Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors – an experience from a tertiary care hospital in South India

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Short Report

Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors – an experience from a tertiary care hospital in South India

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SUMMARY Local prevalences of individual diseases influence the prioritization of the differential diagnoses of a clinical syndrome of acute undifferentiated febrile illness (AFI). This study was conducted in order to delineate the aetiology of AFI that present to a tertiary hospital in southern India and to describe disease-specific clinical profiles. An 1-year prospective, observational study was conducted in adults (age >16 years) who presented with an undifferentiated febrile illness of duration 5–21 days, requiring hospitalization. Blood cultures, malarial parasites and febrile serology (acute and convalescent), in addition to clinical evaluations and basic investigations were performed. Comparisons were made between each disease and the other AFIs. A total of 398 AFI patients were diagnosed with: scrub typhus (47.5%); malaria (17.1%); enteric fever (8.0%); dengue (7.0%); leptospirosis (3.0%); spotted fever rickettsiosis (1.8%); *Hantavirus* (0.3%); alternate diagnosis (7.3%); and unclear diagnoses (8.0%). Leucocytosis, acute respiratory distress syndrome, aseptic meningitis, mild serum transaminase elevation and hypoalbuminaemia were independently associated with scrub typhus. Normal leukocyte counts, moderate to severe thrombocytopenia, renal failure, splenomegaly and hyperbilirubinaemia with mildly elevated serum transaminases were associated with malaria. Rash, overt bleeding manifestations, normal to low leukocyte counts, moderate to severe thrombocytopenia and significantly elevated hepatic transaminases were associated with dengue. Enteric fever was associated with loose stools, normal to low leukocyte counts and normal platelet counts. It is imperative to maintain a sound epidemiological database of AFIs so that evidence-based diagnostic criteria and treatment guidelines can be developed.

Introduction

Acute undifferentiated febrile illnesses (AFIs), such as malaria and dengue, cause considerable morbidity, mortality and economic burden to developing tropical nations.[1] Given the clinical confusion in distinguishing between AFIs, inappropriate use of antibiotics is rampant, frequently corroborated by improperly interpreted tests.[2] Evidence-based decision-making relies on quality information about the epidemiology of region-specific AFIs, of which very little is from South Asia.[1] This study aimed to delineate the regional aetiology of AFI and describe disease-specific profiles that would help clinicians reach diagnoses based on simple clinical evaluation.

Methodology

A prospective, observational study was conducted, following approval of the institutional review board, in a tertiary-care referral hospital (Vellore, South India) during January 2007–January 2008. Consecutive patients aged ≥16 years who had had a febrile illness for 5–21 days, with no evident focus of infection following initial clinical evaluation and who required hospitalization, were recruited after informed consent (study protocol – Figure 1). Immunocompromised patients were excluded. Diagnoses were assigned according to predefined criteria. Odds ratios were derived for clinical features associated with a given AFI compared to the remaining cohort.

Results

We recruited 398 patients (aetiological diagnosis – Figure 1): 242 (60.1%) were male and the mean age was 39.5 (16.9) years. The patients came from the southern Indian states of Tamil Nadu (66.3%) and Andhra Pradesh (30.9%). They

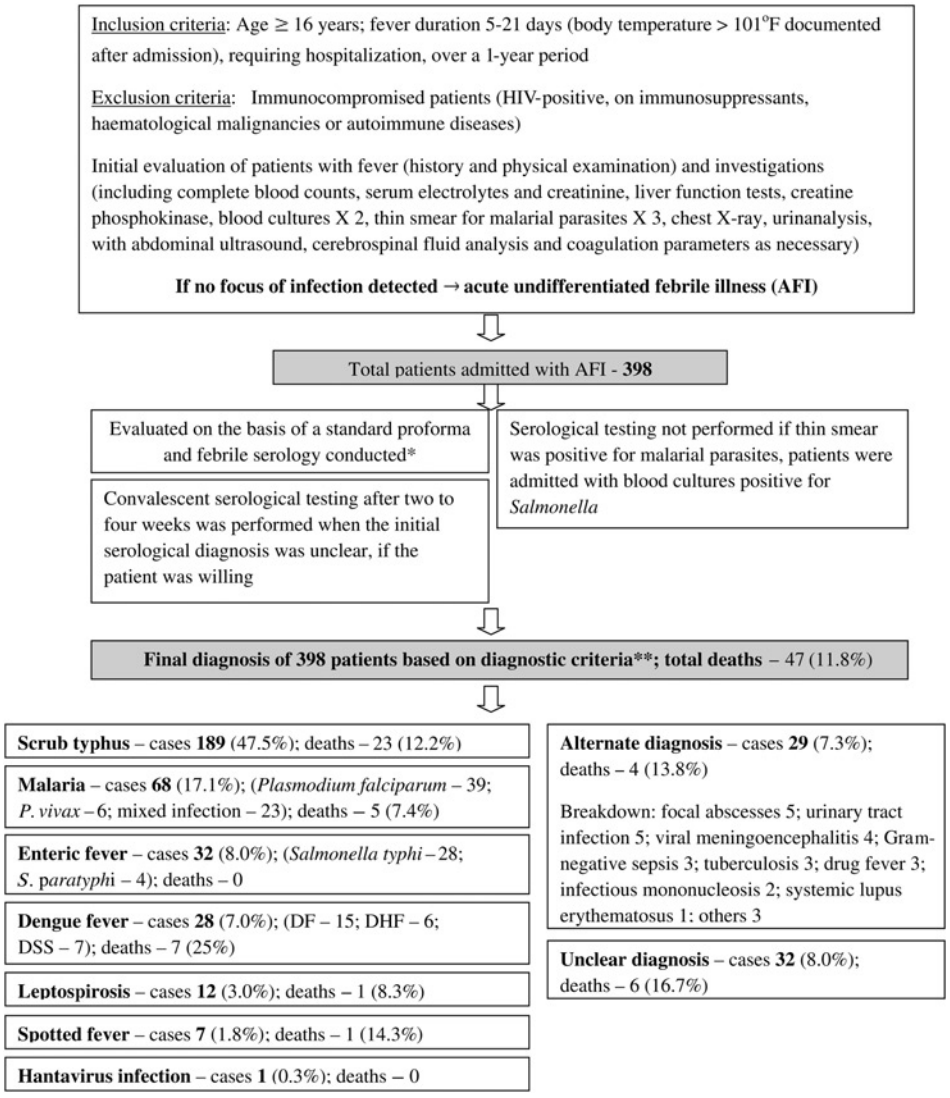

Figure 1 Acute undifferentiated febrile illness

*Febrile serology: scrub typhus IgM ELISA (PanBio Ltd, Brisbane, Australia); Qualitative assays: Leptospira IgM ELISA (Virion\Serion GmbH, Germany), *Hantavirus* IgM and IgG (Focus Technologies, Cypress, California), Typhidot [IgM and IgG] (Malaysia Bio-Diagnostics Research Sdn, Malaysia); Rapid assay: Dengue IgM-IgG ELISA (Dengue Duo Cassette, PanBio Ltd). Spotted fever IgM ELISA (PanBio Ltd) was done for patients with rash.

**Diagnostic criteria for AFI: Scrub typhus – Eschar + Scrub IgM ELISA positive OR Scrub IgM ELISA positive + defervesence within 48 h of initiation of Doxycycline OR Scrub IgM ELISA seroconversion on convalescent sera OR Scrub IgM ELISA with other serologies negative. Malaria – Malaria parasite (trophozoites – Falciparum, Vivax or mixed) visualized on thin blood smears. Enteric fever – Blood culture positive for *Salmonella typhi* or *S. paratyphi* OR Typhidot (IgM) positive + other serologies negative OR fourfold rise in titre on the WIDAL. Dengue fever – Dengue IgM positive + other serologies negative OR seroconversion on convalescent sera; Dengue hemorrhagic fever (DHF) – Above criteria + thrombocytopenia with haemorrhage; Dengue shock syndrome (DSS) – Shock (BP < 90mmHg) + other features of DHF. Leptospirosis – Seroconversion on convalescent sera OR Leptospira IgM positive + other serologies negative. Spotted fever rickettsiosis – Rash + Spotted Fever IgM ELISA positive + other serologies negative OR seroconversion on convalescent sera OR OX19 positive with rash + skin biopsy suggestive of Rickettsial vasculitis. *Hantavirus* – Seroconversion on convalescent sera OR *Hantavirus* IgM positive + other negative serology. Alternate diagnosis – In cases where the diagnosis was not ascertained after basic evaluation, further investigation was conducted by the treating team and an alternated diagnosis was found. Unclear diagnosis – After complete evaluation a definitive diagnosis was not made. This included patients who expired (diagnostic criteria not fulfilled during initial evaluation), who did not have convalescent sera taken (diagnostic criteria was not fulfilled during initial admission) and who had multiple serologies positive without fulfilling the diagnostic criteria. DF, Dengue fever; DHF, Dengue haemorrhagic fever; DSS, Dengue shock syndrome

were mainly unemployed (33.4%) or labourers/farmers (38.7%). AFI predominantly occurred during the monsoon and subsequent months between July to October. The mean time to presentation was 9.3 (3.8) days and mean hospital stay duration was 6.3 (5.4) days. Seventy (19.1%), 58 (15.8%) and 41 (11.2%) patients required mechanical ventilation, inotropes and intensive care, respectively. There were 47 (11.8%) deaths. Univariate/multivariate analyses for individual AFIs are presented in Table 1.

Discussion

AFI disease burden in South Asia

Although rickettsial fevers are being increasingly reported from the Indian subcontinent, the incidence is unknown.[3] Our study showed a high scrub typhus proportion (47.5%), probably due to an epidemic which occurred during the study period, a low disease awareness and, consequentially, a higher referral rate. Up to 80% of reported malaria cases in southern/south-eastern Asia are from India, with the majority from states such as Orissa and Andhra Pradesh.[4] Malaria accounted for 17.1% of AFIs in our study. Dengue fever incidence has been estimated at 14% among AFIs in a rural population-based southern Indian study and 48% in a hospital-based study in urban northern India.[2] The study dengue case numbers, though low (7%), comprised severe cases as evidenced by the high case fatality rate (25%), possibly due to a referral bias. Salmonella, the most common bloodstream bacterial infection in southern Asia,[1] accounted for a tenth of AFIs in a north Indian study[2] – similar to our cohort (8%). Incidence rates for leptospirosis in our study were lower, with predominantly milder non-icteric forms, than that observed in centres with higher rainfall. The seroprevalence of *Hantavirus* in South India is documented, though the incidence of clinical disease is unclear.[5]

Respiratory disease

Respiratory symptoms, signs and abnormal chest radiography were the most common in patients with scrub typhus. Pulmonary involvement, commonly interstitial pneumonitis with possible vasculitis, leading to acute respiratory distress syndrome (ARDS), occurs in up to 55% of scrub typhus patients.[6] Scrub typhus, malaria and dengue contributed 75.8%, 9.7% and 2.9%, respectively, of all patients with ARDS in this cohort. A much higher incidence of ARDS in scrub typhus (24.9%) was documented in our cohort than previously reported.[6] Falciparum malaria associated ARDS is documented in 2.1–11.4% of Indian in-patients, the risk being higher among pregnant and non-immune individuals.[7] The pathophysiology of ARDS in malaria and dengue occurs as a result of endothelial injury, increased alveolar permeability and fluid overload.

Hepatic and renal disease

The predilection of *Orentia tsutsugamushi* for the liver sinusoidal epithelial cell results in mild elevations in hepatic transaminase levels in the majority of patients (70.1% in our study), with relatively mild elevations in alkaline phosphatase and bilirubin. Hepatic injury in malaria causes marginal rises in hepatic transaminases with significant mixed hyperbilirubinaemia due to intravascular haemolysis, hepatocyte dysfunction and bile stasis. In contrast, studies (including ours) have shown that significantly elevated hepatic transaminase levels are common in dengue infections. Normal serum aspartate transaminase (AST) levels are a strong negative predictor for dengue haemorrhagic fever (DHF).[8] Renal failure was seen most commonly in falciparum malaria (38.2%) followed by scrub typhus (19.6%), dengue (17.9%) and leptospirosis (16.7%).

Haematological involvement

Leukocytosis is seen in scrub typhus and leptospirosis, though it is not an invariable feature of scrub typhus. Normal/low leukocyte counts are evident in malaria, dengue and enteric fever. Thrombocytopenia is integral to the presentation of malaria, with up to 70% of patients with falciparum malaria exhibiting this.[9] Marked thrombocytopenia, overt bleeding and haemoconcentration secondary to plasma leak favour DHF/dengue shock syndrome (DSS). Thrombocytopenia in scrub typhus is generally mild.

Central nervous system (CNS) involvement

In this study, 74.6% of the patients with aseptic meningitis and 80% of patients with seizures had scrub typhus. Altered sensorium, including coma, mainly occurred in scrub typhus (53.6%) and falciparum malaria (18.8%). Cerebral malaria, documented in up to 70% of complicated falciparum malaria cases, was uncommon in our cohort. CNS involvement, commonly encephalitis presenting with altered sensorium and seizures, has been documented in 1–25% of dengue admissions.[10] In our study, 7.1% of dengue cases had aseptic meningoencephalitis.

Limitations

The majority of our patients presented late and required hospitalization due to multisystem involvement or complications. Extrapolating this data to patients with mild, shorter duration AFI in the community would be inaccurate.

Conclusion

Scrub typhus contributes a significant, hitherto underrecognized, disease burden in southern India. Respiratory manifestations, including ARDS, aseptic meningitis, mildly elevated hepatic transaminases and leukocytosis, characterize scrub typhus. Eschar detection and a therapeutic response to Doxycycline clinch the diagnosis. A hepato-renal syndrome constituting mixed hyperbilirubinaemia with marginally elevated hepatic transaminases, splenomegaly, renal failure and thrombocytopenia suggests malaria. Dengue, especially DHF/DSS, is characterized by marked thrombocytopenia, leukopenia, high transaminases and overt bleeding. Loose stools with low/normal leukocyte counts suggest enteric fever. Spotted fever (in patients with rash), anicteric leptospirosis and *Hantavirus* infection are important considerations

Table 1 Significant parameters on univariate and multivariate analysis for scrub typhus, malaria, dengue and enteric fever*

	Scrub typhus (189)	*Other AFI (177)*	*P value*	*Adjusted odds ratio (OR)*	*95% confidence interval (CI)*
SCRUB TYPHUS					
Age (mean/standard deviation; years)	45.4 (17.2)	33.4 (14.1)	<0.001		
Cough (N)	57	33	0.011		
Dyspnoea (N)	71	25	<0.001		
Headache (N)	79	42	<0.001		
Seizures (N)	12	2	0.009		
Respiratory crepitations (N)	58	17	<0.001		
Neck stiffness (N)	38	10	<0.001		
Tachycardia (higher rate >100 beats/min; N)	87	63	0.042		
Tachypnoea (respiratory rate >20/min; N)	118	86	0.008		
Shock (blood pressure < 90 mmHg; N)	26	9	0.005		
Haemoglobin (g%)	12.0 (2.3)	11.5 (2.9)	0.045		
Leucocytosis (>11500 cells/mm^3)	70	42	0.006	1.35	0.80–2.26
Neutrophil count (%)	74.14 (13.6)	67.73 (16.4)	<0.001		
Serum creatinine (mg%)	1.26 (1.1)	1.74 (1.9)	0.004		
Serum total bilirubin (mg%)	2.15 (2.4)	5.68 (9.2)	<0.001		
Serum alkaline phosphatase (U/L)	177.96 (127.0)	128.52 (86.8)	<0.001		
Elevated serum alanine aminotransferase (45–200 U/L)	134	81	<0.001	3.78	2.29–6.21
Serum albumin (<3.5 g%)	160	127	0.002	1.76	0.97–3.19
Acute respiratory distress syndrome†	47	12	<0.001	6.56	3.12–13.80
Aseptic meningitis‡	47	17	<0.001	3.65	1.92–6.95
	Malaria (68)	*Other AFI (298)*	*P value*	*Adjusted OR*	*95% CI*
MALARIA (*Plasmodium falciparum*/mixed/*P. vivax*)					
Age (mean/SD; years)	35.84 (14.3)	40.45 (17.3)	0.023		
Fever duration (mean/SD; days)	7.88 (3.9)	9.65 (3.8)	0.001		
Icterus (N)	41	44	<0.001		
Oliguria (N)	15	28	0.003		
Hepatomegaly (N)	40	99	<0.001		
Splenomegaly (N)	25	33	<0.001	6.67	2.56–17.37
Haemoglobin (g%)	10.3 (3.0)	12.1(2.4)	<0.001		
Leukocyte count (<11500 cells/mm^3)	58	192	0.001	2.59	1.05–6.37
Hyperbilirubinaemia (total bilirubin >2.0 mg%; N)	53	86	<0.001	9.40	4.11–21.48
Serum total protein (g%)	5.94 (0.9)	6.36 (1.1)	0.002		
Serum alkaline phosphatase (U/L)	108.09 (51.3)	164.77 (9119.5)	<0.001		
Renal failure (serum creatinine >1.4 mg%; N)	26	60	0.002	9.96	4.15–23.88
Thrombocytopenia (platelet count <50000 cells/mm^3; N)	48	81	<0.001	4.65	1.68–12.86
Serum alanine aminotransferase <100U/L (N)	51	117	<0.001	17.02	6.74–42.97
	Dengue (28)	*Other AFI (270)*	*P value*	*Adjusted OR*	*95% CI*
DENGUE (dengue fever/dengue haemorrhagic fever/dengue shock syndrome)					
Age (mean)	28.61 (12.2)	40.50 (16.9)	<0.001		
Death (N)	7	34	0.026		
Fever duration (mean days)	7.71 (2.9)	9.45 (3.9)	0.021		
Retro-orbital pain (N)	3	0	<0.001		
Leukocyte count (<11500 cells/mm^3)	22	228	0.224	2.92	0.92–9.26
Neutrophils (%)	61.89 (15.6)	71.8 (15.1)	0.001		
Lymphocytes (%)	27.75 (14.1)	19.7 (13.0)	0.002		
Thrombocytopenia (platelet count (<50000 cells/mm^3)	18	111	0.001	2.75	1.07–7.08
Haemoglobin (g%)	13.0 (2.5)	11.64 (2.6)	0.009		
S. AST >500 U/L (N)	12	15	<0.001	13.42	4.69–38.36
Total albumin (g%)	3.27 (0.9)	2.86 (0.7)	0.002		
Overt bleeding manifestations (N)	6	7	<0.001	10.05	2.25–44.98
Petechiae (N)	5	6	0.001		
Rash (N)	6	24	0.019	2.98	0.95–9.34
Abdominal free fluid (N)	3	5	0.017		
Myalgias/body ache (N)	8	54	0.088	2.57	0.89–7.35
	Enteric fever (32)	*Other AFI (266)*	*P value*	*Adjusted OR*	*95% CI*
Enteric fever (*Salmonella typhi*/*S. paratyphi*)					
Age (mean)	26.5 (9.9)	40.84 (16.9)	<0.001		
Fever duration (mean)	12.5 (4.135)	9.01 (3.7)	<0.001		
Loose stools (N)	14	37	<0.001	6.243	2.869–13.586

Continued

Table 1 Continued

	Enteric fever (32)	*Other AFI (266)*	*P value*	*Adjusted OR*	*95% CI*
Respiratory rate (/min) (mean)	20.78 (8.4)	25.58 (9.7)	0.004		
Leukocyte count < 7500 cells/mm^3	20	124	0.005	2.823	1.334–5.971
Platelet count (>130000 cells/mm^3) (N)	18	102	0.002	3.136	1.481–6.641
Serum creatinine (mg%)	1.02 (0.5)	1.54 (1.6)	<0.001		
Total bilirubin (mg%)	2.02 (3.4)	4.02 (7.0)	0.010		
Total protein (g%)	6.99 (.9)	6.22 (1.0)	<0.001		
Total albumin (g%)	3.33 (0.7)	2.84 (0.7)	<0.001		

*Logistic regression models were not created for the small patient cohorts with leptospirosis, spotted fever and *Hantavirus* infection
†Adult respiratory distress syndrome (bilateral pulmonary infiltrates on chest X-ray; peak flow ratio < 200; normal central venous pressure)
‡The diagnosis of aseptic meningitis was assigned to patients diagnosed with scrub typhus in whom cerebrospinal fluid (CSF) analysis revealed a lymphocyte predominant pleocytosis (CSF leucocytes >5) and negative CSF cultures. Lumbar puncture was performed on patients with neck stiffness, altered sensorium or seizures, provided there were no contraindications for the procedure
AFI, acute undifferentiated febrile illness; SD, standard deviation; S. ALT, serum alanine transaminase

in South India. Region-specific epidemiological databases of AFI need to be created so that evidence-based diagnostic criteria and treatment guidelines can be developed.

References

1 Zaidi AK, Awasthi S, deSilva HJ. Burden of infectious diseases in South Asia. *BMJ* 2004;**328**:811–15
2 Joshi R, Colford JM, 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
3 Kamarasu K, Malathi M, Rajagopal V, Subramani K, Jagadeeshramasamy D, Mathai E. Serological evidence for wide distribution of spotted fevers and typhus fever in Tamil Nadu. *Indian J Med Res* 2007;**126**:128–30
4 Lal S, Sonal GS, Phukan PK. Status of malaria in India. *J Indian Acad Clin Med* 2004;**5**:19–23
5 Chandy S, Yoshimatsu K, Boorugu H, *et al.* Acute febrile illness caused by hantavirus: serological and molecular evidence from India. *Trans R Soc Trop Med Hyg* 2009;**103**:407–12
6 Tsay RW, Chang FY. Acute respiratory distress syndrome in scrub typhus. *Q J Med* 2002;**95**:126–8
7 Mohan A, Sharma SK, Bollineni S. Acute lung injury and acute respiratory distress syndrome in malaria. *J Vector Borne Dis* 2008;**45**:179–93
8 Kalayanarooj S, Vaughn DW, Nimmannitya S, *et al.* Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis* 1997;**176**:313–21
9 Memon AR, Afsar S. Thrombocytopenia in hospitalized malaria patients. *Pak J Med Sci* 2006;**22**:141–3
10 Channa R, Wasay M. Central nervous system involvement in dengue infection. *Pak J Neurol Sci* 2006;**1**:84–8