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Hot Topic Commentary

Dengue Viral Infection and Associated Liver Disease

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Dengue virus (DENV), an RNA virus that belongs to the genus Flavivirus, is transmitted primarily by the *Aedes aegypti* mosquito. The disease is endemic in more than 100 countries, with the highest burden reported in South Asia, Southeast Asia, and tropical Latin America.[1] However, with the progression of climate change, the endemicity of the *Aedes* mosquito has been increasingly reported in non-tropical, formerly temperate areas of the world.[1] In the U.S., Puerto Rico, American Samoa, and the U.S. Virgin Islands have reported endemic cases.[2] The majority of people with dengue have mild or no symptoms, which can lead to self-management and underdiagnosis.[3]

Clinically, dengue is classified into three categories: dengue without warning signs (DWoWS), dengue with warning signs (DWWS), and severe dengue.[3] DWoWS, comprising 65% of patients, is characterized by fever, nausea or vomiting, rash, aches, and muscular pains. In severe dengue, liver injury can range from mild aminotransferase elevation to acute hepatitis and liver failure.[1]

The incidence is increasing, and liver injury in dengue infection is common but not commonly appreciated. A recent excellent systematic review discusses the epidemiology and mechanisms, diagnosis, and treatment of hepatic involvement in typical dengue infections.[4] The unique aims of the current commentary are to illustrate differences between the time courses of serological and liver enzyme elevations in mild and severe dengue infections, with an emphasis on the importance of early recognition of progression to acute liver failure (ALF). In addition, the commentary aims to review current recommendations for vaccination and prevention of dengue infection, as well as severe hepatitis and ALF.

After an incubation period of 3–14 days, patients usually develop fever, retro-orbital pain, headache, muscle ache, arthralgia, nausea, vomiting, diarrhea, and rashes. Most cases are mild, and less than 5% progress to severe, life-threatening disease. Fifty to eighty percent develop rashes or petechiae. In severe disease, shortly after defervescence, plasma leakage, with or without bleeding, can occur, resulting in ascites and pleural effusion. This can lead to hypovolemic shock, resulting in multiple organ dysfunction, metabolic acidosis, disseminated intravascular coagulation, and severe bleeding. Hepatic injury manifests as right subcostal pain and hepatomegaly with tenderness.[1]

Autopsy studies in fatal dengue cases have revealed common pathological features, including areas of necrosis mainly in the midzone and centrilobular regions, microvesicular steatosis, Kupffer cell hyperplasia, hepatocyte necrosis, Councilman bodies, absence of fibrosis, and rare cholestasis.[5] DENV antigens have been found in hepatocytes and Kupffer cells. It should be recognized that most histopathological studies of liver biopsies were obtained from severe, not typical, dengue cases. Therefore, the published histopathological findings are likely biased in terms of severity and not reflective of typical cases.

The diagnosis is suspected in patients presenting with fever of two to seven days' duration associated with at least two of the following: petechiae, nausea/vomiting, headache, rash, muscle ache, or arthralgias. Leukopenia and a positive tourniquet test are supportive. Right upper quadrant pain and hepatomegaly are alarming signs that suggest severe disease.[3]

Confirmatory testing includes detecting viral nucleic acids, antigens, or antibodies. Early diagnosis can be made with reverse transcription polymerase chain reaction, non-structural protein 1 enzyme-linked immunosorbent assay, and immunoglobulin M enzyme-linked immunosorbent assay, with a sensitivity/specificity of 95%/89%, 90%/93%, and 71%/91%, respectively (Fig. 1).[1,3,6]

Liver injury from dengue infection is thought to occur through several possible mechanisms, including direct viral hepatotoxicity, immune-mediated response, and hypoperfusion during shock states.[7] The majority (75%) of patients with dengue reportedly develop elevated aminotransferase levels, while only 25% show no elevations. The degree of damage varies depending on disease severity, as reflected by greater increases in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin (Fig. 2).[3,8–10] Levels tend to return to normal 14–21 days after infection. An aspartate aminotransferase above 120 U/L in the early stage of disease, 3–5 days after symptom onset, has an area under the curve (AUC) of 0.93 for predicting severe dengue ($P < 0.001$).[8] Gamma-glutamyl transferase and interleukin-10 are significantly higher, and albumin levels are significantly lower, in severe dengue patients compared to non-severe cases.[9]

The incidence of ALF in patients with dengue varies between 0.31% and 1.1%, and mortality in these patients is as high as 66.7% (Table 1), accounting for 90% of deaths seen in patients who develop severe hepatitis.[11–15] Thus,

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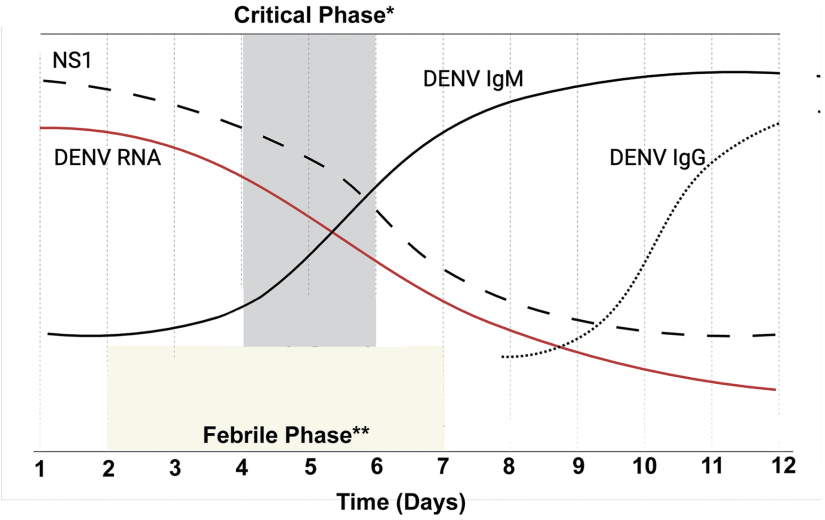

Fig. 1. A time course of fever, antigens, and antibodies in typical dengue infection. NS1, non-structural protein 1; DENV, dengue virus. X axis: days after onset of symptoms, from 1 to 12. ** Febrile phase: two to seven days of fever that could be accompanied by petechiae, nausea/vomiting, headache, rash, muscle ache, arthralgias, leukopenia, or a positive tourniquet test. * Critical phase: during defervescence, a period of increased risk of plasma leakage, ascites, liver failure, and multiple organ dysfunction. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) usually peak between days 4 and 6. Adapted from.[1,3] Created in BioRender. SANTIAGO, M. (2026) https://BioRender.com/907lmmt.

early recognition of patients at risk of progressing to ALF is important. International normalized ratio, total bilirubin, albumin, and creatinine have been described as independent laboratory parameters associated with ALF.[11,13] Patients with chronic hepatitis B virus or hepatitis C virus co-infection and acute dengue infection have been reported to have higher aminotransferase elevations and hepatic dysfunction compared to those without underlying chronic liver disease. A case of ALF was reported in a patient with chronic hepatitis B virus and acute dengue infection.[16] However, most reports have not indicated an increase in liver disease severity or adverse outcomes associated with acute dengue infection in chronic liver disease.[15,17,18] Additionally, an increased risk of severe disease during pregnancy has been reported, with increased maternal death, miscarriage, stillbirth, and neonatal death.[1] Furthermore, the risk of severe dengue has been reported to be increased in individuals with comorbidities, such as diabetes, pulmonary, heart, or renal disease, and in those of low socioeconomic status.[1] A model for end-stage liver disease (MELD) score of 16 has been reported to predict ALF from dengue with 87.5% sensitivity, 89.3% specificity, and an AUC of 0.929 ($P < 0.001$). Moreover, a MELD score cutoff of 18 predicts mortality with an AUC of 0.822 ($P < 0.001$).[11] It should be noted that most available clinical studies were retrospective, which makes them intrinsically susceptible to bias.

There is no specific treatment approved for dengue. Management consists of supportive care. Regardless of the severity of the infection, all patients should be encouraged to maintain hydration and avoid NSAIDs to reduce the risk of bleeding. DWoWS does not require hospitalization and is managed with rest, antipyretics and analgesics for fever and body aches, increased ingestion of liquids, and monitoring for warning signs. DWWS and severe dengue, as well as hepatitis, require hospitalization for at least 48 h and intensive care unit admission, respectively. Prompt volume expansion with isotonic fluids of 10 mL/kg in the first hour and 20 mL/kg in 30 min is recommended for DWWS and severe dengue, respectively.[3]

No antiviral agent has been shown to be effective in DENV infection,[1] and there is no role for intravenous immunoglobulin in terms of survival or improvement of clinical parameters.[1] The use of steroids has been studied in the management of early and late stages of dengue infection.[1,19] In a report of eight studies that enrolled a total of 948 cases of dengue treated with steroids, four trials studied the effects of corticosteroids on survival in dengue-related shock. Unfortunately, the quality of the studies was very low, as they were small and limited to patients younger than 15 years old. Four other trials studied the effects of corticosteroids on complications of severe dengue. Here too, the data were judged to be insufficient to justify conclusions on the effect of corticosteroids on the course of dengue infection.[19] A DengDex trial (NCT05631405) aims to evaluate the efficacy of dexamethasone in the treatment of DWWS.[20]

Although liver transplantation is generally considered to be a life-saving measure in ALF unresponsive to medical management, dengue-associated multiorgan failure, disseminated intravascular coagulopathy, and bleeding add risk to liver transplantation. However, favorable outcomes reported in cases of ALF due to DENV suggest that liver transplantation could be a viable therapeutic alternative in such severe dengue infections.[21]

Regarding the treatment of dengue-induced ALF, small non-controlled studies have reported that the use of N-acetylcysteine (NAC) in severe dengue was associated with recovery,[22] without ill effects of NAC.[23] This is consistent with more extensive data on non-acetaminophen-induced ALF, in which NAC improved transplant-free survival in patients with ALF and grade 1 or 2 encephalopathy. It seems reasonable to recommend NAC for dengue-induced ALF.[24,25]

Preventing dengue infection consists of interfering with the *Aedes* reproduction cycle and transmission of the virus. Control of dengue is mainly achieved by covering water containers and discarding unused outdoor containers to decrease the presence of *Aedes*.[3]

At an individual level, prevention consists mainly of the use of topical repellents containing DEET (N,N'-diethyl-3-methylbenzamide), R3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester), or icaridin (1-piperidinecarboxylic

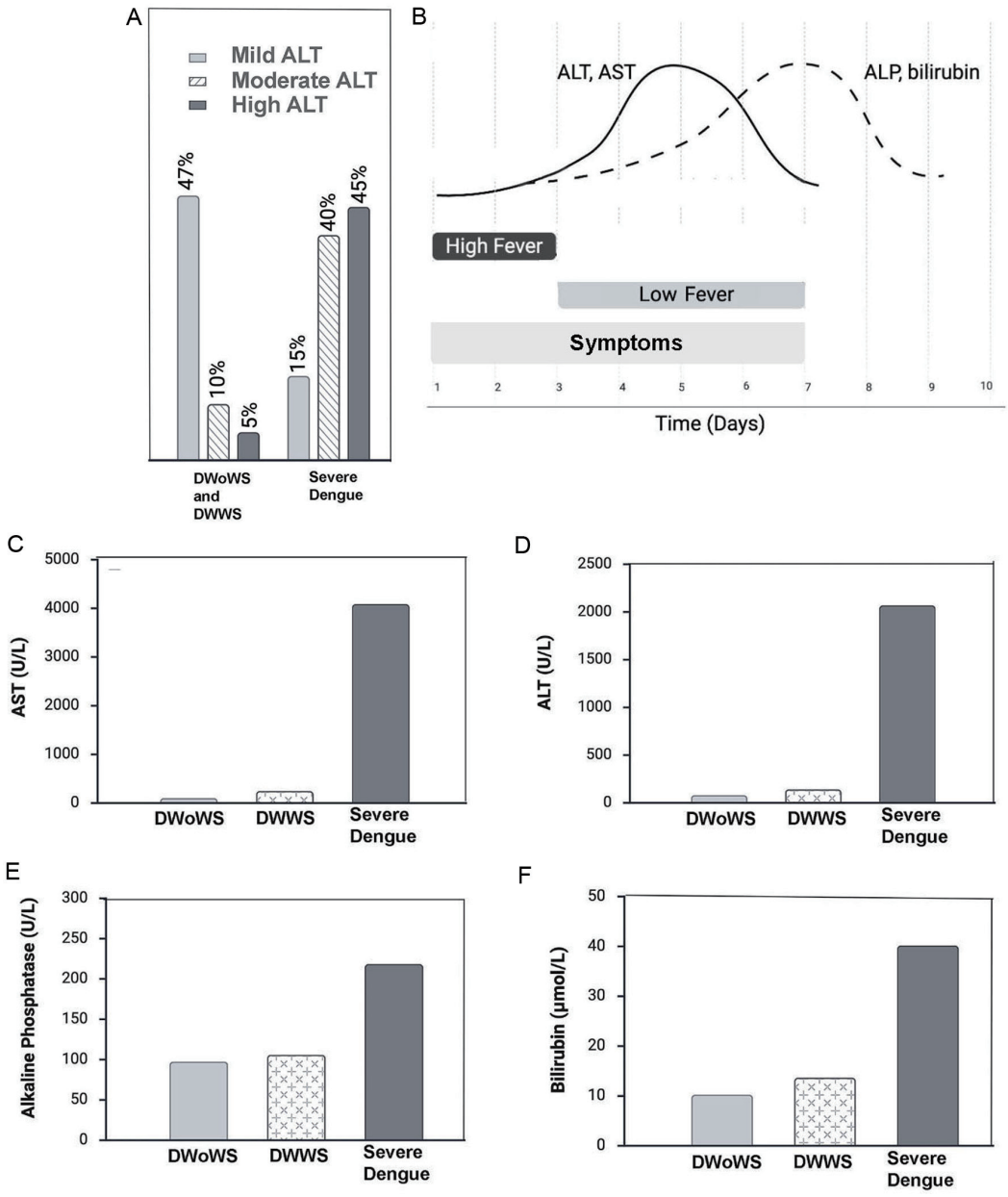

Fig. 2. Markers of liver damage. (A) A comparison of aminotransferase elevations in DWoWS compared to DWWS. (B) A time course of markers of liver injury relative to fever levels and symptoms. Mild ALT (>upper limit of normal, but <160 U/L), moderate ALT (>160 U/L), and high ALT (>400 U/L) elevations. Symptoms include rash, myalgia, arthralgia, headache, nausea, and vomiting. Peak AST and ALT occur on days 5–6 after the onset of symptoms. Peak bilirubin and ALP occur around day 7. (C) AST, (D) ALT, (E) alkaline phosphatase, (F) total bilirubin (µmol/L) in DWoWS, DWWS, and severe dengue infections. DWoWS, dengue without warning signs; DWWS, dengue with warning signs; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase. Adapted from.[3,8–10] Created in BioRender.

Table 1. Incidence of acute liver failure in patients with dengue

Design	Country	Dates	Age	Total Cases	ALF n (%)	ALF death n (%)	References
R	Thailand	2007–2022	≥10	2,447	24 (.98)	13 (54.2)	Teerasarntipan, 2024[11]
R	Thailand	2011–2015	≥15	1,926	6 (.31)	4 (66.7)	Kye Mon, 2016[12]
R	Thailand	1989–2011	<11	3,630	51 (1.1)	28 (54.9)	Laoprasopwattana, 2016[13]
R	India	2014–2017	≥10	10,108	36 (.35)	21 (58.3)	Devarbhavi, 2020[14]
P	Vietnam	2006–2008	>14	644	5 (.77)	1 (20)	Trung, 2010[15]

ALF, acute liver failure; n, number of cases; y, year of publication; R, retrospective; P, prospective.

acid, 2-(2-hydroxyethyl)-1-methylpropyl ester).[3] In addition, the Centers for Disease Control and Prevention recommends wearing permethrin-treated clothes and gear when traveling to endemic areas, as well as using bed netting.[2]

Vaccination is recommended in specific populations. Currently, there are two licensed vaccines against dengue infection, Dengvaxia (CYD-TDV) and Qdenga (TAK-003). Butantan-DV is currently in an ongoing phase three trial with participants aged 2 to 59 years.[26] All are live-attenuated tetravalent vaccines against all four serotypes of DENV. Dengvaxia is approved by the Food and Drug Administration and indicated for individuals 6 to 16 years old with a laboratory-confirmed prior dengue infection who live in endemic areas.[1] The recommended restriction of vaccination to previously dengue-infected individuals is based on data showing that, unlike primary infection, secondary infection is associated with an increased risk of severe dengue due to pre-existing non-neutralizing antibodies enhancing viral entry into cells at an early stage.[1] Likewise, infants have been reported to be more susceptible to severe disease due to antibody-dependent enhancement from waning maternal antibodies.[1]

Qdenga is recommended by the World Health Organization for children 6 to 16 years old living in settings of high dengue transmission. Among seropositive patients with virologically confirmed dengue, Dengvaxia (for ages 9–16 years old) and Butantan-DV (for ages 12–59 years old) have reported overall efficacies of 76% (95% confidence interval (CI) 64–84), 64% (95% CI 58–69), and 89% (95% CI 78–96), respectively. Among seronegative patients with virologically confirmed dengue, Dengvaxia, Qdenga, and Butantan-DV have reported overall efficacies of 39% (95% CI −1–63), 54% (95% CI 42–63), and 74% (95% CI 58–84), respectively.[1]

Because of the rapidly warming climate in currently temperate regions, health care officials and medical providers at the state and local levels will need to become proficient in the diagnosis and treatment of dengue. Education of the general public on methods for suppression of mosquito propagation and avoidance of mosquito contact will be necessary.

In terms of research, vector control remains central to prevention but is challenged by insecticide resistance and potential adverse effects on the environment and ecosystems. Improved mosquito control strategies and repellents that are environmentally safe and medically effective are needed.

Because there are currently no approved direct-acting antiviral therapies against DENV, development of effective antiviral agents is an important challenge. Antiviral therapy is an unmet need, particularly for patients with severe disease and ALF. Although dengue vaccines are available, they are currently limited to use by previously infected individuals. Vaccines, therefore, are needed to prevent infection in individuals with no prior exposure to DENV. This could greatly decrease the number of cases and minimize the development of severe dengue.

Finally, because most data on dengue-associated liver injury come from retrospective studies and case reports, prospective controlled studies are required to validate prognostic markers and guide evidence-based management.

Considering that DENV proliferates in hepatocytes, it is not surprising that a large fraction (75–85%) of dengue infections involve liver damage. However, the majority of these cases are characterized by asymptomatic aminotransferase elevations and are often overlooked by physicians as well as other health care professionals. It is important to realize that although uncommon, severe hepatitis and, rarely, ALF can occur. In this context, early recognition of progression of liver damage is important to minimize mortality, as the degree of aminotransferase elevation generally correlates with dengue disease severity. Thus, regular monitoring of aminotransferases and evaluation of hepatic function with increasing aminotransferases is recommended. A MELD score of 16 has demonstrated strong predictive value for ALF and mortality and should prompt a consultation with a liver specialist and, if necessary, a liver transplant team. No antiviral therapy has been proven to be effective against dengue infection. Consequently, preventive strategies, such as vector control, public health education, and vaccination in selected populations, remain essential to reduce morbidity and mortality.

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Conflict of interest

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Author contributions

Review concept (GYW), information collection, drafting of the manuscript (MDSS), and revision of the manuscript (GYW, MDSS). All authors have approved the final version and publication of the manuscript.

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