Original Article

The diagnosis and outcome of acute undifferentiated febrile illness among children – A hospital based observational study

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Abstract

Aim: To find the epidemiological, clinical, laboratory profile of acute undifferentiated febrile illness that present to a tertiary care hospital in Southern India. **Study population:** Hospitalized acute undifferentiated febrile children, duration<15days, age group 1 to 16 years. **Study design:** Prospective, observational hospital based study. **Study duration:** One year study. **Material and Method:** Children presenting with acute undifferentiated febrile illness were enrolled in the study by consecutive sampling. Detailed history was taken in structured form after getting informed consent. A general physical and systemic examination was performed, which was repeated daily to look for any evidence of underlying etiology of fever. Each child was investigated with complete blood count, erythrocyte sedimentation rate, malaria parasite by Quantitative Buffy Coat method, chest x-ray, urine analysis, ultrasonography of abdomen, urine and blood culture. Serological tests for dengue, typhoid, scrub typhus and leptospirosis, liver function test, done based on clinical suspicion. **Statistical analysis:** Continuous variables assessed for the normality by using SHAPIRO WILK'S test. Categorical variables expressed as percentages. **Results and Conclusion:** Analysis of the distribution of AUFI showed that undifferentiated fever (41.2%) was the commonest cause followed by enteric fever 25.8%, lower respiratory tract infection (LRI) 12.4%, urinary tract infection (UTI) 8.2%, dengue fever 6.2%, and others 6.1% of total cases. Children with undifferentiated febrile illness were most likely to present with complaints of cough/cold, running nose and rash. We found that more than one third of AUFI do not have a specific diagnosis made despite the availability of extensive diagnostic facilities at a tertiary referral hospital. Eosinopenia is a marker for early identification of enteric fever. Complete blood count; blood culture and serology were useful to diagnose more than 50% cases and resulted in an improved health outcome.

Key Words: Febrile illness in children, enteric fever, viral fever, clinical profile of fever in children

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INTRODUCTION

Acute undifferentiated febrile illness is defined as acute onset of fever (fever more than 38 degrees Celsius lasts for less than 2 weeks) and no cause found after full history and physical examination.[1, 2] Local prevalence of individual diseases influences the probability of the differential diagnoses of a clinical case of acute undifferentiated febrile illness (AUFI). There is a need to prioritize signs and symptoms of AUFI for effective management. Several studies confirm the observation that most acute undifferentiated febrile illness in children was of presumed viral etiology and required little more than supportive therapy[3]. Hence, the most important issue for primary physicians is to focus on the fever etiology and to rule out serious diseases. Although distinguishing a child with a viral illness from one with bacterial infection is usually not difficult, there may be considerable overlap in the clinical appearance of children with fever without source due to a viral etiology and those with occult

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bacterial infection. Thus the clinical evaluation of these febrile children is a complex process based on history and physical examination as well as an appreciation of the important variables such as age, severity of fever and observation of the child. This series of steps represents a rich database that allows the healthcare provider to separate those children requiring laboratory evaluation from those who have minor illnesses. Most studies on AUFI have been almost exclusively done in the western countries and limited availability of Indian data. This study was conducted in order to delineate the etiology of AUFI that present to a tertiary care hospital in southern India and to describe disease-specific clinical profiles.

MATERIALS AND METHODS

A prospective observational study was done in Apollo Children's Hospital, Egmore from August 2013 to July 2014. Based on previous year hospital prevalence of AUFI, a total of 97 children selected by consecutive sampling fulfilling the criteria for acute undifferentiated febrile illness were included in the study, after obtaining proper consent and ethical clearance. Entry criteria included patients aged 1 to 16 years hospitalized with AUFI. These included duration of fever ranging 3-14 days with oral temperature over 38.3 degrees Celsius within last 24hrs and no cause found after full history and physical examination. Children with fever of more than 2 week's duration, previous hospitalization in the last 6 months, immunodeficient and those suffering from chronic diseases were excluded. A detailed history was taken from the patients pertaining to cardiovascular, respiratory, abdominal, central nervous and lymphoreticular system. Past history of any infections, including history of travel and family, was elicited. The antenatal, natal, postnatal, developmental and immunization history was recorded. After history, a detailed general physical and systemic examination was performed, and repeated daily for any evidence of underlying etiology of fever. Initial investigation included complete blood count with erythrocyte sedimentation rate, malaria parasite by quantitative Buffy coat method, chest x-ray, urine analysis, ultrasonography of the abdomen, urine and blood culture. Further diagnostic tests performed included liver function test, serological tests for dengue, typhoid, scrub typhus and leptospirosis. Other Imaging including contrast CT or MRI, echocardiography was done if needed. They were based on the results of the initial test and on consultant's suggestion.

Statistical Analysis

All the continuous variables were assessed for the normality by using Shapiro Wilk's test. Continuous variables that are normally distributed were expressed as mean +/- standard deviation and those that are not normally distributed were expressed as median IQR (Inter Quartile Range). All the categorical variables were expressed as either proportions (or) percentages. Comparison of all the normally distributed continuous variables were carried out by independent 't' test or ANOVA based on the number of groups. Those that were not normally distributed were compared by either "Mann' Whitney 'U' Test'' or "Kruskal Wallis H Test" based on the number of groups. Comparison of categorical variables was done by "Chi-Square Test" or "Fisher's Exact Test" based on number of observations.

RESULTS

A total of 97 patients were enrolled (boys 69 and girls 28). The mean age in years was 5.5 +/- 4.1; mean duration of fever in days was 5.9+/- 2.7 and average hospital stay was 3.9+/- 2.4 days. The Pattern and distribution of acute undifferentiated febrile illness in our study is depicted in (Table/Fig-1). Distribution of symptom of AUFI is shown in (Table/Fig-2). Cough, cold with running nose followed by loose stools were the commonest complaints. The signs predominantly noted were nasal and throat congestion with facial flushing (19.8%) followed by lymph node enlargement (13.2%) and skin rashes (11%). Distribution of laboratory features of AUFI is as in (Table/Fig-3). Neutrophilia was the commonest finding in complete blood count with 38 of children having them. Lymphocytosis was found most commonly in viral fever. Eosinopenia (n=22; 22.6%) was100% associated with enteric fever and 88% of children with enteric fever had eosinopenia. Enteric fever diagnosis was clinched with blood cultures (n=14; 56%). Ultra sound scan of the abdomen was found to be normal in 73.6% (n=67).

Table 1: Pattern and distribution of acute undifferentiated febrile illness

Aufi	Number Of Cases(N=97)	Percentage %
Undifferentiated Fever	40	41.2%
Enteric Fever	25	25.8%
Lri	12	12.4%
Uti	8	8.2%
Dengue	6	6.2%
Others	6	6.1%

Table 2: Distribution of symptom of aufi in this study

Symptom	In This Study Total Cases N=97(%)	Non Specific Causes (N=32)		Undiagnosed N=8(8.2%)	Enteric Fever Total Cases N=25	Dengue Fever N=6	Lri N=12	Uti N=8	P Value
		Probable Viral Fever N=25(25.8%)	Probabl E Uri N=7(7.2%)						
Cough, Cold /Running Nose	41(45%)	11(26.8%)	3(7.3%)	4(9.8%)	3(7.3%)	3(7.3%)	11(26.8%)	6(14.6%)	0.000
Vomiting	46(50.5%)	14(30.4%)	4(8.7%)	3(6.5%)	10(20.7%)	4(8.7%)	5(10.9%)	6(13%)	0.545
Loose Stool	20(22%)	7(35%)	1(5%)	3(15%)	6(30%)	1(5%)	2(10%)	-	0.009
Rash	9(9.9%)	7(77%)	-	-	1(11.1%)	1(11.1%)	-	-	0.026
Headache	3(3.3%)	1(33%)	-	-	1(33%)	1(33%)	-	-	0.591
Joint Pain/ Myalgia	8(8.8%)	4(50%)	1(12.5%)	-	2(25%)	1(12.5%)	-	-	0.535
Dysuria	3(3.3%)	-	-	-	1(33.3%)		1(33.3%)	1(33.3%)	0.584
Abdominal Pain	12(13.21%)	1(8.3%)	1(8.3%)	-	8(66.7%)	1(8.3%)	1(8.3%)	-	0.05
Throat Pain	2(2.2%)	1(50%)	1(50%)	-	-	-	-	-	2.20
Seizure	1(1.1%)	-	-	-	-	-	-	1(100%)	1.10

Table 3: Distribution of laboratory features of aufi

Lab	In This Study Total Cases N=97(%)	Non Specific Causes(N=32)		Undiagnosed N=8 (8.2%)	Enteric Fever N=25	Dengue Fever N=6	Lri N=12	Uti N=8
		Probable Viral Fever N=25(25.8%)	Probable Uri N=7 (7.2%)					
Leucopenia	5(5.5%)	3(12%)	-		-	2(33.3%)	-	-
Leukocytosis	29(31.9%)	7(28%)	3(42.8%)	4(50%)	5(20%)	-	5(41.6%)	5(62.5%)
Thrombocytopenia	6(6.6%)	2(8%)	--		-	3(50%)	1(8.3%)	-
Thrombocytosis	2(2.2%)	-	-		1(4%)	1(16.6%)	-	-
Normal	24(26.4%)	4(16%)	2(28.5%)	3(37.5%)	10(40%)	1(16.6%)	3(25%)	1(12.5%)
Neutrophilia	36(39.6%)	8(32%)	4(57.1%)	1(12.5%)	13(52%)	1(16.6%)	6(50%)	3(37.5%)
Lymphocytosis	12((13.2%)	6(24%)	-	1(12.5%)	-	3(50%)	-	2(25%)
Monocytosis	20(22%)	8(32%)	2(28.5%)	1(12.5%)	5(20%)	-	1(8.3%)	3(37.5%)
Eosinopenia	22(22.6%)	-	-	-	22(88%)	-	-	-
Hypoproteinemia	2(2.2%)	-	-	-	-	2(33.3%)	-	-
Elevated Ast/Alt	11(12.1%)	2(8%)	-	-	6(24%)	2(33.3%)	1(8.3%)	-
Elevated Alk Po4	11(12.1%)	2(8%)	-	3(37.5%)	4(16%)	2(33.3%)	-	-
Blood C/S	15(16.5%)	-	-	-	14(56%)	-	1(8.3%)	-
Urine C/S	7(7.7%)	-	-	-	-	-		7(87.5%)
Dengue	6(6.6%)	-	-	--	-	6(100%)	-	-
Lepto		-	-	-	-		-	-
Scrub	1(1.1%)	-	-	-	-	1(100%)	-	-
Widal	18(18.5.0%)	-	-		18(72.0%)	-	-	-

Table 4: Comparison of etiology of aufi with various studies

Etiology Of Aufi	In This Study (Tamilnadu Chennai) Total Cases N=97 (%)	Pediatric Study		Pediatric And Adult Study	Adult Study	
		Manock Sr[4] *et al* (U.K) Total N=533 (%)	Phuong Hl[6] *et al* (Vietnam) Total N=715 (%)	Andrew Ma [7]*et al* (Kerala) Total Number =273(%)	Gopalakrishnan S[2] Et Al (Villupuram, Tamilnadu) Total Number =403	Kashinkundi[1] *et al* (Karnataka) Total Number=100(%)
Undifferentiated Fever	40(41.2%)	-	387(55.5%)	61(63.54%)	84(20.84%)	9(9%)
Enteric Fever	25(25.8%)	-	36(5.16%)	-	83(20.59%)	14(14%)
Lower Respiratory Tract Infection	12(12.4%)	-	1(0.1%)	-	-	-
Urinary Tract Infection	8(8.2%)	-	-	-	-	-
Dengue Fever	6(6.2%)	16(5.3%)	45(6.45%)	12(12.5%)	42(10.4%)	25(25%)

Diarrheal Disease	2(2%)	-	27(3.87%)	-	-	-
Malaria	1(1%)	38(12.5%)	-	-	133(33%)	8(8%)
Leptospirosis	1(1%)	40(13.2%)	9(1.29%)	23(23.96%)	25(6.2%)	-
Scrub Typhus	1(1%)	-	-	-	-	33(33%)

DISCUSSION

A prospective observational study on acute undifferentiated febrile illness among children was done in a tertiary care hospital. Comparison of etiology of AUFI with various other studies is shown in (Table/Fig-4). Undifferentiated fever (unclear diagnosis) constitute (n=40) 41.2% of total cases in our study population, compared to 63.54% in a study from Kerala by *Andrews MA et al*. *Kashinkunti et al* from Karnataka had the least diagnosis of undifferentiated fever among all the studies, most probably because scrub typhus and dengue is more prevalent over there and is easier to diagnose.

Enteric fever was the most common diagnosis made in a child presenting with AUFI (n=25) 25.8%. *Gopalakrishnan S et al* in their study among adults had a similar prevalence as in our study with a 20.59% diagnosis of enteric fever. *Kashinkunti et al* from Karnataka also found that enteric fever was the third most common definitive diagnosis. Dengue fever was found in (n=6) 6.2% of the cases which is comparable with the study from Villupuram. Diagnosis of Dengue as a cause of AUFI was found to be 25% in this study from Karnataka. In our study we have reported lower respiratory tract infection (n=12; 12.4%) and urinary tract infection (n=8; 8.2%) to be a significant cause of AUFI, which was not reported in any of the previous studies. This might be due to the fact that present study is on a pediatric age group and the children might not be able to give proper history about symptoms. In our study the prevalence of scrub typhus is only 1% whereas in Karnataka it is 33%. This again goes to show that for the proper management of AUFI the knowledge of local prevalence of disease is very important and routine screening for the same may not be warranted in clinical scenarios like ours. Vomiting is the most common symptom that children with AUFI present with (50%). This could be due to the fact that most of the diagnoses were viral fevers and post tussive vomiting can occur in LRTI and URI. Vomiting is a known symptom in UTI and enteric fever. Cough / cold, nasal discharges were the second most common symptoms that were seen on symptom analysis. This might be due to the fact that undiagnosed viral infection is the predominant cause for AUFI. In our study joint pain and myalgia was found with lesser frequency (n=8; 8.8%) as compared to other studies. Most probably this is due to the younger age group in the current study (inability to explain joint pain and myalgia), while other studies included adult and pediatric population with extended age group. Probability of Viral fever was found to be high when myalgia was a complaint (62%). In this study rash was found in about 10% of cases. However the *Kashinkunti et al's* study springs a surprise by not having rash in its symptom analysis, with scrub typhus and dengue as the leading diagnosis in their study; and both may have skin rashes.

The diagnosis of undifferentiated fever was made for 41.2% (n=40) of the children. These undifferentiated fevers were redefined clinically to non specific causes (probable viral fever and upper respiratory tract infection) and undiagnosed cases. Probable viral fever diagnosis was made in 62.5 %(n=25) of the undifferentiated group. Undiagnosed cases with history, physical examination and laboratory values were 20% of the undifferentiated fever. The probability of a child being diagnosed as undifferentiated febrile illness was more if they presented with complaints of cough, cold with running nose(p=0.000), rash(p=0.026) and loose stool (p=0.009). Similar finding was observed in *Manock SR*[4] *et al* and *Phuong HL*[6]*et al* in their study also.

On analysis of signs, nasal and throat congestion with facial flushing (p=0.018) and rash (p=0.001) were more common in the undifferentiated fever than the ones with definitive diagnosis. Laboratory features of AUFI predominantly included leucocytosis, neutrophilia, lymphocytosis, eosinopenia and monocytosis. Among these a diagnosis of undifferentiated febrile illness was frequently made if lymphocytosis was seen (p=0.008). Nonspecific causes and undiagnosed cases were short-lived episodes (<2 weeks); both the patient and clinician were usually of opinion that further investigation was not warranted, and an explanation that a patient has a 'viral infection' was generally acceptable, in spite of paucity of data to support this common explanation.

In the present study 100% of eosinopenic undifferentiated fever had a diagnosis of Enteric fever. *Alisgar et al* [8] found eosinopenia in 73% of enteric fever patients whereas our study 88% (22/25) of enteric fever children had eosinopenia. This reinforces the value of early detection of eosinopenia in identifying possible enteric fever. *Bhat J*[9] *A et al* had reported that 13.2% of children admitted with AUFI were UTI. In the present study the prevalence of UTI was 8.2%; possibly because the former selected infants which accounted for 45% of the study population whereas our study had excluded infants. This might have lead to the increased prevalence of UTI in their study.

We found that more than one third of AUFI did not have a definitive diagnosis made despite the availability of extensive diagnostic facilities at a tertiary referral hospital. Interpretation of serial complete blood count, blood culture and serology was used to diagnose about 50% of children who presented with acute undifferentiated febrile illness leading to improved health outcome.

RECOMMENDATIONS

Children must have routine typhoid vaccination. For definitive diagnosis to be made in acute undifferentiated febrile illness, clinical features observed over a period of days and laboratory markers specific to the clinical profile play a vital role. The possibility of Enteric fever should be considered in treating the acute undifferentiated febrile illnesses when eosinopenia is detected early in the course. Causes of acute undifferentiated febrile illnesses vary according to the age, region, endemicity of the diseases and exposure. So knowledge of these is necessary for differentiating the causes. Laboratory investigations like complete blood count and blood culture are primary investigation for narrowing the diagnosis.

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