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Original Article

Clinical profile of fever in patients admitted through the outpatient department in a North Indian tertiary care teaching hospital

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Abstract

Background: Febrile illnesses are a common cause of morbidity and mortality and present diagnostic challenge, especially in the absence of reliable data in India. Fever has varying aetiologies such as infections, connective tissue disorders and malignancies. The infections may be indistinguishable clinically, and appropriate management will depend on the aetiologic profile. This study was planned to know the aetiology and seasonal variations of fever in adult patients.

Methods: A prospective observational study over a period of 15 months was conducted on adult patients aged ≥18 years with febrile illness. Details of history and results of physical examination were recorded. Routine baseline and special investigations were done as clinically indicated. All patients were followed until discharge from the hospital.

Results: Out of 122 patients, 79 were male. The maximum number of patients was in the age group of 31–40 years. The most common symptoms were myalgia, cough and vomiting. The aetiology of febrile illness was acute undifferentiated febrile illness (33.6%), undiagnosed undifferentiated fever (23%) and other diagnosis (43.4%). Common aetiologies of acute undifferentiated febrile illness were dengue fever (10.6%) and enteric fever (9.8%). Amongst other causes, tuberculosis and urinary tract infections were common. Seasonal variation was seen in enteric fever, dengue fever, pneumonia and tuberculosis.

Conclusions: Common aetiologies were dengue, enteric fever and tuberculosis. It is important to understand the profile of febrile illness; so that evidence-based management can be initiated, especially in a resource-limited country like India.

Keywords: Acute undifferentiated febrile illness, dengue fever, enteric fever, seasonal variation, tuberculosis, undiagnosed undifferentiated fever

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Submitted: 05-Mar-2021 **Accepted:** 11-Mar-2021 **Published:** 25-Oct-2021

Access this article online	
Quick Response Code:	Website: www.jcsr.co.in
	DOI: 10.4103/jcsr.jcsr_18_21

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How to cite this article: Salh GK, Gupta V, Kaur H, Ahluwalia S, Ahluwalia S. Clinical profile of fever in patients admitted through the outpatient department in a North Indian tertiary care teaching hospital. J Clin Sci Res 2021;10:227-32.

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INTRODUCTION

Febrile illnesses due to different aetiologic agents are the most common cause of morbidity and mortality in developing tropical and subtropical countries. Such illnesses are a public health challenge as the empirical diagnosis is a common practice and diagnostic facilities are scarce. Fever is a very common presenting symptom in clinical practice. Fever has varying aetiologies like infectious causes (malaria, dengue, scrub typhus, leptospirosis, enteric fever, acute viral hepatitis, sepsis, etc.,) and non-infectious (connective tissue disorders, autoimmune, malignancies and other miscellaneous causes). A uniform strategy to determine the aetiology is difficult as the epidemiology of fever is changing over time.[1]

The term acute undifferentiated fever (AUF) is used to denote fevers that typically do not extend beyond a fortnight and lack localisable or organ-specific clinical features.[2] AUF poses a diagnostic and therapeutic challenge to the health workers, particularly in resource-limited settings. The non-specificity of symptoms and signs and lack of availability of accurate diagnostics not only test the clinical mettle of even astute physicians but often lead to irrational use of antibiotics and antimalarial drugs. On the other hand, AUF syndromes (such as fever-rash, fever-myalgia, fever arthralgia, fever-haemorrhage and fever-jaundice) have overlapping aetiologies, which makes their diagnosis and management even more challenging.[3]

Acute undifferentiated febrile illness (AUFI) accounts for the majority of outpatient visits and inpatient admissions in India. The causes for the same are variable and need a systematic approach to identify the cause of appropriate therapy. AUFI can be potentially fatal if the aetiology is not recognised and if not appropriately treated early.[4]

Some fever syndromes have a more clear localisation to the skin and soft tissue (abscess or cellulitis), meninges or neural tissue (headache, neck stiffness and altered sensorium with or without focal neurological signs), respiratory tract (cough and breathlessness) or urinary tract (dysuria and haematuria). These syndromes have better-developed guidelines for their management.[3] Fevers with proven diagnoses are known as diagnosed AUF; those that defy diagnosis are called undiagnosed undifferentiated fevers (UUF).[5]

The knowledge of the most common aetiologies of fever helps in the appropriate management of patients. It is crucial to determine the prevalence and epidemiology of the causative pathogens to develop protocols for empiric antibiotics.[6] In this context, this study was done to evaluate the aetiology and clinical spectrum of fever in adult patients aged ≥19 years as well as to study the seasonal variation and outcome in these patients.

MATERIAL AND METHODS

A prospective observational study (1 January 2016–31 March 2017) was conducted on adult patients aged ≥19 years with fever admitted in the medical wards through the outpatient department. This study was approved by the institutional ethics committee.

Details of history and results of a thorough physical examination were recorded in a structured proforma. The routine baseline investigations included complete blood count analysis, urine routine examination, peripheral blood film for malarial parasite, serum electrolytes and liver and renal function tests. Other investigations were done as clinically indicated.

The blood sample was collected for serological tests. Various serological assays dengue immunoglobulin M (IgM), leptospira IgM (Panbio Standard diagnostics, Inc Korea), dengue NS1 antigen (J Mitra and Co. Pvt. Ltd. India), scrub typhus IgM (InBios International Inc USA), anti-hepatitis A virus (HAV), hepatitis B surface antigen (HBsAg), anti hepatitis C virus, anti human immunodeficiency virus (HIV) (Roche diagnostic India Pvt. Ltd.), anti hepatitis E virus (Beijing WANTAI Biological Pharmacy Enterprise Co. Ltd.), Malaria-Plasmodium falciparum, Plasmodium vivax Antigen (Medsource Ozone Biomedical Pvt. Ltd. Haryana), chikungunya IgM card (J Mitra and Co. Pvt. Ltd. India) and Widal test (Arkray Healthcare. Pvt. Ltd. Gujarat) were done. All the serological tests were carried out as per the standard procedure guidelines laid down by the manufacturer and interpreted as positive or negative.

Various samples such as sputum, endotracheal secretions, bronchoalveolar lavage, urine, pus, blood and body fluids were processed as per standard protocol. Blood and body fluids were inoculated into blood culture bottles and loaded into the BacT/Alert or BACTEC blood culture system till they were flagged positive or maximum for a period of 7 days. All other samples were inoculated onto blood agar and MacConkey's agar plates and incubated at 37 °C for 24 h. Identification and antibiotic sensitivity testing of isolates was done by Vitek 2 system.

For tuberculosis, smears were stained by Ziehl–Neelsen method and examined for acid-fast bacilli. Concentration and decontamination of specimens was carried out using NALC/NaOH method. The specimen was inoculated on 2 slopes of Lowenstein–Jensen medium and was incubated for 8 weeks.

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Diagnosis of various diseases was as per standard protocol. Patients were grouped into diagnosed AUFI.

UUF-after evaluation, a definitive diagnosis could not be made (UUF illness [UUFI]). Other diagnosis (infectious-localised or organ-specific and non-infectious-connective tissue disorders, autoimmune, malignancy, miscellaneous causes, etc.).

All inpatients were followed up until discharge from the hospital. The outcome studied was variables such as diagnosis at discharge, length of stay in the hospital, correlation with history, physical examination and investigations. The data were described in terms of range; mean ± standard deviation, frequencies (number of cases) and relative frequencies (percentages) as appropriate.

RESULTS

Out of the 122 admitted patients, a maximum number of patients were in the age group of 31–40 years (30.3%), followed by 21–30 years (23%). Out of the 122 patients, 79 were male (64.8%) and 43 were female (35.2%). The length of stay in the ward was 2–28 days with a mean of 6.61 days.

Out of all febrile patients, 16 (13.1%) patients had continuous fever and 106 (86.9%) patients had intermittent fever. About 65 (53.3%) patients had chills/rigors and 13 (10.7%) patients had an evening rise of temperature. Besides fever, the other presenting symptoms were myalgia (46.7%), cough (33.6%), anorexia and vomiting (30.3% each), pain abdomen (20.5%), nausea (18%), headache (13.9%) and weight loss (12.3%) (Figure 1).

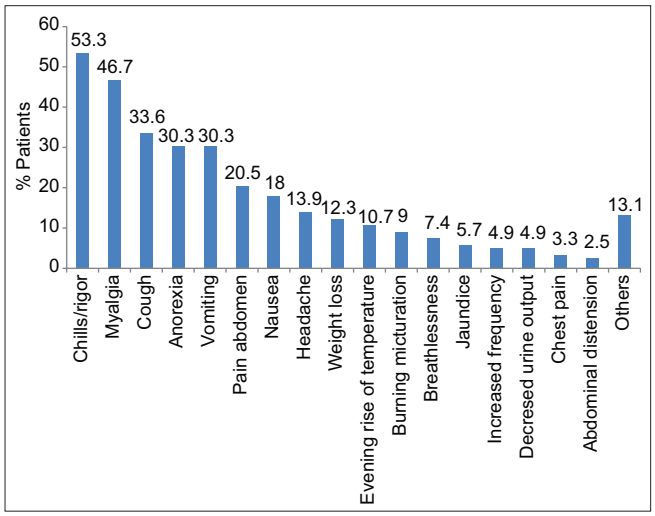

Figure 1: Distribution of subjects according to presenting complaints (*n* = 122)

On serological analysis, dengue IgM and Widal tests were positive in 9 (7.4%) patients each. Dengue NS1 antigen, scrub typhus IgM and anti-HAV were positive in 4 (3.3%) patients each. Leptospira IgM was positive in 3 (2.5%) patients and hepatitis B serology was positive in 2 (1.64%) patients. Malaria and chikungunya serology was positive in one patient each.

Out of 42 blood cultures, 3 (7.1%) were positive and in all, *Salmonella Typhi* was isolated. Out of 22 urine cultures, 4 (18.2%) were positive. *Escherichia coli* was the commonest isolate (50%), followed by *Staphylococcus aureus* (25%) and *Klebsiella pneumonia* (25%).

Of all the 122 patients admitted, acute undifferentiated febrile illness was diagnosed in 41(33.6%) patients; UUF 28 (23%); and other diagnosis 53 (43.4%) The common aetiologies of AUFI were dengue fever (10.6%), enteric fever (9.8%), acute viral hepatitis A, varicella infection and scrub typhus (3.3% each). Amongst other causes, tuberculosis (12.3%) was most common, followed by urinary tract infections (9%) and pneumonia (7.4%) (Table 1).

Table 1: Distribution of subjects according to diagnosis (*n*=122)

Final diagnosis	No. (%)
Acute undifferentiated febrile illness (diagnosed)	41 (33.6)
Dengue fever*	13 (10.6)
Enteric fever	12 (9.8)
Acute viral hepatitis A*	4 (3.3)
Varicella infection	4 (3.3)
Scrub typhus*	4 (3.3)
Leptospirosis*	3 (2.5)
Acute viral hepatitis B	2 (1.64)
Chikungunya	1 (0.8)
Malaria*	1 (0.8)
Other diagnosis	53 (43.4)
Tuberculosis	15 (12.3)
Urinary tract infection	11 (9.0)
Pneumonia	9 (7.4)
Acute pyelonephritis	4 (3.3)
Upper respiratory tract infection	4 (3.3)
Liver abscess	3 (2.5)
Acute gastroenteritis	2 (1.6)
Lymphoma	2 (1.6)
Acute pancreatitis	1 (0.8)
Systemic lupus erythematosus	1 (0.8)
Rapidly progressive glomerulonephritis	1 (0.8)
Undiagnosed undifferentiated fever	28 (23.0)
Total	122 (100)

*Three patients had co-infection: Scrub typhus with dengue fever, scrub typhus with acute viral hepatitis A and malaria with leptospirosis

Amongst tuberculosis patients, 9 (60%) had extra-pulmonary tuberculosis and 6 (40%) were diagnosed with pulmonary tuberculosis. Co-infections were diagnosed in 3 (2.4%) patients. Two patients had scrub typhus associated with

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dengue fever and acute viral hepatitis A. One patient had co-infection of malaria with leptospirosis.

Seasonal variations of various common infections were also studied in the admitted patients. Pneumonia (55.5%), enteric fever (50%) and tuberculosis (46.6%) in months from February to April, leptospirosis (66.6%), urinary tract infection (45.4%) in May to July, scrub typhus (75%) and dengue (69.2%) in August to October and upper respiratory tract infections (75%) in November to January were the common infections (Table 2).

Out of the 122 admitted patients, 2 patients took discharge against medical advice and there had been no mortality.

DISCUSSION

All study patients were evaluated as per protocol and underwent clinical examination and laboratory investigations. Out of the 122 patients, 120 patients were discharged. Two patients got discharged against medical advice and there was no mortality in the hospital. Most of the patients were discharged within a week and the mean length of stay was 6.61 days. This was because of the early detection and availability of rapid diagnostic tests and the initiation of effective antibiotic therapy in our institute.

Seventy-nine (64.8%) patients were male and 43 (35.2%) patients were female. The male-to-female ratio was 1.83. This had been consistent with observations reported in a study[7] which showed that the male-to-female ratio was 1.91.[7] In another study[8] the male-to-female ratio was 1.1. This difference observed in our study can be attributed to the gender difference prevailing in Punjab as well as the more outdoor activities of males making them more prone to vector borne diseases and other infections.

Our study included febrile patients in the age group of ≥19 years. Maximum patients were in the age groups of 31–40 years (30.3%) and 21–30 years (23%). In contrast, a study done in Uttarakhand[9] showed that more patients were in the age group of 21–30 years (25.5%), followed by the age group of 31–40 years (20.7%).[9]

The most common presenting symptoms were fever with chills/rigors (53.3%), myalgia (46.7%), cough (33.6%), anorexia and vomiting (30.3%) and pain abdomen (20.5%). In a study[10] headache (74.3%), myalgia (56.5%) and nausea and vomiting (62.2%) were common presenting symptoms.Another study[11] from Cambodia showed chills and rigors (48.1%), malaise (46.8%) and myalgia (23.2%) as the most commonly associated symptoms with febrile illness.

Acute undifferentiated febrile illness was diagnosed in 41 (33.6%) patients. Aetiological spectrum of acute undifferentiated febrile illness has been similar.[11-14] The common aetiologies were dengue fever (10.6%) and enteric fever (9.8%). Amongst other causes (43.4%), tuberculosis (12.3%), urinary tract infections (9%) and pneumonia (7.4%) were common. No definitive diagnosis could be made in 28 (23%) patients and was labelled as having UUF, whereas in literature, AUFI (83%), UUFI (6.66%) and other infections (10.37%) were seen in a study.

In a study[10] scrub typhus was the most common diagnosis (36.1%), followed by dengue fever (12.2%), urinary tract infections (10.7%) and respiratory tract infections (11.7%) No definitive diagnosis could be made in 5.9% of the patients. In a study[13] done at a tertiary care hospital in Vellore, tuberculosis (19%), lower respiratory tract infections (11%), urinary tract infections (10%) and malaria and scrub typhus (5% each) were most common infections. Non-infectious cause of fever was diagnosed in 15% and unknown aetiology in 13% of patients. Infectious (89.2%) and non-infectious (10.2%) causes of fever were reported in a study[14] from Korea. Amongst infectious causes, influenza, acute viral hepatitis A and scrub typhus were common.

Table 2: Seasonal variation of common infections amongst febrile patients

Infection	Season			
	February–April No. (%)	May–July No. (%)	August–October No. (%)	November–January No. (%)
Tuberculosis (*n* = 15)	7 (46.6)	3 (20)	2 (13.3)	3 (20)
Dengue fever (*n* = 13)	0	0	9 (69.2)	4 (30.7)
Enteric fever (*n* = 12)	6 (50.0)	1 (8.3)	2 (16.6)	3 (25)
Urinary tract infection (*n* = 11)	3 (27.2)	5 (45.4)	1 (9)	2 (18.1)
Pneumonia (*n* = 9)	5 (55.5)	2 (22.2)	1 (11.1)	1 (11.1)
Acute viral hepatitis A (*n* = 4)	0	2 (50)	1 (25)	1 (25)
Scrub typhus (*n* = 4)	0	1 (25.0)	3 (75)	0
Upper respiratory tract infection (*n* = 4)	0	1 (25)	0	3 (75)
Leptospirosis (*n* = 3)	0	2 (66.6)	1 (33.3)	0

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In our study, amongst the AUFI cases, the predominant cause was dengue fever (10.6%) similar to studies conducted by various authors (17.4%,[12] 28.4%[15] and 27%[16]) In India, dengue positivity ranged between 8% and 71% amongst AUFI cases.[7,17]

In our study, enteric fever accounts for 9.8% of cases, whereas only 4% and 3% cases of enteric fever were reported respectively.[12,16] Various studies carried out in India showed 8%–20% cases of enteric fever amongst AUFI.[18]

Scrub typhus was the predominant (47%, 56.6%)[12,14] infection amongst the AUFI cases in the literature, whereas in the present study, only 3.3% cases were diagnosed with scrub typhus. Leptospirosis was diagnosed in 2.5% of AUFI cases in our study which was similar (2%) to that reported in another study.[12] Malaria was diagnosed in 0.8% of patients in our study; in contrast, malaria was seen amongst 2%[16] and 2.4%[14] AUFI cases in the literature.

In our study, 23 (28%) patients had UUF. Patients with UUFs may have infections for which testing is not normally advocated. In short-duration febrile episodes, further investigations are not warranted when the patient clinically improves with symptomatic treatment. Intensive investigative efforts are performed for more prolonged or severe episodes. The lack of PCR technique and advanced molecular biology diagnostic methods was another limiting factor in our study. These advances may lead to the diagnosis of occult infections and previously unknown pathogens. All these factors may have led to the underdiagnosis of cases and hence increased percentage of undiagnosed cases in the present study.

Seasonal variation was seen in cases of tuberculosis, dengue fever, scrub typhus, enteric fever and pneumonia. The maximum number of tuberculosis cases was diagnosed in the months of February to July (66.6%) This can be attributed to the seasonal variation in the incidence of tuberculosis which is high in the spring and summer seasons. This is in concordance with a systematic review of 12 studies[19] which suggested predominant peak of tuberculosis during the spring and summer seasons. The possible reasons of the seasonality of tuberculosis are serum Vitamin D level variability, indoor activities, seasonal changes, immune function, food pattern and delay in diagnosis and treatment of tuberculosis.[19]

A maximum number of dengue cases (69.2%) and scrub typhus (75%) were diagnosed in the months of August to October. This can be attributed to the post-monsoon surge due to increase in the number of mosquito breeding sites. Scrub typhus and dengue were reported during the monsoon and post-monsoon seasons, in accordance with the reported patterns of disease transmission.[20,21] In a study[6] both scrub typhus and dengue fever peaked during the monsoon season and the cooler months. Enteric fever shows seasonal variation in North India with a maximum incidence during early summer and monsoons, i.e., in the months of February to April and July to October. In our study, the maximum number of enteric fever cases (50%) was diagnosed in the months of February to April. This is because of the increased contamination of water during the summer and monsoon seasons leading on to an increase in the number of enteric fever cases.[22] An increased incidence of typhoid fever during the monsoon season was noticed in a study from Assam, India, and also in a study from Pakistan,[23,24] whereas no obvious seasonal trends were detected in the prevalence of enteric fever or malaria.[6]

The maximum number of pneumonia patients (55.5%) was seen from February to April. This had been consistent with results reported in another study.[25] on the seasonal incidence of community-acquired pneumonia which showed an increased incidence of hospitalisations and clustering of cases in the spring and winter seasons. Thus, winter with its low temperature can be said to be the main reason for the development of community-acquired pneumonia in this season.[25]

With comprehensive laboratory investigations, a microbiological cause of AUFI was identified in 33.6% of cases. Our study clearly revealed that predominant cause of AUFI in our area was dengue, followed by typhoid and scrub typhus on the basis of serological tests. The similarity in clinical presentation, diversity of aetiological agents, an inability to identify an aetiology in a significant number of patients, demonstrate the complexity of diagnosis and treatment of AUFI. The aetiological profile will be of use in the development of rational guidelines for infectious disease control and treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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