

Acute Undifferentiated Febrile Illness in Patients Presenting to a Tertiary Care Hospital in South India: Clinical Spectrum and Outcome

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ABSTRACT

Background: Acute undifferentiated febrile illness (AUF) may have similar clinical presentation, and the etiology is varied and region specific. **Materials and Methods:** This prospective observational study was conducted in a tertiary hospital in South India. All adult patients presenting with AUF of 3–14 days duration were evaluated for etiology, and the differences in presentation and outcome were analyzed. **Results:** The study cohort included 1258 patients. A microbiological cause was identified in 82.5% of our patients. Scrub typhus was the most common cause of AUF (35.9%) followed by dengue (30.6%), malaria (10.4%), enteric fever (3.7%), and leptospirosis (0.6%). Both scrub typhus and dengue fever peaked during the monsoon season and the cooler months, whereas no seasonality was observed with enteric fever and malaria. The mean time to presentation was longer in enteric fever (9.9 [4.7] days) and scrub typhus (8.2 [3.2] days). Bleeding manifestations were seen in 7.7% of patients, mostly associated with dengue (14%), scrub typhus (4.2%), and malaria (4.6%). The requirement of supplemental oxygen, invasive ventilation, and inotropes was higher in scrub typhus, leptospirosis, and malaria. The overall mortality rate was 3.3% and was highest with scrub typhus (4.6%) followed by dengue fever (2.3%). Significant clinical predictors of scrub typhus were breathlessness (odds ratio [OR]: 4.96; 95% confidence interval [CI]: 3.38–7.3), total whole blood cell count >10,000 cells/mm³ (OR: 2.31; 95% CI: 1.64–3.24), serum albumin <3.5 g % (OR: 2.32; 95% CI: 1.68–3.2). Overt bleeding manifestations (OR: 2.98; 95% CI: 1.84–4.84), and a platelet count of <150,000 cells/mm³ (OR: 2.09; 95% CI: 1.47–2.98) were independent predictors of dengue fever. **Conclusion:** The similarity in clinical presentation and diversity of etiological agents demonstrates the complexity of diagnosis and treatment of AUF in South India. The etiological profile will be of use in the development of rational guidelines for control and treatment of AUF.

Key words: Acute undifferentiated febrile illness, dengue fever, etiology, scrub typhus, South India

INTRODUCTION

Acute onset of fever, chills, myalgia, and fatigue are common features of many infections that are endemic in India. In many areas of developing countries, where diagnostic facilities are limited, etiologies of

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acute undifferentiated febrile illness (AUFI) remain largely unknown. Physicians often diagnose patients presumptively based on clinical features and assumptions regarding circulating pathogens. These AUFI that includes scrub typhus, dengue fever, malaria, enteric fever, and leptospirosis among others cause significant mortality and morbidity.^[1] These infections may be indistinguishable clinically, and the choice of empiric antibiotics depends on the etiologic profile which is variable and is region specific. Dengue fever and malaria are arthropod-borne diseases and are endemic in many parts of India during the monsoon season. Leptospirosis and scrub typhus are zoonotic infections and are widely prevalent in areas with heavy monsoon and agrarian way of life. A study done by Chrispal *et al.* in 2010 in the same South Indian hospital showed that scrub typhus is responsible for nearly half of the inpatient admissions due to AUFI.^[1] However, the etiological spectrum in the inpatient and outpatient departments (OPDs) is very different. It is crucial to determine the prevalence and epidemiology of the causative pathogens to develop protocols for empiric antibiotics. In this context, we conducted a cross-sectional prospective observational study to investigate the causes of AUFI, clinical predictors, and the seasonal trend through the year.

MATERIALS AND METHODS

This prospective observational study was conducted in Christian Medical College, Vellore, a 2700-bed Tertiary Care Hospital in Tamil Nadu, South India, between October 2012 and September 2013. All adult patients more than 15 years of age presenting with an AUFI lasting between 3 and 14 days with no evident focus of infection following initial clinical evaluation were included in the study. Patients with hematological malignancies, autoimmune disorders, and those on immunosuppressants were excluded from the study. Details of history and results of a thorough physical examination were entered on a standard data collection sheet after obtaining a written informed consent. The routine baseline investigations included complete blood count analysis, serum electrolytes, liver and renal function tests. A thin smear was performed to detect malarial parasites. A single blood culture was obtained from all enrolled patients in an aerobic BacT/Alert 3D (bioMerieux, Hazelwood, MO) bottle and incubated for up to 7 days in the BacT/Alert blood culture system. All commercial enzyme-linked immunosorbent assay (ELISA) tests were performed for agents believed to be endemic to the region and interpreted according to the manufacturer's instruction as positive, equivocal, or negative. These serological tests

were done on or after the 7th day of fever if tests for malarial parasites and blood cultures were negative. These included dengue Ig M ELISA (Panbio[®]; Dengue Duo Cassette), scrub typhus IgM ELISA (InBios International, Inc., Seattle, WA, USA), leptospira IgM ELISA (Panbio[®]), and a Widal test. Convalescent serological testing after 2–4 weeks was performed if the initial serological diagnosis was unclear and if the patient was willing. A 4-fold increase in titer from acute to convalescent sample, or a result change going from negative to positive, was considered indicative of seroconversions. All inpatients were followed up until discharge from the hospital.

Diagnostic criteria

- Scrub typhus: Eschar + scrub IgM ELISA positive or Scrub IgM ELISA positive with other serologies and blood culture negative or scrub IgM ELISA seroconversion on convalescent sera
- Dengue: Clinical features of dengue with dengue IgM positive and other serologies and blood culture negative or seroconversion on convalescent sera
- Malaria: Malaria parasite (trophozoites of *Plasmodium falciparum*, *Plasmodium vivax* or mixed) visualized on thin blood smears
- Enteric fever: Blood culture positive for Salmonella typhi or Salmonella paratyphi or 4-fold rise in titer on the Widal test in convalescent sera
- Leptospirosis: Leptospira IgM positive with other serologies and blood culture negative
- Unclear diagnosis: After complete evaluation, a definitive diagnosis was not made. This included patients who did not have convalescent sera taken (diagnostic criteria were not fulfilled during initial admission) and who had multiple serologies positive without fulfilling the diagnostic criteria.

Statistical methods

Statistical analysis was performed using SPSS software (SPSS Inc., Released 2007. SPSS for Windows, version 16.0, Chicago, IL, USA). Mean (standard deviation [SD]) was calculated for the continuous variables, and *t*-test or Mann–Whitney U-test was used to test the significance. Categorical variables were expressed in proportion, and Chi-square test or Fisher exact test was used to compare dichotomous variables. The clinical and laboratory predictors of diagnosis of the common infections were analyzed by univariate and multivariate logistic regression analysis and their 95% confidence intervals (CI) were calculated. For all tests, a two-sided *P* = 0.05 or less was considered statistically significant.

This study was approved by the Institutional Review Board (IRB Min. No. 8007 dated 19/09/2012) and the patient confidentiality was maintained using unique identifiers and by password protected data entry software with restricted users.

RESULTS

During the study period, 1372 patients presented to the Emergency department and General Medicine OPDs with AUFI. The etiological evaluation could not be done in 114 patients as they either did not give consent or blood samples for confirmation of diagnosis were not given. The final study cohort included 1258 patients [Figure 1].

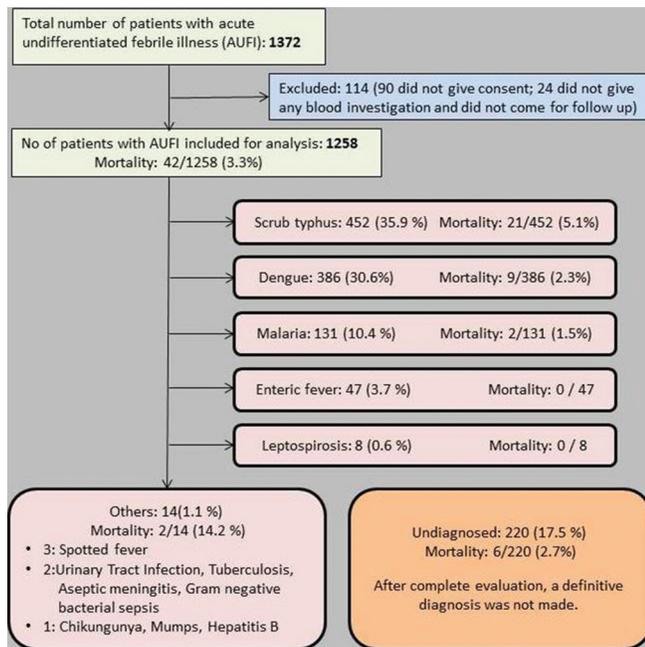


Figure 1: Flow chart of patients presenting with acute undifferentiated febrile illness

Demographic features and etiology

The majority of the patients were from Tamil Nadu (72.4%) and the neighboring state of Andhra Pradesh (26.1%). The remaining 1.5% was from Kerala, Karnataka, Orissa, West Bengal, and Bihar. The patients were mostly housewives (31.7%), manual laborers/agricultural workers (31%), or students (17.2%). The majority of the patients were younger than 40 years (mean = 37.4 years, SD = 20). Common comorbidities included diabetes mellitus (10.7%), essential hypertension (6.5%), ischemic heart disease (1.1%), and chronic liver disease (0.8%) [Table 1].

Scrub typhus was the most common cause of AUFI (35.9%) followed by dengue fever (30.6%), malaria (10.4%), and enteric fever (3.7%) The cause of fever was undetermined in 17.4% patients. Secondary dengue infection (85.7%) was overwhelmingly more common than primary dengue infection (13.9%). Infection with *P. vivax* (63.3%) formed the majority of the malaria cases while *P. falciparum* (26.7%) and mixed infection (10%) with *P. vivax* and *P. falciparum* comprised the rest. Fifty-four percent of the patients were males. A male predominance was seen in leptospirosis (87.5% vs. 12.5%), malaria (84.7% vs. 15.3%), enteric fever (70.2% vs. 29.8%), and dengue (57% vs. 43%). There were 39 pregnant patients (scrub typhus: 23, dengue: 6, malaria: 4, urinary tract infection: 1, and undiagnosed: 5).

Seasonal distribution

The seasonality observed in the more common causes of AUFI is illustrated in Figure 2. Both scrub typhus and dengue fever peaked during the monsoon season and the cooler months. No obvious seasonal trends were detected in the prevalence of enteric fever or malaria.

Table 1: Baseline characteristics of the acute undifferentiated febrile illness patients (n=1258)

Variable	Scrub (n=452)	Dengue (n=386)	Malaria (n=131)	Enteric fever (n=47)	Leptospirosis (n=8)	Other (n=14)	Undiagnosed (n=220)
Age, mean (SD)	42.7 (15.1)	30.9 (12.5)	33.5 (12.7)	29.1 (11.7)	39.4 (14.1)	39.3 (19.0)	41.9 (35.1)
Male, n (%)	186 (41.2)	220 (57)	111 (84.7)	33 (70.2)	7 (87.5)	9 (60)	114 (52.1)
Female, n (%)	266 (58.8)	166 (43)	20 (15.3)	14 (29.8)	1 (12.5)	6 (40)	105 (47.9)
Occupation, n (%)							
Housewife	195 (43.2)	97 (25.1)	17 (13.0)	9 (19.6)	0	6 (40.0)	76 (34.7)
Manual laborer	116 (25.7)	62 (16.1)	47 (35.9)	6 (13.0)	4 (50.0)	3 (20.0)	30 (13.7)
Student	28 (6.2)	122 (31.6)	18 (13.7)	13 (28.3)	1 (12.5)	16.7	34 (15.5)
Others	112 (24.8)	105 (27.2)	49 (37.4)	18 (39.1)	3 (37.5)	5 (33.3)	79 (36.1)
Diabetes, n (%)	66 (14.6)	23 (6)	8 (6.1)	5 (10.6)	2 (25)	3 (20)	28 (12.8)
CLD*, n (%)	3 (0.7)	0	1 (0.8)	0	1 (12.5)	1 (6.7)	5 (2.3)
CKD**, n (%)	3 (0.7)	0	0	2 (4.3)	0	0	1 (0.5)
Pregnant, n (%)	23 (8.6)	6 (3.6)	4 (21.1)	0	0	1 (16.7)	5 (4.8)
CTAS 1***	213 (47.2)	26 (6.7)	26 (19.8)	5 (10.6)	4 (50)	7 (46.7)	38 (17.4)
SOFA****, mean (SD)	5.0 (4.4)	3.0 (2.2)	4.7 (3.3)	1.5 (1.6)	8.6 (5.9)	2.9 (2.8)	2.5 (3.6)

*CLD: Chronic liver disease, **CKD: Chronic kidney disease, ***CTAS: Canadian Triage Assessment Score; **** SOFA: Sequential organ failure assessment score. SD: Standard deviation

Clinical features and laboratory investigations

The mean time to presentation was longer in enteric fever 9.9 (4.7) days and scrub typhus 8.2 (3.2) days compared to the other infections. The clinical features and laboratory investigations are shown in Table 2. Overall, the most common symptoms reported by the enrolled patients included generalized myalgia (77%), headache (59.3%), vomiting (42.9%), abdominal pain (22.4%), breathlessness (23.2%), and altered sensorium (6.9%). Breathlessness was a prominent symptom in 48% of patients with scrub typhus and 37.5% of patients with leptospirosis. A pathognomonic eschar was seen in 57.9%

of patients with scrub typhus. Thrombocytopenia was seen more commonly in dengue (mean: 56,000; SD: 66,200), malaria (mean: 57,000; SD: 64,893), and scrub typhus (mean: 81,000; SD: 77,319). Bleeding manifestations were seen in 98 patients, mostly associated with dengue (14%), scrub typhus (4.2%), and malaria (4.6%). Common sites of bleeding were the gastrointestinal tract (44.9%), gums (18.8%), and the nose (18.8%). Dengue hemorrhagic fever was seen in 11% (43/386) and dengue shock syndrome in 3.6% (14/386) of patients with dengue. The severity at presentation in the first 24 h was assessed by sequential organ failure assessment (SOFA) score. Patients with leptospirosis (mean: 8.6; SD: 5.9), scrub typhus (mean: 5.0; SD: 4.4),

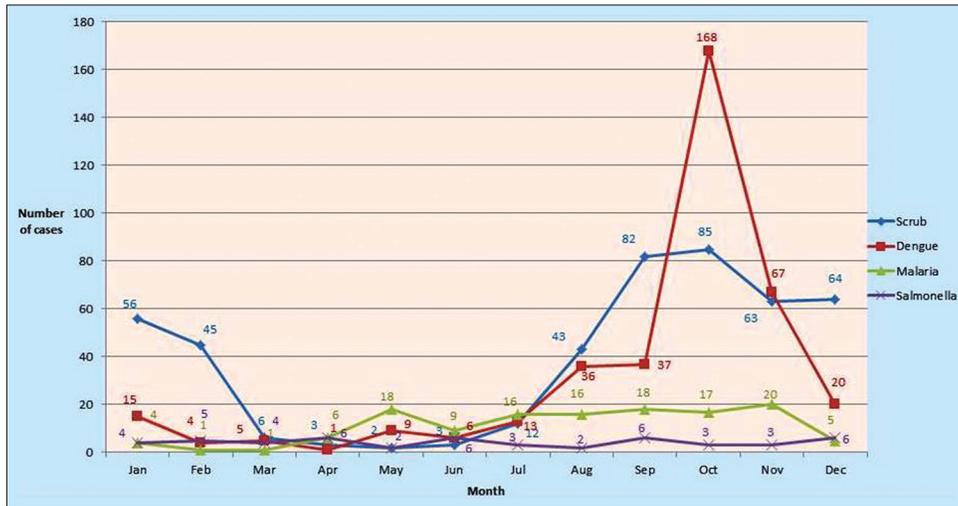


Figure 2: Seasonal distribution of acute undifferentiated febrile illness

Table 2: Clinical features and laboratory investigations of the common acute undifferentiated febrile illnesses

Variable	Scrub (n=452)	Dengue (n=386)	Malaria (n=131)	Enteric fever (n=47)	Leptospirosis (n=8)
Fever duration (days)	8.2 (3.2)	5.8 (2.4)	6.7 (3.2)	9.9 (4.7)	5.5 (2.1)
Headache, n (%)	260 (57.5)	247 (64)	64 (48.9)	25 (53.2)	4 (50)
Seizure, n (%)	17 (3.8)	5 (1.3)	1 (0.8)	1 (2.1)	0
Altered sensorium, n (%)	55 (12.2)	8 (2.1)	9 (6.9)	3 (6.4)	0
Breathlessness, n (%)	217 (48)	27 (7)	15 (11.5)	5 (10.6)	3 (37.5)
Bleeding manifestation, n (%)	19 (4.2)	54 (14)	6 (4.6)	3 (6.4)	2 (25)
Laboratory investigations, mean (SD)					
Hemoglobin (g %)	12.4 (2.3)	14.8 (2.1)	12.4 (3.7)	13.3 (5.2)	12.5 (2.0)
Total WBC count (cells/cumm)	9400 (5421.2)	4200 (3741.4)	5400 (2856.6)	6700 (4327.8)	7350 (3459.5)
Platelets (cells/cumm)	81,000 (77,319)	56,000 (66,200)	57,000 (64,893)	157,000 (89,260)	14,500 (54,400)
Creatinine (mg %)	1.1 (1.3)	1.1 (0.4)	1.1 (0.6)	1.1 (0.5)	1.8 (2.5)
Urea (mg/dL)	36.0 (42.7)	22.0 (15.1)	35.0 (46.9)	22.0 (14.2)	67.0 (63.3)
Sodium (mmol/L)	132.0 (8.2)	135.0 (9.7)	135.0 (4.9)	131.0 (3.8)	136.0 (7.6)
Potassium (mmol/L)	3.8 (1.1)	3.9 (2.0)	3.9 (0.6)	4.0 (0.6)	3.6 (0.5)
Bicarbonate (mmol/L)	20.0 (4.5)	22.0 (3.7)	21.0 (4.6)	22.0 (4.5)	19.5 (6.3)
Total bilirubin (mg/dL)	0.9 (2.6)	0.6 (0.6)	1.8 (22.1)	0.6 (0.7)	2.5 (5.8)
Albumin (g/dL)	3.0 (0.7)	3.9 (1.7)	3.5 (3.9)	3.8 (0.6)	3.3 (0.8)
SGOT (U/L)	107.0 (167.3)	113.5 (517.7)	32.0 (43.4)	66.0 (87.8)	79.5 (39.1)
SGPT (U/L)	63.0 (87.0)	53.0 (282.8)	23.0 (36.8)	57.0 (64.4)	26.0 (23.2)
Alkaline PO ₄ (U/L)	136 (108.2)	74 (72.0)	78 (35.9)	93 (83.3)	83.5 (63.9)

Median (SD). WBC: Whole blood cell, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvate transaminase, SD: Standard deviation

and malaria (mean: 4.7; SD: 3.3) had a higher SOFA score at presentation. Involvement of different organ systems is shown in Figure 3. Respiratory system involvement was seen predominantly in leptospirosis (63%) and scrub typhus (42%). Renal failure, central nervous system, and cardiovascular system involvement were also more common in leptospirosis (63%, 38%, and 38%, respectively) and scrub typhus (31%, 20%, and 42%, respectively).

Significant parameters on univariate and multivariate analysis

Clinical and laboratory predictors of diagnosis using univariate and multivariate analysis are shown in Table 3. Significant parameters for scrub typhus on multivariate analysis were female gender (odds ratio [OR]: 2.25; 95% CI: 1.67–3.03), breathlessness (OR: 4.96; 95% CI: 3.38–7.3), total whole blood cell (WBC) count >10000 cells/mm³ (OR: 2.31; 95% CI: 1.64–3.24), serum albumin <3.5 g % (OR: 2.32; 95% CI: 1.68–3.2).

Overt bleeding manifestations (OR: 2.98; 95% CI: 1.84–4.84), total WBC count <10,000 (OR: 2.37; 95% CI: 1.56–3.59), and a platelet count of <150,000 cells/mm³ (OR: 2.09; 95% CI: 1.47–2.98) to be significantly associated with dengue fever compared with the nondengue group.

Longer duration of fever (OR: 1.17; 95% CI: 1.09–1.26) and symptoms of loose stools (OR: 8.08; 95% CI: 4.14–15.78) were found to be significant predictors of enteric fever.

Management and outcome

Less than half (46.3%) required inpatient care and 110 (8.7%) patients required medical intensive care

treatment. The requirement of inotropes was highest in leptospirosis (25%) followed by scrub typhus (17.4%), malaria (5.3%), and dengue (2.8%). Supplemental oxygen was needed in 62.5% of leptospirosis patients, 39.1% of scrub typhus patients, 5.3% of malaria patients, and 3.4% of patients with dengue fever. Invasive ventilation was required in 37.5%, 13.9%, 3%, and 2.5% of leptospirosis, scrub typhus, malaria, and dengue patients, respectively. Only 7.2% (28/386) of patients with dengue required platelet transfusions. The overall mortality rate was 3.3% and was highest with scrub typhus (21/456; 4.6%) followed by dengue fever (9/386; 2.3%). There were 2 deaths due to Gram-negative bacteremia and one each due to malaria and leptospirosis. The cause of death could not be determined in seven patients.

DISCUSSION

This is one of the largest prospective studies on the clinico-epidemiological profile of AEFI from a Tertiary Care Teaching Hospital of South India. A total of 1258 patients with AEFI were enrolled over a period of 12 months. Except in scrub typhus, male gender comprised the larger proportion of the cases. This is probably explained by the fact that exposure to mosquitoes and transmission of vector-borne diseases are more associated with the predominantly outdoor occupational exposure of males.^[1,2]

With the onset of the monsoon, the number of cases of AEFI increases and this trend persists through the winter months. During this period, scrub typhus (35.9%) was the predominant cause of AEFI followed by dengue fever (30.6%) and malaria (10.4%). Our results are similar

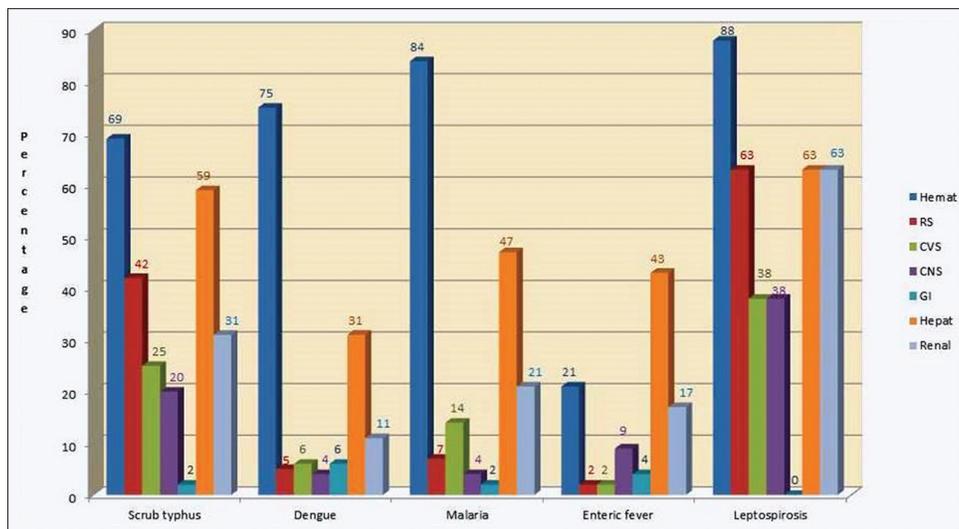


Figure 3: Organ involvement

Table 3: Significant parameters in univariate and multivariate analysis for scrub typhus, dengue, malaria and enteric fever

Scrub typhus	Univariate analysis				Multivariate analysis	
	Scrub typhus (n=451)	Other AUFI (n=807)	P	Un adjusted OR	Adjusted OR	95% CI
Age (mean in years)	42.71 (15.09)	33.84 (14.27)	<0.001	1.04	1.02	1.01-1.03
Female gender, n (%)	266 (58.98)	312 (38.66)	<0.001	2.28	2.25	1.67-3.03
Fever duration (mean in days)	8.14 (3.18)	6.59 (3.04)	<0.001	1.17	1.16	1.11-1.21
Breathlessness, n (%)	217 (48.12)	75 (0.29)	<0.001	9.05	4.96	3.38-7.3
Seizures, n (%)	17 (3.78)	8 (0.99)	0.001	3.92	1.75	0.55-5.59
Altered mental status, n (%)	55 (12.20)	32 (3.97)	<0.001	3.36	1.04	0.57-1.91
Shock (SBP <90 mmHg), n (%)	52 (11.53)	26 (3.23)	<0.001	3.91	0.77	0.41-1.47
Leucocyte count (>10,000 cells/mm ³)	193 (42.89)	111 (13.79)	<0.001	4.69	2.31	1.64-3.24
Serum total bilirubin (mg %), mean (SD)	1.89 (2.62)	1.32 (2.37)	<0.001 ^a	1.1	0.95	0.89-1.02
Serum albumin (<3.5 g %), mean (SD)	316 (70.85)	246 (31.18)	<0.001	5.37	2.32	1.68-3.2
Serum alkaline phosphatase (U/L), mean (SD)	166.79 (108.32)	107.02 (82.79)	<0.001 ^a	1.01	1.003	1.001-1.005
SOFA score >8, n (%)	83 (18.44)	36 (4.46)	<0.001	4.84	0.9	0.48-1.72
Dengue	Dengue (n=386)	Other AUFI (n=872)	P	Un adjusted OR	Adjusted OR	95% CI
Age (mean in years)	30.85 (12.53)	39.75 (15.44)	<0.001	0.96	0.97	0.96-0.98
Fever duration (mean in days)	5.79 (2.36)	7.75 (3.31)	<0.001	0.77	0.81	0.76-0.85
Breathlessness, n (%)	27 (6.99)	265 (30.39)	<0.001	0.17	0.24	0.15-0.37
Overt bleeding manifestations, n (%)	54 (13.99)	44 (5.05)	<0.001	3.06	2.98	1.84-4.84
Leucocyte count (<10,000 cells/mm ³), n (%)	349 (90.89)	602 (69.12)	<0.001	4.46	2.37	1.56-3.59
Platelet count <150,000 cells/mm ³ , n (%)	329 (85.45)	626 (72.04)	<0.001	2.28	2.09	1.47-2.98
Malaria	Malaria (n=131)	Other AUFI (n=1127)	P	Un adjusted OR	Adjusted OR	95% CI
Female gender, n (%)	20 (15.27)	558 (49.51)	<0.001	0.18	0.22	0.13-0.36
Platelet <150,000 cells/mm ³	119 (92.25)	836 (74.31)	<0.001	4.11	3.77	1.92-7.39
Serum total bilirubin (mg %), mean (SD)	3.03 (3.85)	1.36 (2.20)	<0.001 ^a	1.18	1.19	1.11-1.26
Elevated SGPT (3 times upper limit of normal), n (%)	1 (0.79)	179 (16.01)	<0.001	0.04	0.02	0.002-0.18
Enteric fever	Enteric fever (n=47)	Other AUFI (n=1211)	P	Un adjusted OR	Adjusted OR	95% CI
Fever duration (mean in days)	9.87 (4.66)	7.04 (3.06)	<0.001	1.21	1.17	1.09-1.26
Loose stools, n (%)	18 (38.30)	80 (6.61)	<0.001	8.78	8.08	4.14-15.78
Platelet <150,000 cells/mm ³ , n (%)	21 (44.68)	934 (77.38)	<0.001	0.24	0.27	0.14-0.51

^aMann-Whitney U-test. SBP: Systolic blood pressure; SOFA: Sequential organ failure assessment; SGPT: Serum glutamic pyruvate transaminase, OR: Odds ratio, CI: Confidence interval, AUFI: Acute undifferentiated febrile illnesses

to those found in other tropical regions of the developing world, although the relative incidence of specific pathogens varies from place to place.^[2-6] Leptospirosis, malaria, scrub typhus, rickettsial infections, and dengue have been identified as major causes of AUFI in Thailand and Nepal.^[2,3,5] In Peru, South America, spotted fever group *Rickettsia*, leptospirosis, and *Coxiella burnetii* have been identified as major identifiable causes of AUFI.^[6] A study by Chrispal *et al.* in 2010 in the same hospital among inpatients had shown scrub typhus, malaria, and enteric fever to be the three main etiologies.^[1]

Infections such as dengue which reflect public health situation in the country are frequently underreported. In our study, almost one-third of the patients was confirmed to have dengue fever with the majority being secondary dengue cases (85.7%). In an area in Vietnam, dengue accounted for almost one-third of all acute undifferentiated nonmalarial fevers.^[7] In fact, nearly half of the global burden of dengue is borne by the Southeast Asian countries of India, Indonesia, Myanmar, and Thailand.^[8] Reported rates of

hemorrhagic manifestations in Indian studies vary between 6 and 37%.^[9-12] Our study had a higher prevalence of severe dengue cases (11%) compared to that reported by Souza *et al.* (7.6%).^[9] However, the rate of platelet transfusion in our study (7.2%) was much lesser than the rate of 20–51% reported in other studies.^[10-12] In our hospital, platelet transfusion was given only with significant bleeding or for therapeutic interventions such as obtaining a central venous access or performing a gastroscopy. However, in many places, platelets are transfused not based on medical rationale, but as a response to an intense social pressure on the treating physicians by the patients or their relatives. The majority of patients with dengue fever (71.2%) in our study were treated on an OPD basis while the majority of patients with scrub typhus (67.4%) required admission. Souza *et al.* reported much lower rate of the requirement of hospitalization (14.4% among adults and 6.3% among children) of patients presenting with dengue.^[9]

Scrub typhus, dengue, malaria, and leptospirosis are endemic in many parts of South India.^[1] Local public health

authorities have limited data to assess disease burden, to estimate priorities for health resources or to make protocols for empiric antibiotics for patients presenting with AUFI. Accurate diagnosis is complicated by a lack of knowledge of the local etiology of AUFI, similarities in clinical presentation, and unavailability of accurate diagnostic testing, particularly during the early phase of illness. Although leptospirosis has been thought to be widely prevalent in our region, the more definitive microscopic agglutination testing (MAT) was not performed on these samples. *Leptospira* IgM ELISA has been found to have poor diagnostic accuracy compared with MAT testing.^[13] Further laboratory studies and analysis are needed to understand the contribution of Leptospirosis to AUFI in South India.

The majority of the cases of scrub typhus and dengue were reported during the monsoon and postmonsoon seasons, in accordance with the reported patterns of disease transmission.^[14,15] However, we found no significant seasonal variation in malaria and enteric fever. In contrast to our observation, an increased incidence of typhoid fever during the monsoon season was noticed by Sharma *et al.* and Malakar in Assam, India and also by Owais *et al.* in Pakistan.^[16,17]

A microbiological cause of AUFI was identified in the majority (82.5%) of our patients. In other studies, the rates of determining the etiology varied from 40% to 73.3% by Mueller *et al.* in Cambodia.^[2,4,18] In our study, despite extensive evaluation, 17.5% of cases were of undetermined etiology. All the serological tests were negative in 9.6% of patients. More than one serological test being positive, probably due to cross-reactivity or recent infection or dual infections was seen in 7.6% of patients. Physicians need to be aware of the high rate of these phenomena and hence be cautious in making an etiological diagnosis purely based on serological tests. These tests are of little utility early in the course of AUFI but can be useful to establish the etiology during outbreaks and for patients who present after several days of onset of illness.

The overall mortality rate in our study was 3.3% with more than half the deaths resulting due to scrub typhus. However, the case fatality rate among inpatients of scrub typhus in our hospital decreased from 12.2% in 2008 to 6.9% in our study.^[15] This is probably due to a greater awareness and early recognition of this re-emerging infection. An eschar is the most useful diagnostic physical clue in areas endemic for scrub typhus.^[19] Since scrub typhus is the predominant etiology in our population, a thorough physical search for an eschar is mandatory so that appropriate antibiotics may

be promptly initiated. The mortality with dengue fever in our study (2.3%) is comparable with the mortality rate due to dengue, in recent studies.^[20,21]

Our study has certain limitations. Many potential pathogens (spotted fever, hantan virus, and chikungunya virus) were not routinely tested, and samples were not subjected to a broader battery of serologic testing due to financial constraints. Some patients did not come back for a second visit, and hence, convalescent sera could not be obtained for confirmation of diagnosis. A single thin smear was done to rule out malaria due to logistical constraints in most patients and hence, malaria may have been underdiagnosed.

CONCLUSION

With comprehensive laboratory investigation, a microbiological cause of AUFI was identified in 82.5% of cases. The similarity in clinical presentation, diversity of etiological agents, an inability to identify an etiology in a significant number of patients, demonstrate the complexity of diagnosis, and treatment of AUFI in South India. The etiological profile will be of use in the development of rational guidelines for infectious disease control and treatment.

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Conflicts of interest

There are no conflicts of interest.

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