

Acute undifferentiated febrile illness: Protocol in emergency department

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Abstract

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.^[1] Acute undifferentiated febrile illness (AUFI) is defined as fever with non-localizing signs and symptoms. There are multiple causes of AUFI in the emergency

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department in developing countries. The significant illnesses are dengue fever, malaria, enteric fever, scrub typhus fever, leptospirosis and Japanese encephalitis.^[2,3] 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.^[4,5] 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]

Aims and objectives

The primary goal of the study was to formulate a standardized protocol for evaluation, assessment of patients with AUFI.

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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.^[7] 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. Renal impairment was defined as oliguria with acidosis and/or a rise in blood urea nitrogen (BUN) and serum creatinine as per laboratory normal values. Respiratory involvement (respiratory distress) was defined as tachypnoea (>20/min) along with a fall in oxygen saturation to > 90%. Liver dysfunction defined as two-fold rise in alanine transaminases or isolated hyper bilirubinaemia in the absence of liver dysfunction if transaminases were with in normal limits. CNS dysfunction defined as single or multiple episodes of generalised tonic - clonic seizures or altered sensorium or unconscious presentation.^[7] Detailed history and clinical examination was done in all the patients of fever. Patient with history of fever of more than 5 days were subjected to blood culture investigations. All the patients were followed till defervescence, although morbidity parameters were not compared. Data in the form of day of fever, whether investigated or not, whether antibiotics given or not, multi-organ involvement and final diagnosis at discharge was collected and tabulated, retrospectively from the hospital record section.

Results

This retrospective study was carried out at a tertiary care hospital of Uttarakhand over a period of 6 months from April 2018 to September 2018. A total of 212 patients aged more than 18 years of acute febrile illness, who neither had localizing signs and symptoms, not fulfilled the criteria of sepsis were enrolled in the study group; 96 (45.2%) patients of AUFI presented with first a second day history of fever; 43 (20.8%) patients presented with 3 days history of fever; 43 (20.8%) patients presented with solution of the formation of the formation of the study of fever for the study of fever formation of the study of fever formation of the study of formation of the study of fever formation of the study of the study of fever formation of the study of fever formation of the study of the study of the study of fever formation of the study of

Table 1: Day of fever presentation				
No. of patients (n=212) (%)				
27 (12.7)				
69 (32.5)				
43 (20.8)				
24 (11.3)				
31 (14.6)				
18 (8.4)				

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 defervescense 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 significance 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.^[4,8]

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.^[9,10] 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 deferverscence without investigations and 54 (72%) showed

Table 2: Profile of patients presenting on Day-1 or 2 of fever (<i>n</i> =96)				
Patient investigated (n=35, 36.4%)	Investigations not useful	6 (17.1%)		
	Investigations useful	29 (82.8%)		
Patients not investigated (n=61, 63.5%)	Patients improved without investigation	49 (80.30%)		
	Patients eventually required investigated	12 (19.6%)		
Total number of patients improved without investigation	nc	75 (78%)		
Patients receiving antibiotic initially		18 (24.1%)		
Did not receive antibiotic initially		54 (72%)		
Lost to follow up		3 (4%)		
Patients improved without antibiotics		54 (72%)		
Males		54 (56.2%)		
Females		42 (43.7%)		
Malaria		5 (5.2%)		
Dengue		2 (2%)		
Non-specific		61 (63.5%)		
UTI		7 (7.2%)		
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%)
66-75 years	13 (6.1%)
>76 years	3 (1.4%)
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 (37.2%)
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%)

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 AUFI. Symptoms such as cough (16.6%) dyspnea (20.0%) and headache (48.3%) were more commonly associated with scrub typhus fever.

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.*^[13] that 78 (98.7%) patients

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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 (<i>n</i> =79)	Enteric fever (n=20)	Р			
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%)	(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 (62.02%)	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 (%)	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 (0.1%)	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

of dengue fever had thrombocytopenia. Previous studies have highlighted the correlation of thrombocytopenia and dengue hemorrhage fever.^[14]

Around 5% patients of scrub typhus and dengue fever in our study had aseptic meningitis. This result was not in accordance of previous studies as our study had smaller sample size.^[11]

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, SpO₂ levels and altered sensorium.^[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 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.

References

- 1. Grandey KA. Fever [Internet]. In: Sherman SC, Weber JM, Schindlbeck MA, Rahul GP, editors. Clinical Emergency Medicine. New York, NY: McGraw-Hill Education; 2014.
- 2. Manock SR, Jacobsen KH, de Bravo NB, Russell KL, Negrete M, Olson JG, *et al.* Etiology of acute undifferentiated febrile illness in the Amazon basin of Ecuador. Am J Trop Med Hyg 2009;81:146-51.
- 3. Gasem MH, Wagenaar JF, Goris MG, Adi MS, Isbandrio BB, Hartskeerl RA, *et al.* Murine typhus and leptospirosis as causes of acute undifferentiated fever, Indonesia. Emerg Infect Dis 2009;15:975-7.
- 4. Joshi R, Colford JM Jr, Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: Diagnostic uncertainty and overtreatment with

antimalarial agents. Am J Trop Med Hyg 2008;78:393-9.

- 5. Phuong HL, de Vries PJ, Nagelkerke N, Giao PT, Hung le Q, Binh TQ, *et al.* Acute undifferentiated fever in Binh Thuan province, Vietnam: Imprecise clinical diagnosis and irrational pharmaco-therapy. Trop Med Int Health 2006;11:869-79.
- 6. Zaidi AK, Awasthi S, de Silva HJ. Burden of infectious diseases in South Asia. BMJ 2004;328:811-5.
- 7. Ahmad S, Dhar M, Mittal G, Bhat NK, Shirazi N, Kalra V, *et al.* A comparative hospital-based observational study of mono- and co-infections of malaria, dengue virus and scrub typhus causing acute undifferentiated fever. Eur J Clin Microbiol Infect Dis 2016;35:705-11.
- 8. Jones AE, Troyer JL, Kline JA. Cost-effectiveness of an emergency department-based early sepsis resuscitation protocol. Crit Care Med 2011;39:1306-12.
- 9. Kikuchi T, Toba S, Sekiguchi Y, Iwashita T, Imamura H, Kitamura M, *et al.* Protocol-based noninvasive positive pressure ventilation for acute respiratory failure. J Anesth 2011;25:42-9.
- 10. Thangarasu S, Natarajan P, Rajavelu P, Rajagopalan A, Seelinger Devey JS. A protocol for the emergency department management of acute undifferentiated febrile illness in India. Int J Emerg Med 2011;4:57.
- 11. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, *et al.* Acute undifferentiated febrile illness in adult hospitalized patients: The disease spectrum and diagnostic predictors-an experience from a tertiary care hospital in South India. Trop Doct 2010;40:230-4.
- 12. Acharya A, Satyanarayana PVV, Subrahmanyam V. A prospective study of pattern of hepatic dysfunction in dengue fever patient in coastal Andhra Pradesh, India. Int J Adv Med 2018;5:663-7.
- 13. Mitra S, Gautam I, Jambugulam M, Abhilash K, Jayaseeelan V. Clinical score to differentiate scrub typhus and dengue: A tool to differentiate scrub typhus and dengue. J Glob Infect Dis 2017;9:12-7.
- 14. Khan DM, Kuppusamy K, Sumathi S, Mrinalini VR. Evaluation of thrombocytopenia in dengue infection along with seasonal variation in rural Melmaruvathur. J Clin Diagn Res 2014;8:39-42.