e-ISSN: 2988-3237

Sriwijaya Journal of Internal Medicine (SJIM)

Journal website: https://phlox.or.id/index.php/sjim

The Many Faces of Expanded Dengue Syndrome: A Two-Case Series of Renal and Hepatic–Neurological Organ Involvement in Adult Patients

Putu Nindya Ayu Ningrum Subadra[1*], Anak Agung Ayu Yuli Gayatri[2], I Ketut Agus Somia[3], I Made Susila Utama[2], Ni Made Dewi Dian Sukmawati[2]

[1]General Internal Medicine Specialist Program, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

[2]Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

[3]Head Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

ARTICLE INFO

Keywords:
Acute kidney injury
Acute liver failure
Antibody-dependent enhancement
Expanded dengue syndrome
Hepatic encephalopathy

***Corresponding author:**
Putu Nindya Ayu Ningrum Subadra

E-mail address:
nindyaningrum98@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjim.v4i1.278

A B S T R A C T

Introduction: The rising global incidence of dengue has been accompanied by increasing recognition of atypical, organ-dominant presentations collectively termed expanded dengue syndrome (EDS), in which severe involvement of the liver, kidney, heart, lung or central nervous system dominates the clinical picture and drives mortality. We describe two adult men who illustrate contrasting EDS phenotypes.

Case presentation: Case I, a 30-year-old man with serologically confirmed secondary dengue infection (IgM-negative, IgG-positive), presented with gross haematuria, dysuria and warning signs and developed acute kidney injury (oliguria, rising creatinine, proteinuria, marked erythrocyturia) superimposed on leucopenia, severe thrombocytopenia and haemoconcentration; he recovered fully with carefully titrated crystalloid and renoprotective measures. Case II, a 23-year-old man with a primary infection, deteriorated on the sixth day with agitated delirium and acute liver failure (transaminases exceeding 100 times the upper limit, hyperbilirubinaemia, coagulopathy, hypoalbuminaemia) complicated by hepatic encephalopathy; he improved with supportive care, electrolyte correction and multidisciplinary management.

Conclusion: EDS may arise from either secondary or primary infection, and organ dysfunction tends to resolve in step with the natural history of dengue. Meticulous fluid stewardship stratified by clinical group, with systematic evaluation for intensive-care needs using clinical, laboratory and imaging parameters, is the cornerstone of management. Early recognition of organ-specific complications is essential to reduce preventable morbidity and mortality.

1. Introduction

Dengue is the most rapidly expanding arthropod-borne viral infection of humans and constitutes a major and growing burden for tropical and subtropical health systems. The causative agent, dengue virus (DENV), is a single-stranded RNA flavivirus transmitted principally by the mosquitoes *Aedes aegypti* and *Aedes albopictus* and circulates as four antigenically distinct serotypes (DENV-1 to DENV-4). Approximately half of the world's population now lives in areas at risk of transmission, and tens of millions of symptomatic infections are estimated to occur annually, with a substantial and rising contribution to global years lived with disability.[1] Indonesia, where dengue is

hyperendemic and all four serotypes co-circulate, continues to report large annual epidemics with tens of thousands of hospitalisations and a persistent, if proportionally small, burden of fatalities.[2]

Following an incubation period of three to fourteen days, the virus replicates in cells of the reticuloendothelial system before a secondary viraemia triggers the release of inflammatory mediators and the onset of the febrile illness. The clinical spectrum is famously protean, ranging from a self-limiting febrile syndrome to the plasma-leakage phenotypes historically labelled dengue haemorrhagic fever and dengue shock syndrome. Classic features include an abrupt high fever, often with a biphasic or saddleback pattern, frontal and retro-orbital headache, myalgia, a transient macular rash, and minor mucocutaneous bleeding such as petechiae, gingival oozing or epistaxis. The cardinal laboratory triad of leucopenia, progressive thrombocytopenia and rising haematocrit reflects the underlying immunopathology and heralds the critical phase of capillary leak.[3]

As the global incidence has climbed, reports of atypical, organ-dominant presentations that fall outside the traditional classification have multiplied. These are collectively designated expanded dengue syndrome (EDS) and are characterised by severe dysfunction of one or more major organ systems—most commonly the liver, kidney, heart, lungs and central nervous system. Although EDS is more frequently encountered against a background of severe dengue, it may also complicate apparently uncomplicated dengue fever, and it is increasingly described in adults and in patients with comorbidities.[4,5] The pathogenesis is believed to involve an exuberant, T-cell-driven immune response and a cytokine storm that produce systemic endothelial dysfunction, glycocalyx degradation, increased vascular permeability and coagulopathy, upon which organ-specific injury is superimposed.[6,7]

Reported manifestations of EDS are remarkably diverse and include dengue-associated acute kidney injury, fulminant hepatitis and acute liver failure, encephalitis and encephalopathy, myocarditis and conduction disturbances, and acute respiratory complications such as the acute chest syndrome and acute respiratory distress syndrome.[8,9,10,11] Mortality in EDS is driven largely by these severe complications in vital organs—encephalopathy, fulminant hepatic failure with disseminated intravascular coagulation, and refractory shock—and is amplified by older age and by comorbidities such as diabetes mellitus, chronic kidney disease and immunosuppression.[3,4] Because effective antiviral therapy is lacking, outcomes hinge on early recognition, meticulous supportive care and organ-specific intervention. The relative rarity of individual organ phenotypes, however, means that the literature guiding their bedside management remains limited and is dominated by single case reports.

The present series addresses this gap by describing two adult men managed within a short interval at the same tertiary centre in Bali who developed two of the most clinically consequential—and pathophysiologically contrasting—phenotypes of EDS: severe renal involvement with acute kidney injury arising from a serologically confirmed secondary infection, and acute liver failure with hepatic encephalopathy complicating a primary infection. The novelty of this report lies in the side-by-side presentation of renal-predominant and hepatic–neurological EDS within a single institutional experience, allowing a direct comparison of their diagnostic reasoning, monitoring strategy and organ-tailored supportive management, and in situating both within current mechanistic understanding of antibody-dependent enhancement and cytokine-mediated organ injury. The aim of this study is therefore to characterise the clinical evolution, laboratory trajectory and management of these two EDS phenotypes, and to distil practical lessons that may help clinicians recognise and treat organ-dominant dengue earlier and more confidently.

2. Case Presentation

Case I — Renal-predominant expanded dengue syndrome

A 30-year-old man presented to the emergency department with macroscopic haematuria containing blood clots and dysuria. The illness had begun four days earlier with an abrupt, continuous high fever accompanied by generalised and retro-orbital headache and myalgia. Over the following days the course was complicated by the appearance of warning signs—epigastric pain, nausea, persistent vomiting and spontaneous gingival bleeding. He had been treated empirically elsewhere with an intravenous proton-pump inhibitor, an antiemetic and intravenous antipyretics without improvement. He recalled a previous, milder dengue infection in 2019 that had not been complicated by bleeding.

On examination he was fully conscious and haemodynamically relatively stable, with a blood pressure of 112/71 mmHg (mean arterial pressure above 65 mmHg), but was febrile at 38.1 °C and tachycardic at 102 beats per minute. Cardiac and pulmonary examinations were unremarkable. The abdomen showed minimal distension with epigastric and right-upper-quadrant tenderness, and shifting dullness was positive, indicating ascites. There were no petechiae; the extremities were warm with a capillary refill time of less than two seconds. The electrocardiogram was normal.

Laboratory testing on the fourth day of fever demonstrated the characteristic profile of dengue, with leucopenia (1,730/μL), severe thrombocytopenia (22,000/μL) and haemoconcentration (haemoglobin 15.9 g/dL). Evidence of organ involvement was provided by elevated serum transaminases (aspartate aminotransferase 456 U/L, alanine aminotransferase 205 U/L) and by acute kidney injury, confirmed by a raised serum creatinine (1.2 mg/dL) and oliguria (urine output 0.4 mL/kg/h). Urinalysis revealed proteinuria (2+) with haematuria (3+) and a strikingly high erythrocyte sediment count of 1,631/μL. The chest radiograph showed no cardiac or pulmonary abnormality, while abdominal ultrasonography confirmed ascites without structural abnormality of the kidneys or other intra-abdominal organs.

On the basis of the clinical picture and supporting investigations, a diagnosis of dengue with warning signs was made, supported by ascites, spontaneous gingival bleeding and haematuria, with a renal manifestation consistent with acute kidney injury. The presence of this severe, atypical renal involvement placed the case within the spectrum of expanded dengue syndrome. The definitive diagnosis was confirmed serologically by a negative anti-dengue IgM with a positive anti-dengue IgG, a pattern indicating secondary infection.

Management focused on intravenous crystalloid resuscitation with 0.9% sodium chloride, beginning at 5–7 mL/kg/h (500 mL) over one to two hours, reduced to 3–5 mL/kg/h (300 mL) over two to four hours, then to 2–3 mL/kg/h, before transition to a daily maintenance requirement of approximately 2,400 mL over 24 hours. Fluids were titrated against clinical response, urine output and serial haematocrit. Supportive therapy comprised oral paracetamol 500 mg every eight hours, intravenous metoclopramide 10 mg every eight hours, a curcuma tablet once daily, and the angiotensin-converting-enzyme inhibitor lisinopril 10 mg once daily as a renoprotective measure. The critical phase manifested on the fifth day with worsening haemoconcentration (a rise in haematocrit exceeding 20%, reaching 50.1%) and a progressive fall in the platelet count to a nadir of 13,000/μL on the sixth day (Table 1; Figure 1A,B), even as the patient's symptoms began to improve.

By the seventh day of illness the clinical course had turned: the patient had been afebrile for three days, the gastrointestinal symptoms and haematuria had resolved, and renal function had recovered with a fall in serum creatinine to 0.98 mg/dL. The haemoconcentration had resolved and the platelet count had begun to climb. He was discharged once clinically stable with a rising platelet count, and outpatient review documented

complete recovery with normalisation of the haematological profile (platelets 214,000/µL) and a clear urinalysis without proteinuria or haematuria. Table 1 presents the serial complete blood count for this patient, and the temporal relationship between platelet nadir and haematocrit peak is depicted graphically in Figure 1.

Table 1. Serial complete blood count during admission — Case I (renal-predominant expanded dengue syndrome).

Parameter	Reference range	HD1	HD2	HD3	HD4	HD5	HD6	HD7
WBC (×10³/µL)	4.0–10.0	2.36	5.29	5.29	3.82	3.91	3.48	3.98
Haemoglobin (g/dL)	13.5–17.5	16.1	16.5	14.5	14.4	14.0	13.3	13.0
Haematocrit (%)	40–52	48.3	50.1	43.2	43.5	41.6	40.0	40.2
Platelets (×10³/µL)	150–400	15	22	13	16	19	48	96

Notes: HD = hospital day of serial sampling. The platelet nadir of 13,000/µL coincided with the haematocrit peak of 50.1% during the critical phase.

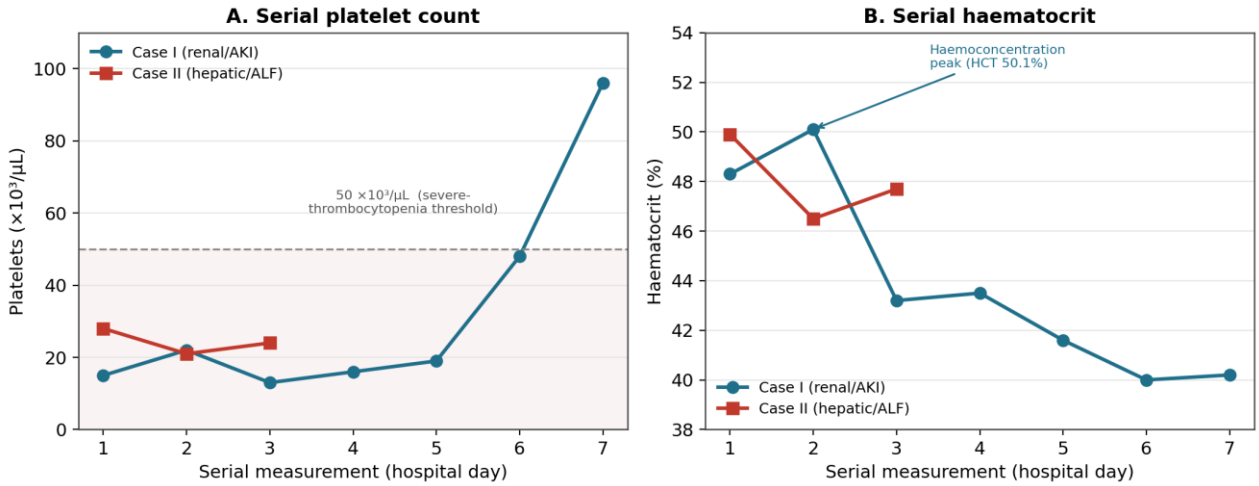

Figure 1. Serial laboratory trends for both cases. (A) Platelet count, showing the characteristic critical-phase nadir (13,000/µL in Case I and 21,000/µL in Case II) below the 50,000/µL severe-thrombocytopenia threshold, followed by recovery. (B) Haematocrit, showing the haemoconcentration peak (50.1% in Case I) and subsequent plasma reabsorption. The horizontal axis denotes serial in-hospital measurements corresponding to the columns of Table 1 (Case I).

Case II — Hepatic–neurological expanded dengue syndrome

A 23-year-old man was referred from a private hospital with a four-day history of fever that had begun on 25 January 2025. The fever had been continuous and only transiently responsive to antipyretics. On the sixth day of illness he deteriorated clinically with a reduction in consciousness manifesting as agitated delirium, which prompted referral to our tertiary centre. By the time of evaluation the fever had abated. Associated symptoms included headache and an episode of epistaxis on the fourth day of illness. He worked as a construction labourer with environmental exposure to mosquito-breeding sites (standing water), although he denied any known contact with a dengue patient or any previous dengue infection.

On admission he was haemodynamically stable, with a blood pressure of 120/77 mmHg, a heart rate of 89 beats per minute, a respiratory rate of 18 breaths per minute, an oxygen saturation of 95% on room air, and a temperature of 36.5 °C. Petechiae were noted over the thorax. Cardiac and pulmonary

examinations were normal. The abdomen was neither distended nor ascitic, but there was right-hypochondriac tenderness without organomegaly. Urine output was adequate at 1,500 mL over 24 hours (approximately 0.7 mL/kg/h).

The complete blood count on the sixth day of illness (30 January 2025) showed a leucocyte count of 6,680/µL, a haemoglobin of 17.2 g/dL, a haematocrit of 49.9% and severe thrombocytopenia (28,000/µL), the elevated haematocrit indicating haemoconcentration, although no baseline haemoglobin or haematocrit was available for comparison. On the seventh day the haemoglobin fell to 16.0 g/dL and the haematocrit to 46.5%, signalling the plasma-reabsorption phase, while the platelet count declined further to 21,000/µL; a repeat sample at our hospital on the same day showed a haemoglobin of 15.9 g/dL, a haematocrit of 47.7% and an early rise in the platelet count to 24,000/µL.

Liver function testing revealed severe hepatocellular injury, with serum transaminases far exceeding the upper reference limit (aspartate aminotransferase 6,304 U/L and alanine aminotransferase 1,752 U/L; Table 2). There was evidence of impaired hepatic synthetic function, with mild prolongation of coagulation parameters (prothrombin time 13.0 seconds, international normalised ratio 1.23, activated partial thromboplastin time 45.7 seconds) and hypoalbuminaemia (albumin 2.8 g/dL). Hyperbilirubinaemia was present (total bilirubin 3.10 mg/dL) with a predominant direct fraction (2.42 mg/dL); the alkaline phosphatase was normal at 69 U/L and the gamma-glutamyl transferase was 238 U/L. Renal function was preserved (blood urea nitrogen 19 mg/dL, serum creatinine 1.32 mg/dL, estimated glomerular filtration rate 75.5 mL/min). Serum electrolytes showed hyponatraemia (123 mmol/L) and hypokalaemia (3.06 mmol/L). To exclude viral hepatitis, hepatitis B surface antigen and anti-hepatitis C antibody were both negative. Urinalysis demonstrated proteinuria (2+) and blood (2+) with negative nitrite, negative leucocyte esterase and minimal sediment, effectively excluding urinary tract infection.

Integrating the history, examination and investigations, the diagnosis pointed to severe dengue. This was supported by the biphasic fever pattern, severe thrombocytopenia, haemoconcentration and minor bleeding (epistaxis and petechiae), together with evidence of severe organ involvement in the form of transaminases above 1,000 U/L and impaired consciousness. The combination of altered mental status with severe hepatocellular injury indicated acute liver failure complicated by hepatic encephalopathy, and the severe, atypical hepatic involvement classified the case as expanded dengue syndrome.

Initial treatment at the referring hospital comprised intravenous hydration with Ringer's lactate, paracetamol, domperidone and ranitidine. During admission to our centre the patient received multidisciplinary care, including a neurology consultation for the altered consciousness, with empirical intravenous dexamethasone 10 mg every eight hours and intravenous ceftriaxone 2 g every twelve hours to cover the possibility of a secondary central-nervous-system infection. Other measures included maintenance Ringer's lactate at 20 drops per minute, a curcuma tablet every eight hours, oral potassium chloride 600 mg every eight hours for the hypokalaemia, and symptomatic paracetamol 750 mg as required for fever. His symptoms improved, he remained afebrile throughout admission, and he was discharged after four days of inpatient care. The serial haematological course of this patient is plotted alongside that of Case I in Figure 1.

Table 2 contrasts the principal clinical, laboratory and management features of the two cases, highlighting the divergent organ phenotypes that emerged from a shared dengue pathophysiology.

Table 2. Comparative clinical, laboratory and management features of the two cases.

Feature	Case I	Case II
Age/gender	30 years, male	23 years, male
Dominant organ phenotype	Renal — acute kidney injury	Hepatic + CNS — acute liver failure with encephalopathy
Infection type	Secondary (IgM−/IgG+)	Primary (no prior dengue)
Presentation	Day 4 of fever	Day 6 of illness (referred)
Warning signs/bleeding	Epigastric pain, gingival bleeding, gross haematuria, ascites	Epistaxis, petechiae, agitated delirium
Transaminases	AST 456 / ALT 205 U/L	AST 6,304 / ALT 1,752 U/L
Platelet nadir	13,000/μL	21,000/μL
Haematocrit peak	50.1%	49.9%
Renal markers	Creatinine 1.2 → 0.98 mg/dL; proteinuria 2+/haematuria 3+; oliguria	Creatinine 1.32 mg/dL; eGFR 75.5 mL/min (preserved)
Other biochemistry	—	Bilirubin 3.10 (direct 2.42) mg/dL; albumin 2.8 g/dL; INR 1.23; Na 123; K 3.06 mmol/L
Key supportive therapy	Titrated crystalloid; lisinopril (renoprotection)	Titrated Ringer's lactate; empirical dexamethasone + ceftriaxone; potassium replacement
Outcome	Full recovery; platelets 214,000/μL at follow-up	Afebrile, discharged after 4 days; recovered

3. Discussion

Dengue is caused by a flavivirus with four distinct serotypes transmitted by *Aedes* mosquitoes, and its clinical spectrum extends from asymptomatic infection through classic dengue fever to the severe phenotypes of dengue haemorrhagic fever, dengue shock syndrome and expanded dengue syndrome, any of which may culminate in multi-organ dysfunction.[3,4] The two patients described here exemplify how a single virus can produce strikingly different organ-dominant illnesses—severe renal involvement in one and fulminant hepatic failure with encephalopathy in the other—and how careful, individualised supportive care can deliver excellent outcomes even in the absence of specific antiviral therapy. Figure 2 illustrates the pathogenetic cascade that links the shared immunological trigger to the divergent organ phenotypes observed in this series.

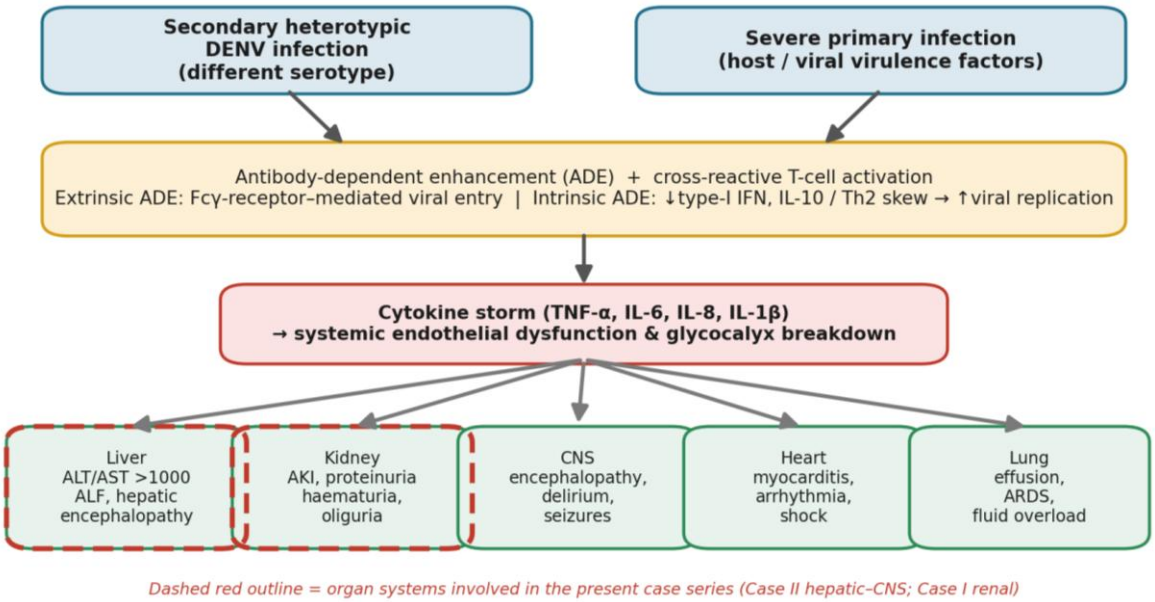

Figure 2. Original schematic (created by the authors) of the pathogenetic cascade of expanded dengue syndrome. Secondary heterotypic infection—or a severe primary infection driven by host and viral factors—triggers antibody-dependent enhancement and cross-reactive T-cell activation, producing a cytokine storm with systemic endothelial dysfunction and glycocalyx breakdown, upon which organ-specific injury is superimposed. Dashed red outlines indicate the organ systems involved in the present series (Case I, renal; Case II, hepatic–neurological).

The severity of any given dengue infection is shaped by a complex interaction among three groups of determinants. Viral factors include the infecting serotype and strain virulence; DENV-2, for example, is frequently associated with more intense immune responses and severe disease. Host factors encompass genetic predisposition, older age, nutritional status including obesity, and comorbidities such as diabetes mellitus, chronic kidney disease and immunodeficiency, all of which raise the risk of progression to severe or atypical disease. Environmental factors—season, climate and population density—govern vector dynamics and transmission intensity.[3,6] Against this background, a widely invoked explanation for severe secondary infection is the phenomenon of antibody-dependent enhancement (ADE).

In ADE, non-neutralising or sub-neutralising antibodies generated during a previous heterotypic infection bind to a different infecting serotype without effectively neutralising it. The resulting virus–antibody immune complexes are recognised by Fcγ receptors on monocytes and macrophages, facilitating viral internalisation, amplifying replication and increasing the probability of severe disease.[6,12] Two mechanistic forms are recognised. Extrinsic ADE operates outside the phagocyte by enhancing the interaction between immune complexes and Fcγ receptors, increasing the number of infected cells. Intrinsic ADE acts within the phagocyte, where internalised immune complexes suppress innate antiviral effectors such as type-I interferon while inducing interleukin-10 and skewing the response toward a T-helper-2 phenotype, thereby further supporting viral replication; intrinsic ADE is thought to make the larger contribution to amplification of dengue viral load.[6] Large prospective human cohort data have provided direct epidemiological support for ADE, showing that a narrow range of pre-existing anti-dengue antibody titres is associated with an increased risk of subsequent severe disease.[2,12] Case I, with serologically confirmed secondary infection and a severe clinical course, is consistent with this paradigm. By contrast, the severe presentation of Case II appears to have arisen from a primary infection, for which the mechanistic basis of severe disease is less completely understood and is likely to reflect host and viral factors and an exuberant innate inflammatory response rather than antibody-mediated enhancement.

Beyond ADE, the final common pathway to severe organ injury is an inflammatory one. Activated cross-reactive T cells and infected monocytes release a surge of pro-inflammatory cytokines—including tumour necrosis factor-α, interleukin-6, interleukin-8 and interleukin-1β—that produce endothelial activation and degradation of the endothelial glycocalyx, with consequent increased vascular permeability, plasma leakage and coagulopathy. Prospective biomarker studies in severe dengue have shown that the magnitude of this inflammatory response, indexed by interleukin-6 and ferritin and by markers of endothelial activation and glycocalyx breakdown such as angiopoietin-2 and syndecan-1, correlates with disease severity, the degree of vascular leak and mortality, reinforcing the central pathogenic role of hyperinflammation and identifying potential targets for future host-directed therapy.[7] This systemic endothelial and inflammatory milieu provides the substrate upon which the organ-specific injuries seen in our two patients developed.

Diagnosis in both cases rested on the integration of clinical and laboratory findings. Clinically, both men exhibited continuous fever for three to four days, spontaneous bleeding (gingival bleeding in Case I and petechiae in Case II) and warning signs such as epigastric pain, while the laboratory hallmark of thrombocytopenia with haemoconcentration was present in each. The definitive diagnosis in Case I was reinforced by serology. The kinetics of the antibody response are central to interpretation: in primary infection, specific IgM becomes detectable only after about the fifth to sixth day of symptoms, rises over the second week and persists for two to three months, whereas IgG appears later, after roughly the second week,

and persists for years. In secondary infection, by contrast, IgG rises rapidly and is detectable within the first few days of symptoms; thus a positive IgG with negative IgM, as in Case I, supports a secondary infection.[13] non-structural protein 1 (NS1) antigen testing was not performed in either patient because both presented after the viraemic window had closed, illustrating a common real-world limitation in which the timing of presentation dictates which diagnostic modality is informative.[13]

The renal involvement in Case I merits particular attention because dengue-associated acute kidney injury (AKI), although increasingly recognised, remains under-appreciated at the bedside. Systematic reviews and meta-analyses indicate that AKI complicates a clinically meaningful proportion of hospitalised dengue cases and is independently associated with adverse outcomes, with severe disease, older age, rhabdomyolysis, multi-organ involvement and male sex among the consistently reported predictors.[14-16] The pathogenesis is multifactorial, as outlined in Figure 2. Pre-renal mechanisms predominate, with hypovolaemia from plasma leakage and impaired renal perfusion during the critical phase; the cytokine storm—mediated by tumour necrosis factor-α, interleukin-6, interleukin-8 and interleukin-1β—contributes to endothelial dysfunction and reduced renal perfusion. Direct viral and immune-mediated glomerular injury may also occur, with mesangial proliferation, capillary endothelial swelling, inflammatory-cell infiltration and immune-complex deposition narrowing Bowman's capsule, reducing the glomerular filtration rate and producing proteinuria and haematuria; acute tubular necrosis, rhabdomyolysis and, rarely, haemolytic-uraemic-type pictures complete the spectrum.[15,16] Although a definitive diagnosis of glomerulopathy would require renal biopsy, the resolution of the urinary abnormalities in tandem with clinical recovery in our patient strongly suggests a reversible, functional process rather than established structural damage—a pattern typical of dengue-associated AKI in the tropics.[14,16]

The hepatic and neurological involvement in Case II represents the other end of the EDS spectrum and carries a higher intrinsic mortality. Some degree of hepatic involvement is almost universal in dengue, reflecting both direct hepatocyte infection and immune-mediated injury, and mild to moderate transaminase elevation is the rule. Acute liver failure, however—defined by severe hepatocellular injury with coagulopathy and encephalopathy in the absence of pre-existing liver disease—is a rare but feared complication, with reported case-fatality rates that are substantially higher in adults and are amplified by delayed presentation and comorbidity.[17-19] In our patient, the transaminases exceeded 1,000 U/L by a wide margin, accompanied by hyperbilirubinaemia, hypoalbuminaemia and coagulopathy, and the absence of clinical stigmata of cirrhosis argued against chronic liver disease. A careful exclusion of alternative or contributory aetiologies is essential in such cases. Malaria typically does not raise transaminases to this degree and is usually accompanied by extravascular haemolysis and other organ dysfunction; leptospirosis was unlikely given the absence of conjunctival suffusion, calf tenderness and the characteristic leucocytosis, and given preserved renal function; viral hepatitis B and C were serologically excluded; and drug-induced liver injury, including paracetamol toxicity, was considered unlikely on the basis of the medication history. The combination of fever, thrombocytopenia and haemoconcentration, in the appropriate epidemiological context, pointed firmly to dengue as the cause.[19,20]

The neurological manifestation—agitated delirium consistent with hepatic encephalopathy in the setting of acute liver failure—deserves separate consideration because dengue can affect the nervous system through several distinct mechanisms. Neurological complications of dengue are conventionally grouped into those arising from direct viral neurotropism (encephalitis), those that are metabolic or systemic in origin (encephalopathy from hepatic failure, shock, electrolyte disturbance or cerebral oedema), and immune-mediated post-

infectious syndromes.[8] In our patient, the encephalopathy is best attributed to acute liver failure, although the coexisting hyponatraemia is likely to have contributed, and direct central-nervous-system involvement could not be entirely excluded without cerebrospinal-fluid analysis. Dengue encephalopathy may present with cognitive impairment, behavioural change, anxiety or frank psychosis, and the proposed neuropathogenesis includes viral penetration of the blood–brain barrier, which can be confirmed by intrathecal studies when these are clinically warranted.[8] The empirical use of dexamethasone and an antibiotic in this case reflected the clinical need to cover a possible central-nervous-system infection while the diagnostic picture was clarified.

The cornerstone of dengue management is supportive, and the first decision is to stratify patients by the presence or absence of warning signs in order to determine the need for admission and the intensity of monitoring. Patients without warning signs (Group A) can be managed as outpatients with education about warning signs, whereas those with warning signs (Group B) require admission for intravenous fluid therapy and close observation. For Group B, isotonic crystalloid (Ringer's lactate or 0.9% sodium chloride) is begun at about 5–7 mL/kg/h and titrated downward in steps—to 3–5 mL/kg/h and then 2–3 mL/kg/h—as clinical improvement and a urine output above 0.5 mL/kg/h are achieved, before transition to maintenance over the following 24 to 48 hours; an inadequate response signals progression to severe dengue (Group C).[4,21] In Group C, resuscitation begins more aggressively, at 10–20 mL/kg/h, with a similar stepwise de-escalation once perfusion is restored; colloids are reserved for shock refractory to crystalloid, and packed red cells (5–10 mL/kg) are indicated where a falling haematocrit suggests significant bleeding.[21] Crucially, both of our patients, despite features of severe dengue, did not exhibit massive plasma leakage or hypotension, so aggressive fluid loading was neither indicated nor administered; instead, fluids were carefully titrated to avoid the very real hazard of iatrogenic fluid overload, a balance that lies at the heart of good dengue care.

In EDS specifically, supportive care is supplemented by organ-directed interventions, and the early identification of patients who require intensive care is pivotal. Indicators that should prompt consideration of intensive-care admission include clinical features of shock (hypotension, prolonged capillary refill, a thready pulse) combined with altered consciousness, with or without massive bleeding; laboratory features such as severe thrombocytopenia below 50,000/μL, a rising haematocrit and hepatic dysfunction, with transaminases above 1,000 U/L frequently signalling significant organ damage; and imaging features on ultrasonography such as gallbladder-wall thickening, pleural effusion and ascites, which are strong predictors of severe disease and the need for intensive monitoring.[4,19] Applying these criteria, Case II—with transaminases far above 1,000 U/L and encephalopathy (Table 2)—warranted the heightened multidisciplinary observation it received, whereas Case I was monitored closely for the renal and haematological trajectory without requiring critical-care escalation.

Organ-specific management follows from recognising the dominant phenotype. For renal involvement, which is often pre-renal and perfusion-related, adequate but carefully monitored fluid administration is the mainstay, with vigilance for fluid overload and for electrolyte disturbances such as hyperkalaemia; renal function generally recovers in step with the natural history of the disease, and no specific therapy has been established.[15,16] In Case I, recovery accompanied hydration together with a renoprotective angiotensin-converting-enzyme inhibitor; the rationale for an ACE inhibitor rests on reduction of intraglomerular pressure through efferent-arteriolar dilatation, which lowers the filtration fraction and can reduce proteinuria, although such agents must be used cautiously in the setting of evolving AKI and volume depletion. For hepatic involvement progressing to acute liver failure, management is largely supportive—correction of coagulopathy and electrolytes,

treatment of hepatic encephalopathy with measures such as lactulose, and meticulous avoidance of hepatotoxins—while N-acetylcysteine has been proposed as an adjunct. By replenishing glutathione, scavenging free radicals and improving hepatic oxygen delivery through its vasodilatory action, N-acetylcysteine may mitigate the oxidative stress induced by viral infection and the inflammatory response, and small studies and case series have suggested potential benefit in dengue-related liver injury, although high-quality randomised evidence is still lacking.[18,22] For intracranial involvement, measures may include mannitol for cerebral oedema and, in selected cases, immunomodulation, with electroencephalography or neuroimaging to establish the diagnosis; and for the cardiac complications that can accompany severe or secondary infection, inotropic or vasopressor support may be required to maintain the circulation.[8,9] Across all phenotypes, the unifying principle is anticipatory, organ-tailored supportive care delivered within a framework of close clinical, laboratory and imaging surveillance.

Although the present series concerns renal and hepatic–neurological disease, it is worth situating these phenotypes within the wider catalogue of organ involvement that defines EDS, because the same vigilance applies across systems. Cardiac involvement ranges from asymptomatic troponin elevation and conduction disturbances to overt myocarditis and cardiogenic shock, and is more likely in secondary infection and in patients with comorbidity; it may masquerade as, or compound, the haemodynamic instability of plasma leakage and therefore warrants electrocardiographic and, where available, echocardiographic assessment when the circulatory picture is discordant with the degree of leak.[9] Pulmonary complications include pleural effusion, the acute chest syndrome and acute respiratory distress syndrome, which may be precipitated or aggravated by injudicious fluid administration—again emphasising that fluid stewardship is simultaneously therapeutic and potentially iatrogenic.[10] Haematological extremes such as severe haemolysis and haemophagocytic lymphohistiocytosis-like pictures further widen the differential and may demand specific intervention.[11] The recognition that a single dengue infection can express itself through any of these organ systems, sometimes simultaneously, is the conceptual core of the expanded-dengue construct and the justification for a systematic, head-to-toe reassessment in any patient whose course deviates from the expected trajectory.

A further point concerns the monitoring framework that underpinned the favourable outcomes in both patients. Serial complete blood counts, performed at least daily and more frequently during the critical phase, allowed the platelet nadir and haematocrit peak to be tracked in real time and fluid therapy to be adjusted accordingly, as depicted in Figure 1. The decision to transfuse is guided not by the platelet count in isolation but by the presence of clinically significant bleeding; prophylactic platelet transfusion for thrombocytopenia alone, even when severe, is not supported by the evidence and may cause harm, and neither patient required it. Equally, the haematocrit must always be interpreted in the light of any fluid already given and of bleeding, since a falling haematocrit may reflect either appropriate plasma reabsorption or occult haemorrhage—two situations that demand opposite responses.[3,21] This disciplined, parameter-driven approach, rather than any specific drug, was the decisive element of care.

Finally, these cases carry implications beyond the individual patient. In a hyperendemic setting such as Indonesia, where all four serotypes co-circulate and the population carries a high prevalence of prior exposure, the conditions that favour secondary heterotypic infection and antibody-dependent enhancement are ubiquitous, and the absolute burden of atypical, organ-dominant disease can be expected to rise as transmission intensifies with urbanisation and climate change.[1,2] Strengthening clinician awareness of EDS, embedding warning-sign-based triage and structured fluid protocols into routine practice, and ensuring timely access to laboratory and imaging support are pragmatic measures that

can reduce preventable mortality even before disease-modifying therapies or broadly effective vaccines become widely available.[12] Documenting well-characterised cases such as these contributes to the collective experience on which such improvements depend.

Several practical lessons emerge from juxtaposing these two cases. First, EDS is not the exclusive preserve of secondary infection: while Case I fits the ADE-driven secondary-infection model, Case II demonstrates that severe organ failure can complicate a primary infection, so a reassuring serological or exposure history must not lower clinical vigilance. Second, the organ phenotype dictates both the monitoring strategy and the therapeutic emphasis—serial creatinine and urinalysis with renoprotection in renal-predominant disease, versus serial transaminases, coagulation, ammonia-conscious neurological assessment and consideration of N-acetylcysteine in hepatic–neurological disease. Third, and perhaps most importantly, both patients recovered fully, underscoring the encouraging observation that organ dysfunction in EDS commonly resolves in concert with the natural resolution of the dengue illness, provided that the critical phase is navigated with disciplined fluid stewardship and that life-threatening complications are anticipated and supported. Criteria for recovery include stable vital signs, the absence of constitutional symptoms, a normalising haematocrit and the appearance of a convalescent rash, with discharge appropriate once the patient has been afebrile for more than 24 hours, has shown clinical improvement, and has a platelet count rising above 50,000/μL.[3,21]

Limitations

This report has limitations inherent to its design. As a two-patient series it cannot support inferences about incidence, risk factors or the comparative effectiveness of specific interventions, and the management decisions described reflect the practice of a single tertiary centre. Serotype identification and molecular confirmation were not available, NS1 testing was precluded by late presentation, and the attribution of encephalopathy in Case II to hepatic failure, while clinically reasonable, was not corroborated by cerebrospinal-fluid analysis or neuroimaging. Nonetheless, the value of the series lies in its detailed, contrasting documentation of two clinically important EDS phenotypes managed to full recovery, and in the practical diagnostic and therapeutic reasoning it makes explicit for clinicians who encounter organ-dominant dengue.

4. Conclusion

The clinical spectrum of dengue extends from asymptomatic infection and dengue fever to the severe phenotypes of dengue haemorrhagic fever, dengue shock syndrome and expanded dengue syndrome, the last of which may involve the liver, kidney, heart, lung or central nervous system. The two adult men described here illustrate two of the most consequential and pathophysiologically distinct EDS phenotypes—renal-predominant disease with acute kidney injury arising from a secondary infection, and acute liver failure with hepatic encephalopathy complicating a primary infection—and both recovered completely. Disease severity is governed by the interplay of viral, host and environmental factors, with secondary infection by a heterotypic serotype provoking a more intense immune response and, through antibody-dependent enhancement, a higher risk of severe disease, although primary infection can also culminate in organ failure. The natural history is characterised by a biphasic (saddleback) fever with defervescence around days four to six heralding the critical phase, during which close monitoring for plasma leakage and shock is essential. Management remains principally supportive, with appropriately titrated fluid therapy as its foundation and clinical improvement generally tracking the natural resolution of the illness; N-acetylcysteine may be considered in hepatic EDS with acute liver failure, while renal involvement demands vigilant monitoring of urine output, serum creatinine and the markers of acute kidney injury in the absence of any specific therapy. A comprehensive understanding of EDS, and the capacity to detect dengue infection and its potential severe

complications as early as possible, are indispensable to delivering timely and appropriate care.

Declarations

Ethics approval and consent to participate

This case series was prepared in accordance with the Declaration of Helsinki and the institutional standards for case reports at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar. As a retrospective report of routine clinical care, it did not require formal ethics-committee review at the authors' institution.

Consent for publication

Written informed consent for the publication of de-identified clinical information was obtained from both patients; signed SJIM Patient Consent for Publication forms have been uploaded. No identifying details or images are included in this report.

Availability of data and materials

The clinical data supporting this report are contained within the article; further details are available from the corresponding author upon reasonable request, subject to patient confidentiality.

Competing interests

The authors declare that they have no competing interests.

Funding

This report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

P.N.A.N.S.: conceptualization, data curation, and writing — original draft; A.A.A.Y.G.: supervision and writing — review & editing; I.K.A.S.: validation and supervision; I.M.S.U.: investigation and writing — review & editing; N.M.D.D.S.: methodology and writing — review & editing. All authors reviewed and approved the final version of the manuscript.

Use of artificial intelligence

A generative-AI assistant was not used for developing the manuscript; all clinical data, interpretations, and references were independently verified and approved by the authors.

Acknowledgements

The authors thank the staff of the Division of Tropical and Infectious Diseases, Department of Internal Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, involved in the care of the patients.

5. References

1. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133-61. doi:10.1016/S0140-6736(24)00757-8
2. Forrat R, Dayan GH, DiazGranados CA, et al. Analysis of hospitalized and severe dengue cases over the 6 years of follow-up of the tetravalent dengue vaccine (CYD-TDV) efficacy trials in Asia and Latin America. Clin Infect Dis. 2021;73(6):1003-12. doi:10.1093/cid/ciab288
3. Sangkaew S, Ming D, Boonyasiri A, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(7):1014-26. doi:10.1016/S1473-3099(20)30601-0
4. Mahajan V, Singh J, Guglani V. Clinical profile of expanded dengue syndrome in children. Pediatr Infect Dis J. 2024;43(9):883-7. doi:10.1097/INF.0000000000004421
5. Nelwan EJ, Pramanta P, Safitri WJ, et al. Expanded dengue syndrome in a diabetic patient with a history of COVID-19 infection: a case report. Ann Med Surg (Lond). 2023;85(10):5187-90. doi:10.1097/MS9.0000000000001201

6. Dash MK, Samal S, Rout S, et al. Immunomodulation in dengue: towards deciphering dengue severity markers. Cell Commun Signal. 2024;22(1):451. doi:10.1186/s12964-024-01779-4
7. McBride A, Duyen HTL, Vuong NL, et al. Endothelial and inflammatory pathophysiology in dengue shock: new insights from a prospective cohort study in Vietnam. PLoS Negl Trop Dis. 2024;18(3):e0012071. doi:10.1371/journal.pntd.0012071
8. Kulkarni R, Pujari S, Gupta D. Neurological manifestations of dengue fever. Ann Indian Acad Neurol. 2021;24(5):693-702. doi:10.4103/aian.AIAN_157_21
9. Cristodulo R, Luoma-Overstreet G, Leite F, et al. Dengue myocarditis: a case report and major review. Glob Heart. 2023;18(1):41. doi:10.5334/gh.1254
10. Singh S, Nayak V, Acharya V, et al. Expanded dengue syndrome: dengue-triggered acute chest syndrome. QJM. 2024;117(12):887-8. doi:10.1093/qjmed/hcae184
11. Arora N, Gulati P, Suri V, et al. Hemolytic anemia in expanded dengue syndrome. QJM. 2022;115(2):103-4. doi:10.1093/qjmed/hcab298
12. Aggarwal C, Ahmed H, Sharma P, et al. Severe disease during both primary and secondary dengue virus infections in pediatric populations. Nat Med. 2024;30(3):670-4. doi:10.1038/s41591-024-02798-x
13. Gomes LF, Mundim JV, do Carmo Silva L, et al. Diagnostic performance of the Bioline Dengue Duo rapid test on symptomatic patients assisted at Armed Forces Hospital (HFA) in Brasilia, Brazil. Braz J Microbiol. 2024;55(2):1801-9. doi:10.1007/s42770-024-01351-9
14. Bushi G, Shabil M, Padhi BK, et al. Prevalence of acute kidney injury among dengue cases: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg. 2024;118(1):1-11. doi:10.1093/trstmh/trad067
15. Awad AA, Khatib MN, Gaidhane AM, et al. Predictors of acute kidney injury in dengue patients: a systematic review and meta-analysis. Virol J. 2024;21(1):223. doi:10.1186/s12985-024-02488-7
16. Batra N, Kaur N, Pethekar A. Acute kidney injury in dengue fever: a one-year hospital-based prospective cross-sectional study. J Assoc Physicians India. 2022;70(6):11-2. doi:10.5005/japi-11001-0024
17. Juneja D, Jain R, Nasa P. Dengue induced acute liver failure: a meta summary of case reports. World J Virol. 2024;13(1):91457. doi:10.5501/wjv.v13.i1.91457
18. Giri S, Anirvan P, Vaidya A, et al. Dengue-related acute liver failure - a scoping review. Indian J Gastroenterol. 2024;43(2):407-24. doi:10.1007/s12664-024-01570-w
19. Wagle C, Ghimire DP, Sah AK, et al. Elevated liver enzyme (AST and ALT) as biomarkers for severe dengue in Nepalese patients: a cross-sectional study. BMC Infect Dis. 2025;25(1):1118. doi:10.1186/s12879-025-11549-3
20. Seth S, Maharshi S, Sharma KK, et al. Changing etiological spectrum of acute liver failure. Indian J Gastroenterol. 2024;43(2):452-8. doi:10.1007/s12664-024-01578-2
21. Nouh AK, Haj Mohamad H, Toubah AM, et al. Successful management of severe dengue with gastrointestinal bleeding: a case report highlighting endoscopic hemostasis. Cureus. 2024;16(11):e74142. doi:10.7759/cureus.74142
22. Gupta M, Gupta S, Sood D, et al. Role of N-acetylcysteine in liver injury due to dengue fever. Trop Doct. 2023;53(4):475-80. doi:10.1177/00494755231176317