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Original Research Article

Clinico-Etiological Spectrum in Children Presenting with Acute Undifferentiated Febrile Illness

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Abstract:

Background: Acute undifferentiated febrile illness (AUFI) is a common clinical presentation among children in tropical regions. Overlapping symptoms and the absence of localizing signs often make etiological diagnosis difficult. Knowledge of regional disease patterns is important for appropriate investigation and management.

Aim: To evaluate the clinico-etiological spectrum of acute undifferentiated febrile illness in children and assess the association between underlying etiology and clinical outcomes.

Materials and Methods: This prospective observational study was conducted at the Indira Gandhi Institute of Child Health, Bengaluru, from April 2024 to September 2025. A total of 400 children aged 1 month to 18 years presenting with fever lasting less than 14 days without an identifiable focus were included. Demographic characteristics, clinical findings, laboratory parameters, etiological diagnoses, complications, and outcomes were recorded. A two-tier diagnostic approach involving routine investigations and selected serological and molecular tests was followed.

Results: Of the 400 children, 219 (54.8%) were males, and the largest proportion belonged to the 6–10-year age group (39.0%). Dengue fever was the predominant etiology (57.0%), followed by rickettsial fever (4.8%), while 37.0% remained etiologically undiagnosed. Hepatomegaly (66.8%) and rash (20.5%) were common clinical findings. Among 330 hospitalized children, thrombocytopenia was observed in 59.7%, and elevated AST levels in 73.3%. PICU admission was required in 17.3%, while 13.0% developed shock. Overall mortality was 1.0%, with three deaths attributed to severe dengue and one to leptospirosis.

Conclusion: Dengue was the leading identified cause of pediatric AUFI, followed by rickettsial fever. Although most children recovered, severe infections were associated with significant complications. Early clinical assessment, appropriate diagnostic investigations, and timely management remained important in improving outcomes.

Keywords: Acute undifferentiated febrile illness; Children; Dengue; Rickettsial fever; Scrub typhus; Clinical outcomes; Tropical infections.

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Introduction

Fever is among the most common reasons for pediatric consultations and hospital admissions. Although most febrile illnesses in children are infectious, identifying the underlying cause can be difficult when specific clinical features are absent. Acute undifferentiated febrile illness (AUFI) refers to fever of short duration without an identifiable focus following initial clinical evaluation. Its presentation ranges from mild, self-limiting infections to severe systemic illnesses requiring intensive care. Jayashree et al. [1] emphasized the importance of systematic clinical assessment in children presenting with fever, while Shoman et al. [2] described the diagnostic difficulties associated

with pediatric febrile illnesses of uncertain origin. The etiological spectrum of AUFI varies considerably across geographical regions, seasons, and age groups. In tropical countries such as India, dengue, scrub typhus, malaria, enteric fever, leptospirosis, and other viral infections account for a substantial proportion of cases. Changes in disease transmission and seasonal outbreaks further influence the distribution of febrile illnesses. Verma et al. [3] examined the potential of surveillance-related data for predicting acute febrile illness outbreaks in northern India. Abhilash et al. [4] reported considerable variation in the clinical presentation and outcomes of acute undifferentiated fever in a tertiary care hospital in South India.

Distinguishing between different infectious causes remains challenging because symptoms such as headache, vomiting, myalgia, abdominal pain, and rash frequently overlap. Laboratory findings, including thrombocytopenia, leukopenia, elevated liver enzymes, and inflammatory markers, may provide diagnostic clues but are rarely specific to a single infection. Bhaskaran et al. [5] reviewed the diagnostic approaches used for acute febrile illnesses in South India and identified limitations in the availability and application of diagnostic tests. Rauf et al. [6] also demonstrated the varied infectious causes of acute febrile illness among hospitalized children in northern India.

Early etiological identification is particularly important in children because certain infections can progress rapidly to shock, neurological complications, respiratory failure, or multiorgan dysfunction. Appropriate use of serological and molecular investigations may improve diagnostic accuracy and support timely treatment. Kavirayani et al. [7] examined the clinical profile and diagnostic role of serological testing in pediatric acute febrile illness. Sánchez-González et al. [8] described the viral etiologies and seasonal patterns of pediatric febrile illnesses, demonstrating the importance of local epidemiological surveillance.

Despite improvements in diagnostic facilities, a considerable proportion of children with AUFI remain without a confirmed etiological diagnosis. Region-specific information on clinical characteristics, laboratory abnormalities, complications, and outcomes is therefore needed to guide clinical management. The present study was undertaken to evaluate the clinico-etiological spectrum of AUFI among children attending a tertiary care pediatric hospital in Bengaluru and to examine the association between underlying etiology and clinical outcomes.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted at the Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, over 18 months, from April 2024 to September 2025. Children presenting to the outpatient department, emergency department, general pediatric wards, and pediatric intensive care unit were evaluated for acute undifferentiated febrile illness.

Study Population and Sample Size: A total of 400 children aged 1 month to 18 years were enrolled. The sample size was calculated using a prevalence-based formula, considering an anticipated prevalence of 36%, a 95% confidence level, and an absolute precision of 5%. After allowing for a 10% attrition rate, the calculated sample size was rounded to 400 participants.

Inclusion and Exclusion Criteria: Children presenting with fever above 38°C (100.4°F) for less than 14 days, without an identifiable focus of infection on history and clinical examination, were included after obtaining informed consent from their parents or guardians and age-appropriate assent.

Children with an identifiable localized infection, hematological malignancy, autoimmune disorders, immunocompromised conditions, recurrent fever, or transfusion-related febrile reactions were excluded.

Data Collection and Clinical Evaluation: Demographic characteristics, duration of fever, associated symptoms, clinical examination findings, and relevant medical history were recorded using a structured proforma. Each child underwent a detailed clinical assessment to identify possible infectious etiologies and signs of disease severity.

Laboratory Investigations: A two-tier diagnostic approach was followed. Initial investigations included complete blood count, peripheral smear, C-reactive protein, liver and renal function tests, urine examination, dengue NS1 antigen testing, malaria rapid diagnostic testing, and Weil–Felix testing. Blood culture, chest radiography, and cerebrospinal fluid examination were performed when clinically indicated.

Additional serological and molecular investigations were carried out in collaboration with the Department of Neurovirology/Microbiology at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. These included testing for scrub typhus, chikungunya, dengue, Salmonella, Brucella, leptospirosis, and Epstein–Barr virus, as appropriate.

Outcome Assessment: The underlying etiology, clinical manifestations, laboratory abnormalities, complications, requirement for intensive care, duration of hospitalization, and final clinical outcomes were recorded. Associations between

etiological diagnoses and clinical outcomes were assessed.

Ethical Considerations: The study was conducted after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from parents or legal guardians, and assent was obtained from eligible children. Patient information was kept confidential throughout the study.

Results

A total of 400 children presenting with acute undifferentiated febrile illness (AUFI) were included in the study. Of these, 219 (54.8%) were males and 181 (45.2%) were females, with a male-to-female ratio of 1.2:1. The largest proportion of children belonged to the 6–10-year age group (39.0%), followed by the 1–5-year age group (30.8%).

Dengue fever was the most common identified etiology, accounting for 57.0% of cases, followed by rickettsial fever (4.8%). An etiological diagnosis could not be established in 37.0% of children.

Table 1: Demographic Characteristics and Etiological Distribution of the Study Population (N = 400)

Characteristics	Number (n)	Percentage (%)
Age group		
<1 year	21	5.3
1–5 years	123	30.8
6–10 years	156	39.0
11–14 years	60	15.0
15–18 years	40	10.0
Sex		
Male	219	54.8
Female	181	45.2
Etiological diagnosis		
Dengue fever	228	57.0
Rickettsial fever	19	4.8
Viral hepatitis	3	0.8
Leptospirosis	2	0.5
Sero-negative AUFI	148	37.0

Hepatomegaly was the most frequently observed clinical finding, present in 267 (66.8%) children, followed by rash in 82 (20.5%).

Splenomegaly was documented in 17 (4.3%) children, while bleeding manifestations were observed in 15 (3.8%). Eschar was identified in nine children, all of whom were diagnosed with rickettsial fever. Among the 330 hospitalized children, thrombocytopenia was observed in 197 (59.7%), while elevated aspartate aminotransferase (AST) levels were recorded in 242 (73.3%).

C-reactive protein (CRP) levels were considerably higher among children with rickettsial fever than among those with dengue.

Table 2: Clinical Features and Laboratory Findings among Children with AUFI

Clinical and laboratory parameters	Number (n)	Percentage (%)
Clinical findings (N = 400)		
Hepatomegaly	267	66.8
Rash	82	20.5
Splenomegaly	17	4.3
Bleeding manifestations	15	3.8
Eschar	9	2.3
Laboratory findings (N = 330 hospitalized children)		
Severe thrombocytopenia (<20,000/mm³)	29	8.8
Moderate thrombocytopenia (20,000–50,000/mm³)	88	26.7
Mild thrombocytopenia (50,000–100,000/mm³)	80	24.2
Normal platelet count	133	40.3
Elevated AST (>60 U/L)	242	73.3
Normal AST (≤60 U/L)	88	26.7

Of the 330 hospitalized children, 57 (17.3%) required admission to the pediatric intensive care unit (PICU). Shock was documented in 43 (13.0%) children, while 21 (6.4%) developed respiratory complications.

Mechanical ventilation was required in 14 (4.2%) children. Neurological complications were recorded in 12 (3.6%), and multiorgan dysfunction syndrome developed in nine (2.7%).

Table 3: Complications and Intensive Care Requirements among Hospitalized Children (N = 330)

Complications and interventions	Number (n)	Percentage (%)
PICU admission	57	17.3
Shock	43	13.0
Antibiotic treatment required	24	7.3
Respiratory complications	21	6.4
Mechanical ventilation	14	4.2
Central nervous system complications	12	3.6
Multiorgan dysfunction syndrome	9	2.7
Inotropic support	7	2.1
Acute kidney injury	6	1.8
Platelet transfusion	4	1.2

Clinical outcomes were generally favorable, with 396 (99.0%) children recovering and four (1.0%) deaths recorded. Three deaths occurred among children with severe dengue, while one occurred in a child with leptospirosis. No deaths were reported among children with mild or moderate dengue, rickettsial fever, viral hepatitis, or sero-negative AUFI. The mean duration of hospitalization was longest among children with severe dengue (6.5 days), followed by rickettsial fever (5.4 days).

Table 4: Clinical Outcomes According to Etiological Diagnosis (N = 400)

Etiological diagnosis	Total (n)	Recovered n (%)	Deaths n (%)	Mean hospital stay (days)
Mild dengue	95	95 (100.0)	0 (0.0)	3.0
Moderate dengue	104	104 (100.0)	0 (0.0)	4.3
Severe dengue	29	26 (89.7)	3 (10.3)	6.5
Rickettsial fever	19	19 (100.0)	0 (0.0)	5.4
Leptospirosis	2	1 (50.0)	1 (50.0)	5.0
Viral hepatitis	3	3 (100.0)	0 (0.0)	5.0
Sero-negative AUFI	148	148 (100.0)	0 (0.0)	4.6
Total	**400**	**396 (99.0)**	**4 (1.0)**	—

Overall, dengue accounted for most AUFI cases, while rickettsial fever was associated with substantial clinical morbidity. Thrombocytopenia and elevated liver enzymes were common among hospitalized children. Although most patients recovered, severe dengue and leptospirosis accounted for all recorded deaths.

Discussion

The present study evaluated the clinico-etiological spectrum and clinical outcomes of acute undifferentiated febrile illness (AUFI) among 400 children attending a tertiary care pediatric hospital in Bengaluru. Dengue fever was the predominant etiology (57.0%), followed by rickettsial fever (4.8%), while 37.0% of cases remained without an identified cause. Most children belonged to the 6–10-year age group (39.0%), with a slight male predominance (54.8%). These findings reflected the substantial burden of vector-borne infections among children in tropical regions.

Rickettsial fever accounted for 4.8% of cases but was associated with considerable clinical morbidity. Chrispal et al. [9] described the clinical manifestations and predictors of mortality in scrub typhus, emphasizing the potential for severe systemic complications. Ranjan and Prakash [10] also discussed the re-emergence of scrub typhus in India. In the present study, eschar was identified in 47.4% of children with rickettsial fever, while hepatomegaly and splenomegaly were frequent findings. These observations suggested that careful clinical examination, supported by appropriate laboratory testing, remained important for identifying rickettsial infections. Laboratory abnormalities were common among hospitalized children. Thrombocytopenia was observed in 59.7%, while elevated AST levels were recorded in 73.3%.

These findings were consistent with the hematological and hepatic involvement associated with tropical febrile illnesses. Jairajpuri et al. [11] examined the diagnostic relevance of hematological parameters in malaria, demonstrating their potential usefulness in evaluating febrile patients. However, such abnormalities were not disease-specific and required interpretation alongside clinical findings and etiological investigations. Fever represented an important physiological response to infection, although its clinical significance depended on the underlying disease and associated complications.

Mackowiak [12] discussed the protective and potentially harmful effects of fever, while Baraff [13] emphasized the importance of systematic assessment in children presenting without an identifiable source. Dinarello [14] described the inflammatory mechanisms responsible for fever generation. In the present study, the overlapping clinical manifestations of dengue and rickettsial fever demonstrated the limitations of relying on symptoms alone for etiological diagnosis.

A marked seasonal concentration of dengue cases was observed during the monsoon and post-monsoon months. This pattern was compatible with the temperature-dependent transmission of mosquito-borne infections discussed by Mordecai et al. [15]. Seasonal variation therefore remained an important consideration when evaluating children with AUFI in Bengaluru.

Complications occurred in a proportion of hospitalized children, with PICU admission required in 17.3%, shock in 13.0%, and respiratory complications in 6.4%. Mechanical ventilation was required in 4.2%. Jain et al. [16] described the clinical burden of serious pediatric respiratory infections requiring hospitalization, providing broader context for respiratory complications among febrile children. In the present study, severe dengue accounted for three of the four deaths, while one death occurred in a child with leptospirosis. The overall mortality was 1.0%, although mortality was considerably higher within the small severe dengue and leptospirosis subgroups.

Despite the use of a two-tier diagnostic approach, 37.0% of children remained without an identified etiology. Damhorst et al. [17] discussed the potential role of point-of-care technologies in improving the diagnosis of serious acute illnesses. Ghoshal et al. [18] demonstrated the diagnostic utility of multiplex molecular testing in infectious disease, although their investigation focused on infectious diarrhoea rather than pediatric AUFI. These studies provided broader support for expanding diagnostic capabilities, particularly where conventional investigations failed to establish an infectious cause.

The study was limited by its single-centre design and the substantial proportion of cases without etiological confirmation.

Nevertheless, the findings provided useful information regarding the local distribution of pediatric AUFI, associated clinical abnormalities, and outcomes. The predominance of dengue and the morbidity associated with rickettsial infections supported the need for early clinical assessment, appropriate diagnostic testing, and close monitoring of children presenting with undifferentiated fever.

Conclusion

Dengue fever was the most common identified cause of acute undifferentiated febrile illness among children attending the tertiary care pediatric hospital, followed by rickettsial fever. Hepatomegaly, thrombocytopenia, and elevated liver enzymes were frequent findings.

Although most children recovered, severe dengue and leptospirosis were associated with mortality. A considerable proportion of cases remained etiologically undiagnosed despite laboratory evaluation. Early recognition of complications and the appropriate use of serological and molecular investigations may help guide treatment and improve clinical management.

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