

# A Case of Dengue Hemorrhagic Fever and the Use of Supportive Therapy

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## INTRODUCTION

Dengue fever is a mosquito-bound viral illness that occurs in tropical climates. It is endemic in 110 countries.<sup>1</sup> Fifty to three hundred and ninety million people are infected worldwide every year,<sup>2</sup> leading to ~25,000 deaths.<sup>3</sup> It is often an asymptomatic self-limited illness, which can present with myalgias, arthralgias, and hemorrhagic manifestations such as petechiae. In a fraction of cases, dengue fever can proceed to dengue hemorrhagic fever (DHF), which can be life threatening causing thrombocytopenia, bleeding and increased vascular permeability. Dengue shock syndrome (DSS) can then ensue, if hypotension occurs, and is fatal in >10% of patients.<sup>4</sup>

Here we present a case of Dengue fever, which proceeded to DHF and finally DSS. Our case demonstrates the supportive nature of treatment and how catastrophic severe dengue fever can be.

## CASE PRESENTATION

A 64 year-old Pakistani female with a history of diabetes mellitus presented to her local hospital with severe body aches and malaise three days after returning from a two month long trip to Pakistan. During her stay, several family members had a self-limited febrile illness and one was diagnosed with dengue fever. On admission she was found to be febrile and thrombocytopenic, raising concern for dengue fever. She rapidly deteriorated with acute renal failure, acute liver failure (**Table 1**), new onset seizures, and required intubation and mechanical ventilation. She was then transferred to Thomas Jefferson University Hospital where she was emergently started on molecular adsorbent recycling system (MARS) therapy and continuous veno-venous hemodialysis (CVVHD).

Table 1. Labs on Admission

Lab Parameter	Value (normal range)	Lab Parameter	Value (normal range)
AST	11035 IU/L (7 – 35)	Sodium	138 mmol/L (135-146)
ALT	1925 IU/L (1 – 30)	Potassium	3.3 mmol/L (3.5 – 5)
Total Bilirubin	6.5 → 14.7 mg/dL (0.1 – 0.9)	Chloride	84 mmol/L (89 – 109)
Direct Bilirubin	5.3 → 13.2 mg/dL (0.0 – 0.3)	Bicarbonate	13 mmol/L (24 – 32)
Alkaline phosphatase	230 → 239 IU/L (25 – 120)	BUN	22 mg/dL (7 – 26)
GGT	254 IU/L (5 – 55)	Creatinine	2.3 mg/dL (0.7 – 1.4)
LDH	8490 IU/L (105 – 333)	Glucose	179 mg/dL (70 – 100)
Lactate	27.6 mmol/L (0.5 – 2.2)	Anion Gap	13 mmol/L (4 – 16)
PT	25.9 seconds (8.6 – 13.0)	WBC	6.7 B/L (4 – 11)
INR	2.44 sec (0.79 – 1.21)	Bands	30 % (0 – 9)
PTT	39 sec (28 – 38)	Hemoglobin	8.4 g/dL (12.5 – 15)
Fibrinogen	180 mg/dL (203 – 451)	Hematocrit	25.5 % (36 – 46)
D dimer	2661 ng/mL (<331)	Platelets	33 B/L (140 – 400)

### DIFFERENTIAL DIAGNOSIS

The patient's recent history of travel suggested an infectious etiology, particularly dengue as it is endemic in Pakistan. In addition, history obtained provided evidence of a local outbreak. Furthermore, her timeline of fevers and thrombocytopenia 3-7 days after her return supported the diagnosis of DHF. The incubation period for dengue is typically 3-14 days.<sup>5</sup> Congo fever was also considered but was less likely as it isn't commonly seen in the area she visited in Pakistan. As her hospital course progressed and she became more thrombocytopenic with increasing evidence of severe vascular permeability (Figure 1), the diagnosis of DHF became more apparent. In addition, her serum dengue IgG and IgM were reported positive several days after admission.

### OUTCOME AND FOLLOW-UP

Although her aminotransferase levels improved rapidly on MARS (Table 2), the patient's hospital course was complicated by seizures and a new large ischemic stroke in the left medial temporal region. After one week of MARS therapy with no improvement in her mental status, she underwent a transjugular liver biopsy that showed 50-75% necrosis of liver parenchyma. Given her poor prognosis secondary to severe dengue infection, as well as the aforementioned stroke, she was deemed unsuitable for liver transplant. Post-ischemic stroke she did not have focal deficits, but it was difficult to fully neurologically assess her because of unresponsiveness. She was maintained on MARS/CVVHD for one more



Figure 1. The tourniquet test also known as the capillary-fragility test. Seen in areas of pressure, such as tourniquets or blood pressure cuffs.

week with the hope that longer therapy would improve her outcome. Her hospital course was complicated by tracheobronchitis and septic shock requiring multiple vasopressors. As she still had no sign of neurologic recovery, the family decided to withdraw life support.

Table 2: Lab Values Pre and Post Therapy		
Lab	Pre-supportive Therapy (normal range)	Post-supportive therapy (normal range)
AST	10705 IU/L (7 – 35)	101 IU/L (7 – 35)
ALT	1924 IU/L (1 – 30)	73 IU/L (1 – 30)
Total Bilirubin	6.5 mg/dL (0.1 – 0.9)	14.7 mg/dL (0.1 – 0.9)
Direct Bilirubin	5.3 mg/dL (0.0 – 0.3)	13.2 mg/dL (0.0 – 0.3)
Lactate	24.8 mmol/L (0.5 – 2.2)	7.2 mmol/L (0.5 – 2.2)
Creatinine	2.3 mg/dL (0.7 – 1.4)	0.8 mg/dL (0.7 – 1.4)
Pre-support therapy: before MARS and CVVHD were initiated Post-supportive therapy: after MARS and CVVHD were initiated		

## DISCUSSION

Dengue fever is caused by the dengue virus, which is carried by several species of the mosquito in the genus *Aedes*. Classic dengue fever is a self-limited febrile illness that may last up to one week. However, it can become more severe and proceed to the hemorrhagic form where profound increases in vascular permeability can lead to shock and possibly multi-organ failure. The mechanism behind the vascular permeability is unknown but is thought to be secondary to the overwhelming inflammatory response to the virus.<sup>6</sup>

The treatment for dengue is entirely supportive, consisting of aggressive fluid resuscitation. MARS and CVVHD therapy may also be used for life threatening sequelae with potential improvement of acute liver failure, acute kidney failure, and disseminated intravascular coagulation.<sup>5</sup>

There is little evidence regarding the use of MARS in the setting of dengue fever. One case report demonstrated rapid improvement in a patient with dengue-associated hepatic encephalopathy and fulminant hepatic failure after treatment with MARS and CVVHD.<sup>7</sup> The patient's transaminitis rapidly corrected with MARS, with associated resolution of hepatic encephalopathy. The length of MARS with concurrent CVVHD in this case was three days. In our patient, MARS therapy corrected the transaminitis but did not affect her mental status. It was also surprising that her bilirubin levels remained elevated despite MARS which usually removes albumin-based substances such as bilirubin and bile acids.<sup>8</sup> It was unclear if her altered mental status was secondary to hepatic encephalopathy, stroke, uremia, or infection.

In hindsight, MARS may not have been indicated in this patient for an additional week after no clinical improvement in the first few days. There are no clear guidelines on the use of MARS or hemodialysis in a patient with acute liver failure. In one study evaluating the improvement in mental status in patients with acute liver failure and encephalopathy who were placed on hemodialysis, 61.5% had either total (43.6%) or partial (17.9%) regaining of consciousness.<sup>9</sup> Comparisons have been made between MARS in combination with continuous veno-venous hemodiafiltration (CVVHDF), CVVHDF alone, and single-pass albumin dialysis (SPAD).<sup>7</sup> All three forms are similar because they remove some

type of waste product from the circulation. SPAD uses a standard renal replacement machine with an albumin dialysate solution and no additional recirculation pump, whereas MARS uses standard dialysis solution, an albumin solution, and an additional recirculation pump. MARS and SPAD were both efficient *in vitro* at removing albumin-bound substances, such as bilirubin; SPAD was actually superior to MARS in removing bile acid waste. Both SPAD and CVVHDF were better than MARS in taking out water-soluble solutes such as ammonia. The most notable difference was that SPAD cost significantly less than MARS; for a seven-hour session, SPAD cost \$810 whereas MARS cost \$2641. In our patient, MARS was an expensive treatment to continue without any proven correlation between prolonged length of use and improvement in mortality. Cost-effectiveness must be taken into consideration when alternate therapies are available for fractions of the cost.

As an adjuvant therapy for her fulminant hepatic failure, our patient also received eight days of N-acetylcysteine (NAC). NAC has been shown to be beneficial in patients when liver transplant is not available for non-acetaminophen associated acute liver failure. In a retrospective analysis of eight patients with dengue-associated acute liver failure, NAC was shown to be beneficial in early stages of liver failure but not in advanced stages.<sup>10</sup> The patient in this analysis had a maximum length of NAC use of 72 hours. No analysis exists comparing MARS versus NAC, or using both treatments, for improved outcomes in acute liver failure.

## KEY POINTS

The treatment for dengue hemorrhagic fever is entirely supportive. Guidelines for the length of MARS treatment in dengue patients in fulminant hepatic failure needs to be further evaluated, as MARS is an expensive treatment only available at a few tertiary level centers.

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*"Serenity on Howe Sound, British Columbia"*  
photograph by Andrew Zabolotsky

