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CASE REPORT | LIVER

# Acute Liver Failure in a Patient With Dengue Shock Syndrome

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## ABSTRACT

Dengue is an arboviral disease of significant burden in tropical countries. It commonly affects the liver, ranging in presentation from asymptomatic transaminitis to acute liver failure. We present a young woman from India who developed acute liver failure because of dengue shock syndrome and improved without a liver transplant. We review the disease characteristics and management of dengue, with a focus on the natural history of illness and how to approach the possible need for liver transplant in these patients.

## INTRODUCTION

Dengue is a febrile illness caused by infection with 1 of 4 dengue viruses transmitted by the *Aedes* mosquito, with dengue virus 2 having the highest risk for severe infection.[1] It is an arboviral disease of a significant burden in tropical countries with an increasing prevalence: the global estimate of dengue infections was approximately 75 million in 1997 and approximately 150 million in 2008.[2] This increase is secondary to poor hygiene, inadequate health systems, and increased international travel, which has facilitated *Aedes* mosquito proliferation. Seventy percent of cases are in Asia, with India alone having 34% of the global total.[2] Dengue fever is defined by fever and at least 2 of the following symptoms: ocular pain, headache, muscle/joint pain, rash, or leukopenia. There is an incubation period of 3–7 days, and the symptoms are divided into 3 phases: febrile phase (2–7 days), critical phase (day 3–7 of illness, with vascular leakage, shock, and/or organ damage), followed by a convalescent phase.[3] The disease most commonly affects the liver compared with other organs.[3] Dengue causes liver damage through multiple mechanisms: direct viral effects on hepatocytes and Kupffer cells, immunologic hyperactivity via a T cell-mediated cytokine storm, and circulatory failure that leads to decreased hepatic perfusion.[4] Effects on the liver range from asymptomatic transaminitis to acute liver failure (ALF). We present a young woman who developed ALF secondary to dengue shock syndrome (DSS).

## CASE REPORT

A 23-year-old woman arrived in the United States from India 3 days before admission and presented with fever, nausea, emesis, diffuse abdominal pain, myalgias, and weakness. On presentation, her temperature was 39.6°C, heart rate was 110 beats per minute, and blood pressure was 97/58 mm Hg. Examination demonstrated right upper quadrant abdominal tenderness, hepatomegaly, and scattered petechiae over her lower extremities. Laboratory evaluation was pertinent for a platelet count of 13 K/mm$^3$, aspartate aminotransferase (AST) 1520 U/L, alanine aminotransferase (ALT) 605 U/L, albumin 2.1 g/dL, alkaline phosphatase 53 U/L, total bilirubin 1.6 mg/dL, and international normalized ratio (INR) 2.2. Her acetaminophen (APAP) level was 9 μg/mL. Viral hepatitis panel and a broad infectious workup were negative. Computed tomography scan demonstrated moderate ascites, pericholecystic fluid, bilateral pleural effusions, and subtle lucency around the portal vein branches with an otherwise normal liver (Figure 1).

Given the patient's recent move from India in the setting of her clinical presentation and laboratory findings, she was tested for dengue fever antibodies immunoglobulin G and immunoglobulin M, which were both positive (viral subtype testing was not performed). She received platelets and N-acetylcysteine (NAC) for supportive therapy, as well as APAP and external cooling for fever. Fluids were administered for sustained tachycardia to 150 beats per minute and persistently elevated lactate above 4.0 mmol/L; she then experienced transient hypoxic

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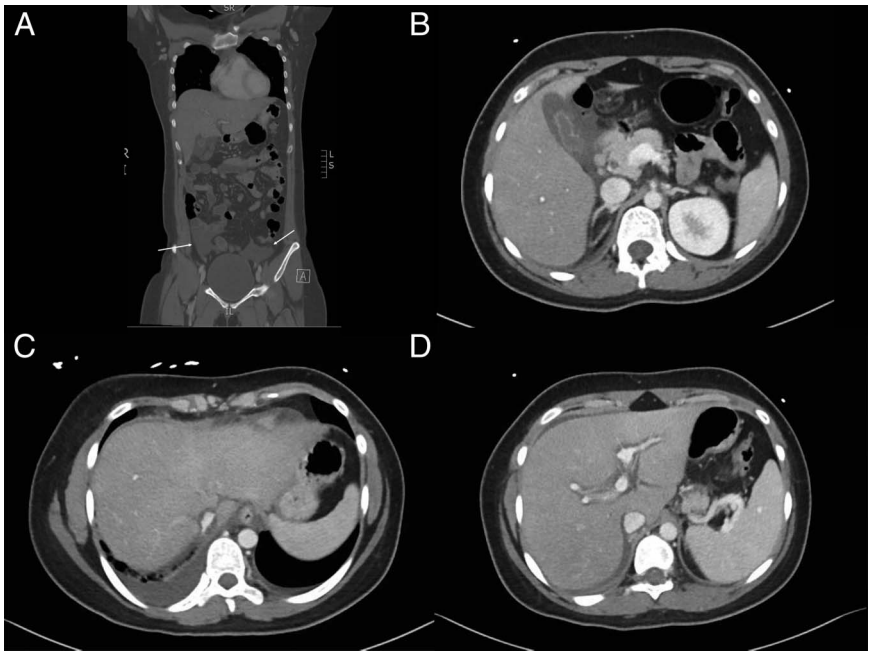


**Figure 1.** Abdominal computed tomography showing (A) moderate ascites, which is most prominent in the pelvic area (see arrows) in coronal view, (B) pericholecystic fluid, (C) bilateral pleural effusions, right greater than left, and (D) periportal effusion, seen as areas of hypoattenuation around the portal vein branches, and a normal-appearing liver.

respiratory distress that improved with diuresis and supplemental oxygen. Her transaminitis worsened, peaking at AST 15,700 U/L and ALT 3100 U/L. She developed stage III hepatic encephalopathy, and her INR peaked at 3.5, consistent with the progression to ALF; she was subsequently listed for liver transplant while supportive care was continued. One day after listing, her liver tests began to improve, with the resolution of fevers, tachycardia, and altered mental status over the following 24 hours. She gradually made a complete recovery without requiring a transplant.

## DISCUSSION

Dengue infection is associated with a spectrum of illness severity. In addition to dengue fever, dengue hemorrhagic fever is defined by fever, signs of hemorrhage, thrombocytopenia, and plasma leakage secondary to increased vascular permeability, which was seen on our patient's computed tomography scan. The most severe form of dengue is DSS, which is dengue hemorrhagic fever with circulatory collapse.[3] Our patient progressed to DSS, as evidenced by her requiring fluids for hemodynamic support.

From a liver perspective, patients with dengue typically endorse abdominal pain, nausea, emesis, and anorexia, with hepatomegaly with or without jaundice. Laboratory findings include transaminitis, hyperbilirubinemia, hypoalbuminemia, and elevated INR. Our patient demonstrated these classic findings, but her presentation was unique in the severity of her transaminitis. Although elevated AST and ALT levels are seen in 63%–97% and 45%–96% of dengue patients, respectively, only 4% of cases have a 10-fold transaminitis increase; our patient's peak AST and ALT levels were 380 and 50, respectively, times the upper limit of normal.[3,5] Her severe liver injury was likely multifactorial. In addition to dengue's direct hepatic effects, she had significant hemodynamic compromise that was concerning for possible ischemic hepatitis. Moreover, liver injury decreases APAP metabolism and APAP-related hepatotoxicity can happen with multiple, small overdoses.[6] Given her initial detectable APAP level, and that she received 3 doses of 650 mg in-house (to control fever before concern for APAP-related liver injury), this potentially contributed to hepatic injury.

Treatment of dengue is supportive because there is no direct antiviral therapy. Oral fluids are encouraged, with intravenous fluids and blood products given if needed. Fluids should be used judiciously during the critical illness phase, given that vascular leakage combined with fluids predisposes patients to respiratory compromise, which happened with our patient.

Another component of therapy is NAC. NAC prevents hepatic damage by scavenging free radicals, improving systemic hemodynamics, and optimizing tissue oxygen delivery.[7] Case reports suggest giving NAC early in the course of ALF-associated DSS, as was done with our patient.[8]

Although dengue commonly results in liver damage, ALF rarely develops. The risk of progression to dengue-associated ALF is difficult to estimate because the literature is limited to case series and case reports. One study in Thailand estimated a 0.31% incidence of ALF secondary to dengue.[9] A case series of 8 patients with ALF secondary to dengue showed that the median duration from fever onset to ALF was 7.5 days, with the majority presenting with severe hepatitis (peaking 5–13 days from fever onset) and hepatic encephalopathy.[10] Those who survived the

first 1–2 days of the critical illness phase entered the convalescent phase just after transaminitis peak and then improved with supportive therapy alone; this occurred with our patient. In that case series, only one patient had the most severe form of dengue, DSS, and that patient improved without requiring a transplant.[10] There are only a few cases of adult patients with DSS-associated ALF that recover with supportive therapy alone; our case thus supports the idea that transplant can be avoided in DSS-associated ALF. Recognizing that clinical improvement is likely to occur within 24–48 hours after transaminitis peak is critical to medical decision-making and optimizing limited resources.

However, in the rare circumstance of deterioration during the critical illness phase, a liver transplant can be considered, with a recently reported successful transplant in dengue-associated ALF.[11]

## DISCLOSURES

Author contributions: J. Lewis wrote the manuscript and is the article guarantor. A. Mitra and M. Chang edited the manuscript.

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Informed consent was obtained for this case report.

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