Review Article:

Expanded Dengue Syndrome: A Comprehensive Review

Nargis Akter[1], Ahmed Imran[2], Tripti Moni Saha[3], Masuma Sultana[4], Tania Alam[5]

Abstract:

Background: Expanded Dengue Syndrome (EDS) encompasses a wide spectrum of atypical and severe clinical manifestations of dengue virus infection involving various organ systems beyond the classical definitions of dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Recognized by the World Health Organization, EDS includes neurological, hepatic, renal, cardiac, pulmonary, and hematological complications that may occur with or without plasma leakage. Increasing dengue incidence worldwide has led to a parallel rise in these unusual presentations, posing significant diagnostic and therapeutic challenges, particularly in endemic countries such as Bangladesh. This review summarizes current knowledge on the epidemiology, pathophysiology, clinical manifestations, diagnostic approach, management strategies, and prognosis of Expanded Dengue Syndrome, highlighting the importance of early recognition and multidisciplinary care to reduce morbidity and mortality.

Key words: Expanded dengue syndrome, severe dengue, atypical dengue, multiorgan failure, Bangladesh.

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1. Dr Nargis Akter
   Lecturer,
   Department of Pharmacology and Therapeutics
   Dhaka Medical College, Dhaka
2. Dr Ahmed Imran
   Assistant Professor,
   Department of Radiology and Imaging
   Comilla Medical College, Cumilla
3. Dr Tripti Moni Saha
   Assistant Professor,
   Department of Pharmacology and Therapeutics
   Bikrampur Bhuiyan Medical College, Munshiganj
4. Dr Masuma Sultana
   Lecturer,
   Department of Pharmacology and Therapeutics
   Mymensingh Medical College, Mymensingh
5. Dr Tania Alam
   Assistant Professor, Department of Physiology
   National Institute of Mental Health and Hospital, Sher-e-bangla Nagar, Dhaka

Address of correspondence:
Dr Nargis Akter
Lecturer,
Department of Pharmacology and Therapeutics
Dhaka Medical College, Dhaka
Email: anargis87@gmail.com;
Cell: 01674962954
ORCID ID: 0009-0006-5776-1814

Introduction:

Dengue is the most rapidly spreading mosquito-borne viral disease globally, caused by four antigenically distinct serotypes of dengue virus (DENV-1 to DENV-4) belonging to the *Flaviviridae* family[1]. Classical dengue infection ranges from asymptomatic illness to dengue fever characterized by acute febrile illness, headache, retro-orbital pain, myalgia, arthralgia, rash, leukopenia, and thrombocytopenia[2]. Severe dengue is traditionally described as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), primarily associated with plasma leakage, bleeding, and shock[3].

However, with increasing dengue burden and improved surveillance, clinicians have recognized a variety of atypical and severe organ-specific manifestations that do not conform to classical classifications. To address this gap, the World Health Organization introduced the term **Expanded Dengue Syndrome (EDS)** to describe unusual manifestations involving the central nervous system, liver, kidneys, heart, lungs, and hematological system[4]. These manifestations significantly increase disease complexity, diagnostic uncertainty, and mortality risk, particularly in resource-limited settings.

Epidemiology:

Dengue is endemic in more than 100 countries, with approximately 3.9 billion people at risk worldwide[1]. South-East Asia bears a disproportionate burden of

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disease, and Bangladesh has experienced recurrent outbreaks with increasing severity and mortality[5]. Although the exact prevalence of EDS is unknown, hospital-based studies suggest that atypical manifestations account for a significant proportion of severe dengue admissions[6],[7].

The rising incidence of EDS may be attributed to multiple factors, including secondary dengue infection, changing viral virulence, host immune factors, aging populations, comorbid illnesses, and delayed presentation to healthcare facilities[8].

Definition and Classification:

Expanded Dengue Syndrome refers to dengue infection associated with **unusual or atypical organ involvement** that cannot be fully explained by plasma leakage, hemorrhage, or shock alone[4]. Unlike classical severe dengue, EDS may occur even in the absence of hemoconcentration or hypotension.

The WHO 2009 dengue classification indirectly acknowledges EDS by listing "severe organ involvement" such as severe hepatitis, encephalitis, myocarditis, and acute kidney injury under severe dengue[4]. However, the term EDS provides a broader conceptual framework to understand multisystem involvement.

Pathophysiology:

The pathogenesis of EDS is multifactorial and incompletely understood. Proposed mechanisms include:

- **Direct viral invasion** of organs such as the liver, brain, and myocardium[9]
- **Immune-mediated injury**, including cytokine storm and antibody-dependent enhancement[10]
- **Endothelial dysfunction** and microvascular leakage affecting multiple organs[11]
- **Coagulopathy and disseminated intravascular coagulation** leading to organ ischemia[12]

Host factors such as age, pregnancy, diabetes mellitus, chronic liver disease, and cardiovascular disease increase susceptibility to EDS and worsen outcomes[13].

Clinical Manifestations:

Neurological Manifestations

Neurological involvement is one of the most serious forms of EDS. Manifestations include encephalopathy, encephalitis, seizures, intracranial hemorrhage, meningitis, Guillain–Barré syndrome, and transverse myelitis[14]–[16]. These may result from direct neurotropism of dengue virus or secondary metabolic and immune-mediated effects.

Hepatic and Gastrointestinal Involvement

Mild to moderate elevation of transaminases is common in dengue, but EDS may present with acute hepatitis, fulminant hepatic failure, acalculous cholecystitis, and acute pancreatitis[17],[18]. Severe hepatic involvement is associated with high mortality, especially in children and pregnant women.

Renal Manifestations

Acute kidney injury is increasingly recognized in severe dengue and EDS, ranging from mild creatinine elevation to oliguric renal failure requiring dialysis[19]. Rhabdomyolysis-associated AKI and hemoglobinuria have also been reported[20].

Cardiac Manifestations

Cardiac involvement includes myocarditis, arrhythmias, conduction abnormalities, pericarditis, and cardiogenic shock[21],[22]. Subclinical myocardial dysfunction may be underdiagnosed without cardiac biomarkers or echocardiography.

Pulmonary Manifestations

Pulmonary involvement may present as pleural effusion, pneumonitis, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS)[23]. These features may occur independently of plasma leakage.

Hematological and Immune Complications

Severe thrombocytopenia, pancytopenia, disseminated intravascular coagulation, and hemophagocytic lymphohistiocytosis (HLH) are recognized components of EDS[24],[25].

Diagnosis:

Diagnosis of EDS requires confirmation of dengue infection using NS1 antigen, dengue IgM/IgG serology, or RT-PCR, along with evidence of atypical organ dysfunction[4]. Differential diagnoses include malaria, leptospirosis, viral hepatitis, sepsis, and autoimmune disorders.

Early recognition relies on clinical suspicion, particularly during outbreaks, and systematic evaluation of organ function including liver enzymes, renal

parameters, cardiac markers, neuroimaging, and coagulation profile.

Management:

There is no specific antiviral therapy for dengue or EDS. Management is primarily **supportive and organ-specific**, including:

- Careful fluid management to avoid fluid overload[4]
- Early intensive care support for multiorgan dysfunction
- Renal replacement therapy for severe AKI
- Mechanical ventilation for respiratory failure
- Blood component therapy for significant bleeding

A **multidisciplinary approach** involving intensivists, hepatologists, nephrologists, neurologists, and cardiologists is essential for optimal outcomes[26].

Prognosis:

Expanded Dengue Syndrome is associated with significantly higher morbidity and mortality compared to classical dengue. Prognosis depends on the number of organs involved, early diagnosis, and access to critical care facilities[27]. Delayed recognition remains a major contributor to adverse outcomes in low-resource settings.

Challenges and Future Directions:

Key challenges include under-recognition of EDS, lack of standardized diagnostic criteria, and limited access to advanced supportive care. Future research should focus on identifying early biomarkers, understanding pathogenesis, and developing targeted therapies. Strengthening surveillance systems and clinician awareness is crucial in endemic countries.

Conclusion:

Expanded Dengue Syndrome represents an important and increasingly recognized dimension of dengue infection. Awareness of its diverse manifestations, early diagnosis, and prompt supportive management are critical to reducing mortality. As dengue continues to expand globally, EDS should be considered in all dengue patients presenting with unexplained organ dysfunction.

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