RISK FACTORS FOR SEVERE DENGUE

Kamolwish Laoprasopwattana[1] and Alan Geater[2]

[1]Department of Pediatrics; [2]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

Abstract. Dengue viral infection (DVI) is a common cause of morbidity and mortality in both children and adults in tropical countries. Severe dengue is defined as dengue patients with dengue shock syndrome (DSS) and/or organ failure/dysfunction. The mortality rate of severe DVI found in various studies varies from 0.5-13%, depending on the severity of disease in the enrolled patients, the experience of the medical team, age group, and underlying disease(s). In this narrative review, we describe and discuss the risk factors and outcomes of severe DVI in children and adults. In both children and adults, DSS leading to organ failure has a poor outcome with a high mortality rate of 60-70%; severe hepatitis and/or coagulopathy are commonly found in patients with severe bleeding; and patients with non-DSS-caused organ failure have a good prognosis. Obese children are at higher risk of developing severe DVI and subsequent organ failure, notably acute kidney injury (AKI) and acute liver failure (ALF). In adults, severe DVI is caused not only by DSS, but can also result from co-bacteremia and/or underlying diseases. Children rarely have these comorbidities, and adults are thus more vulnerable to organ dysfunction. To reduce the number of DVI patients progressing to severe DVI, early detection of patients at risk of developing severe DVI is important. During the febrile stage, dengue patients should be carefully checked daily. If they have any of the warning signs or risk factors of severe DVI, they should be hospitalized with close monitoring.

Keywords: dengue hemorrhagic fever, dengue, organ failure, risk factors, severe dengue, shock syndrome

DEFINITION OF SEVERE DENGUE VIRAL INFECTION

The definition of severe dengue viral infection (DVI) according to WHO 2009 is a dengue patient who has dengue shock syndrome (DSS), including those with signs of impending shock or dengue hemorrhagic fever grade III (DHF Gr III) and profound shock (DHF Gr IV), fluid accumulation with respiratory distress, severe bleeding and severe organ involvement such as acute respiratory failure (ARF), acute liver failure (ALF) or transaminase enzymes >1,000 units/l, acute kidney injury (AKI), and impaired consciousness (WHO, 2009).

Correspondence: Kamolwish Laoprasopwattana, MD, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Tel: +66 (0) 74 451250; Fax: +66 (0) 74 429618
E-mail: *kamolwish@gmail.com; lkamolwi@medicine.psu.ac.th*

ARF is defined by severe hypoxemia requiring a mechanical ventilator. Hematologic failure is defined by severe bleeding requiring packed red cells and/or other blood components to control. AKI is defined by a sudden increase in serum creatinine (Cr) level >2 mg/dl or a serum Cr concentration >2 times previous or subsequent values and that is also higher than the upper limit of normal values for the patient's age (Chan *et al*, 2002). ALF is defined as the rapid development of severe acute liver injury with impaired synthetic function (INR ≥1.5 or PT >15 seconds) and encephalopathy or INR ≥2.0 or PT >20 seconds irrespective of hepatic encephalopathy in patients with no history of liver disease (Suchy, 2016).

COMPLICATIONS OF SEVERE DENGUE VIRAL INFECTION

Severe bleeding

Endothelium injury leading to consumptive thrombocytopenia and coagulopathy as well as

increased fibrinolysis, and acute liver injury causing coagulopathy and disseminated intravascular coagulation play a major role in hemorrhage in DVI. Mild mucosal bleeding is common in DVI. However, severe bleeding is not common and can be fatal if uncontrolled. The most common severe bleeding sites leading to death are the upper gastrointestinal tract, the lower respiratory tract, and within the skull (Lee *et al*, 2012; Fariz-Safhan *et al,* 2014; Laoprasopwattana *et al,* 2014).

In an earlier unpublished study from our institution on DVI in children, profound shock, platelets <20,000/mm^3 and INR ≥1.5 were the major risk factors of severe bleeding [odds ratio (OR) = 3.4; 95% CI: 1.4-8.6, 2.6; 95%CI: 1.1-6.2], and 10.6; 95%CI: 4.0-28.4, respectively] (Laoprasopwattana *et al*, 2017). Similarly, a study of DVI in adults also found that platelets <20,000/mm^3 and/or prothrombin time (PT) prolongation were associated with severe bleeding (Lee *et al,* 2012).

Our study also found that INR had a high correlation with transaminase enzymes (Laoprasopwattana *et al*, 2017). This finding is supported by a recent study in adults in which an increase of aspartate aminotransaminase was associated with an increased risk of severe bleeding (OR = 1.008; 95% CI: 1.005-1.01) (Fariz-Safhan *et al,* 2014). Taken together, these various factors suggest that acute liver injury plays a key role in hemorrhage in DVI patients by causing decreased synthesis and increased consumption of coagulation factors. These subsequently cause prolonged PT and prolonged activated partial thromboplastin time (aPTT).

Acute liver failure

Currently, the most common infectious disease causing ALF in Thailand is DVI (Poovorawan *et al,* 2006). The liver is the target organ of the dengue virus, and mildly elevated transaminase levels are common in patients with DVI with levels of transaminase enzymes usually returning to <200 U/l in 2 weeks (Laoprasopwattana *et al,* 2016). ALF is rare (<1%) in DVI, but severe complications do occur in some patients. These are associated with high fatality rates, especially high-grade hepatic encephalopathy, which has a fatality rate of 50.0-66.7% (Poovorawan *et al,* 2006; Chongsrisawat *et al,* 2009; Laoprasopwattana *et al,* 2016).

Profound shock is a major risk factor of ALF and most DSS-caused ALF patients develop ALF within 48 hours after onset of shock (Laoprasopwattana *et al,* 2016). This suggests that the major cause of ALF in DVI is ischemic hepatic injury. ALF may also result from the immune system through a process in which the dengue virus stimulates Fas ligand formation on hepatocytes, causing cell apoptosis by immune-mediated hepatocytic injury (Pagliari *et al,* 2014).

Acute kidney injury

AKI is rare although mild serum creatinine elevation is common in DHF. The major cause of AKI in both children and adults is DSS (Lee *et al,* 2009; Laoprasopwattana *et al,* 2010). The reported major causes of non-DSS AKI are rhabdomyolysis, acute hemolysis, and direct kidney injury from dengue virus. Immune complex-mediated acute glomerulonephritis, sepsis, or nephrotoxic medications can cause AKI too. Non-DSS-caused AKI has a good prognosis with a very low mortality rate. AKI itself does not increase the risk of fatality in DVI in patients who must have renal replacement therapy, but profound shock subsequently causing respiratory failure and massive bleeding are the major causes of fatal DVI (Laoprasopwattana *et al,* 2010).

AKI was found in 0.9% (25/2,893) of hospitalized children with DVI with a high mortality rate of 64.0%. The main risk factors of AKI were profound shock and obesity (OR 16.9; 95% CI: 4.2-68.5 and OR = 6.3; 95%CI: 1.4-28.8, respectively). Most DSS-caused AKI patients developed AKI within 24 hours after onset of shock. Fatality was more likely in children with profound shock, oliguric AKI, respiratory failure, or prolongation of PT or aPTT of more than twice that of the reference specimen. Among the survivors, none had chronic kidney disease, and serum creatinine levels returned to normal in 1 to 48 days (mean 32 days) (Laoprasopwattana *et al,* 2010).

Lee *et al* (2009) found an AKI rate of 3.3% (10/304) in adult patients hospitalized with DHF with a mortality rate of 60.0%. The higher proportion

of AKI in adults can be explained by the other risk factors of adults that increase their vulnerability to AKI during renal hypoperfusion such as older age, having an underlying disease(s) such as hypertension, diabetes mellitus and chronic kidney disease, as well as/or co-bacterial infection (Table 1).

Fatal outcome

DVI fatality rates generally depend on various factors such as age group or severity of DVI, availability of intensive medical care, and the experience of the medical team. The overall fatality rate of DVI varies from 0.2-2% in tropical countries (WHO, 2009).

Both adult and child fatal DVI patients have a higher proportion of severe DVI at first presentation and higher median leukocyte counts than those who survive the disease (Thein *et al,* 2013; Laoprasopwattana *et al,* 2014). Most fatal cases in children have DSS at presentation while more than half of fatal cases in adults have an underlying disease or diseases, making them prone to unfavorable outcomes (Table 2). The higher leukocyte count in fatal DVI patients could be explained by the high levels of inflammatory cytokines and stress hormones, and concurrent bacterial infection if present. Although documented the numbers of bacteremia cases in the two studies are low (Thein *et al,* 2013; Laoprasopwattana *et al,* 2014) (Table 2), empirical treatment with antibiotics is common in treating DVI patients with multiple organ failure. This is because these patients are more vulnerable to nosocomial infection.

The DVI children at highest risk of death are those with DHF grade IV who subsequently have multiple organ failure. Our previous study of 238 children with severe DVI found that 30 of these patients subsequently died. Organ failure occurred in nearly one-third of the severe DVI patients. Organ failure, notably ARF, AKI, and ALF, are accompanied by severe bleeding, occurring in 16-18% of severe DVI patients with a high mortality rate of 60-70% (Table 3). We found that patients with both ARF and severe bleeding had an 82% fatality rate, but if they did not have these two risk factors, the chance to survive was 99% (Laoprasopwattana *et al,* 2014).

The causes of fatal DVI in adult patients are not only DSS and subsequent multiple organ failure, but also concurrent or secondary bacteremia and underlying diseases contributing to death (Wang *et al,* 2007; Leo *et al,* 2011; Lee *et al,* 2012; Thein *et al,* 2013). Wang *et al* (2007) found that of 11

Table 1. Risk factors of acute kidney injury in children and adults hospitalized with DVI.

Risk factor	Laoprasopwattana *et al*, 2010[a]		Lee *et al*, 2009	
	AKI (*n*=25)	No AKI (*n*=50)	AKI (*n*=10)	No AKI (*n*=294)
Age median (range), years	10.0 (0.5-13.1)	10.0 (0.3-13.0)	69.5 (33-78)[b]	55.0 (19-88)
Chronic renal disease *n* (%)	0.0	0.0	2 (20.0)[b]	9 (5.7)
DSS *n* (%)	19 (76.0)[b]	10 (20.0)	8 (80)[b]	10 (3.4)
Severe bleeding *n* (%)	21 (84.0)[b]	6 (12.0)	8 (80) [b]	45 (15.3)
Bacteremia *n* (%)[c]	1 (4.0)	0.0	3/7 (42.8)[b]	3/67 (4.5)

AKI, acute kidney injury; DSS, dengue shock syndrome.

[a]To determine the risk factors of AKI, children who had DHF-caused AKI were matched with patients with DHF by age at a ratio of 1:2.

[b]Significant when comparing children and adults with AKI (p <0.05).

[c]Significantly higher in AKI than non-AKI groups (p <0.05).

Table 2. Risk factors contributing to fatal outcome in children and adults.

Risk factor	Laoprasopwattana *et al*, 2014		Leo *et al*, 2012 Thein *et al*, 2013	
	Died (*n* =30)	Survived (*n* =208)	Died (*n* =28)	Survived (*n* =80)
Age range, years	0.5 -13	0.3-15	21-86	21-86
Underlying disease(s)[a]				
Cardiac disorder *n* (%)	0	0	10 (47.6)[b]	7 (8.8)
Renal disorder *n* (%)	1 (3.3)	0	8 (40)[b]	2 (2.5)
At presentation				
Severe dengue *n* (%)	25 (83.3)[b]	121 (59.2)	22 (78.6)[b]	8 (10)
DHF gr. I-II *n* (%)	5 (16.7)	87 (41.8)	5 (17.9)	6 (7.5)
DSS[#] *n* (%)	25 (83.3)[b]	121 (59.2)	2 (7.1)	0
Bacteremia/meningitis *n* (%)	1 (3.3)	0	4 (14.3)	NA
Leukocyte count (10^9/l)[c]	18.8[b] (10.4-24.7)	6.6 (4.6-10.3)	8.8[b] (2.8-31.7)	2.5 (1.1-7.6)

DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; not applicable.
[a]Significant when comparing children and adults with fatal outcome (p <0.05).
[b]Significantly higher in non-survival than survival group (p <0.05).
[c]In children, the highest leukocyte count; in adults, leukocyte count at presentation.

Table 3. Mortality rate of severe DVI and organ failure in children and adults.

Study	Patient population characteristics	*n* of fatal outcomes/n of condition (%)	
Laoprasopwattana *et al*, 2014	238 severe DVI Thai children aged <15 y with DSS 228 (95.8%); referred *n*=70	Severe bleeding ARF ALF AKI Severe DVI	28/44 (63.6) 30/44 (68.1) 28/41 (63.6) 23/39 (58.9) 30/238 (12.6)
Lam *et al*, 2013	1,719 DSS Vietnamese children aged <15 years	DSS	8 (0.5)
Lee *et al*, 2009	304 hospitalized Taiwanese adults >18 years	AKI	6/10 (60)
Wang *et al*, 2007	661 hospitalized Taiwanese adults >18 years	ARF	8/11 (72.7)

AKI, acute kidney injury; ALF, acute liver failure; ARF, acute respiratory failure; DSS, dengue shock syndrome; DVI, dengue viral infection.

dengue patients with ARF, severe bleeding, AKI, and bacteremia were found in 8, 7, and 6 patients, respectively. The major causes of ARF were sepsis (*n*=6) and upper gastrointestinal tract bleeding (*n*=3), and the mortality rate of ARF was 72.7%.

PREVENTION OF SEVERE DVI

The severity of DVI is associated with the degree of endothelial cell injury, leading to plasma leakage and bleeding disorders. During the febrile period, early differentiation of DVI from other acute febrile illnesses and then monitoring for any warning signs of impending severe DVI are important.

Warning signs of severe DVI include persistent vomiting, abdominal pain/tenderness, hepatomegaly, fluid accumulation, lethargy/ restlessness, mucosal bleeding, and increased hematocrit with rapid decrease in platelets (WHO, 2009). Patients with any warning signs of severe DVI or with any risk factors of unfavorable outcomes such as obesity, having an underlying disease(s) prone to causing organ failure/dysfunction, and old age should be hospitalized for close monitoring and have appropriate treatment readily available to prevent progression to severe DVI and minimize the risk of a fatal outcome.

In summary, DSS is the major cause of severe DVI in children. However, DSS and underlying disease(s) that tend to cause organ failure are the major causes of severe DVI in adults. Profound shock is the major cause of organ failure due to poor tissue perfusion and hypoxia in both children and adults. Obese children are at higher risk to develop AKI or ALF while adults with co-infection with bacteremia and/or an underlying disease(s) that makes them vulnerable to organ dysfunction are at risk of developing severe DVI.

Patients with severe hepatitis/ALF are also prone to develop severe bleeding. Multiple organ failure, especially involving ARF and severe bleeding, is associated with a high risk of death in both children and adults. Early detection of DVI patients who have warning signs of severe DVI is essential. These patients should be closely monitored, so early treatment can be applied to prevent severe DVI and a fatal outcome.

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