

Aetiology and clinical spectrum of acute undifferentiated febrile illness in hospitalized children

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Abstract

Introduction: Acute fever of 2 weeks duration with non-specific signs and symptoms is known as acute undifferentiated febrile illness (AUF). Owing to non-specific presentation, it remains a diagnostic challenge. Hence the present study focuses on etiology and clinical profile of undifferentiated febrile illness. **Methodology:** All children aged 2-12 years admitted with fever of 5-15 days duration, for which no cause was found after a thorough history and clinical examination were included from July 2015 to June 2016 prospectively. History, examination findings, investigations and the treatment details were recorded. Data analyzed using SSPS software. **Results:** Total sample size was 263. The mean age was 6.7 ± 3.4 years. Most common symptoms were cough and vomiting. The most common diagnosis arrived at was Scrub typhus (22.4%) followed by Dengue (11%), Enteric fever (11%), Co- infections (6.1%), Urinary tract infections (3%) and Lower respiratory tract infections (2.3%). Fever was still undiagnosed in 116 children (44.1%). No malarial infection was noted. **Conclusion:** Non-malarial infections are common in this part of the country in children with AUF.

Key words: Fever, acute disease, Child, scrub typhus, Dengue, Enteric fever

Introduction

Fever whether low or high grade is a distressing symptom for parents. It is the most common presentation in children attending the pediatric outpatient service and in children with infectious disease. Acute fever of 2 weeks duration with non-specific signs and symptoms is known as acute undifferentiated febrile illness (AUF) [1]. This is distinguished from pyrexia of unknown origin which refers to fever of at least 3 weeks for which no cause is identified even after investigation [2]. Since the presentation is non-specific, AUFs remain a diagnostic challenge unless information of the regional etiological pattern of the AUFs is known. It can then serve as a clinical and therapeutic guide. Otherwise, treatment may get delayed and contribute to mortality in the child. In developed countries, viral fever is reportedly the most common cause for AUF in children [3]. In South Asian

regions, common causes are Dengue, Enteric fever, Scrub typhus, Leptospirosis, and Malaria in varying proportions which are potentially treatable [4,5].

Several studies are available on AUF in adults [4-6] whereas data are limited in children. There is thus an urgent need to describe the demography, clinical profile, and identification of etiology in children seeking health care facility for AUF. Hence the present study will focus on etiology and clinical profile of undifferentiated febrile illness.

Methodology

Type of study: Prospective study of observational design.

Place of study: Pediatric department of Indira Gandhi Medical College and Research Institute, Puducherry after institute ethics committee approval.

Study duration: July 2015 to June 2016.

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Inclusion criteria: All children aged 2-12 years admitted with fever 38° Celsius or more, of 5-15 days duration with no cause found after a thorough history and clinical examination.

Exclusion criteria: Children with fever less than 5 days, those with fever more than 15 days, children with clear localizing signs and critically ill children and infants.

Sampling Methods: All children satisfying inclusion criteria were included.

Methods

Detailed history was recorded concerning fever pattern, duration and other presenting complaints after informed consent from parents.

History pertaining to respiratory, cardio-vascular, gastro-intestinal and central nervous system, development and immunization was recorded. Past history of infections, contact with tuberculosis, family history and history of travel was noted. Detailed general and systemic examination findings were recorded. Initial investigations recorded were complete blood count, peripheral smear, urine

Results

A total of 263 children were included. Their mean age was 6.7 ± 3.4 years and ranged from 2-12 years. Children aged 2-5 years were 116 (44.1%) and 6-12 years were 147 (55.9%). Male children were 155 (58.9%) and female children were 108 (41.1%). There were 189 patients (71.9%) from Puducherry and 74 patients (28.1%) from neighboring Tamil Nadu. All were developmentally normal and immunized for age. None had received any Typhoid vaccine.

Clinical features- Mean duration of fever for all the children was 8.3 ± 3.6 days. Mean peak temperature was $39.2 \pm 0.9^{\circ}\text{C}$ and the maximum recorded was 44°C . Fever was intermittent in 211 children (80.2%) and continuous in 52 (19.8%). Fever was associated with chills in 122 children (46.4%) and rigors in 107 (40.7%).

Other symptoms at presentation and hospital stay were cough (n=163, 62%), vomiting (n=114, 43.3%), headache (n=69, 26.2%), abdominal pain (n=61, 23.2%), muscle pain (n=50, 19%), loose stools (n=33, 12.5%), arthralgia (n=15, 5.7%), rash (n=6, 2.3%), and seizures (n=2, 0.8%) in that order. History of fever was present in other family members in 4 of the index children (1.5%). History of contact with Pulmonary Tuberculosis was seen in 6 children (2.3%). Previous admission with fever was seen in 4 children (1.5%). All were developmentally normal with normal nutritional status. No history of travel was recorded in any of these children.

Shock was seen in 12 children (4.6%) during the course of hospital stay, throat congestion in 11 (4.2%), conjunctival congestion in 8 (3%), coated tongue in 7 children (2.7%), rash in 6 (2.3%), epigastric tenderness in 4 (1.5%), and cheilitis in 1 (0.4%).

Lab findings- Anemia was seen in 99 children (37.6%). Neutrophil leukocytosis was seen in 60 children (22.8%), leukopenia in 30 (11.4%), eosinopenia in 38 (14.4%), and thrombocytopenia in 65 (24.7%). Peripheral smear for malarial parasite and RDT malaria was negative in all the children. Urine culture grew pathogenic organisms in 8

analysis, smear and rapid diagnostic test (RDT) for malarial parasite, urine culture and blood culture. Further investigations included chest X-ray, Ultra sonogram (USG) of abdomen, liver function test (LFT), renal function test (RFT) and serological analysis including blood Widal, Dengue Ns1Ag detection/IgM Elisa and Scrub typhus IgM Elisa which were done as per clinical discretion. Other serological tests were not done in the hospital.

Treatment details pertaining to antimicrobial use was recorded. The peak temperature, time for defervescence and duration of hospital stay were noted.

Statistical analyses- SPSS software was used for analyzing data collected. Mean and standard deviation was used for continuous variables which were compared using t test. Proportions were used for categorical variables which were compared using Chi test.

Univariate and multivariate logistic regression was done to find significant association of variables in common etiological patterns identified. p value less than 0.05 was considered significant.

children (3%). The organism isolated were E.coli (n=6, 4.9%), Klebsiella (n=1, 0.4%) and Pseudomonas (n=1, 0.4%). Blood culture grew Salmonella typhi in 2 children (0.8%), S.paratyphi in 1 (0.4%) and Coagulase negative Staphylococcus aureus in 1 (0.4%). Mantoux was done in 27 children (10.3%) and was negative in all of them. Liver function test was done in 25 children (9.5%) and enzymes were elevated in 11 of them (44% of LFTs done). Renal function test were done in 34 children (12.9%) and was normal in all. Koch's screening was negative in all the 6 children who had history of contact with Tuberculosis.

Blood Widal was done in 189 children (71.9%) and was positive for enteric fever in 39 children (20.6% of Widal tests done). Dengue testing was done in 136 children (51.7%) and was positive in 38 children (14.4%). Dengue Ns1Ag was positive in 26 children (19.1%), IgM positive in 11 (4.2%) and both were positive in one (0.4%). Scrub typhus IgM Elisa was done in 108 children (41.1%) and was positive in 72 children (66.7%). Screening Xray Chest showed infiltrates/patchiness in 13 children (4.9%). USG Abdomen was done in 17 children (3.8%). USG finding was ascites in 4 children (1.5%), GB wall edema in 1 (0.4%), pleural effusion in 2 (0.8%), mesenteric adenitis in 2 (0.8%), and normal in rest 8 (3%).

Diagnosis- The pattern of acute undifferentiated fever is shown in Figure 1.

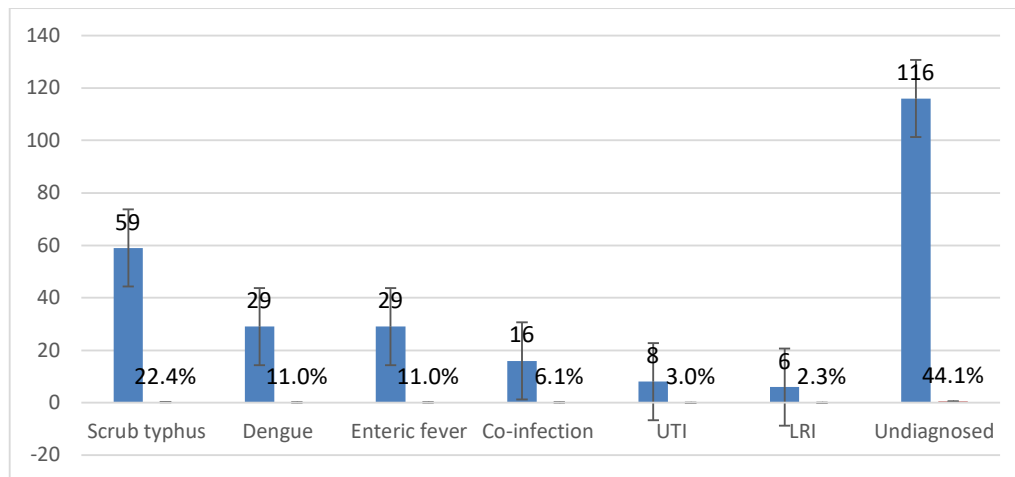


Figure-1: Aetiological Pattern of Acute undifferentiated febrile illness

The most common diagnosis arrived at was Scrub typhus (n=59, 22.4%) followed by Dengue (n=29, 11%), Enteric fever (n=29, 11%), Co-infections (n=16, 6.1%), Urinary Tract infection (UTI)(n=8, 3%)and Lower Respiratory Tract Infection (LRTI)(n=6, 2.3%). Fever was still undiagnosed in 116 children (44.1%).Co-infections were Enteric fever with Scrub typhus (n=7, 44%), Dengue with Scrub typhus (n=6, 37%) and Enteric fever with Dengue (n=3, 19%).

Gender, age group and regional differences

There was no gender difference noted for any of the etiological patterns ($p>0.05$). More number of female children presented with chills ($\chi^2 3.944$, $p=0.047$).

Dengue was more commonly observed in older age group (6-12 years) than younger age group of 2-5 years (age group categorical, $\chi^2 5.272$, $p=0.022$). No difference was noted for any of the other diagnosis ($p>0.05$). Significantly higher proportion of younger children presented with cough ($\chi^2 4.301$, $p=0.038$). Significantly higher proportion of older children had headache ($\chi^2 12.320$, $p=0.000$), abdominal pain ($\chi^2 6.866$, $p=0.009$), shock ($\chi^2 9.922$, $p=0.002$) and leucopenia ($\chi^2 10.342$, $p=0.001$). Scrub Typhus patients were significantly from local population rather than neighboring Tamil Nadu ($p=0.006$).

The clinico-lab profile in different etiologies of AUFI is shown in table 1-3

Table-1: Distribution of symptoms and signs in different patterns of AUFI

Variable †	Scrub typhus n=59	Dengue n=29	Enteric fever n=29	UTI n=8	LRTI n=6	Co-infections n=16	Undiagnosed fever n=116
Cough	35(59.3%)	18(62.1%)	16(55.2%)	2(25%)	5 (83.3%)	6 (37.5%)	81(69.8%)
Vomiting	24(40.7%)	19(65.5%)	14(48.3%)	2 (25%)	1 (16.7%)	11 (68.8%)	43(37.1%)
Headache	13 (22%)	12(41.4%)	10(34.5%)	1(12.5%)	1 (16.7%)	2 (12.5%)	30 (25.9%)
Abdominal Pain	23 (39%)	11(37.9%)	5(17.2%)	1(12.5%)	1 (16.7%)	2 (12.5%)	18 (15.5%)
Muscle pain	6 (10.2%)	7 (24.1%)	3(10.3%)	0 (0%)	2 (33.3%)	2 (12.5%)	30 (25.9%)
Loose stools	4 (6.8%)	5 (17.2%)	4(13.8%)	2 (25%)	1 (16.7%)	1 (6.2%)	16 (13.8%)
Joint pain	1 (1.7%)	2 (6.9%)	3(10.3%)	0 (0%)	0 (0%)	0 (0%)	9 (7.8%)
Rash	2 (3.4%)	1 (3.4%)	0(0%)	0 (0%)	0 (0%)	1(6.2%)	2(1.7%)
Jaundice	1 (1.7%)	0 (0%)	0(0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Conjunctival injection	6(10.2%)	0(0%)	0(0%)	0(0%)	0(0%)	1(6.2%)	1(0.9%)
Shock	4 (6.8%)	2 (6.9%)	3 (10.3%)	0 (0%)	0 (0%)	0 (0%)	3 (2.6%)
Empirical antibiotics	0 (0%)	7 (24.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (17.4%)
Empirical antimalarials	0 (0%)	01(3.4%)	0 (0%)	1(12.5%)	0 (0%)	0 (0%)	3 (2.6%)

†All variables are expressed as frequency (n) and percentage (%)

Table-2: Duration of events in AUFI

Variable †	Scrub typhus n=59	Dengue n=29	Enteric fever n=29	UTI n=8	LRTI n=6	Co-infection n=16	Undiagnosed fever n=116	Total n=263	F/Sig
Fever duration at presentation in days	8.5±3.5	6.2±2.5	7.7±3.0	10.1±3.6	8.5±3.4	9.1±4.5	8.6± 3.7	8.3±3.6	2.575 0.019*
Time for defervescence	3.2±1.9	3.2±1.5	5.5±3.3	3.4±1.2	4.7±2.3	4±2.9	3.5±1.7	3.7±2.1	5.303 0.000**
Hospital stay	7.2±2.4	7.1±3.5	9.1±3.5	8.1±2.8	9.7±5.5	7.4±1.9	5.2±2.5	6.7±3.1	11.120 0.000**

Duration of fever at presentation was longest in UTI (10.1±3.6 days) and shortest in Dengue (6.2±2.5 days).

†All Variables expressed as Mean ± SD

* p<0.05

** p<0.01

Table-3: Distribution of laboratory findings in patterns of AUFI.

Variable †	Scrub typhus n=59	Dengue n=29	Enteric fever n=29	UTI n=8	LTRI n=6	Co-infection n=16	Undiagnosed fever n=116
Leukocytosis	12 (20.3%)	3 (10.3%)	5 (17.2%)	6 (75%)	3 (50%)	6 (37.5%)	25 (21.6%)
Leukopenia	4 (6.8%)	10 (34.5%)	3 (10.3%)	0 (0%)	0 (0%)	0 (0%)	13 (11.2%)
Eosinopenia	7 (11.9%)	4 (13.8%)	22(75.9%)	1 (12.5%)	0 (0%)	1 (6.2%)	3 (2.6%)
Thrombocytopenia	18 (30.5%)	16 (55.2%)	5 (17.2%)	1 (12.5%)	0 (0%)	3 (18.8%)	22 (19%)
Urine c/s	0 (0%)	0 (0%)	0 (0%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)
Blood c/s	0 (0%)	0 (0%)	3 (10.3%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Blood Widal	0 (0%)	0 (0%)	29 (100%)	0 (0%)	0 (0%)	10 (62.5%)	0 (0%)
Dengue Testing	0 (0%)	29 (100%)	0 (0%)	0 (0%)	0 (0%)	9 (56.2%)	0 (0%)
Scrub Typhus IgM	59(100%)	0(0%)	0(0%)	0(0%)	0(0%)	1 (81.2%)	0(0%)
Chest Xray	3 (5.1%)	3 (10.3%)	1 (3.4%)	0 (0%)	6 (100%)	0 (0%)	0 (0%)
Liver function	5 (8.5%)	4 (13.8%)	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)	1 (0.9%)
Renal function	9 (15.3%)	3 (10.3%)	7 (24.1%)	2 (25%)	0 (0%)	3 (18.8%)	12 (10.3%)

†All variables are expresses as frequency (n) and percentage (%)

After univariate and multivariate logistic regression, local residence, abdominal pain and conjunctival congestion were significantly higher in scrub typhus (Table 4). Leucopenia and thrombocytopenia were significantly higher in Dengue (Table 4).

Table-4: Multivariate analysis for scrub typhus and Dengue

Variable	Wald	Sig p value	Exp (B)	95% C.I.for EXP(B)	
				Lower	Upper
<i>Scrub Typhus</i>					
Region (Puducherry)	6.462	0.011*	0.438	0.232	0.828
Abdominal pain	7.715	0.005**	0.393	0.203	0.760
Conjunctivitis	7.083	0.008**	0.100	0.018	0.545
<i>Dengue</i>					
Leukopenia	6.271	0.012*	0.277	0.102	0.757
Thrombocytopenia	8.441	0.004**	0.278	0.117	0.660

*p<0.05 **p<0.01

Treatment- Antimicrobials were started in 133 children (50.6%). Chloroquine was used additionally in 5 children (1.9%). Scrub Typhus was treated with Doxycycline or Azithromycin. Dengue was treated symptomatically and with fluids according to Dengue protocol. Enteric fever was treated with Ceftriaxone. If fever persisted even after 6 days of antibiotics, then Azithromycin was added. UTI was treated with Ceftriaxone or Amikacin. LRTI was treated with Ampicillin with or without Gentamycin or only Amoxicillin. In the undiagnosed fever category, 19 (16.4%) received empirical antibiotics and 3 (2.6%) received Chloroquine.

Outcome- The mean duration of fever after hospital admission was 3.1 ± 2.3 days. The mean hospital stay was 6.7 ± 3.1 days and was longest in LRTI (9.7 ± 5.5 days) and shortest in undifferentiated illness (5.2 ± 2.5 days). No mortality was recorded in present study.

Discussion

Final diagnosis was possible in 147 children (55.9%). The most common diagnosis was scrub typhus (22.4%). This is similar to finding reported by Kashinkunti in Karnataka [1]. However, regional patterns vary. In Chennai, enteric fever was identified as most common specific etiology in children [7]. All these children diagnosed with Scrub typhus in this study did not have eschar. Various studies have reported presence of eschar as ranging from 11-44% only [8, 9]. Therefore, high index of suspicion is necessary to make a prompt diagnosis of Scrub typhus in the absence of eschar. Serology is useful in this regard to confirm the clinical suspicion. This is vital as early treatment reduces morbidity and mortality associated with Scrub typhus.

After Scrub typhus, Enteric fever (11%) and Dengue (11%) were the common specific diagnosis reported in our study. Prevalence in other studies range from 5-26% [5,7]. None of the children in our study had received typhoid vaccination. However, the low prevalence may be related to absence of specific reliable serological test and low yield of blood culture. Though Widal is only supportive investigation, eosinopenia was a valuable guide in diagnosis. Typhidot which is considered superior to Widal was not available in the hospital.

Prevalence of Dengue in AEFI ranged from 10-25% in adults [1,10]. A lower proportion was reported in children in Chennai [7]. Thus, there is wide regional variation in the prevalence. The common infections noted in AEFI are malaria and non-malarial infections such as Scrub typhus, Enteric fever, Dengue and Leptospirosis in South India [1,7,10], North India [11] and even other Asian countries like Cambodia and Vietnam [5,12].

It is noteworthy that no case of malaria was reported in our study during this time period though mosquito-borne Dengue was noted in 11% of the children. It may be because of different mosquito species and different breeding habits of the mosquitoes involved. Respiratory tract infections and urinary tract infections were other identifiable causes in our study, similar to that reported by

Shamikumar [7]. Co-infections were observed in 6.1% comparable to 7.6% reported by Abhilash et al [6]. It is highly probable that these might not be true co-infections but only serological cross-reactivity. However, true co-infection have been reported [13,14].

Cough and vomiting were the two principal symptoms with which children with AEFI presented, similar to that reported by Shamikumar [7]. In their study, vomiting and cough were predominant in that order. Abdominal pain and conjunctival suffusion were significantly associated with scrub typhus in our study while Abhilash observed breathlessness as significant in adults [6]. Lab finding of leukopenia and thrombocytopenia was significantly associated with Dengue similar to that reported by Gopalakrishnan in adults [10].

Undiagnosed fever was seen in 44.1% in our study. Similar proportion was reported by other studies ranging from 50-60% [7, 15]. Higher proportion of undiagnosed cases can be explained by the limited diagnostic facilities available.

Most of the undiagnosed fever in our study were treated as viral fever and was indeed self-limiting. Shamikumar also reported a similar observation where non-specific viral illness and URI formed the major category of children with AEFI [7]. In our study, a small number of them, received empirical antibiotics (16.4%) and empirical Chloroquine (2.6%). Overall, empirical antibiotics were given in 26 children (9.9%) and empirical chloroquine in 5 (1.9%). Observation from our study emphasizes that empirical antimicrobials can well be avoided in children presenting with AEFI as most of them are self-limiting.

Limitations in our study- There are certain limitations in our study such as limited diagnostic facilities. Serology for Leptospirosis, Brucella, Chikungunya and other viral studies would have increased the specific diagnosis that could have been made. These were not available in the Institute and were not ordered outside as per ethical committee considerations.

Conclusion

Non-malarial infections are common causes of AEFI in children in this part of the country. The most common specific infection was Scrub typhus, followed by Dengue and Enteric fever. Proportion of undiagnosed fever, most of which were presumed non-specific viral fever, still remain high owing to limited diagnostic facilities. Due to high prevalence of Scrub typhus in this area, a thorough search for eschar should be made in all patients of AEFI. Empirical Chloroquine can be safely avoided unless tested positive for malaria. Similarly, empirical antibiotics can be avoided in children presenting with AEFI.

Recommendations- All children should receive Typhoid vaccination. Dengue control and mite control measures should be undertaken to curb the same.

What this study adds- Non-malarial infections are presently the leading causes of AEFI in children in this region. Empirical chloroquine can be avoided. As most of the AEFI are self-limiting, even empirical antimicrobials can be avoided.

Abbreviations used

AEFI-Acute undifferentiated febrile illness, **RDT**-Rapid Diagnostic Test, **USG**-Ultra sonogram, **LFT**-Liver Function Test, **RFT**-Renal Function Test, **LRTI**-lower respiratory Tract infection, **UTI**-Urinary tract infection,

Each Authors's contribution

- S.Prabha -concept, design, data acquisition, analysis,drafting, revising critically and final approval of version to be published
- C.Barathy contributed to design, data acquisition, analysis,drafting,revising critically and final approval of version to be published
- P.Sriram-drafting, revising critically and final approval of the version to be published
- Antonio Jude Raja-Data acquisition and drafting
- All authors read and approved the final manuscript.

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