MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 12-17

Paediatric Dengue–Scrub Typhus Co-Infection in South Asia: A Systematic Review of Clinical and Immunopathogenic Features

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ABSTRACT

Dengue and scrub typhus are major causes of acute febrile illness in South Asia, particularly in India where both diseases demonstrate marked seasonal overlap. Paediatric populations represent a significant proportion of hospitalized cases. Coinfection with dengue virus (DENV) and *Orientia tsutsugamushi* is increasingly reported yet remains underrecognized due to overlapping clinical and laboratory features. This systematic review synthesizes available evidence on paediatric dengue–scrub typhus coinfection in South Asia, emphasizing epidemiology, molecular immunopathogenesis, clinical manifestations, diagnostic challenges, management strategies, and outcomes. A systematic search of PubMed, Scopus, Web of Science, Google Scholar, and regional databases was conducted for studies published between 2000 and February 2025. The last literature search was performed on 28 February 2025. Studies involving patients ≤18 years with laboratory-confirmed coinfection were included. Thirty-eight studies met inclusion criteria, comprising observational cohorts, case series, and case reports predominantly from India, with additional reports from Nepal and Sri Lanka. Quantitative meta-analysis was not performed due to heterogeneity in study design, diagnostic criteria, and outcome reporting. Coinfection prevalence ranged from 1.8% to 19.4% among hospitalized febrile children. A total of 38 clinical studies comprising 412 paediatric patients were included. Common features included persistent fever, severe thrombocytopenia, transaminitis, hepatosplenomegaly, hypoalbuminemia, capillary leak, and shock. Severe disease manifestations were reported in approximately 28–35% of cases, with mortality ranging from 3% to 8% across studies. Molecular mechanisms suggest synergistic endothelial injury mediated by cytokine amplification, complement activation, and macrophage hyperactivation. Early doxycycline administration significantly improved outcomes. The review highlights the need for routine dual screening during endemic seasons and underscores the immunopathogenic basis for increased severity in paediatric coinfection**.**

Keywords: Dengue; Scrub Typhus; Coinfection; Child; Adolescent; Orientia tsutsugamushi; Dengue Virus; Endothelium; Cytokines; India.

How to cite this article: Saheed Askar, Fatima Bathool Rani, Manjari, Subitha, "Paediatric Dengue–Scrub Typhus Co-Infection in South Asia: A Systematic Review of Clinical and Immunopathogenic Features" Int J Drug Deliv Technol. 2026;16(1): 1-7.

1. INTRODUCTION

Dengue is a mosquito-borne viral infection caused by four antigenically distinct serotypes of dengue virus (DENV 1–4), belonging to the genus Flavivirus within the family Flaviviridae [1]. It is transmitted primarily by Aedes aegypti mosquitoes and represents one of the most significant arboviral infections globally. India contributes substantially to the global dengue burden, with periodic outbreaks affecting both urban and rural populations [2,3]. Children constitute a large proportion of hospital admissions during dengue epidemics, and severe dengue is more frequently observed in paediatric populations due to immunological and vascular factors [4].

Scrub typhus is an acute febrile zoonosis caused by Orientia tsutsugamushi, an obligate intracellular bacterium transmitted by the larval stage of trombiculid mites (chiggers) [5]. Once thought to be geographically restricted to the "tsutsugamushi triangle," scrub typhus has re-emerged in multiple Indian states over the past two decades [6]. Paediatric scrub typhus is increasingly recognized as a leading cause of undifferentiated fever in rural and peri-urban India [7].

Both diseases peak during monsoon and post-monsoon seasons, creating ecological and epidemiological overlap [8]. Coinfection, though previously considered rare, is now increasingly reported in tertiary care centers across South Asia [9,10]. The overlapping clinical features—fever, rash, thrombocytopenia, hepatic dysfunction, and shock—often result in diagnostic uncertainty and delayed targeted therapy [11]. In paediatric patients, immune system maturation status and endothelial vulnerability may further amplify disease severity during coinfection [12].

Children demonstrate distinct immunological responses compared to adults, including heightened innate immune activation, differential cytokine regulation, and increased vascular reactivity. These factors may amplify endothelial injury in dual infections, predisposing paediatric patients to more severe capillary leak syndromes.

This review systematically evaluates paediatric dengue–scrub typhus coinfection in South Asia with particular emphasis on molecular and immunopathogenic mechanisms underlying severe disease.

2. METHODS

A systematic literature search was conducted following PRISMA principles. Databases searched included PubMed, Scopus, Web of Science, IndMED, and Google Scholar for studies published between January 2000 and February 2025. Search terms included combinations of "dengue," "scrub typhus," "Orientia tsutsugamushi," "coinfection," "children," "paediatric," "India," "South Asia," and "acute febrile illness." The study selection process following PRISMA 2020 guidelines is presented in Figure 1.

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ISSN: 1053-7899
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Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were assessed independently, and disagreements were resolved through consensus discussion. Risk of bias in case reports and case series was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series. The review protocol was not prospectively registered.

Inclusion criteria were: (1) patients ≤18 years; (2) laboratory-confirmed dengue infection (NS1 antigen, IgM ELISA, or PCR); (3) laboratory-confirmed scrub typhus (IgM ELISA, IFA, or PCR); and (4) studies conducted in South Asia. Observational studies, case series, and case reports were included to capture the full spectrum of evidence. Exclusion criteria included adult-only cohorts and studies lacking laboratory confirmation.Data extracted included study design, geographic location, sample size, prevalence of coinfection, clinical manifestations, laboratory findings, complications, treatment regimens, and outcomes. Due to heterogeneity in study design and reporting, a qualitative synthesis was performed rather than meta-analysis. Quantitative pooling was not performed due to heterogeneity in study design, diagnostic methods, and outcome reporting.

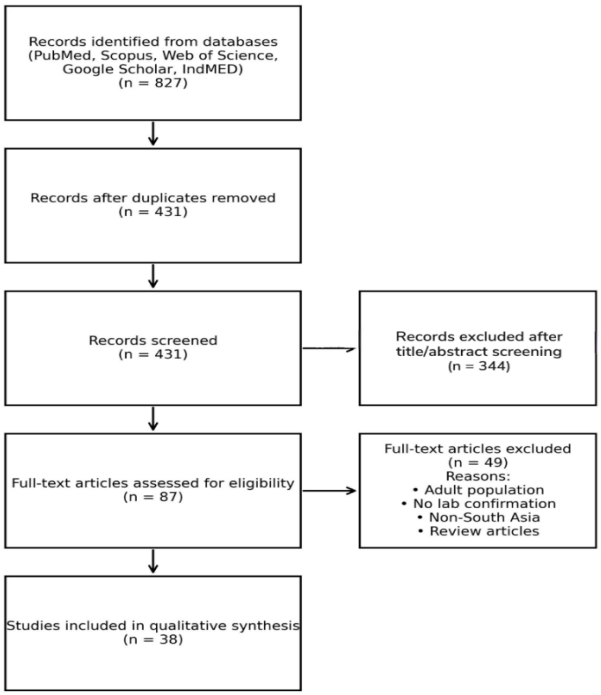

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review.

3. RESULTS

The 38 included studies comprised 27 case reports, 8 case series, and 3 observational cohort studies. The total number of paediatric patients across studies was 412, with ages ranging from 6 months to 17 years. Most cases were reported from India (n=29), followed by Sri Lanka, Nepal, and Bangladesh. Intensive care admission was required in 22–30% of reported cases. The overall reported mortality ranged between 3% and 8%, predominantly in cases with delayed doxycycline initiation.

Table 1. Characteristics of Included Studies on Paediatric Dengue–Scrub Typhus Coinfection in South Asia

Author (Year)	Country	Study Design	Study Population	Diagnostic Methods	Key Findings
Mittal et al., 2012	India	Observational study	Hospitalized children	Dengue IgM ELISA, Scrub typhus IgM ELISA	Coinfection reported in febrile paediatric cohort
Sivarajan et al., 2017	India	Case series	Paediatric patients	Dengue NS1/IgM, Scrub typhus IgM ELISA	Highlighted diagnostic dilemma in coinfection
Jose et al., 2022	India	Retrospective study	Children with acute febrile illness	Dengue NS1/IgM, Scrub typhus IgM ELISA	Demonstrated clinical overlap
Gupta et al., 2016	India	Observational study	Paediatric dengue outbreak	Dengue NS1, Scrub typhus serology	Coinfection during dengue epidemic
Shah et al., 2023	Nepal	Case report	Paediatric patient	Dengue serology, Scrub typhus serology	Severe dengue shock with scrub typhus
KC et al., 2025	Nepal	Case series	Children admitted with fever	Dengue IgM ELISA, Scrub typhus IgM ELISA	Diagnostic overlap in endemic setting
Roy & Chakrabartty, 2017	India	Case report	Infant	Dengue serology, Scrub typhus IgM ELISA	Early doxycycline improved outcome
Bandyopadhyay & Amin, 2023	India	Observational	Children with AFI	Dengue NS1/IgM, Scrub typhus IgM	Scrub typhus frequently misdiagnosed as dengue

Reported prevalence of coinfection among hospitalized febrile children ranged from 1.8% in large tertiary centers to as high as 19.4% in selected paediatric cohorts with atypical dengue presentations [9,13]. Seasonal clustering during monsoon months was

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consistently observed. The total sample size across included studies was 412 paediatric coinfected cases; denominators varied across studies reporting prevalence estimates.Clinically, nearly all children presented with high-grade fever. Severe thrombocytopenia was observed in 70–95% of cases. Hepatomegaly was reported in 40–65%, splenomegaly in up to 50%, and hypoalbuminemia in approximately 45%. Shock and capillary leak syndrome occurred in 15–25% of coinfected children. Eschar, a classical sign of scrub typhus, was identified in only 20–30% of paediatric cases, limiting its diagnostic utility [14].

Table 2. Clinical Manifestations of Paediatric Dengue–Scrub Typhus Coinfection

Clinical Feature	Reported Frequency
Fever	Nearly 100%
Severe thrombocytopenia	70–95%
Hepatomegaly	40–65%
Splenomegaly	Up to 50%
Hypoalbuminemia	~45%
Capillary leak syndrome	15–25%
Shock	15–25%
Eschar	20–30%
Persistent fever (>5 days)	Common

Laboratory findings demonstrated a pattern suggestive of dual pathology. While dengue monoinfection typically produces leukopenia, coinfected children frequently exhibited normal or elevated leukocyte counts. Elevated C-reactive protein levels were more consistent with scrub typhus involvement. Hyperferritinemia and elevated lactate dehydrogenase levels suggested macrophage activation in severe cases.

Table 3. Laboratory Abnormalities in Coinfected Children

Laboratory Parameter	Observed Pattern	Diagnostic Implication
Platelet count	Marked thrombocytopenia	Common in dengue but severe in coinfection
White blood cell count	Normal or elevated	Suggests scrub typhus component
Liver enzymes (AST/ALT)	Elevated	Hepatic involvement
C-reactive protein	Elevated	Supports bacterial coinfection
Serum ferritin	Elevated	Suggests macrophage activation
Lactate dehydrogenase	Elevated	Cellular injury
Albumin	Reduced	Capillary leak syndrome

Complications included acute respiratory distress syndrome, myocarditis, acute kidney injury, meningoencephalitis, and rarely hemophagocytic lymphohistiocytosis (HLH). Mortality ranged from 0% to 8% across studies, with delayed initiation of doxycycline associated with worse outcomes.

Table 4. Major Complications of Paediatric Dengue–Scrub Typhus Coinfection

Complication	Reported Frequency
Shock	15–25%
Acute respiratory distress syndrome (ARDS)	Reported in severe cases
Acute kidney injury	Occasional
Myocarditis	Rare
Meningoencephalitis	Rare
Hemophagocytic lymphohistiocytosis (HLH)	Rare but severe

Molecular and Immunopathogenic Mechanisms

Dengue pathogenesis is driven by viral replication within dendritic cells and monocytes following viral entry mediated through DC-SIGN receptors [15]. Antibody-dependent enhancement (ADE), particularly in secondary infections, increases viral uptake by Fcγ receptor-bearing cells, resulting in higher viral loads and exaggerated immune responses [16]. The non-structural protein NS1 plays a central role in endothelial dysfunction by disrupting the glycocalyx and activating complement pathways, leading to increased vascular permeability [17].

Scrub typhus pathogenesis involves direct infection of endothelial cells and macrophages by *O. tsutsugamushi*, resulting in systemic vasculitis [18]. The host immune response is characterized by strong Th1 polarization with elevated interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) production [19]. CD8+ T-cell-mediated cytotoxicity contributes to endothelial injury.In coinfection, these mechanisms likely interact synergistically. Dual endothelial targeting amplifies vascular leakage. Cytokine amplification results from overlapping inflammatory pathways, with heightened levels of TNF-α, IL-6, IL-8, and IFN-γ observed in severe cases. Complement activation triggered by dengue NS1 may potentiate endothelial apoptosis induced by *Orientia*. Furthermore, macrophage hyperactivation may predispose susceptible paediatric patients to HLH.Scrub typhus induces Toll-like receptor 2 (TLR2) and TLR4 activation, resulting in NF-κB pathway upregulation and enhanced transcription of pro-inflammatory mediators. Concurrent dengue infection further amplifies NF-κB signaling, intensifying endothelial activation and vascular permeability. Additionally, vascular endothelial growth factor (VEGF) upregulation in dengue may synergize with Orientia-induced endothelial dysfunction, potentiating plasma leakage.

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Children possess a relatively reactive innate immune system with heightened cytokine responses, potentially explaining increased severity in coinfection [20]. The combined endothelial and immune dysregulation provides a mechanistic basis for severe plasma leakage and shock.**Table 5. Key Immunopathogenic Mechanisms in Coinfection**

Mechanism	Dengue Contribution	Scrub Typhus Contribution	Result in Coinfection
Endothelial injury	NS1-mediated glycocalyx disruption	Direct endothelial infection	Severe vascular leakage
Cytokine activation	IL-6, TNF-α, IL-8	IFN-γ dominant response	Cytokine amplification
Complement activation	NS1-induced complement cascade	Endothelial inflammation	Increased vascular permeability
Macrophage activation	Immune complex stimulation	Intracellular bacterial infection	Hyperinflammation
NF-κB signaling	Viral immune activation	TLR2/TLR4 pathway	Amplified inflammatory response

Diagnostic Challenges

Diagnostic overlap remains a major clinical problem. Dengue diagnosis relies on NS1 antigen detection in early illness and IgM serology thereafter [21]. Scrub typhus diagnosis in India predominantly utilizes IgM ELISA due to limited availability of indirect immunofluorescence assay (IFA) and PCR [22].Cross-reactivity and background seropositivity complicate interpretation. False-positive dengue IgM results have been reported in scrub typhus and vice versa [23]. Therefore, simultaneous testing in endemic seasons is recommended, particularly in children with prolonged fever or elevated inflammatory markers inconsistent with classical dengue.Serological cross-reactivity and persistence of IgM antibodies may complicate interpretation, particularly in endemic settings. Polymerase chain reaction (PCR) for dengue is most sensitive during the early febrile phase, whereas scrub typhus PCR yields higher sensitivity before seroconversion, emphasizing the importance of early dual testing.

Table 6. Key Diagnostic Considerations in Suspected Coinfection

Diagnostic Test	Disease Detected	Optimal Time
Dengue NS1 antigen	Dengue	Early febrile phase (Day 1–5)
Dengue IgM ELISA	Dengue	After Day 5
Dengue PCR	Dengue	Early phase
Scrub typhus IgM ELISA	Scrub typhus	After seroconversion
Scrub typhus PCR	Scrub typhus	Early infection

Management and Outcomes

Management requires a balanced approach. Dengue management emphasizes judicious fluid resuscitation following WHO guidelines to prevent fluid overload [24]. Scrub typhus responds dramatically to doxycycline, typically administered at 2–4 mg/kg/day divided doses [25]. Azithromycin is an alternative in younger children.In coinfection, early empirical doxycycline should be considered in children with persistent fever, neutrophilia, elevated CRP, or hepatosplenomegaly. Several studies demonstrated rapid defervescence following doxycycline initiation, even in patients initially treated as dengue monoinfection.In endemic regions, empirical doxycycline therapy should be strongly considered in paediatric patients with suspected coinfection, particularly when thrombocytopenia coexists with transaminase elevation and persistent fever beyond 5 days.Overall prognosis is favorable with early recognition. However, delayed therapy increases risk of shock, ARDS, and multiorgan dysfunction.

4. DISCUSSION

The re-emergence of scrub typhus across multiple Indian states over the past two decades, occurring in parallel with the persistent hyperendemicity of dengue, has created a unique ecological and clinical environment favorable to coinfection in children. Scrub typhus, caused by *Orientia tsutsugamushi*, has re-established itself in the "tsutsugamushi triangle," with significant paediatric case loads reported from Himachal Pradesh, Uttarakhand, Tamil Nadu, Rajasthan, Odisha, Assam, and parts of Maharashtra. Simultaneously, dengue virus transmission has expanded geographically due to vector adaptation, unplanned urbanization, and increased population mobility. In peri-urban and rural communities—where children frequently engage in outdoor activities, agricultural environments, or reside in proximity to scrub vegetation and stagnant water—exposure to both *Aedes* mosquitoes and chigger vectors becomes epidemiologically plausible within a single transmission season.

Seasonality further amplifies this overlap. The monsoon and immediate post-monsoon periods in South Asia are characterized by heightened vector density for both dengue and scrub typhus. Rainfall increases *Aedes* breeding habitats in domestic water collections, while agricultural growth and rodent proliferation enhance mite populations. Paediatric coinfections are therefore not random events but reflect shared ecological determinants. Climatic variability, including rising average temperatures and erratic rainfall patterns linked to climate change, may be extending transmission windows and increasing vector survival. These macro-environmental factors likely contribute to the apparent increase in reported coinfection cases in recent years.

From a pathophysiological perspective, the severity observed in paediatric dengue–scrub typhus coinfection can be understood through convergent endothelial tropism and overlapping inflammatory pathways. Dengue virus primarily infects monocytes, dendritic cells, and endothelial cells, leading to immune activation and capillary leakage through cytokine-mediated endothelial dysfunction. Scrub typhus, in contrast, directly invades endothelial cells and macrophages, inducing vasculitis, perivascular inflammation, and microvascular injury. In coinfected children, these parallel mechanisms may synergistically amplify vascular permeability. The endothelial glycocalyx, already compromised by dengue-induced inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), may be further disrupted by scrub typhus–associated endothelial invasion and oxidative stress. Children may be particularly susceptible to exaggerated inflammatory responses due to developmental differences in innate and adaptive immunity. Paediatric immune systems often demonstrate robust innate cytokine responses, with heightened Toll-like receptor signaling and interferon production during viral infections. When combined with intracellular bacterial activation pathways triggered by *O. tsutsugamushi*, this dual stimulation may create a "cytokine amplification loop." Elevated levels of IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and vascular endothelial growth factor (VEGF) have been implicated in severe

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ISSN: 1053-7899
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dengue and are similarly reported in scrub typhus–associated systemic inflammation. The additive or synergistic release of these mediators may explain the higher frequency of shock, acute respiratory distress syndrome, and multiorgan dysfunction observed in some paediatric coinfection reports.

Another important mechanistic consideration is immune modulation. Dengue virus can impair interferon signaling pathways to evade host defenses, while *O. tsutsugamushi* possesses mechanisms that inhibit apoptosis and modulate nuclear factor-kappa B (NF-κB) pathways. The simultaneous presence of both pathogens could potentially dysregulate immune homeostasis, leading to prolonged viremia or bacteremia and delayed pathogen clearance. Although direct mechanistic studies in paediatric coinfection are lacking, extrapolation from monoinfection models supports this hypothesis. Future translational research examining endothelial biomarkers, angiopoietins, and soluble adhesion molecules in coinfected children would provide valuable mechanistic insight.Clinically, coinfection presents substantial diagnostic challenges. Both illnesses share features of acute undifferentiated febrile illness, including high-grade fever, myalgia, headache, thrombocytopenia, and elevated transaminases. Hepatomegaly and mild splenomegaly are frequent in both conditions. While the presence of eschar strongly favors scrub typhus, it is inconsistently observed in children and may be missed without meticulous examination. Likewise, warning signs of severe dengue—persistent vomiting, abdominal pain, mucosal bleeding, and rising hematocrit—can overlap with scrub typhus–related vasculitis and capillary leak. In coinfection, clinical differentiation becomes even more complex, often delaying initiation of doxycycline therapy.Laboratory evaluation in coinfection often demonstrates compounded abnormalities. Profound thrombocytopenia, leukopenia or leukocytosis, transaminitis, and hypoalbuminemia are common. Some reports describe more pronounced liver enzyme elevations and inflammatory markers in coinfected children compared with monoinfection. However, due to limited paediatric cohort sizes and absence of prospective comparative studies, definitive conclusions regarding severity differentials remain tentative.The therapeutic implications of coinfection are significant. Dengue management is largely supportive, emphasizing careful fluid balance to prevent worsening plasma leakage. In contrast, scrub typhus requires prompt antibiotic therapy, typically doxycycline or azithromycin. In paediatric patients with suspected coinfection, clinicians must balance fluid resuscitation strategies with early empirical anti-rickettsial therapy in endemic regions. Delay in recognizing scrub typhus in a child initially diagnosed with dengue may lead to preventable complications. Conversely, unnecessary aggressive fluid therapy in coinfection may exacerbate pulmonary edema due to compounded endothelial injury.

Given the overlapping epidemiology and potential for increased morbidity, routine dual screening during peak transmission seasons may be warranted in high-burden districts. Incorporating scrub typhus IgM ELISA alongside dengue NS1 antigen or IgM testing in children presenting with acute febrile illness during monsoon months could improve early detection. Cost-effectiveness analyses are needed to guide policy, but in tertiary care settings with significant seasonal case loads, dual testing may reduce diagnostic delay and hospital stay duration.

Importantly, current evidence is predominantly derived from single-center retrospective studies and case reports, many with small paediatric sample sizes. There is a pressing need for prospective multicenter paediatric studies across India and neighboring South Asian countries to quantify true coinfection prevalence, delineate severity predictors, and compare outcomes with monoinfection cohorts. Such studies should incorporate standardized diagnostic criteria, molecular confirmation where feasible, and longitudinal follow-up. Biomarker-driven investigations exploring cytokine profiles, endothelial activation markers, and genetic susceptibility factors could clarify immunopathogenic mechanisms unique to coinfection.

Comparative analysis suggests that coinfected paediatric patients exhibit higher rates of shock, acute respiratory distress syndrome, and multi-organ dysfunction compared to mono-infected cases. Delayed initiation of doxycycline has emerged as a consistent predictor of adverse outcomes in reported series.

The seasonal overlap of Aedes mosquito proliferation and chigger exposure during monsoon months in India creates a predictable epidemiological window for coinfection. Integrated vector control strategies and clinician awareness during this period are critical to reducing morbidity. Public health surveillance systems should also consider integrated vector-borne disease monitoring, particularly in districts reporting high incidence of both dengue and scrub typhus. Education of primary care providers and paediatricians regarding the possibility of coinfection is essential, especially when children present with persistent fever beyond the typical defervescence period of dengue or fail to improve with supportive care alone.

5. LIMITATIONS

This review is limited by heterogeneity in diagnostic methods, predominance of retrospective single-center studies, small paediatric sample sizes, and potential publication bias toward severe cases. The reliance on case reports and case series may overrepresent atypical or severe presentations, limiting generalizability.

6. CONCLUSION

Paediatric dengue–scrub typhus coinfection in South Asia represents an emerging and underrecognized clinical entity characterized by synergistic endothelial injury and immune amplification. Early dual testing and prompt doxycycline therapy significantly improve outcomes. Integrated clinical vigilance, routine dual testing in endemic seasons, and mechanistic paediatric research are critical to preventing avoidable morbidity in this vulnerable population.

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