

LIVER COMPLICATIONS IN ADULT DENGUE AND CURRENT MANAGEMENT

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Abstract. Adult dengue patients have a lower prevalence of bleeding tendency and greater prevalence of abnormal liver function tests than children with dengue infections. At least two-thirds of adult dengue patients have abnormal liver function tests. Our article aims to detail the clinical findings of liver complications in adult patients with dengue infection. The predictors of liver complications and the associations with failure of other organs were reviewed; for example, high-level ALT during the febrile stage has been associated with shock. In addition, this review includes the current interventions for treatment of acute liver failure in adult dengue patients including N-acetylcysteine, and artificial liver dialysis.

Keywords: liver complication, adult dengue, treatment

INTRODUCTION

Dengue infection is the most common mosquito-borne viral disease in the world. Fifty million infections occur annually, with 500,000 cases of dengue hemorrhagic fever (DHF) and 22,000 deaths (CDC, 2014). The overall incidence rates of dengue infection in adult patients (aged ≥ 15 years) are up to one-third of the incidence rates in child patients. Clinical manifestations in adult patients may differ from child patients, and the data are still limited. Severe infection, DHF, or dengue shock syndrome (DSS) were more prevalent in adults than

in children. Liver involvement is common in dengue infection, including hepatomegaly, jaundice, abnormal liver enzymes (60%), and acute severe hepatitis with an at least 10 times elevated level of transaminase (4%) (Wichmann *et al*, 2004).

Previous studies have shown more liver involvement in adult patients characterized by high rates of elevation in transaminase levels of which the average elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were about two times that of the upper normal limit (AST 93 U/l and ALT 86 U/l) (Souza *et al*, 2004). This review article aims to detail the clinical findings of liver complications in adult patients with dengue infection. The predictors of liver complications and associations with the failure of other organs were reviewed; for example, high-level ALT during the febrile stage has been

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associated with shock. In addition, this review includes the current treatments of acute liver failure in dengue adult patients.

MATERIALS AND METHODS

We retrospectively reviewed data from a Medline and PubMed search that was performed to identify relevant literature using search terms “liver complications” and “dengue” during a 20-year period, from 1995 to 2014. All relevant literatures of adult dengue patients with liver complications were reviewed. Specific terms were defined: 1) adult was defined as age greater than or equal to 15 years; 2) abnormal AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) were defined as their level above the normal value with blood tests taken within 7 days after the onset of fever; 3) dengue infection was defined by WHO criteria with serological confirmation by ELISA test or rapid immunochromatographic test; and 4) the 1997 and 2009 WHO classifications were used to categorize dengue patients as dengue fever (DF) or DHF Grades I-IV (Treeprasertsuk *et al*, 2003).

RESULTS

Prevalence of liver function test abnormalities and liver pathophysiology in adult patients with dengue infection

Our study at the Hospital for Tropical Diseases in Bangkok, Thailand showed that the mean age of 127 adult dengue patients was 26.4 ± 11.5 years, and 66% of them had a severe form of dengue infection. Most of them (96%) had no underlying liver disease. Abnormal transaminase levels, including AST and ALT, were commonly

found. These accounted for 88% and 69% of patients respectively, with the average ratio of AST to ALT of 1.8:1 (Table 1). In addition, our study found that the dengue-infected patients with abnormal ALT had significantly older age and had a longer duration of fever of at least 7 days (Treeprasertsuk *et al*, 2003).

Those patients with significant or acute severe hepatitis with an at least 10 times elevated transaminase level accounted for 7% of adult dengue infected patients, which is consistent with previous reports of a prevalence of 4%-15% (Kuo *et al*, 1992; Treeprasertsuk *et al*, 2003; Souza *et al*, 2004; Parkash *et al*, 2010). A previous study showed that the level of AST was more prominent than that of ALT in the first week and the maximum transaminase levels occurred on the ninth day after the onset of fever (Treeprasertsuk *et al*, 2003), gradually decreasing to normal levels within two weeks. However, some reports have shown that about one-third of dengue infections had persistent symptoms of fatigue, and abnormal liver tests remained in 7.6% of patients with dengue infections at the end of the second month of follow-up (Tristao-Sa *et al*, 2012). Elevated AST levels tend to return to normal more rapidly than ALT levels possibly due to AST having a shorter half-life than ALT. Hyperbilirubinemia has been found in 0.7%-13.4% of adult dengue infections without significant association with severity (Kuo *et al*, 1992; Wahid *et al*, 2000; Trung *et al*, 2010).

Liver pathophysiology

The patients with dengue infection who had complications or severe acute hepatitis were usually infected with dengue serotype 3 or serotype 4 (Gasperino *et al*, 2007;

Soundravally *et al*, 2010). The characteristic histological change to the liver parenchyma in these patients was midzonal (Zone 2) hepatic necrosis, which is the classic pathological finding (Gasperino *et al*, 2007). The possible pathophysiological factors associated with acute liver injury in dengue patients were the direct viral effect on liver cells or an adverse consequence of dysregulated host immune responses against the virus (Seneviratne *et al*, 2006) along with the severity of diseases including prolonged shock or ischemic hepatitis, drugs induced liver injury and preexisting liver damage (Ahmed *et al*, 2014).

Clinical findings of liver complications in adult patients with dengue infection

Hepatomegaly was significantly more commonly found in children with dengue infection than adults (43%-92% in children vs 28%-72% in adults) (Wichmann and Jelinek, 2004; Wichmann *et al*, 2004; Wang *et al*, 2009). An abnormal liver test can be used as one of the associated factors for dengue severity with an odds ratio of 1.9 (CI 0.97-0.99) (Khan *et al*, 2013). In addition, our study found an association between the patients with severe hepatitis during the febrile stage and clinical bleeding (Treeprasertsuk *et al*, 2003). Patients with at least a 10-fold elevation of ALT had a significantly greater proportion of hypotension than those with low-level ALT (25% vs 5%, respectively). Moreover, patients with high-level transaminases had a significantly longer duration of fever and a higher hematocrit level than those with low-level ALT.

In clinical practice, the common causes of abnormal liver tests in critical patients were ischemic hepatitis, sepsis, and drugs

induced liver injury (Thomson *et al*, 2009). If the clinical course of a dengue patient is worsening despite full supportive treatments, the clinician must exclude co-infection with other tropical diseases or complications; for example, malaria (Assir *et al*, 2014), bacterial sepsis (Ahmed *et al*, 2014), acute acalculous cholecystitis (Tan *et al*, 2005), leptospirosis, and acute hepatitis E (Behera *et al*, 2009; Parkash *et al*, 2010). One study of acute hepatitis severity in dengue fever and its outcomes reported that two-thirds of the deceased patients had severe acute hepatitis while one-third had mild to moderate acute hepatitis [elevated transaminase of at least 10 times had a higher mortality rate than those with low ALT level (HR 4.9; 95% CI 1.7-13.9; $p=0.003$) (Parkash *et al*, 2010)]. These findings are consistent with a previous report that the transaminase levels were associated with the severity of vascular leakage and the increased severity of bleeding (Trung *et al*, 2010).

Current treatment of acute liver failure in dengue adult patients

Principle management for hospitalized critically ill patients with abnormal liver tests (Berry *et al*, 2013):

A. Identify those patients with underlying chronic liver disease (Thomson *et al*, 2010). Due to the high risk to mortality in cirrhotic patients, the clinician has to identify the evidence of underlying chronic liver disease: for example, splenomegaly, low platelet count, or evidence of cirrhosis from abdominal ultrasonography (Agrawal *et al*, 2011).

B. Exclude treatable and/or emergency hepato-biliary diseases: for example, gallstone cholangitis or acute liver failure. The high-risk group for developing acute

Table 1
Laboratory findings of 127 adult dengue patients admitted to the Hospital for Tropical Diseases, Bangkok, Thailand.

Lab test	Days 1-7			Days 8-14		
	n	Mean±SD	Range	n	Mean±SD	Range
Hematocrit (%)	126	42.7±5.2	21.1-56.7	80	41.5±5.7	21.6-55.5
WBC (cell/mm ³)	126	3,983±1,925	1,200-11,550	34	6,432±3,096	2,875-18,700
Lymphocyte (%)	125	31.3±0.9	3-56	34	41.1±11.6	10-63
Atypical lymphocyte (%)	125	5.8±7.9	0-40	34	8.0±6.9	0-32
Platelet (cell/mm ³)	126	61,905±39,561	10,000-234,500	76	76,555±65,201	12,500-355,000
AST (IU/l)	127	243±372	14-2,215	18	651±1,463	52-6,468
ALT (IU/l)	127	152±215	5-1,580	18	512±1,030	80-4,586

Days 1-7, day 1-to -day 7 from onset of fever; days 8-14, day 8-to-day 14 from onset of fever; SD, standard deviation; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Source: Treeprasertsuk *et al* (2003).

Table 2
The outcomes of treatment with N-acetylcysteine (NAC) in patients with dengue infection and severe hepatitis.

Studies	Case report	LFT - presentations	Complications	Outcomes
Habaragamuwa <i>et al</i> , 2014	54-year female	Acute liver failure: AST 16,261 U/l, ALT 4,545 U/l, INR 1.7, TB 6 mg/dl	GCS= 11	Survive with normal liver tests in 2 weeks
Lim and Lee, 2012	6-year-old boy	Acute liver failure	No details	Survive
Kumarasena <i>et al</i> , 2010	n=7 cases; ages 6 months-12 yrs	Acute liver failure	Low GCS, prolonged shock	Survive

GCS (Glasgow Coma Scale) provides a score in the range 3-15; patients with scores of 3-8 are usually in a coma.

liver failure from dengue infection is those patients with a comorbidity, especially diabetes mellitus (Sam *et al*, 2013).

C. Identify the common causes of abnormal liver tests in critically ill patients, especially the causes from ischemic hepatitis and sepsis (Thomson *et al*, 2009).

D. Consider the risk of complication from the specific hosts: for example, pregnancy (Malhotra *et al*, 2006), AIDS, or elderly patients, all of whom may present with variable clinical courses. The few reports of HIV patients with dengue infection have shown that they usually present with mild symptoms (Mendes Wda *et al*, 2006; Siong *et al*, 2008). However, opportunistic infections in HIV patients must be excluded.

E. Exclude drug-induced liver injury (DILI). Recently, two reports have found evidence that acetaminophen overdose may play an important role in causing acute liver failure in dengue infection patients (Ranganathan *et al*, 2006; Gan *et al*, 2013). Supra-therapeutic doses of acetaminophen to control fever in children (the average dose was 145 mg/kg/day) were found in all child fulminant hepatitis patients compared with none in the control group (Ranganathan *et al*, 2006).

Recent suggestions for the treatment of dengue patients with acute liver failure

1. N-acetylcysteine (NAC).

2. Providing temporary liver support as a bridge to liver transplantation: artificial liver support. However, studies of both treatments have some limitations including lack of randomization, small sample size, and the nature of multiple organ failure in severe forms of dengue infection. These new treatment modalities should be considered for use on a case-by-case basis.

The rationale for N-acetylcysteine (NAC) use as an adjunctive therapy is its ability to restore hepatocellular glutathione, and its action as a free radical scavenger. In addition, NAC may improve antioxidant defense (Senanayake *et al*, 2013; Habaragamuwa and Dissanayaka, 2014). In non-acetaminophen related acute liver failure, the following NAC dosage regimen has been used: an intravenous (IV) loading dose of 150 mg/kg/day in 5% dextrose in water for up to 72 hours or 7 days (Lee *et al*, 2009; Squires *et al*, 2013).

The prescribed dosage in children was 100 mg/kg/24 hours until an INR of <1.4 was achieved (Kortsalioudaki *et al*, 2008). Previous studies have shown that dengue patients with acute liver failure who were prescribed NAC had favorable outcomes as shown in Table 2 (Sklar and Subramaniam, 2004; Senanayake *et al*, 2013; Habaragamuwa and Dissanayaka, 2014).

The standard dosage and duration for NAC regimens remain controversial, but have been suggested as follows:

1. IV NAC 100 mg/kg/day infusion for 5 days in adult patients (Habaragamuwa and Dissanayaka, 2014);

2. IV 150 mg/kg bolus over 15 minutes followed by 12.5 mg/kg/hour for 4 hours and then 6.25 mg/kg/hour for 72 hours in children (Kumarasena *et al*, 2010);

3. Or, 100 mg/kg/day for 6 days in children (Lim and Lee, 2012).

Artificial liver support

Artificial liver support aims to provide temporary support of liver function while maintaining the treatment of specific causes of liver failure. It can provide detoxification through different dialysis proce-

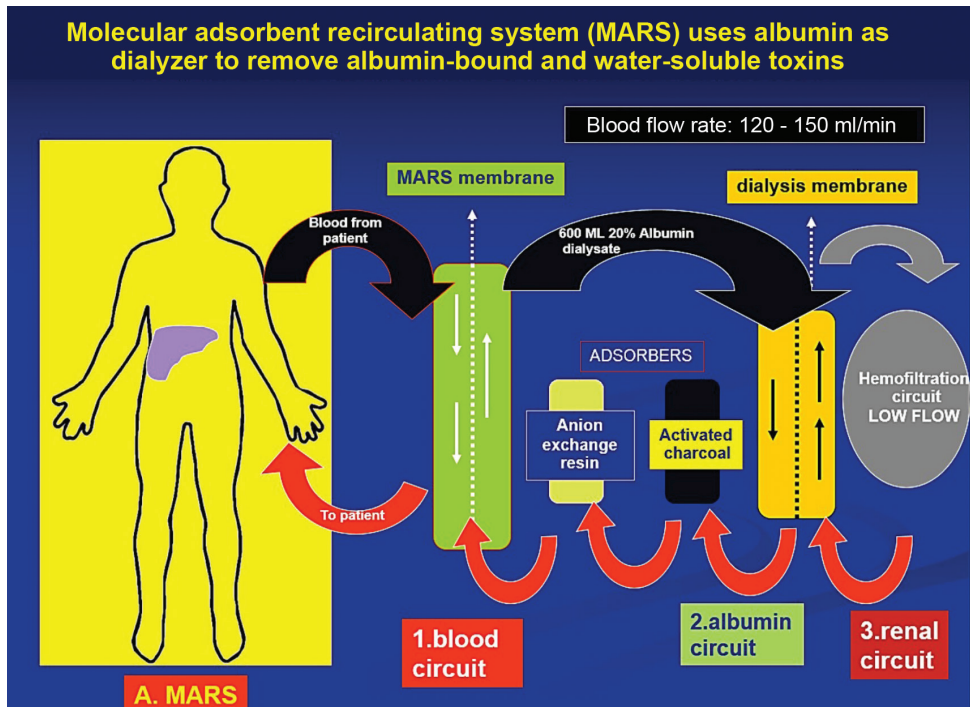


Fig 1—The Molecular Adsorbent Recirculating System: a nonbiological artificial liver support system.

dures, and it is different from the bioartificial liver support because there is no addition of the viable porcine cellular component into the system, the addition of which may have a safety concern with xenotransplantation of porcine cells (Banares *et al*, 2013; Wang *et al*, 2013).

The current use of nonbiological systems including the hemodiafiltration, albumin dialysis, and plasma exchange are available worldwide as follows (Carpentier *et al*, 2009):

Molecular Adsorbent Recirculating System (MARS, Gambro, Sweden), which was developed by Falkenhagen *et al* (1999).

Prometheus (Fresenius, Germany), which was developed by Falkenhagen *et al* (1999).

SPAD (Single pass albumin dialysis).

These nonbiological systems have been used as a treatment for different types of liver failure. The overall outcome of using these devices is safe. In addition, they have shown several clinical benefits including improvement of jaundice, improvement of hemodynamic instability, reduction of portal pressure, reduction of intracranial pressure, and improvement of hepatic encephalopathy (Nevens and Laleman, 2012). Penafiel *et al* (2006) reported that supportive treatment of a dengue infected patient with fulminant liver failure by MARS (Fig 1) demonstrated a favorable outcome including rapid reversal of the biochemical profile and an improvement of encephalopathy; however, MARS has some limitations including a high cost and some technical difficulty in usage (Penafiel *et al*, 2006).

At King Chulalongkorn Memorial Hospital in Thailand, we use albumin dialysis more often than other modalities due to the availability of equipment, lower cost, and ease of usage (Boonsrirat *et al*, 2009). Albumin dialysis utilizes the scavenging function of albumin to remove toxins, and it can reduce hyperbilirubinemia as well as improve encephalopathy in liver failure patients (Sen *et al*, 2005). Our previous study of using SPAD in patients with acute liver failure showed favorable outcomes and had no serious complications (Boonsrirat *et al*, 2009).

We used 2% human serum albumin dialysate for 6 hours, and SPAD reduced the level of total bilirubin by an average of 23% (Boonsrirat *et al*, 2009). We noted no significant changes in mean arterial pressure, and treatment modality was hemodynamically well tolerated. Recently, we have used SPAD in two dengue infected patients with liver failure, and these cases had good outcomes (local data).

CONCLUSION

At least two-thirds of adult dengue patients have shown abnormal liver function tests. Acute severe hepatitis with an at least 10 times elevation of transaminase levels has occurred in 4%-15% of adult dengue infected patients, and this should be a concern for the treating physician. Transaminases gradually decrease to normal levels within two weeks. The clinical findings of acute severe hepatitis or jaundice can be used as associated factors for dengue severity with an odds ratio of 1.9. The evidence of acetaminophen overdose, co-infection, or underlying chronic liver disease may play important role in caus-

ing acute liver failure in dengue infected patients. N-acetylcysteine and artificial liver support are currently used as a bridge to liver transplantation. However, studies of both treatments have had some limitations including lack of randomization, small sample size, and the nature of multiple organ failure in severe forms of dengue infection. These new treatment modalities should be considered for use on a case-by-case basis, and more data is needed to support their usage.

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