

CURRENT MANAGEMENT OF LIVER COMPLICATIONS IN ADULT DENGUE INFECTION

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Abstract. Adult dengue patients have a high prevalence of abnormal liver function tests in about 75-80% for aspartate aminotransferase (AST), followed by 52-54% for alanine aminotransferase (ALT) whereas the incidence of patients with acute liver failure (ALF) caused by dengue infection was 0.31%. The average duration from onset of fever to clinical symptoms of ALF was 7.5 days with a mortality rate of 67%. Our article aims to detail the clinical findings of liver involvement, especially those presenting with ALF, and the current management including N-acetylcysteine (NAC) and artificial liver dialysis.

Keywords: liver complications, adults, dengue

INTRODUCTION

Dengue infection is a major mosquito-borne viral disease of the tropical countries and is becoming a global problem (Stanaway *et al*, 2016; Subedi and Taylor-Robinson, 2016; Zambrano *et al*, 2016) with an estimated number of 60 million symptomatic dengue infections annually as well as 10,000 deaths per year. Clinical presentations in adult patients are different from child patients (Martinez Vega *et al*, 2016). Severe infection, namely DHF or dengue shock syndrome (DSS), were more prevalent in adults than in children (Wichmann *et al*, 2004).

Liver involvement is common in dengue infection, and acute liver failure (ALF) is one of the serious and emergent complications of dengue (Souza *et al*, 2004). This review article aims to describe the prevalence and severity of abnormalities of liver function test in adult patients with dengue infection. In addition, we aim to describe the current management of the severe

dengue-infected patients with liver involvements, especially those presenting with ALF.

MATERIALS AND METHODS

We retrospectively reviewed data from a PubMed search, which includes Medline, that was performed to identify relevant literature using search terms “**liver and dengue infection and burden**” during a 20-year period from 1996 to 2016. All relevant literatures of adult dengue patients with liver involvement were reviewed. Specific terms were defined: 1) adult was defined as age greater than or equal to 15 years; 2) abnormal AST and/or alanine aminotransferase (ALT) 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 World Health Organization (WHO) criteria with serological confirmation by enzyme-linked immunosorbent assay test or rapid immunochromatographic test; and 4) the 2009 WHO classifications were used to categorize dengue patients as dengue (with or without warning signs) and severe dengue.

RESULTS

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

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Recently, the data from 15 articles related to liver tests abnormalities in dengue-infected patients during 1997-2013 showed a high prevalence of 75-80% for the presence of an abnormal AST, followed by 52-54% for the presence of an abnormal ALT (Martinez Vega *et al*, 2016; Wang *et al*, 2016). Additionally, liver impairment in adult dengue patients was more frequently found compared with child dengue patients [liver impairment defined as ALT > 2 × upper limit of normal (ULN)], 47.1 vs. 25.5%; or severe hepatitis defined as AST/ALT >10 × ULN, 16.5 versus 4.3% (Martinez Vega *et al*, 2016; Wang *et al*, 2016).

Our previous report showed that the mean age of adult dengue patients ±SD was 26.4±11.5 years, two-thirds of them had a severe form of dengue infection, and most of them had no underlying liver disease (Kittittrakul *et al*, 2015). Recently, data from Thailand showed that the incidence of patients with ALF caused by dengue infection was 0.31% (Kye Mon *et al*, 2016).

The dengue-infected patients with high levels of transaminitis usually presented with longer duration of fever of at least 1 week (Kittittrakul *et al*, 2015). The average duration from onset of fever to clinical symptoms of ALF was 7.5 days with a mortality rate of 67% (Kye Mon *et al*, 2016). Previous studies have shown that the dengue-infected patients presenting with severe acute hepatitis were usually infected with dengue serotypes 3 or 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). However, there was an evidence of multi-serotype dengue viral infections from Indonesia showing the concurrent presence of dengue serotype 2 and type 3 infections, both of which may contribute to the severity of disease (Lardo *et al*, 2016). Recent studies have shown the pattern of abnormal liver tests, in which the highest AST levels were seen on day 6 of the illness, and AST were significantly higher in patients with severe dengue than those with non-severe dengue (Fernando *et al*, 2016).

The clinical findings of liver complications in adult patients with dengue infection

The common clinical findings of liver complications in patients with dengue infection are hepatomegaly (28-72%) (Wichmann *et al*, 2004; Wichmann and Jelinek, 2004; Wang *et al*, 2009), abnormal liver tests (52-80%) (Wang *et al*, 2016), and severe hepatitis defined as AST/ALT >10 × ULN (16.5%) (Wang *et al*, 2016). The clinical presentation of severe hepatitis in dengue-infected patients had a significantly greater proportion of hypotension than those with low level ALT (25% vs 5%, respectively) (Kittittrakul *et al*, 2015). These findings are consistent with a previous report that the transaminase levels were associated with severity of vascular leakage and increased severity of bleeding (Trung *et al*, 2010).

In clinical practice, the primary physicians should be aware of and work up for the common causes of abnormal liver tests in critical patients, including ischemic hepatitis, liver test abnormality related to bacteremia, and drug-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 (Parkash *et al*, 2010; Behera *et al*, 2010).

The Current principles of management of ALT in adult patients with dengue infection

A. The current principles of management for hospitalized critically ill patients with acute hepatitis are the following:

1. Identify those patients with underlying chronic liver disease (Thomson *et al*, 2010). There is an evidence from a retrospective study showing that the cirrhotic patients presenting with dengue infection had poor clinical outcomes from acute liver decompensation with a mortality rate of 25%, which was higher than that reported in patients without chronic liver diseases (1.4%) (Table 1) (Kulkarni *et al*, 2016).
2. Exclude treatable and/or emergency hepato-

Table 1. Outcomes of DHF infection in cirrhosis patients: acute hepatic decompensation – retrospective study; 7/2015-4/2016 – India.

Outcome	Gr 1 No liver disease (n=71)	Gr 2 Chronic hepatitis (n=12)	Gr 3 Cirrhosis (n=12)	p value
Age, year (SD)	39.2 (1.6)	40.8 (16.3)	50.9 (7.9)	0.02
Jaundice, n (%)	6 (8.5)	1 (8.3)	7 (58)	<0.001
Ascites, n (%)	5 (7%)	0	7 (58)	<0.001
Death, n (%)	1 (1.4)	0	3 (25)	0.001
Survived, n (%)	70 (98.6)	12 (100)	9 (75)	

Modified from Kulkarni, *et al*, 2016. *Hepatology* 2016; 63(suppl): 1012, 206.

biliary diseases, for example, gallstone cholangitis or ALF. The high-risk group for developing ALF from dengue infection is those patients with a comorbidity, especially diabetes mellitus (Sam *et al*, 2013).

3. Identify the common causes of abnormal liver tests in critically ill patients, especially the causes from ischemic hepatitis and sepsis (Thomson *et al*, 2009). In addition, the specific host characteristics may influence the etiologies of abnormal liver tests, for example, pregnancy (Malhotra *et al*, 2006), AIDS, or elderly patients. There have been few studies focusing on co-infection of dengue virus and HIV infection. However, the seroprevalence of dengue virus infection in HIV-infected children was not different from that in healthy children (Thisyakorn *et al*, 2016; Torrentes-Carvalho *et al*, 2016; Delgado-Enciso *et al*, 2017). Finally, the physician should look for the possibility of abnormal liver tests caused by drug-induced liver injury. Recently, two reports have found evidences that acetaminophen overdose may play an important role in dengue-infected patients presenting with ALF (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/d) were reported in all children with fulminant hepatitis compared with none in the control group (Ranganathan *et al*, 2006).

B. The current principles of management of ALF in adult patients with dengue infection are the following:

1. N-acetylcysteine (NAC).
2. Provide temporary liver support as a bridge to liver transplantation: artificial liver support.

Both treatment modalities are mainly reported in case series that have limitations to inform guidelines because of the lack of good study design, small sample size, and the different definitions of ALF used in each study.

1. *N-acetylcysteine (NAC)*

The rationale for 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 ALF, the following NAC dosage regimen has been used: an intravenous (iv) loading dose of 150 mg/kg/d 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/24h until an INR of < 1.4 was achieved.

Previous studies have shown that dengue patients with ALF who were prescribed NAC had favorable outcomes as shown in Table 2 (Sklar and Subramaniam, 2004; Senanayake *et al*, 2013;

Table 2. The outcomes of treatment with 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	Survived with normal liver tests in 2 weeks
Manoj, <i>et al</i> , 2014	37-year male	FHF-AST 220 U/l, ALT 157 U/l, TO Day 7; AST/ALT 12,500/ 2,700 U/l, INR 1.7, TB 10 mg/dl	Gr III HE, Resp fail, UGIB-massive	Survived with discharge – Day 18
Lim, <i>et al</i> , 2012	6-year boy	Acute liver failure	No details	Survived
Abeysekera, <i>et al</i> , 2012	52-year; HT male	Acute liver failure	Gr II HE	Survived
Kumarasena, <i>et al</i> , 2010	N = 7 cases; Age: 6 mo-12 y	Acute liver failure	Low GCS, prolonged shock	Survived

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

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/d infusion for 5 days (Habaragamuwa and Dissanayaka, 2014).

2. IV NAC with 150 mg/kg loading dose, followed by iv administration over 15 minutes, then followed by 12.5 mg/kg/h for 4 hours, and finally iv drip administration 6.25 mg/kg/h for up to 72 hours (Kumarasena *et al*, 2010).

The second regimen was reported in a retrospective study of eight consecutive dengue-infected patients with ALF who showed complete recovery without adverse events from NAC treatment (Kumarasena *et al*, 2010).

2. 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 procedures. It is different from 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 non-biological systems including the albumin dialysis and plasma exchange are available worldwide as follows (Carpentier *et al*, 2009):

2.1 Molecular Adsorbent Recirculating System (MARS, Gambro, Sweden).

This was developed by Stange and Mitzner in 1993 (Fig 1). The key principle of this system is albumin dialysis, in which albumin plays an important role in scavenging function, and it can remove toxins as well as reduce hyperbilirubinemia in ALF patients (Sen *et al*, 2005). There was a case report that described the use of MARS in a critically ill dengue-infected patient who had a rapid improvement of biochemical tests and encephalopathy (Penafiel *et al*, 2006). MARS has some limitations including high cost and some technical difficulty in its usage (Penafiel *et al*, 2006). Recently, a meta-analytic study reported



Fig 1–The Molecular Adsorbent Recirculating System (MARS) in an intensive care unit.

the outcomes of MARS treatment in patients with ALF from 10 randomized control trials. It showed that MARS improved survival, but MARS did not show a survival benefit in cirrhotic patients with acute decompensation (He *et al*, 2015).

2.2 Prometheus (Fresenius, Germany). This was developed by Falkenhagen, *et al* in 1999. It uses the principle of fractionated plasma separation, adsorption, and hemodialysis (Tsipotis *et al*, 2015). Currently, there are no reports about the use of Prometheus in dengue-infected patients with ALF.

2.3 SPAD (Single pass albumin dialysis). These non-biological 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). Recently, there was a non-inferiority crossover study design comparing MARS with SPAD system procedures for total bilirubin reduction and clinical outcomes (Sponholz *et al*, 2016). The major findings showed that both systems were safe and had similar efficacy in plasma bilirubin reduction. However, MARS had better efficacy in reduction of serum bile acids, albumin-binding capacity than that by SPAD (Sponholz *et al*, 2016). At King Chulalongkorn

Memorial Hospital in Thailand, we have used albumin dialysis more often than other modalities due to the availability of equipment, lower cost, and ease of usage (Boonsrirat *et al*, 2009). Our previous study of using SPAD in patients with ALF 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% without serious complications (Boonsrirat *et al*, 2009).

Recently, a meta-analysis (7 trials of MARS and 3 trials of Prometheus), showed that albumin dialysis was superior in reducing serum total bilirubin level and improving hepatic encephalopathy compared with the standard medical therapy of 8.0 mg/dl; however, it did not show superior efficacy in reducing serum ammonia or bile acids (Tsipotis *et al*, 2015).

In summary, at least two-thirds of adult dengue patients have shown abnormal liver function tests. Acute severe hepatitis with an elevation of transaminase levels of at least 10 times has occurred in 4-15% of adult dengue-infected patients, and this should be a concern for the physician. Transaminases gradually decrease to normal levels within 2 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 diseases

may play important roles in causing ALF in dengue-infected patients. NAC and artificial liver support is 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 are needed to support their usage.

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