

## CLINICAL PREDICTORS AND OUTCOMES OF ACUTE UNDIFFERENTIATED FEBRILE ILLNESS: A TERTIARY CARE EXPERIENCE

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### ABSTRACT

**Background:** Fever is a common major presenting complaint in the fast-developing world. Due to high prevalence of local individual diseases there is a need of differential diagnoses for acute undifferentiated febrile illness (AFI). Acute undifferentiated febrile illness is aptly defined as acute onset of fever (fever more than 38 degree Celsius lasting for less than 2 weeks) and no obvious cause found after full clinical history and physical examination. This study was carried out to find out the etiology of AFI that present to a tertiary hospital in north Karnataka and to describe disease specific clinical profiles. This was a 1-year prospective, observational study conducted in adults (age >14 years) who presented with an undifferentiated febrile illness of duration <15 days, requiring hospitalization. **Materials and Methods:** The study consisted of 100 patients. Data was collected to identify sex, age range and duration of fever. The diagnosis was done history, physical and laboratory examination. Blood cultures, malarial parasites and febrile serology, in addition to clinical evaluations and basic investigations were performed. **Results:** Scrub typhus (36%), dengue (24%), enteric fever (23%), malaria (2.0%), spotted fever rickettsiosis (3.0%), H1N1 (2.0%), and unclear diagnoses (10.0%). Leukocytosis, acute respiratory distress syndrome, aseptic meningitis, mild serum transaminase elevation and hypoalbuminemia were associated with scrub typhus and dengue. Normal leukocyte counts, moderate to severe thrombocytopenia, renal failure, splenomegaly and hyperbilirubinaemia with mildly elevated serum transaminases were associated with malaria. Enteric fever was associated with diarrhea, normal to low leukocyte counts and normal platelet counts. **Conclusion:** It is important to maintain a proper epidemiological data of AFIs so that evidence-based diagnostic criteria and treatment guidelines can be developed.

## INTRODUCTION

Fever is a common presenting complaint in the india and is one of the most common presentations to the emergency department (ED) at our institution. In the Western world, AUFI is often due to self-limited viral conditions. However, in the developing world, the differential diagnosis for AUFI includes potentially significant illnesses such as malaria, dengue fever, enteric fever, leptospirosis, rickettsiosis, Hantavirus, and Japanese encephalitis.<sup>[1,2]</sup>

Limited available resources and the great diversity of AFI etiologies in tropical regions challenge diagnosis, treatment, and public health responses to endemic and epidemic diseases. Further confounding this is the fact that a majority of the

patients present with non-descript symptoms (e.g., low-grade fever, general malaise, headache, and myalgia) and usually no focal point of infection. Health care providers lacking proper diagnostic tools are usually unable to determine specific etiologies, often diagnosing patients presumptively based on clinical features and assumptions regarding circulating pathogens. Syndrome based disease surveillance provides a useful methodology to systematically identify and document causes of acute fever.

This approach has been used by Trop Net Europa,<sup>[3,4]</sup> to diagnose fevers of unknown origin in Turkey,<sup>[5]</sup> China,<sup>[6]</sup> and India and a project designed by the U.S. Centers for Disease Control and Prevention (CDC, Atlanta, GA) for the same purpose along the United States-Mexico border. In

Southeast (SE) Asia, a prospective study of Thai patients presenting with acute undifferentiated febrile illness determined the etiologies of over 40% of cases, with the most prevalent being influenza, dengue, and rickettsial infections.<sup>[7]</sup>

In Latin America, surveillance identified the etiology of acute undifferentiated febrile illness in Ecuador in 40% of enrolled patients which was not previously been isolated in the country.<sup>[8]</sup>

Emerging and re-emerging diseases are a concern in SE Asia during a dynamic time of population growth, urbanization, and global migration. Infections from dengue virus, malaria parasites, influenza viruses, hepatitis viruses, rickettsiae, and *Leptospira* have previously been shown to impact populations across SE Asia.

However, among the SE Asian nations, limited data exists on the etiologies of AFI in the India.

Herein, we describe the demographics, symptoms, and identified etiologies of the patients seeking health care for AFI to a tertiary care hospital of north Karnataka. An attempt is made to increase the awareness of emerging infections which has caused increased morbidity and mortality.

## MATERIALS AND METHODS

Acute undifferentiated febrile illness was investigated in tertiary care hospital of north Karnataka. Adult patients age > 16years who presented to us with acute fever (of <15 days duration) were included in the study. Fever more than 2 weeks and those who failed to give consent were excluded from study. The study protocol was approved by the Ethical Review committee and written informed consent was obtained from each patient investigated.

**Clinical Investigations:** A detailed history and the results of all physical examinations and laboratory investigations were recorded for each patient, on standardized code sheets. The routine baseline investigations included complete blood-cell and platelet counts, blood cultures, evaluation of the plasma concentrations of glucose and electrolytes and the serum concentrations of urea and creatinine, liver-function tests, urine analysis, and chest radiography.

**Serology:** Scrub and murine typhus were diagnosed using a micro-immunofluorescence assay (MIA) with, respectively, three *O. tsutsugamushi* strains and *R. typhi* as antigen source. The titers of total immunoglobulin, IgG and IgM reacting with the rickettsial antigens were evaluated. Individuals found to having titers of anti-rickettsial antibodies in their convalescent sera that were at least four-fold greater than those seen in their acute sera, and those ever found to have titers of anti-rickettsial antibodies of at least 1:320 were considered to be confirmed cases of scrub or murine typhus.

Tests for anti-*Leptospira* antibodies using microscopic agglutination tests (MAT) and IFAT.

Dengue infection was diagnosed using a commercial antibody-capture ELISA NS 1 antigen, IgM antibody and influenza using another commercial kit based on an ELISA, for the detection of specific IgM.

## Statistical Analysis

Descriptive statistics were used to summarize the results of the study. Microsoft excel and SPSS 15.0 were used.

## RESULTS

From January 2025, hundred patients were enrolled. All patients enrolled met the criteria of fever (> 38.0C). There were 58 male patients and 42 female patients. The maximum patients were in the interquartile range 21–40 years of age (36%). Study subject occupation reporting a specific occupation, cattle farmers were most common (34%).

The most common symptoms reported by enrolled patients included malaise and headache (61%), cough (58%), sore throat (46%), chills (48%), and jaundice (19%). Among enrolled participants, 60% presented with signs and symptoms characteristic of influenza-like illness, 12% with gastroenteritis, and 19% with jaundice. Close contact with an individual who had similar symptoms was reported among 4% of participants. Laboratory testing was performed for agents believed to be endemic to the region in addition to a variety of emerging pathogens. A total of 100 AFI patients were diagnosed with: scrub typhus (33%); dengue (25%); enteric fever (14%); malaria (8.0%); spotted fever rickettsiosis (6.0%); H1N1 (5.0%); and unclear diagnoses (9.0%). [Figure 1]

Laboratory investigations showed total leukocyte count <4000 cells/cu mm in 20% and >11000 cells/cumm in 35%, low platelet count of <50000 cells/ml was seen in 54% of the patients. Evidence of acute kidney injury was seen in 26%, hepatic dysfunction was observed in nearly 25% patients in the form of either raised bilirubin, transaminases or low albumin. [Table 1]

Multi organ dysfunction was seen in 51%. [Table 2]

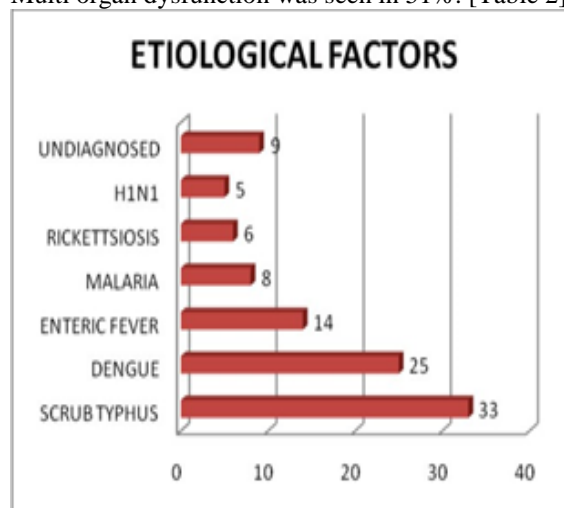


Figure 1: Spectrum of AFI

**Table 1: Laboratory investigations**

Laboratory parameters	Total leucocyte count (cells/cu.mm)	No of Patients
	< 4000	26
	4000-11000	41
	>11000	33
Platelet count (cells/ml)		
	<50000	55
	50000- 100000	24
	>100000	18
Serum creatinine (mg/dl)		
	>1.5	23
Total bilirubin (mg/dl)		
	>1.5	29
	↑AST/ ↑ALT/ ↑ALP Albumin <3.0 gm/dl	28/ 24/ 39 25

**Table 2: Organ dysfunction**

Number of organ failure	Total no of patients
1	20
2	27
≥3	48

## DISCUSSION

The aims and objective of this study was to identify the infectious etiologies of AFI among patients 16 years of age and older in parts of north Karnataka. Scrub typhus and leptospirosis have already been reported as major causes of acute febrile illness in South-east Asia, not only among residents but also among military personnel deployed to the region. About 10%–19% of all the investigated cases of acute undifferentiated fever in this area have been attributed to scrub typhus, with leptospirosis a slightly less common cause.<sup>[9-12]</sup>

In the present study scrub typhus was again identified as the most common causes of acute fever, followed by Dengue. Scrub typhus and Dengue are emerging as an important pathogen of acute febrile illness in this part of north Karnataka. Two major reasons for such under-reporting are a general lack of physician awareness and a general lack of a widely available specific serological test to confirm a suspected case of scrub typhus.

The present study was not very different from those found in other tropical regions of the developing world, although the relative incidence of specific pathogens varies considerably. Leptospirosis, malaria, scrub typhus, murine typhus, Rickettsia typhi, and dengue have been identified as major causes of AEFI in Thailand, Malaysia, and Nepal.<sup>[13-17]</sup> Dengue was found to cause one third of all cases of acute undifferentiated non-malarial fever in Vietnam.<sup>[18]</sup> In South America, spotted fever group Rickettsia, leptospirosis, and Coxiella burnetii have been identified as major identifiable causes of AEFI in a subtropical area of northwestern Peru.<sup>[19]</sup> Accurate diagnosis is complicated by a lack of knowledge of the scope of local pathogens, absence of etiology-specific signs and symptoms, and unavailability of accurate diagnostic testing, particularly during the early phase of illness.

## CONCLUSION

This study reports for the first time a number of important pathogens that have been overlooked in parts of north Karnataka. These results are necessary to bring about the awareness among treating health care officers regarding the potential pathogens in local area. The discovery of dengue requires a need to launch a major vector control effort. Local clinical laboratories now offer serologic testing for dengue, malaria and enteric fever. Such testing is admittedly of little utility early in the course of AEFI, but can be useful to establish the etiology during outbreaks and for patients who present after several days of illness. Local clinicians have also altered their approach to the treatment of AEFI. Typically this now involves ruling out malaria with a blood smear, then treating adults empirically for possible leptospirosis, Q fever, or other Rickettsial diseases with doxycycline and acetaminophen. If typhoid is in the differential diagnosis a third-generation cephalosporin or azithromycin is added to the treatment regimen. Until simple, rapid and affordable tests become available to accurately determine the etiology of AEFI early in its course, a combination of epidemiologic surveillance, focused public health efforts, and broad spectrum empiric therapy will have to suffice.

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