood pressure

Hemorrhagic complications

Gastrointestinal tract and vagina in adult females are usual sources of major bleeding in dengue. Patients with peptic ulcer, those on non-steroidal anti-inflammatory agents or anticoagulant therapy and those with trauma are at higher risk of major bleeding.[14] Gastrointestinal bleeding is a leading cause of death in dengue. Early identification of patients with high risk of gastrointestinal bleeding is crucial as it will provide an opportunity for early effective intervention and will be useful in reducing morbidity and mortality in adult dengue patients.[15] The requirement of packed red blood cells and fresh frozen plasma is higher in patients with peptic ulcer with recent hemorrhage compared to those without recent hemorrhage.[16]

Predictors of gastrointestinal hemorrhage among adult patients[15]
1. Age >60 years
2. End stage renal disease with comorbidities
3. Previous stroke with comorbidities
4. Platelet count <50 × 10^9 cells/L

As per WHO 2009 guidelines severe bleeding can be recognized by decrease in hematocrit after fluid resuscitation, refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 ml/kg, hypotensive shock with low/normal hematocrit before fluid resuscitation and persistent or worsening metabolic acidosis especially in those with severe abdominal tenderness and distention.[14] Blood transfusion is required in patients with severe bleeding, however judicious use of transfusion is necessary to avoid risk of fluid overload.[14]

Hemophagocytic Lymphohistiocytosis in dengue

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory condition with high mortality that can develop in some patients with severe dengue. Persistent high fever, cytopenia, hyperferritinemia, and hemophagocytosis may indicate HLH and clinicians should be aware and suspect HLH in such patients. Prompt treatment with corticosteroids such as dexamethasone has demonstrated can be lifesaving and has demonstrated improved survival in patients with HLH.[17]

Cardiac manifestations in dengue

Myocarditis and rhythm disturbances can occur in patients with dengue, and therefore close cardiac monitoring is necessary.[18] Other cardiac manifestations such sinus bradycardia, atrio-ventricular block, T wave, and ST-segment abnormalities have also been reported. Subclinical myocarditis, myocardial edema, or circulating myocardial depressant factors can lead to functional myocardial impairment and electrocardiographic abnormalities.[19] Elderly patients (age ≥65 years) and those with comorbidities are at high risk of complications. If ECG is not normal in high-risk groups and in those with cardiac symptoms, cardiac biomarkers and echocardiography should be performed in patients with severe disease and refractory shock. Patients with cardiac manifestations require careful attention to fluid balance and hemodynamic monitoring. [19]

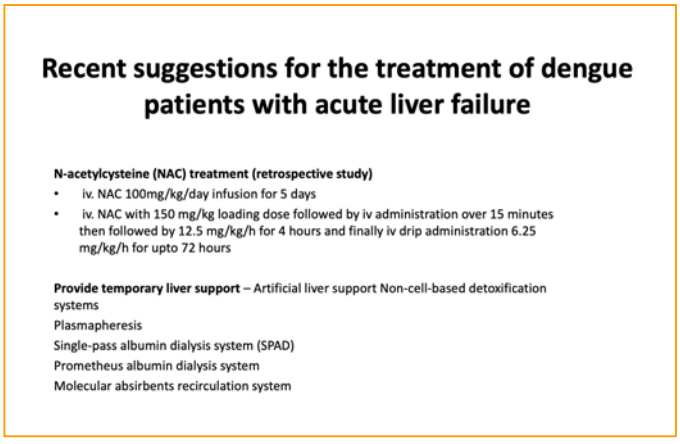
Hepatic and renal involvement in dengue

Dengue virus has some hepatotoxic effects. Liver involvement in dengue is usually asymptomatic with elevated bilirubin and transaminase levels but fulminant hepatic failure has also been reported. Liver involvement is more common in children than in adults. Non-steroidal anti-inflammatory drugs, such as ibuprofen or antipyretics and other drugs, which might worsen the liver damage should be avoided in dengue fever.[20] Use of standard dose of paracetamol has shown increased incidence of transaminase elevation and therefore paracetamol should be used with caution in dengue patients.[21]

Renal involvement in dengue ranges from elevation of the serum creatinine level, acute kidney injury, acute tubular necrosis, hemolytic uremic syndrome, proteinuria, to glomerulopathy and nephrotic syndrome.[22] Acute kidney injury is a serious complication of dengue and its pathogenesis is multifactorial, resulting from hemodynamic instability, hemolysis, rhabdomyolysis and acute glomerulitis. Assessment of warning signs of dengue and careful fluid resuscitation is essential to prevent acute kidney injury.[22]

Bacterial and viral co-infections with dengue

Being critically ill at hospital presentation is associated with 15 times increased risk of concurrent bacteremia, which is associated with more deaths and longer hospital stay. Therefore, blood cultures and empiric antibiotic therapy should be considered in critically ill patients.[23] More recently, co-infection of COVID-19 and dengue virus has presented a double challenge of managing two severe and complex diseases.



MANAGEMENT OF SEVERE DENGUE: THE RESEARCH PERSPECTIVE

Prof. Bridget Wills
Professor of Tropical Medicine and Honorary Consultant in Pediatrics
Centre for Tropical Medicine and Global Health
University of Oxford

Thrombocytopenia in dengue

Platelet count is invariably reduced in dengue patients and thrombocytopenia is linked to the severity of the disease and clinical outcome. A rapid decline in platelet count or platelet count <150,000/ml have been described by WHO guidelines.[24] Several mechanisms have been implicated in development of thrombocytopenia and bleeding manifestations. Bone marrow hypoplasia, functional disruption and increased platelet consumption due to intravascular coagulation (DIC), platelet destruction, complement activation and development of antiplatelet antibodies contribute to thrombocytopenia in dengue.[24]

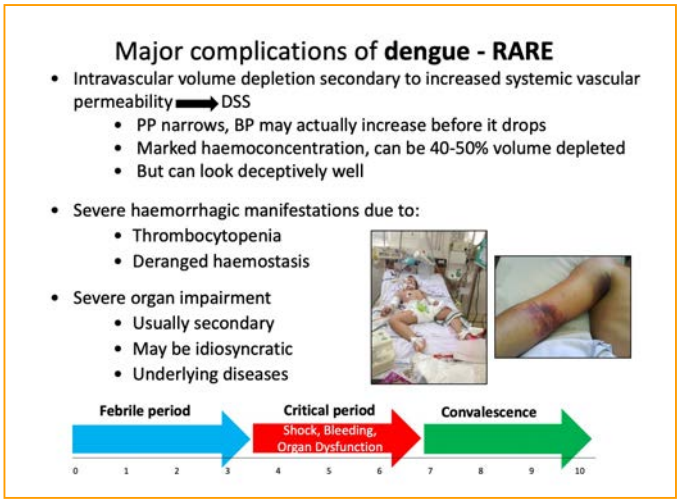
Platelet transfusions are recommended in patients with thrombocytopenia who develop bleeding manifestations. However, role of platelet transfusions as prophylactic therapy is unclear. In an open-label, multicenter, randomized, superiority trial in five hospitals in Singapore and Malaysia, 372 patients with dengue, platelet count < 20,000 without persistent mild bleeding or any severe bleeding were randomly allocated to receive 4 units of platelets each day (transfusion group) or supportive care alone (control group). [25] Clinical bleeding was not different between transfusion and control groups. (21% vs.26%; p=0·16) However, adverse events were significantly higher in patients who received transfusion. (6.26% vs. 5.81%; p=0·0064). This provides evidence that prophylactic platelets are not superior in patients without bleeding.[25]

An open-label, randomized controlled phase-II trial in patients with dengue fever (DF) and dengue hemorrhagic fever (DHF) evaluated the safety and efficacy of eltrombopag, a thrombopoietin receptor agonist in treatment of thrombocytopenia. [26] 109 patients with platelet count< 100 × 10^9/L without comorbidity, pregnancy, and liver abnormalities were randomly allocated to receive two doses of eltrombopag - 25 mg/day (group 1), 50 mg/day (group 2) and standard dengue treatment without eltrombopag (control group). On day 7, patients in group 1 (332 × 10^9/L ± 92) and group 2 (371 × 10^9/L ± 111) had significantly higher platelet count than control group (194 × 10^9/L ± 96). 91% patients in groups 1 and 2 achieved the primary end point of platelet count above 150 × 10^9/L compared to 55% patients in control group. This trial shows the beneficial effect of eltrombopag in restoring platelet counts in DF and DHF.[26] Some studies on role of dexamethasone, recombinant activated factor VII, anti-D immune globulin and recombinant human IL-11 have been conducted, but further research on their role in thrombocytopenia is necessary.

The quality of evidence from trials using corticosteroids in dengue at an early stage and dengue related shock was low and inconclusive.
(Cochrane Database Syst Rev. 2014 Jul 1;2014(7):CD003488)

Dengue shock syndrome

Dengue shock syndrome (DSS) is a serious complication of dengue infection and is associated with high mortality. It is characterized by increased capillary permeability leading to hypovolemia and shock. Prompt and judicious fluid resuscitation plays a crucial role

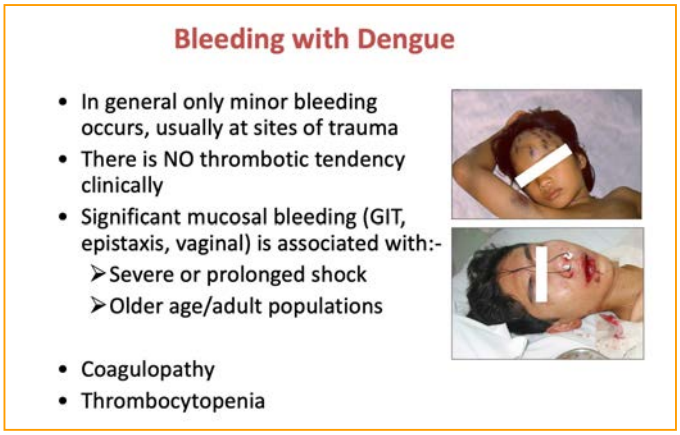


in management of DSS.[27] Most DSS cases have a good response to careful management with isotonic crystalloid solutions alone, however patients with profound shock are more likely to receive rescue colloid. In patients with severe shock the choice between crystalloids and colloids depends on personal experience, familiarity with products, local availability, and cost.[27] Several trials have compared the impact of choice of resuscitation fluids on clinical outcomes in critically ill patients, which provide some insight on management of these patients.

- **Early treatment with colloids improved outcome in patients who presented with pulse pressure <10 mmHg, thus pointing towards a possible benefit of colloids in these children.[28]** A randomized, double blind trial compared the efficacy of dextran 70, 3% gelatin, lactated Ringer's, and normal saline for initial resuscitation in 230 Vietnamese children with DSS. Results were similar for 4 fluids with all patients undergoing full recovery, but the longest recovery times were observed with lactated Ringer's group. 20% children in Ringer's lactate group took >1 hour to recover, compared to only 5.4%–7.1% children in the other 3 groups. Response to treatment was largely determined by pulse pressure at shock. Children who presented with pulse pressure <10 mmHg were at increased risk of not recovering from shock within 1 hour and increased risk of re-shock.[28]
- **Ringer lactate was as efficient as crystalloids for moderately severe shock, but patients with severe shock needed significantly more rescue colloid.[27]** A double blind, randomized trial compared Ringer's lactate, 6 percent dextran 70 and 6 percent hydroxyethyl starch in management of DSS in Vietnamese children. The primary outcome was requirement for rescue colloid, which was similar across the groups. The adverse effects were similar in between the two colloid groups but adverse reactions were more with dextran.[27]
- **Use of HSL in resuscitation of patients with DSS was associated with minimal fluid overload.[29]** A randomized single blind clinical trial compared the effectiveness of Ringer lactate (RL) with hypertonic sodium lactate solution (HSL) in 50 Indonesian children with DSS. Hemodynamic recovery, plasma expansion, clinical outcome, and survival rate were comparable in both groups but cumulative fluid balance was significantly less in the HSL group than the RL group.[29]
- **SAFE study observed that albumin and saline were clinically equivalent for intravascular volume resuscitation in ICU patients.[30]** The Saline versus Albumin Fluid Evaluation (SAFE) Study was a multicenter, randomized, double blind trial that compared the impact of albumin versus saline on organ function in 7000 ICU patients with severe sepsis. The 28-day

all cause mortality was 21.1% in saline group versus 20.9% in albumin group. There was no significant difference in survival times, need for mechanical ventilation and renal-replacement therapy, and time spent in the ICU between the two groups. Additionally, there was no difference in new single-organ or multiple-organ failure in both groups.[30]

- **In critically ill children with impaired perfusion, fluid boluses are associated with increased 48-hour mortality in a resource-limited setting.[31]** The Fluid Expansion as Supportive Therapy (FEAST) study was a randomized controlled trial in 3000 African children that compared the effect of fluid boluses in critically ill children. Patients were randomized to either receive 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) or no bolus (control group).[31] 48-hour mortality was 10.6% in albumin-bolus group 10.5% in saline bolus-group versus 7.3% in no bolus control group. The risk of neurological sequelae and/or death at 4 weeks increased by 4 percentage points in bolus groups.[31]



"The most important factor in reducing mortality in patients with dengue shock syndrome is assiduous medical and nursing care. Ongoing research is crucial."
Prof. Bridget Wills

Q AND A SESSION

Q1. What is the role of platelet transfusion in severe adult dengue with thrombocytopenia and what is the cut-off point for platelet transfusion?

Prof. Terapong Tantawichien: In patients with active bleeding platelet cut-off <50,000 is an indication for platelet transfusion. We also use platelet transfusion in patients with acute liver failure as they may have more severe bleeding due to other form of coagulopathies. Platelet transfusion is not used if there is no bleeding.

Q2. Is there any role of steroids in managing myocarditis in severe dengue in adult patients?

Prof. Terapong Tantawichien: In myocarditis, the cardiac enzymes are raised but usually patients have no symptoms, some may have arrhythmias. Only indication for steroids in dengue in adults is Hemophagocytic lymphohistiocytosis (HLH).

Q3. What is the role of CVP in guiding fluid management in DSS in children?

Prf. Lucy Lum: It is practically challenging to insert a central line in hypovolemic patients. However, ultrasound guided insertion of central line is possible, especially when patients need a central line for hemodialysis for renal support. Insertion of central line has to be done very skillfully to prevent bleeding complications at the puncture sites.

Q4. What is the role of echocardiography in looking at inferior vena cava (IVC) collapsibility in assisting fluid replacement in DSS?

Prof. Lucy Lum: IVC collapsibility can be used to guide fluid replacement in DSS. However, the interpretation of IVC collapsibility can be challenging in cases where there are changes in the intra-thoracic pressure (E.g. patients with acidotic breathing, ventilated patients)

Q5. What is the role of N-acetylcysteine (NAC) in children with severe liver failure?

Prof. Lucy Lum: The quantity of diluent fluid required during administration of N-acetylcysteine (NAC) can cause fluid overload and can therefore be counterproductive in managing dengue patients. I do not use it until there is documented paracetamol toxicity.

Prof. Terapong Tantawichien: Plasmapheresis can be used in adult patients with acute liver failure.

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