International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Case Study *DOI: 10.61336/im/26-06-121*

Severe Dengue Fever with Hepatitis in Infants and the Role of N-Acetylcysteine in Non-Acetaminophen Acute Liver Failure: A Case Series

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Received: **May 08, 2026**
Revised: **May 19, 2026**
Accepted: **June 08, 2026**
Published: **June 20, 2026**

Abstract

Dengue virus infection can cause significant hepatic injury through cytokine-mediated inflammatory pathways, occasionally progressing to pediatric acute liver failure (PALF). PALF in the context of severe dengue is associated with coagulopathy, encephalopathy, and high morbidity and mortality. We report two infants with severe dengue who presented with marked thrombocytopenia, deranged coagulation profiles, and transaminase levels elevated more than fivefold above baseline. Both infants demonstrated hepatomegaly and clinical jaundice, with an international normalized ratio (INR) persistently >1.5. N-acetylcysteine (NAC) therapy was initiated on day 8 of hospitalization in Case 1 and on day 4 in Case 2. Both infants showed rapid biochemical and clinical improvement following NAC infusion, with normalization of liver function tests and coagulation parameters within 72 hours. Although the role of NAC is well established in acetaminophen-induced acute liver failure, its utility in non-acetaminophen PALF—particularly dengue-associated hepatitis—is less frequently reported in children. Our findings support the potential benefit of early NAC administration in dengue-induced PALF and highlight the need for larger systematic studies.

Keywords: NAC - N-acetylcysteine, PALF -Pediatric acute liver failure, IL- Interleukins

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INTRODUCTION

Dengue is a mosquito-borne viral infection and remains the most prevalent arthropod-borne disease worldwide. The primary vectors, *Aedes aegypti* and *Aedes albopictus*, are widely distributed across tropical and subtropical regions. Dengue continues to be a major public health challenge, with children disproportionately affected. Globally, an estimated 25,000 pediatric deaths occur annually, and more than 100 countries report endemic transmission (1-3).

Pediatric acute liver failure (PALF) is an uncommon but severe and often fatal complication of dengue. The underlying mechanisms include dysregulated cytokine responses, direct viral cytopathic injury, hypoxic–ischemic damage during shock, and immune-mediated hepatocyte apoptosis (4,5). Elevated levels of inflammatory cytokines—particularly interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor-α (TNF-α), and interferon-γ—are closely associated with increased disease severity. Among these, IL-6, IL-8, IL-10, and IL-17 show the strongest association with severe dengue, bleeding manifestations, plasma leakage, and dengue-associated hepatic injury (8-10).

Although the overall prevalence of dengue-associated acute liver failure is low (approximately 0.31%), morbidity and mortality remain high, particularly in patients younger than 40 years.[7] Hepatic injury in dengue classically peaks around the sixth to seventh day of illness, coinciding with cytokine surges and the critical phase of the disease (6,7).

The role of N-acetylcysteine (NAC) as an antidote in acetaminophen-induced acute liver failure is well established. However, its utility in non-acetaminophen PALF—including dengue-associated hepatitis—has been less clearly defined. Emerging evidence suggests that NAC may have hepatoprotective effects by replenishing glutathione stores, reducing oxidative stress, and modulating cytokine cascades (5,8).

In this case series, we present two infants with severe dengue who developed significant hepatic dysfunction and responded favorably to NAC infusion, highlighting its potential therapeutic role in dengue-associated PALF.

Case 1

A 2-month-9-day-old female infant presented with a 3-day history of fever, rash, and vomiting. On admission she had persistent hypertension (>99th percentile) and hepatomegaly measuring 4 cm below the right costal margin (RCM), progressing to 8 cm by day 4. Abdominal distension developed by day 3. Ultrasound on day 6 showed mild ascites, hepatomegaly, and a distended gallbladder.

CBC revealed borderline thrombocytopenia (1.56 lakh/µL), declining to 16,000/µL by day 4. Dengue NS1 antigen was positive. LFTs showed rising AST, ALT, and total bilirubin, peaking on day 4 (Figure 1 & 2). The coagulation profile was deranged, with APTT reaching 200–247 seconds and INR consistently >1.5 (Figure 3).

Supportive treatment included IV fluids, fresh frozen plasma, and vitamin K. Despite this, hepatic parameters continued to worsen. NAC (100 mg/kg infused over 24 hours for 3 days) was initiated on day 8. Within 72 hours, liver enzymes, bilirubin, and coagulation parameters showed marked improvement. Liver size regressed to 4 cm by discharge.

Hypertension was managed with oral amlodipine.

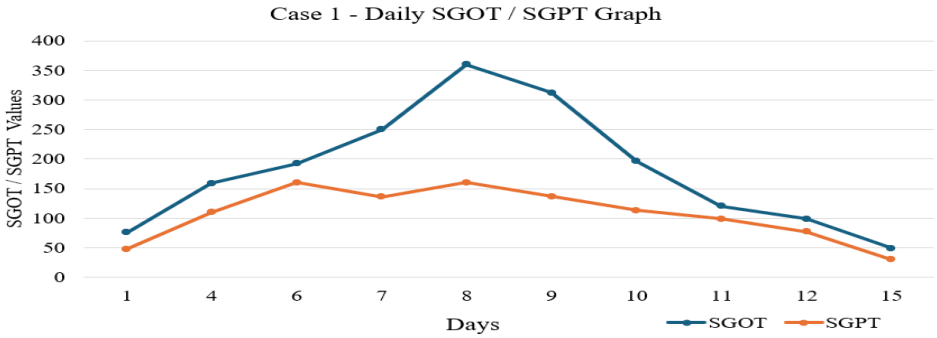

Figure 1 - Case 1 showing rising trend of liver enzymes and declining trend after adding NAC on day 8 of hospitalization and day 11 of illness.

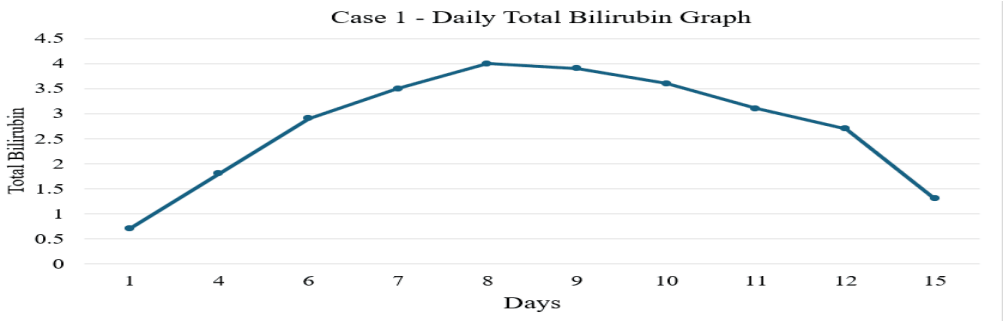

Figure 2 - Case 1 showing rising trend of Total bilirubin and declining trend after adding NAC on day 8 of hospitalization and day 11 of illness.

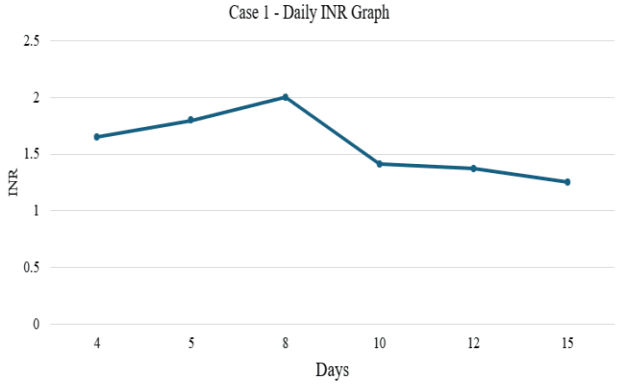

Figure 3 - Case 1 showing rising trend of INR and declining trend after adding NAC on day 8 of hopsitalization and day 11 of illness

Case 2

A 2-month-2-day-old male infant presented with 5 days of fever and decreased activity. Hepatomegaly of 7–8 cm below the RCM was noted. The child was irritable and refused feeds.

Initial platelets were 1.24 lakh/µL, decreasing to 13,000/µL by day 3. Dengue NS1 antigen was positive. Liver enzymes rose to more than 5.5-fold above baseline. Total bilirubin increased to 5.1 mg/dL, and the infant exhibited grade I encephalopathy. INR remained >1.5 on serial monitoring.

Supportive care did not result in improvement. NAC therapy (100 mg/kg/day infused over 24 hours for 72 hours) was initiated on day 4. The infant improved dramatically, with rapid normalization of AST, ALT, bilirubin, and INR. Hepatomegaly improved to 3 cm below the RCM, and the child resumed breastfeeding.The infant recovered fully without adverse effects related to NAC therapy.

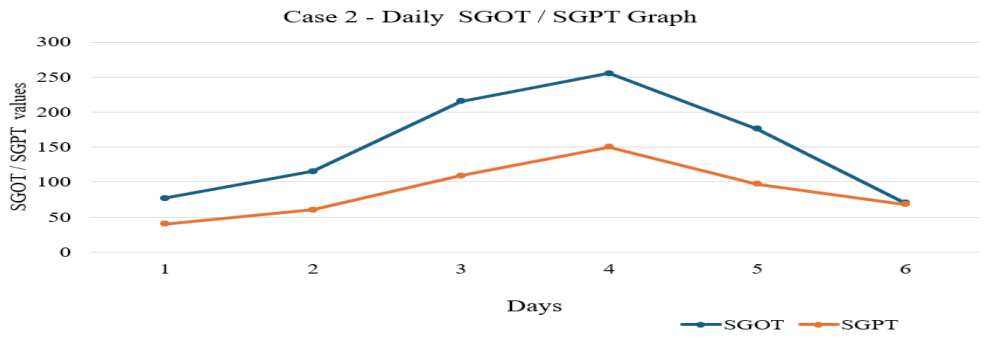

Figure 4 - Case 2 showing rising trend of liver enzymes and declining trend after adding NAC on day 4 of hospitalization and day 9 of illness.

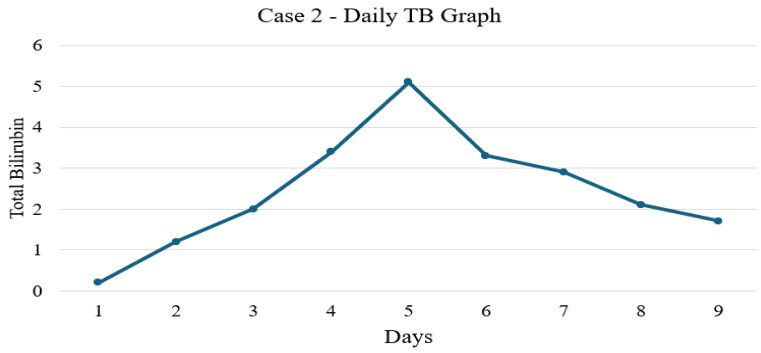

Figure 5 - Case 2 showing rising trend of TB and declining trend after adding NAC on day 4 of hospitalization and day 9 of illness.

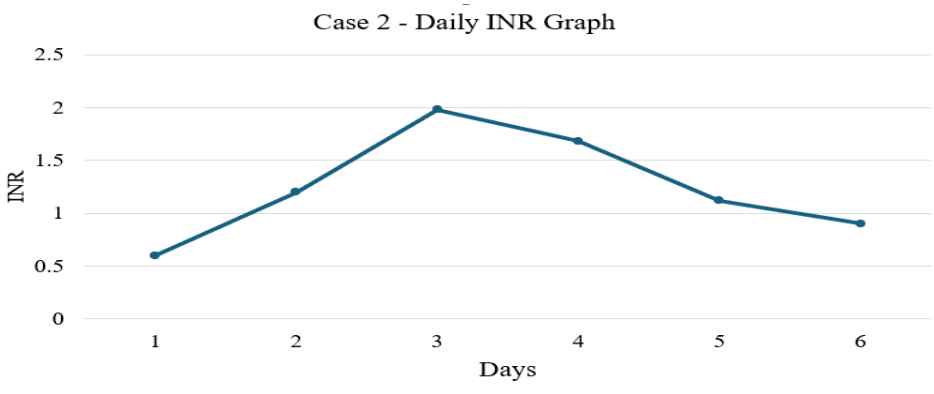

Figure 6 - Case 2 showing rising trend of TB and declining trend after adding NAC on day 4 of hospitalization and day 9 of illness

Child was started on IV fluids and supportive care did not result in improvement. NAC therapy (100 mg/kg/day infused over 24 hours for 72 hours) was initiated on day 4. The infant improved dramatically, with rapid normalization of AST, ALT, bilirubin, and INR. Hepatomegaly improved to 3 cm below the RCM, and the child resumed breastfeeding.

DISCUSSION

In both cases presented, the infants developed significant hepatic involvement secondary to severe dengue infection. Dengue virus can directly infect hepatocytes and Kupffer cells, leading to cellular injury. In addition, multiple indirect mechanisms—including hypoxic and ischemic injury during shock, oxidative stress, and dysregulated immune responses—contribute to hepatocellular damage and progression to pediatric acute liver failure (PALF). The resulting cytokine surge, particularly elevations in IL-6, IL-8, IL-10, and IL-17, exacerbates liver injury and correlates with the severity of dengue.[8–10]

During the acute phase of dengue infection, hepatic antioxidant enzymes such as glutathione peroxidase and glutathione reductase are diminished, while AST and ALT levels rise substantially. N-acetylcysteine (NAC), a precursor of glutathione, replenishes intracellular glutathione stores, mitigates oxidative stress, and supports redox reactions. These mechanisms may explain its therapeutic benefit beyond acetaminophen toxicity.[11] In our infants, the initiation of NAC was followed by rapid improvements in transaminases, bilirubin levels, coagulation parameters, and clinical status.

Several previous reports support the use of NAC in dengue-associated liver failure. Senanayake et al. described seven children with severe dengue complicated by ALF and altered consciousness; all received NAC, with four responding after a single dose and the remaining three requiring two or three doses. All patients showed eventual recovery.[12]

Stravitz et al. conducted a randomized trial involving 79 patients with non-acetaminophen–induced ALF. The etiologies included autoimmune hepatitis, hepatitis A and B, idiosyncratic drug reactions, and other causes. The study demonstrated that patients receiving NAC showed a more rapid decline in IL-17 levels compared with placebo ($p = 0.045$). Elevated IL-17 in early and late serum samples correlated with mortality or liver transplantation, suggesting that IL-17 may serve as a prognostic biomarker.[5]

In another important trial, Lee et al. conducted a randomized, double-blind study of 173 patients with acute liver failure of various etiologies. The NAC group demonstrated a higher transplant-free survival rate (52%) compared with the placebo group (30%). Liver transplantation occurred less frequently in the NAC group (32% vs 45%).[6] These findings support the hepatoprotective and immunomodulatory role of NAC in non-acetaminophen ALF.

In the context of dengue, Kye Mon et al. observed that severe dengue infection was strongly associated with acute liver failure ($p < 0.001$). Among 1,926 serologically confirmed dengue cases, six developed ALF, and four of these patients died.[7] Imad et al. found that rising IL-8 levels were associated with a nearly 100-fold increase in transaminase levels. They noted that IL-8 likely originates from damaged hepatocytes and recruits neutrophils, further amplifying hepatocellular injury.[8]

In our case series, both infants demonstrated significant hepatic dysfunction and coagulopathy, meeting criteria for PALF. Despite supportive care—including fluids, vitamin K, FFP, and close monitoring—hepatic parameters continued to worsen. The initiation of NAC resulted in rapid biochemical and clinical improvement in both cases, without adverse effects. Although reports of NAC use in pediatric non-acetaminophen liver failure remain limited, our findings add to the growing evidence supporting its therapeutic potential in dengue-associated ALF.

Larger, controlled studies are warranted to better define the efficacy, optimal timing, and dosing of NAC in pediatric dengue-associated hepatitis. Nonetheless, early consideration of NAC in severe dengue with progressive hepatic dysfunction may improve outcomes in this vulnerable population.

CONCLUSION

Dengue associated PALF carries high morbidity and mortality. In these two infants, early administration of NAC led to rapid improvement in hepatic function and clinical status. Given its favorable safety profile and biologically plausible mechanisms, NAC should be considered in severe dengue with evolving hepatic failure. Larger pediatric studies are needed to further validate its role.

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