Fever accounts for around 15% of emergency visits in elderly age group and around 5% in adults. The spectrum of etiologies ranges from non-infectious to infectious etiologies. There are very few studies done in the past highlighting the approach of patients with acute febrile illness without any localizing signs and symptoms. **Objectives:** The aim of the study was to formulate a targeted approach for evaluation and treatment of patients with acute undifferentiated febrile illness without evidence of localizing symptoms and signs. The secondary objective was to study the etiology and final outcome of patients with acute undifferentiated febrile illness. **Materials and Methods:** A protocol was devised for patients aged more than 18 years, who presented in emergency department with complaints of fever without localizing symptoms or signs of sepsis over a period of 6 months from April 2018 to September 2018. Patient’s data were collected retrospectively from the hospital record section. **Results:** A total of 212 patients of undifferentiated acute febrile illness were enrolled in the study. Maximum number of patients \( n = 69 \) (32.5%), presented on second day of illness. All the patients presenting within 1 or 2 days of fever experienced defervescence. Out of these 69 patients, 35 (36.4%) were investigated of which in 29 (82.2%) investigations were not found to be useful; 75 (78.1%) patients with 1 or 2 days history of fever improved without investigations. Surprisingly, 54 patients (72%) with 1 or 2 days’ history of acute febrile illness experienced defervescence without the need of antibiotics. **Conclusion:** There is an urgent need to devise a standardized protocol for diagnosis and treatment of patients with acute undifferentiated febrile illness in order to avoid unnecessary investigations and antimicrobial use.

**Keywords:** Dengue, fever, malaria, scrub typhus

**Introduction**

Fever is an important and one of the most common complaints of patients presenting to emergency department. It amounts to 15% complaints in the elderly age group and around 5% complaints in the adults. It has a wide spectrum of differential diagnosis from infectious to non-infectious causes.[4,5] Acute undifferentiated febrile illness (AUFI) is defined as fever with non-localizing signs and symptoms. There are multiple causes of AUFI in the emergency department in developing countries. The significant illnesses are dengue fever, malaria, enteric fever, scrub typhus fever, leptospirosis and Japanese encephalitis.[6,8] These patients get over-investigated and receive unnecessary antimicrobials. There are very few studies highlighting the importance of a standardized protocol of approach and treatment of these patients in the emergency department.[6,5] The indiscriminate use of antimicrobial not only leads to increased burden on health expenditure but also leads to rise in drug resistance, drug interactions and adverse drug reactions in these patients.[6,9]

**Aims and objectives**

The primary goal of the study was to formulate a standardized protocol for evaluation, assessment of patients with AUFI.
The secondary goal of the study was to study the clinical and biochemical profile of patients with AUFI in a tertiary care hospital of Uttarakhand.

Materials and Methods

All patients more than 18 years of age, presenting to emergency department with complaints of fever without localizing signs were included in the study. The study was carried out over a period of 6 months from April 2018 to September 2018. For all practical purposes, AUFI defined as fever duration of more than 2 weeks without any localizing signs of infection.[9,10] Patients with clear-cut diagnosis of sepsis or septic shock and who did not give consent for participation in the study were excluded from the study. As per the devised protocol, patients with 2 days history of fever were neither investigated nor prescribed antibiotics. However, patients presenting with 3 or more days’ history of fever underwent routine and diagnostic investigations in the form of complete blood count, thick film for malaria, urine analysis, rapid diagnostic test for scrub typhus confirmed by enzyme-linked immunosorbent assay (ELISA), dengue serology and other biochemical tests in the form of liver function and kidney function tests. Acute malaria was diagnosed by Leishman stained smear positivity, dengue by positive IgM serology and scrub typhus by positive IgM ELISA.

Fever such as malaria, scrub and dengue lead to significant mortality and morbidity in these patients. However, the exhaustive clinical and diagnostic evaluation as well as rampant use of antibiotics increases the economic burden especially on the healthcare system of developing countries. The diagnostic work-up and treatment of patients with AUFI depend upon the local prevalence of various diseases in the geographical area. The protocol thus should be guided by the prevalence of individual diseases such as malaria, dengue fever, scrub typhus and enteric fever. This will improve the diagnostic evaluation and treatment making in these patients.[10,8]

AUFI is one of the most common illnesses, encountered by both emergency physicians as well as family physician. A protocol-based approach to AUFI can limit the economic burden and mortality in these patients.[10,8] Thus, in this study we studied a rational and stepwise protocol for diagnosis and treatment of patients with AUFI influenced by local and geographical parameters.

In our study, 96 (45.2%) patients presented with 1 or 2 days history of fever. Out of these patients, 75 (78.1%) showed defervescence with investigations and 54 (72%) showed were neither investigated nor prescribed antimicrobial and were only treated symptomatically. They were categorized as category ‘A’ patients. Patients, presenting with 3 or 4 days history of fever were categorized as category ‘B’. They underwent investigations in the form of complete blood count and work up for malaria, dengue and scrub typhus. Third category was ‘C’ patients who underwent blood and urine culture. Out of 96 (45.2%) patients of category ‘A’, 35 (36.4%) patients were investigated, of which 29 (82.8%) had improved without investigations being useful; 61 (63.5%) patients were not investigated, of which 49 (80.3%) patients showed defervescence without investigation. Thus, around three-fourth [\( n = 75 \) (78.1%)] patients of category ‘A’ had improved and 54 (72%) patients showed defervescence without the need of antibiotics [Table 2] clearly, males outnumbered female patients. Maximum number of patients were in the age group of 26-35 years [\( n = 68 \), 32%]. Nausea and vomiting [\( n = 96 \), 45.2%] were the most common symptoms. In all, 93 (43.8%) patients had hepatomegaly and 75 (35.3%) had splenomegaly. Dengue fever (37.2%), malaria (6.1%), enteric fever (9.4%) and scrub typhus (16.9%) were common causes of AUFI [Table 3].

Discussion

The differential diagnosis of AUFI is varied and confusing. Fever such as malaria, scrub and dengue lead to significant mortality and morbidity in these patients. However, the exhaustive clinical and diagnostic evaluation as well as rampant use of antibiotics increases the economic burden especially on the healthcare system of developing countries. The diagnostic work-up and treatment of patients with AUFI depend upon the local prevalence of various diseases in the geographical area. The protocol thus should be guided by the prevalence of the individual diseases such as malaria, dengue fever, scrub typhus and enteric fever. This will improve the diagnostic evaluation and treatment making in these patients.[10,8]
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Table 2: Profile of patients presenting on Day-1 or 2 of fever (n=96)

| Patient investigated (n=35, 36.4%) | Investigations not useful | Investigations useful |
|-----------------------------------|---------------------------|-----------------------|
| Patients not investigated (n=61, 63.5%) | Patients improved without investigation | Patients eventually required investigated |
| Total number of patients improved without investigation | 6 (17.1%) | 29 (82.8%) |
| Patients receiving antibiotic initially | 49 (80.30%) | 12 (19.6%) |
| Did not receive antibiotic initially | 54 (72%) | 3 (4%) |
| Lost to follow up | 54 (72%) | 54 (56.2%) |
| Patients improved without antibiotics | 42 (43.7%) | 5 (5.2%) |
| Males | Dengue | 2 (2%) |
| Females | Non-specific | 61 (63.5%) |
| Malaria | UTI | 7 (7.2%) |
| Dengue | Scrub typhus | 5 (5.2%) |
| Enteric fever | | 20 (9.4%) |

Table 3: Clinical and demographic profile of patients of acute undifferentiated fever in emergency

| Parameters | No. of patients (n=212) |
|------------|-------------------------|
| Male       | 122 (57.5%)             |
| Female     | 90 (42.4%)              |
| Age distribution |                     |
| 17-25 years | 49 (23.1%)             |
| 26-35 years | 68 (32.0%)             |
| 36-45 years | 35 (16.5%)             |
| 46-55 years | 29 (13.6%)             |
| 56-65 years | 15 (7.0%)              |
| >66 years | 13 (6.1%)               |
| Loose stools | 56 (26.4%)            |
| Nausea/vomiting | 96 (45.2%)         |
| Cough      | 39 (18.3%)              |
| Oliguria   | 31 (14.6%)              |
| Hepatomegaly | 93 (43.8%)        |
| Splenomegaly | 75 (35.3%)          |
| Dengue fever | 99 (45.72%)        |
| Malaria    | 13 (61%)                |
| Scrub typhus | 36 (16.9%)            |
| Undiagnosed | 30 (14.1%)             |
| Thrombocytopenia | 92 (43.3%)     |
| Transaminitis | 112 (52.8%)          |
| Acute kidney injury | 102 (48.1%) |

Significantly more number of patients with scrub typhus had increased neutrophil count (n = 24, 40%), elevated alkaline phosphatase levels (n = 48, 80%) and low serum albumin (n = 39, 65%) levels. Splenomegaly (15, 65.2%) was more common in patients with malaria. Loose motions were more commonly seen in patients with enteric fever (n = 12, 60%). Cleanly, feature such as thrombocytopenia (n = 78, 98%), overt bleeding manifestations (n = 28, 35.4%) and myalgia and body ache (n = 56, 70.8%) were more commonly seen in patients with dengue fever.

In a study conducted by Chrispal et al., significantly more number of patients with enteric fever had loose stools. As observed in this study, thrombocytopenia and overt bleeding manifestations were more common in patients with dengue fever. Hepatic manifestations, hepatomegaly and splenomegaly were more commonly seen in patients with malaria. Leukocytosis, raised alkaline phosphatase levels, adult respiratory distress syndrome and aseptic meningitis were primary clinical manifestations of patients with scrub typhus fever. Acute respiratory distress syndrome (ARDS) was seen in 26 (43.3%) patients of with scrub typhus and 3 (3.7%) patients with dengue fever.[11]

Hepatic dysfunction in the form of mild deviations of transaminases with elevated alkaline phosphate levels (n = 48, 80%) was found to be associated with scrub typhus fever. Almost similar number (n = 49, 62.02%) of patients with dengue fever had hepatic dysfunctions. A study by Acharya et al. has also highlighted hepatic dysfunctions in patients with dengue fever.[12]

In our study, 16 (26.6%) patients with scrub typhus fever had leukocytosis as compared with 4 (17.3%) patients of malaria and 3 (3.7%) patients of dengue fever; 70 patients with scrub typhus had leukocytosis as compared with dengue fever as shown in a study conducted by Chrispal et al.[11] Similar results were reported by a study conducted by Mitra et al.[18] that 78 (98.7%) patients

improvement without antibiotics. A similar study was conducted by Thangarasu et al.[11]

Our study reported the incidence of dengue fever (37.2%) malaria (61%), scrub typhus (16.9%) and enteric fever (9.4%). Similar causes of acute febrile illness have been described by study conducted in South India by Chrispal et al. The study described the incidence of scrub typhus (47.5%), malaria (17.1%), enteric fever (8.0%) and dengue fever (7%).[12]

Table 4 shows clinical profile of patients of AUIF. Symptoms such as cough (16.6%) dyspnea (20.0%) and headache (48.3%) were more commonly associated with scrub typhus fever.
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Around 5% patients of scrub typhus and dengue fever in our study had thrombocytopenia. Previous studies have highlighted the correlation of thrombocytopenia and dengue hemorrhage fever.\textsuperscript{[14]}

Finally, a scoring system should be made in order to differentiate between scrub typhus, malaria and dengue fever. The score should include total leucocyte count, platelet count, ALT, AST, serum bilirubin, $\text{SpO}_2$ levels and altered sensorium.\textsuperscript{[13]}

AUFi is one of the most common presentations in tertiary care hospitals of various northern and southern parts of India especially during seasonal outbreaks. These patients have varied presentation. They present as complicated multisystem illness especially to tertiary care hospital. ARDS, aseptic meningitis, hematological complications, hepatic and renal dysfunction are common causes of referral of AUFi to the emergency department of an apex institute. These require immediate attention. The stable patients can be screened by point of care tests at triage, managed by emergency as well as family physicians and community care workers who can pick up subtle signs of the febrile illness and make quicker diagnosis, thus aiding in preventing further comorbidities and mortalities. One of the contributing causes of mortality and morbidity in India are infectious diseases. However, there is lack of data on infectious diseases. Unaffordable and non-diagnostic methods and tools to diagnose those infections will be adding on financial burden. Hence, these

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**Table 4: Clinical and biochemical profile of patients with AUFi**

| Parameters                        | Scrub typhus ($n=36+24$) | Malaria ($n=13+10=23$) | Dengue ($n=79$) | Enteric fever ($n=20$) | $P$     |
|-----------------------------------|--------------------------|------------------------|----------------|------------------------|---------|
| Cough                             | 10 (16.6%)               | 0                      | 2 (2.5%)       | 1 (5%)                 | <0.001  |
| Dyspnea                           | 12 (20%)                 | 1 (4.3%)               | 3 (3.7%)       | 0                      | <0.001  |
| Headache                          | 29 (48.3%)               | 2 (8.6%)               | 24 (30.3%)     | 0                      | NS      |
| Seizures                          | 11 (18.3%)               | 1 (4.3%)               | 5 (6.3%)       | 0                      | <0.001  |
| Respiratory crepitation           | 5 (8.3%)                 | 2 (8.6%)               | 12 (15.1%)     | 0 (5%)                 | NS      |
| Neck stiffness                    | 3 (5%)                   | 1 (4.3%)               | 4 (5%)         | 0                      | NS      |
| Tachycardia                       | 38 (63.3%)               | 14 (60.8%)             | 56 (10.8%)     | 0                      | NS      |
| Shock                             | 22 (36.6%)               | 2 (8.6%)               | 33 (41.7%)     | 0                      | 0.002   |
| Hemoglobin                        | 2 (20%)                  | 0                      | 13 (16.4%)     | 0                      | NS      |
| Leukocytosis                      | 16 (26.6%)               | 4 (17.3%)              | 3 (3.7%)       | 1 (0.003)              |
| Neutrophil count                  | 24 (40%)                 | 2 (8.6%)               | 0              | 0                      | <0.001  |
| Renal dysfunction                 | 11 (18.3%)               | 4 (17.3%)              | 12 (15.1%)     | 0                      | NS      |
| Hepatic dysfunction               | 39 (65%)                 | 8 (34.7%)              | 49 (62.0%)     | 4                      | NS      |
| Elevated ALP                      | 48 (80%)                 | 5 (21.7%)              | 23 (29.1%)     | 1                      | <0.001  |
| Serum albumins                    | 39 (65%)                 | 8 (26%)                | 15 (18.9%)     | 0                      | <0.001  |
| ARDS (Respiratory)                | 26 (43.3%)               | 0 (0%)                 | 3 (3.7%)       | 0                      | NS      |
| Aseptic meningitis                | 3 (5%)                   | 1 (4.3%)               | 4 (5%)         | 0                      | NS      |
| Icterus                           | 39 (65%)                 | 8 (34.7%)              | 49 (62%)       | 3 (15%)                | NS      |
| Oliguria                          | 6 (10%)                  | 3 (13%)                | 8 (29%)        | 0 (15%)                | NS      |
| Hepatomegaly                      | 6 (10.1%)                | 18 (65.2%)             | 23 (29%)       | 3 (15%)                | 0.003   |
| Splenomegaly                      | 2 (3.3%)                 | 15 (65.2%)             | 1 (1.2%)       | 0                      | <0.001  |
| Thrombocytopenia                  | 49 (81.6%)               | 20 (86.9%)             | 78 (98.7%)     | 0                      | <0.001  |
| Overt bleeding manifestation      | 0                        | 3 (13%)                | 28 (35.4%)     | 0                      | 0.0002  |
| Rash                              | 3 (5%)                   | 1 (4.3%)               | 48 (60.7)      | 0                      | <0.001  |
| Abdominal body fluid              | 22 (36.6%)               | 3 (13.3%)              | 38 (48%)       | 2 (10%)                | <0.001  |
| Myalgia/body ache                 | 32 (53.3%)               | 5 (21.7%)              | 57 (70.8%)     | 5 (25%)                | <0.0001 |
| Loose stools                      | 1 (1.6%)                 | 0                      | 3 (3.7%)       | 12 (60%)               | <0.001  |

Flow chart 1: Protocol for AUFi
patients get nonspecific treatment in form of antibiotics over conventional treatments from peripheral centers. This lack of knowledge and inappropriate use of antibiotics lead to increased antimicrobial resistance in India. This further reinstates importance of standardized protocols for diagnosis and treatment in AUFI.

**Conclusion**

We studied a standard protocol for diagnosis and evaluation of patients with AUFI. This study highlights the need to defer unnecessary investigations and antibiotic usage in these patients. Family physician should device a protocol in patients with AUFI in order to avoid indiscriminate usage of investigations and antibiotics.

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**Conflicts of interest**

There are no conflicts of interest.

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