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Original Article

Internal Medicine Section

Acute Febrile Illness in Immunocompetent Adults with Special Reference to Neutropaenia: A Cross-sectional Study

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ABSTRACT

Introduction: Fever is a common symptom with multifactorial aetiologies. In tropical country like India, most of the cases of acute febrile illness are due to seasonal viral diseases and vector-borne infections.

Aim: To know the causes of acute onset fever in immunocompetent adults and to study the prevalence of neutropaenia.

Materials and Methods: A cross-sectional study was done on 403 patients presenting with Acute Febrile Illness (AFI) of <14 days duration admitted to a tertiary care hospital, Pune, Maharashtra, India from January 2019 to January 2020. Total Leukocyte Count (TLC), Absolute Neutrophil Count (ANC) and investigations for dengue, malaria, leptospirosis, enteric fever, atypical infections like brucella, rickettsia and relevant body fluid cultures were done. The categorical and continuous variables were expressed as frequency, percentage, and standard deviation.

Results: Out of 403 patients, 214 were males (53.1%) and 189 females (46.9%) with mean age of 28.57±11.26 years. Cause of fever was found in 254 (63%) patients. Dengue fever was the most common cause in 221 (54.8%) followed by Acute Undifferentiated Febrile Illness (AUFI) in 149 (37%). Transient neutropaenia was present in 38.5% cases, mostly with dengue. Only 5.2% patients with AFI required antibiotics.

Conclusion: Dengue fever was found to be, the most common cause of AFI chiefly affecting young adults. Neutropaenia in AFI in immunocompetent adult was transient and benign. Antibiotics were not required in majority of the cases of AFI without organ specific aetiologies.

Keywords: Dengue, Enzyme linked immunosorbent assay, Fever, Malaria

INTRODUCTION

Fever is a pervasive and ubiquitous theme in human myth, art and science and there are accurate description of febrile patients even in early recorded history. An oral morning temperature of more than 37.2°C (98.9°F) or an evening temperature of greater than 37.7°C (>99.9°F) would define a fever, and occurs with increase in hypothalamic set point. The normal daily temperature variation, also called circadian rhythm, is typically 0.5°C (0.9°F). Axillary temperature is 0.5°C lower than oral temperature [1]. The term Acute Undifferentiated Febrile Illness (AUFI) denotes fever of <14 days duration without any evidence of organ or system specific aetiology [2]. Acute febrile illness (AFI) in immunocompetent patients may be because of serious bacterial, viral or vector-borne infections like dengue fever, typhoid fever, respiratory tract infection, Urinary Tract Infection (UTI), meningitis, leptospirosis, chikungunya, etc. [3-5]. In India, vector-borne infections are common causes of acute febrile illnesses.

Neutropaenia is defined as an Absolute Neutrophil Count (ANC) of less than 1500/µL. Mild neutropaenia is ANC of 1000-1500/µL, moderate neutropaenia is ANC of 500-1000/µL and severe neutropaenia is ANC of <500/µL [6]. Neutropaenia often accompanies fever, known as febrile neutropaenia. Febrile neutropaenia is common in people on chemotherapy for malignant diseases and other immunosuppressive states [7]. Acute transient neutropaenia in an immunocompetent adult is usually defined as an ANC of less than 1500/µL and is usually benign, transient and self-limiting.

Several studies have been done on immunocompetent children and immunocompromised adults with febrile and non febrile neutropaenia to elucidate its aetiology, clinical features and outcomes [8,9]. However, studies on neutropaenia in immunocompetent adults with acute febrile illness are few. In a study with 200 cases of short duration fever, excluding immunocompromised patients, the common cause of fever was unspecified viral fever (45%) followed by dengue fever (26.5%), enteric fever (7%) and UTI (5.5%) [10].

The aim of the current study was to determine the causes of AFI in immunocompetent adults, study the prevalence of neutropaenia in these patients and to assosciate it with the outcome of AFI. AFI in Indian subcontinent is usually due to viral infections and vector-borne diseases. So, the accompanying neutropaenia is transient and self-limiting. This will help the clinicians to avoid advising investigations and treatments to the immunocompetent adults having neutropaenia during AFI.

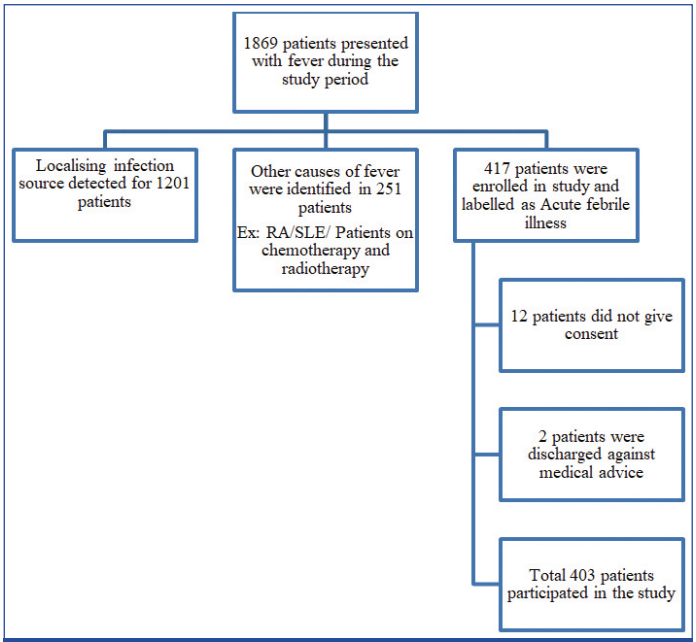
MATERIALS AND METHODS

This cross-sectional study was conducted from January 2019 to January 2020 at tertiary care hospital in Pune, Maharashtra, India. A written informed consent was taken from all the study participants. Institutional Ethics Committee approval was taken prior to the commencement of the study (I.E.S.C./W/81/2022).

Inclusion and Exclusion criteria: All patients above the age of 18 years, with fever of <2 weeks duration, without any organ specific aetiology were enrolled in the study. [Table/Fig-1] shows the patient selection algorithm. Patients with organ specific and localised source of fever (UTI, pneumonia, meningitis, abscess, etc.), malignancies, post-transplant, patients on chemotherapy, radiotherapy, and on immunosuppressive drugs and patients with Human Immunodeficiency Virus Infection (HIV) were excluded from the study.

Procedure

Total 403 patients were included in the study. A detailed clinical history and general physical examination was done for all the study



[Table/Fig-1]: Patient selection algorithm.

participants. Following investigations were done-White Blood Cell count per microlitre (WBC) by photometry, absolute neutrophil count per microlitre, blood cultures (under aseptic precautions, two 15 mL blood samples were collected from two separate sites at 1 hour interval and inoculated into Bactec specific blood culture and sent to the laboratory), rapid malarial antigen test (by Bi-card method), peripheral blood smear for malarial parasite detection, Enzyme Linked Immunosorbent Assay (ELISA) test for serology of dengue, leptospirosis, chikungunya and typhoid fever (Serum widal test), if fever persist for more than seven days, tube agglutination method was used. Also urine test for routine and microscopy, liver and renal function tests, chest x-ray and ultrasound of the abdomen were done.

If no cause of the AFI was found after the above mentioned investigations, the following tests were done for diagnosis of Brucella-tube agglutination test (titre>1:160 was considered positive) and for Rickettsial infections-IgM and IgG antibodies (by using a micro immunofluorescence assay). As these tests were negative, no data was recorded of Brucella and Rickettssia. A final diagnosis of fever aetiology was made using the clinical picture of the patients and a confirmed positive relevant laboratory test.

Patients were defined as having neutropaenia, if their ANC <1500/µL anytime during their stay in the hospital. The Complete Blood Count (CBC) was repeated on day 3 and before discharge from the hospital. The patient outcomes were described as discharged, worsened/shifted to ICU and death.

The patients were sub-grouped into three groups based on their lowest neutrophil count as:

- Mild neutropaenia (1000-1500/µL),
- Moderate neutropaenia (500-1000/µL), and
- Severe neutropaenia (<500/µL) .

Patients were diagnosed to have Acute Undifferentiated Febrile Illness (AUFI), if no cause was identified after the above mentioned investigations.

STATISTICAL ANALYSIS

The data was entered in MS Excel worksheet and was analysed using Statistical Package for Social Sciences (SPSS) software version 2021-1.0.0.1406. The categorical variables were expressed in terms of frequency and percentage, and continuous variables were expressed in terms of Mean±Standard Deviation (SD). Chi-square test was applied to study the association between the categorical variables. All the tests were two tailed and p-value of less than 0.05 was considered to be statistically significant at 95% confidence interval.

RESULTS

Out of 403 study participants, 214 were males (53.1%) and 189 were females (46.9%). [Table/Fig-2]. The mean age of the study participants was 28.57±11.26 years and the age range was 18-74 years. Majority of study participants were in the age group of 18 to 29 years (59.5%) and among them, 92 (22.8%) patients had neutropaenia. There were seven patients in the geriatric age group (>60 years of age). Common symptoms on presentation, apart from fever were constitutional (74.44%), dry cough (31.26%), and headache (21.33%).

Parameters	N (%)
Gender	
Male	214 (53.1)
Female	189 (46.9)
Age group (in years)	
18-29	240 (59.5)
30-39	96 (23.8)
40-49	40 (9.9)
50-59	20 (5.0)
60-69	06 (1.5)
>70	01 (0.3)
Pre-existing medical illness	101
Diabetes	23 (22.8)
Hypertension	19 (18.8)
Thyroid disorders	54 (53.5)
Ischaemic heart disease	05 (4.9)
Presenting symptoms	
Fever	403 (100)
Constitutional	300 (74.4)
Skin rash	167 (41.4)
Dry cough	126 (31.26)
Headache	86 (21.3)
Nausea, vomiting or loose stools	65 (16.1)
Yellow discolouration of eyes	09 (2.2)
Mean duration of hospital stay (days)	4.41±1.71
Positive blood culture	13 (2.2)
Antibiotics	21 (5.2)
Complications	6 (1.48)
Outcome	
Discharged	403 (100)
Worsened and shifted to ICU	06 (1.5)
Death	0

[Table/Fig-2]: Demographic and clinical data of the study participants.

Total 356 (88.3%) study participants were admitted in the hospital for less than seven days and 47 (11.7%) study participants for more than seven days. Total 101 (25%) patients had pre-existing medical illness. Most common pre-existing medical illness in the study participants were thyroid disorders (53.5%).

[Table/Fig-3] shows that dengue fever was the most common cause of acute febrile illness 221 (54.8%) followed by undifferentiated fever 149 (37%), Plasmodium vivax malaria was found in 3% cases. The cause of AFI was identified in 254 of the 403 total participants (63%). The mean stay in the hospital was minimum for patients with undifferentiated fever (3.73±1.72 days), and maximum for patients diagnosed with leptospirosis (8.0±1.66 days) and enteric fever (7.28±1.78 days).

Diagnosis	Number n (%)	No. of days of stay in hospital (Mean±SD)	No. of patients with neutropaenia (%)
Dengue fever	221 (54.8)	4.22±1.71	93 (23.1)
AUFI	149 (37)	3.73±1.72	53 (13.1)
Enteric fever	14 (3.5)	7.28±1.78	06 (1.5)
P. vivax malaria	12 (3)	5.08±1.73	02 (0.5)
Chikungunya	05 (1.2)	4.8±1.61	01 (0.2)
Leptospirosis	02 (0.5)	8.0±1.66	0
Total	403	-	155

[Table/Fig-3]: Causes of fever in the study participants, their respective duration of hospital stay and presence of neutropaenia.

A total of 155 of 403 (38.5%) had neutropaenia during their hospital stay. Out of 155 study participants with neutropaenia, severe neutropaenia was present in 26 (16.77%) patients [Table/Fig-4].

Severity of neutropaenia	Number of patients (n=155)	Percentage (%)
Mild neutropaenia (1000-1500/µL)	84	54.2
Moderate neutropaenia (500-1000/µL)	45	29
Severe neutropaenia (<500/µL)	26	16.77

[Table/Fig-4]: Number of study participants according to severity of neutropaenia.

Neutropaenia most commonly occurred in dengue fever (23.1%) followed by undifferentiated fever (13.2%). However, as shown in [Table/Fig-5], when the presence of neutropaenia was compared between the patients with and without dengue fever, it was found that the neutropaenia did not occur with greater frequency in dengue patients (p-value >0.05).

Variables	With neutropaenia (n=155)	Without neutropaenia (n=248)	Chi-square test (p-value)
With dengue infection	93	128	0.09
Without dengue infection	62	120	

[Table/Fig-5]: Association between neutropaenia and dengue fever.
Total number of cases having other causes of AFI was less and so statistical analysis for clinical significance was not possible

Blood culture was positive in total 13 of 403 (3.2%) patients, eight patients of *Salmonella typhi*, two patients of *Klebsiella pneumoniae*, two of *Escherichia coli* and one of *Streptococcus pyogenes.* All the patients with positive blood culture had neutropaenia.

Out of 403 patients, only 21 patients required antibiotics (5.2%) during their hospital stay. All these patients were either diagnosed with enteric fever, leptospirosis or a positive bacterial growth in the blood culture. Among 26 severe neutropaenia patients, 6 (23.1%) had to be shifted to the Medical Intensive Care Unit (MICU) due to unstable and unfavourable haemodynamic and biochemical profile. Sepsis in four and acute kidney injury in two patients were the complications developed with severe neutropaenia. There were no deaths recorded in the study subjects. All the patients were discharged from the hospital and had a favourable outcome including those shifted to the MICU.

DISCUSSION

The current study is one of its kind on immunocompetent adults suffering from AFI to elucidate the causes, the outcomes and to determine the prevalence of neutropaenia. The cause of AFI was identified in 63% cases after the work-up. In a large Indonesian cohort of 1486 patients suffering from acute febrile illness, the cause of fever was identified in 67.5% subjects [11]. In a study conducted among 1324 adults with AFI in Kerala, India, the aetiology for the fever was identified in 70.1% subjects [12]. [Table/Fig-6] shows comparative analysis of similar studies done on patients of all ages with AFI [11-13]. This may be due to economic and resource constraints in those countries [13-15]. The higher rate of identification of the cause in the current study can be due to comprehensive blood tests. There was no gender difference in the prevalence of fever. Young adults (18-29 years) commonly suffered from AFI with neutropaenia. AFI can affect any age group, however, serious organ specific, viral and bacterial infections like UTI, bacterial pneumonias are more common in elderly patients [16,17].

Constitutional symptoms were common with fever in the current study. It was found only in 4.2% patients in an Indonesian study which was in contrast to our findings. The gastrointestinal symptoms like nausea (61.9%) and anorexia (33.4%) were found in their study [7]. In a study done in Israel for comparison of aetiological and clinical outcome in febrile vs non febrile neutropaenia in hospitalised immunocompetent children, bronchiolitis (31 cases) and vomiting (25 cases) were the common symptoms [18]. Thus, the accompanying symptoms with AFI may vary depending on the age, geographical distribution, level of immunity and the underlying aetiology.

Dengue was the most common cause of fever, which was similar to the findings of other Asian studies [11,19]. This finding highlights the importance of dengue virus as a causative agent of AFI. Rapid diagnostic strategies, better management protocols and serosurveillance for dengue infections should be undertaken at state and national levels to prevent it from becoming a major public health problem. Dengue infection is endemic in India. The first reported dengue epidemic in India occurred in 1963-64 [20]. Since then

Similar studies author details/Number of patients	No. of study participants (n)	Location/Year of the study	Common clinical features accompanying fever	Common aetiologies	Age and gender distribution	Average hospital stay	Mortality
Gasem MH et al., [11]	1486	Indonesia/2013	Nausea (61.9%), Headache (39.9%), and Anorexia (33.4%)	Dengue (31.5%) Salmonella enteric (6.9%) Rickettsia species (6.9%)	1-98 years Male (55.9%), Female (44.1%)	6 days	5.9%
Andrews MA and Ittyachen AM, [12]	1324	Kerala, India/2014	Headache (41.5%), and Vomiting (36.6%)	Dengue (43.5%) Undiagnosed fever (29.9%) Leptospirosis (17.9%)	20-49 years Male (63.2%) Female (36.8)	NA	1.65%
Mayxay M et al., [13]	229	Southern Laos/2003	Weakness (80%), Headache (79%) and Dizziness (64%)	Dengue (30.1%), Leptospirosis (7.0%) and Japanese encephalitis virus (3.5%)	1-80 years Male (57%) Female (43%)	NA	NA
Kasper MR et al., [15]	9997	Cambodia/2006-2009	Headache (69.5%), Chills (48.1%), and Malaise (46.8%)	Influenza (19.9%), Dengue (17.3%) and Malaria (7.2%)	19.6±16.9 years Male (54%) Female (46%)	NA	NA
Current study	403	Pune, India/2019-2020	Constitutional (74.4%) Skin rash (41.4%) Dry cough (31.3%)	Dengue (54.8%) AUFI (37%) Enteric fever (3.5%)	18-74 years Male (53.1%) Female (46.9%)	4.41±1.71	0%

[Table/Fig-6]: Various studies done on patients with AFI and their findings [11-13,15].
*NA: Not available

many Indian states have become endemic where all the serotypes of dengue are prevalent [20]. Prevention of dengue involves control the breeding sites of the vector by improving public and household environmental sanitation and water supply, and through sustained modification of human behaviour [21].

The AUFI was the second common cause of fever in current study. AUFI is a commonly encountered illness in most of the hospitals. A clinician should be aware of the locally endemic infections to advise appropriate work-up and treatment.

Neutrophils are the first line of defence against the pathogens. Viral infections are a common cause of neutropaenia due to either bone marrow suppression or peripheral destruction [21]. Most common causes of neutropaenia in the current study were dengue and AUFI. Clinical observations and experimental data shed light on the possible mechanisms by which dengue virus can suppress bone marrow. The stroma of the bone marrow is found to be infected by dengue virus, which then fails to support hematopoiesis and also affects the cytokine production in the bone marrow. Thus, there is a down regulation of haematopoiesis protective mechanism of the microenvironment, causing harm to the marrow stem/progenitor cell compartment during the subsequent process of virus elimination leading to neutropaenia and thrombocytopenia [22].

Most of the researches on neutropaenia have been done on children and immunocompromised adults. In children, the neutropaenia is predominantly due to parasitic, viral and bacterial infections and is usually benign and self-limited. Infections in children may affect one or more cell lines, resulting in transient haematological abnormalities which usually resolve within two months of onset [23,24]. In immunocompromised adults, neutropaenia is usually due to cytotoxic chemotherapy, infections with atypical organisms, immune reactions and bone marrow infiltrative diseases and if left untreated can lead to fatal infections whereas, vector-borne diseases and common bacterial and viral infections are common in immunocompetent patients having AFI [25].

Most of the patients with AFI with neutropaenia were successfully managed in the wards and did not require intensive care. The reason for good outcome may be that most of the viral infections causing fever and neutropaenia are self-limiting and uncomplicated. Early diagnosis, better patient care and immunity in the adult patients prevent the emergence of complications and ensure a good outcome.

In a large study of 2000 hospitalised adult patients with laboratory confirmed dengue infection, it was concluded that prophylactic antibiotics are not indicated in patients with severe neutropaenia [26,27]. Since most of the patients in the current study had viral aetiology of AFI, antibiotics were not required. Thus, all febrile patients may not require antibiotics and should be managed symptomatically initially. There is no role of Granulocyte-Colony Stimulating Factor (G-CSF) in immunocompetent patients having AFI with neutropaenia. It is only reserved for immunocompromised patients with neutropaenia [28].

Limitation(s)

Special investigations for the detection of viruses like adenovirus, influenza virus, herpes virus etc., were not done due to financial constraints.

CONCLUSION(S)

Dengue was the most common cause of AFI affecting patients less than 30 years of age. Neutropaenia was found in more than one third of the patients. It was benign, transient and self-limiting in all the patients with AFI. Most of the patients were treated symptomatically and without antibiotics. Short duration fever cases, without any clinical signs of bacterial infection or haemodynamic compromise, should be managed by acetaminophen, and other symptomatic therapy, while awaiting investigations. Diagnosed cases of viral infections do not require antibiotics to prevent the emergence of secondary bacterial infection. A good physician should know “when not to use antibiotics”, otherwise, the world will have to battle with superbugs in the near future.

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