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ORIGINAL ARTICLE

Clinical features and risk factors for death in acute undifferentiated fever: A prospective observational study in rural community hospitals in six states of India

Kristine Mørch [a,b,*], Anand Manoharan[c], Sara Chandy[c], Ashita Singh[d], Cijoy Kuriakose[e], Suvarna Patil[f], Anil Henry[g], Novin Chacko[h], Gerardo Alvarez-Uria[i], Joel Nesaraj[j], Bjørn Blomberg[a,b], Siby Kurian[c], Christel Gill Haanshuus[a], George Vasanthan Antony[c], Nina Langeland [a,b], and Dilip Mathai[c]

[a]Norwegian National Advisory Unit on Tropical Infectious Diseases, Department of Medicine, Haukeland University Hospital, 5021, Bergen, Norway; [b]Department of Clinical Science, University of Bergen, 5021, Bergen, Norway; [c]Infectious Diseases Training and Research Centre, Department of Medicine, Christian Medical College, 632004, Vellore, India; [d]Baptist Christian Hospital, 784001, Tezpur, Assam, India; [e]Christian Fellowship Hospital, 624619, Oddanchatram, Tamil Nadu, India; [f]B.K.L. Walawalkar Hospital, 415612, Ratnagiri, Maharashtra, India; [g]Christian Hospital, Mungeli, 495001, Chhattisgarh, India; [h]Duncan Hospital, Raxaul, 803101, Bihar, India; [i]Rural Development Trust Hospital, 510051, Anantapur, Andhra Pradesh, India; [j]Bethesda Hospital, 635802, Ambur, Tamil Nadu, India

*Corresponding author: Tel: +0047 55 97 56 60; E-mail: kristine.morch@helse-bergen.no

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Background: Acute undifferentiated fever (AUF) ranges from self-limiting illness to life-threatening infections, such as sepsis, malaria, dengue, leptospirosis and rickettsioses. Similar clinical presentation challenges the clinical management. This study describes risk factors for death in patients hospitalized with AUF in India.

Methods: Patients aged ≥5 y admitted with fever for 2–14 d without localizing signs were included in a prospective observational study at seven hospitals in India during 2011–2012. Predictors identified by univariate analysis were analyzed by multivariate logistic regression for survival analysis.

Results: Mortality was 2.4% (37/1521) and 46.9% (15/32) died within 2 d. History of heart disease (p=0.013), steroid use (p=0.011), altered consciousness (p<0.0001), bleeding (p<0.0001), oliguria (p=0.020) and breathlessness (p=0.015) were predictors of death, as were reduced Glasgow coma score (p=0.005), low urinary output (p=0.004), abnormal breathing (p=0.006), abdominal tenderness (p=0.023), leucocytosis (p<0.0001) and thrombocytopenia (p=0.001) at admission. Etiology was identified in 48.6% (18/37) of fatal cases.

Conclusions: Bleeding, cerebral dysfunction, respiratory failure and oliguria at admission, suggestive of severe organ failure secondary to systemic infection, were predictors of death. Almost half of the patients who died, died shortly after admission, which, together with organ failure, suggests that delay in hospitalization and, consequently, delayed treatment, contribute to death from AUF.

Keywords: Acute undifferentiated fever, India, malaria, mortality, scrub typhus, sepsis

Introduction

Infectious diseases are leading causes of morbidity and death in India, accounting for half of the deaths among children aged 5–14 y.[1] Common infections presenting as acute undifferentiated fever (AUF) characterized by fever without localizing signs and symptoms may be mild and self-limiting, while others can be rapidly fatal if left untreated.[2] Malaria, leptospirosis, scrub typhus, dengue and bacterial blood stream infections including enteric fever are the most common causes of AUF in hospitalized patients in India.[2–7] In South East Asia, the reported case-fatality rates in hospitalized patients presenting with AUF are 5–12% in bacterial bloodstream infections,[7,8] 2–22% in malaria,[2,4,6,7] 4–12% in scrub typhus,[2,4,9] 8–22% in leptospirosis[4,6] and 0–25% in dengue.[2,4,10,11] In cases of infections with drug-resistant bacteria, mortality in resource-constrained settings can reach 18–70%.[12,13]

Unfortunately, due to the similar clinical presentation and optimal confirmatory tests being inaccessible and unaffordable,[14] the etiology of AUF frequently remains uncertain.[3,7]

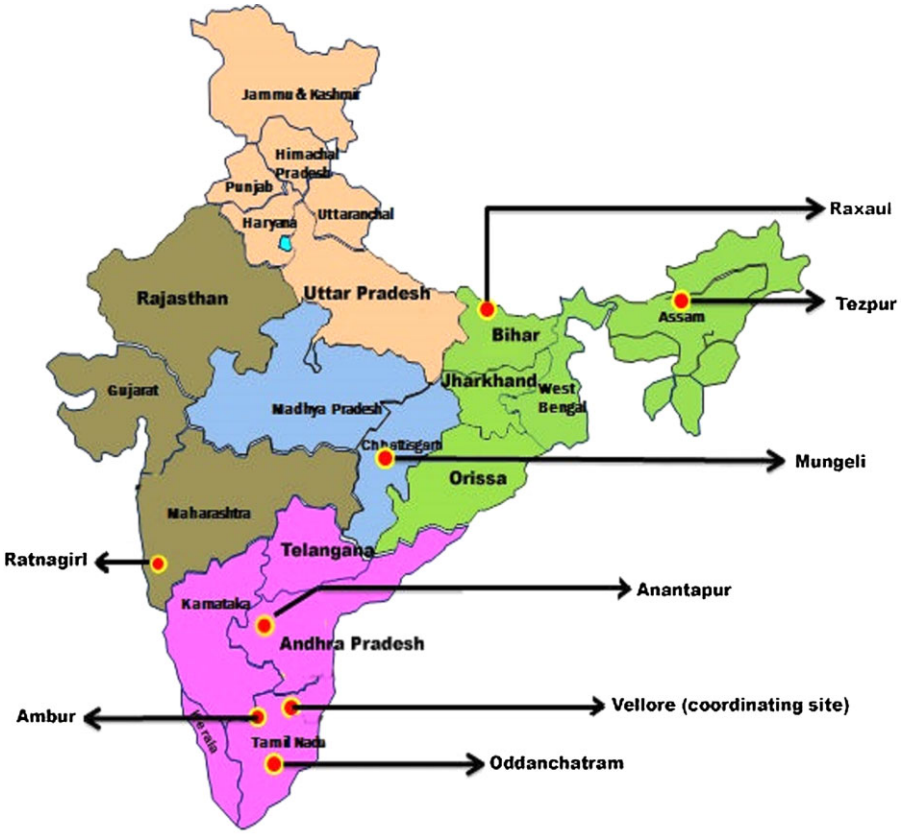

Figure 1. Location of hospitals in India participating in the study.

Consequently, there is considerable uncertainty around estimates of the morbidity and mortality that can be attributed to each pathogen.

Focus on clinical evaluation and identification of risk factors for severe prognosis of bacterial, viral and parasitic infections is particularly important to prioritize the right patients for treatment in hospital and to triage the right patients for intensive care treatment.

The objective of this study was to investigate the clinical features, treatment and risk factors for death among patients admitted with AUF in rural hospitals in India.

Materials and methods

Study sites and participants

Patients aged ≥5 y with AUF were consecutively included at admission to hospital during April 2011–November 2012. Patients were admitted to the following seven secondary community 100–500-bed hospitals in six states: Baptist Christian hospital in Tezpur (Assam, North East India), Duncan hospital in Raxaul (Bihar, North India), Christian hospital in Mungeli (Chhattisgarh, Central India), B.K.L. Walawalkar hospital in Ratnagiri (Maharashtra, Western India), Rural Development Trust hospital in Anantapur (Andhra Pradesh, South India), Christian Fellowship hospital in Oddanchatram (Tamil Nadu, South India) and Bethesda hospital in Ambur (Tamil Nadu, South India) (Figure 1).

The study monitoring center and reference laboratory was the Infectious Diseases Training and Research Centre and the Dr Benjamin M. Pulimood Laboratories for Infection Immunity and Inflammation, Department of Medicine and Infectious diseases, Christian Medical College (CMC), Vellore, India. Details of the climate variation among the study sites have been published previously.[15] AUF was defined as a temperature ≥38°C of 2–14 d duration before admission, with no localized infection as judged by the treating physician at the time of evaluation for inclusion. Patients with abdominal pain, diarrhea, hematochezia, nausea or vomiting, rhinorrhea, dyspnea, ocular pain, altered sensorium, headache, stiff neck, rash, arthralgia, myalgia, petechiae, ecchymosis, epistaxis, gingival bleeding or jaundice were not excluded. Patients with presentations suggestive of pneumonia, urinary tract infections, soft tissue infections and other localized causes were excluded.

Study procedures

The treating physicians prospectively recorded predefined clinical data. Reason for visit, fever duration, 13 specified symptoms, 12 specified prehospital comorbidities, travel history, animal exposure, alcohol and smoking habits, clinical findings upon admission, radiological, biochemical and microbiological test results,

tentative differential diagnoses, treatment including 11 specified antibiotics and seven specified antimalarials, outcome and condition at discharge, were recorded in a standardized case report form at all sites. One site (Tezpur) included information on all WHO-defined criteria for severe malaria.

This was a prospective observational study, and clinical work up and treatment were performed according to the hospital's routines. Point of care tests were performed in the hospitals, while microbiological case definitions based on analyses performed later in the reference laboratory were not available at the hospitals while treating the patients.

The following investigations were performed at the study hospitals on all patients: malaria blood smears, scrub typhus IgM ELISA (In Bios, USA), *Leptospira* IgM ELISA (Alere, Australia), chikungunya IgM ELISA (NIV, India), dengue rapid NS1 antigen and IgM Combo test (SD bioline, USA) and blood cultures. Blood cultures were collected before starting antibiotics and were cultured with the conventional method or by Bactec (Becton Dickinson, MD, USA); if growth was identified at the site it was frozen, then sent by cold chain to the study reference laboratory for new identification.

The following investigations were performed at the reference laboratory: scrub typhus IgM ELISA, *Leptospira* IgM ELISA, chikungunya IgM ELISA and dengue NS1/IgM Combo test if not performed at site. Dengue IgM capture ELISA (MAC-ELISA) on all samples. Scrub typhus immunofluorescence (IFA) on IgM ELISA positive samples, *Leptospira* microscopic agglutination test (MAT) on IgM ELISA positive samples. A genus-specific mitochondrial malaria PCR method, and the immunochromatographic rapid diagnostic test (RDT) Parahit Total (Span Diagnostics Ltd, Surat, India), were performed on all samples. A species-specific 18S PCR method, or sequencing, was performed on malaria genus PCR positive samples.

Case definitions were defined as follows: Leptospirosis, positive ELISA and positive MAT; scrub typhus, positive ELISA and positive IFA; dengue, positive RDT and/or positive MAC-ELISA; chikungunya, positive ELISA; bacteremia, growth of bacteria not considered to be contaminants in blood culture; malaria, positive malaria genus-specific PCR.

Microbiological methods and findings in this study have been reported previously.[3,15,16]

The study was reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist.

Statistical analysis

In descriptive analysis, dichotomous variables were given as proportions and continuous variables as medians with IQR. Univariate and multivariate analysis of risk factors for death included demographic variables, comorbidity, signs, symptoms, clinical and biochemical findings, laboratory-confirmed diagnosis and duration of hospitalization. Risk factors were analyzed group-wise for (i) demographic characteristics and comorbidities, (ii) history of illness, (iii) clinical findings on admission and (iv) microbiological and biochemical test results. Missing values were analyzed as missing values, except for imputation in merged variables, where missing values were coded as negative. In univariable analyses we calculated unadjusted OR, 95% CI and p-values, using logistic regression for both dichotomous variables and continuous explanatory factors. Age, gender and significant risk factors with $p<0.05$ in the univariable analyses were included in multivariable analyses. For multivariable analysis, we used logistic regression and presented results as adjusted OR (aOR), 95% CI and p-values. Statistical analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY, USA).

Results

Characteristics and outcome

A total of 1564 patients were included in the study. In-hospital mortality was 2% (37/1521), and additionally, 2% (25/1525) were discharged in a state of deteriorating health with unknown outcome. Discrepancies from the total (n=1564) in the numbers of patients included in each analysis are due to missing values and are shown in the tables. Characteristics and outcome at each study site are shown in Table 1.

The majority (82%, 1219/1495) of the population lived in rural areas. Median age was 31 y and 14% (199/1422) were aged ≤14 y. Fatal cases were not significantly older (median age 34 y) than survivors (31 y, p=0.197) (Table 2).

Fifty-nine percent (895/1527) were men and 41% (632/1527) women. There was no significant difference in case-fatality rates between male (2%, 18/887) and female patients (3%, 19/630) (p=0.223).

Antibiotics had been used before admission by 23% (335/1486); 33% (12/1477) among those who died and by 22% (320/1477) of survivors, but the difference was not a significant risk factor (OR 1.75, 95% CI 0.87 to 3.54) for death (Table 2). Eight percent (115/1476) had used antimalarial treatment before admission, and this was not associated with risk of death (p=0.900).

Among comorbid conditions, heart disease (aOR 5.85, 95% CI 1.46 to 23.48) and steroid use before admission (aOR 9.25, 95% CI 1.65 to 51.82) were significant risk factors for death (Table 2). One study site found 47% (75/160) of patients to have positive HIV status upon admission; none of these patients died.

Symptoms before admission

A history of altered consciousness (aOR 21.68, 95% CI 8.72 to 53.92), bleeding (aOR 14.08, 95% CI 4.21 to 47.13), oliguria (aOR 3.41, 95% CI 1.21 to 9.61) and breathlessness (aOR 2.91, 95% CI 1.24 to 6.87) were significant risk factors for death in both univariable and multivariable analyses (Table 3).

History of seizures, jaundice, prostration and vomiting were significant risk factors for death in univariable analyses but were not significant when included in the multivariable analysis (Table 3). Median duration of fever was 5 d among both survivors and those who died.

Clinical and laboratory findings

The following clinical signs at admission were predictors of death in the multivariable analysis: Glasgow Coma Scale (GCS) score (aOR 0.76, 95% CI 0.63 to 0.92), decreased urinary output (aOR

Table 1. Characteristics and outcome among patients with AUF in seven secondary hospitals in India (N=1564)

Characteristics	N[a]	Oddancha-tram (N=330) N (%)	Ambur (N=316) N (%)	Tezpur (N=336) N (%)	Mungeli (N=62) N (%)	Anantapur (N=160) N (%)	Ratnagiri (N=251) N (%)	Raxaul (N=109) N (%)	Total (N=1564) N (%)
Gender	1527								
Male	895	176 (53)	170 (55)	195 (59)	27 (52)	108 (72)	154 (62)	65 (61)	895 (59)
Female	632	154 (47)	139 (45)	135 (41)	25 (48)	42 (28)	96 (38)	41 (39)	632 (41)
Age, median (IQR), y	1422	31 (17–45)	32 (20–50)	30 (20–46)	27 (18–53)	30 (20–40)	36 (24–49)	26 (17–38)	31 (20–45)
≤14		71 (22)	33 (16)	41 (12)	10 (19)	22 (15)	10 (4)	12 (11)	199 (14)
>14		259 (78)	176 (84)	287 (88)	42 (81)	126 (85)	239 (96)	94 (89)	1223 (86)
Residency	1495								
Urban		57 (17)	107 (37)	25 (8)	8 (15)	35 (24)	39 (16)	5 (5)	276 (18)
Rural		271 (83)	186 (64)	294 (92)	44 (85)	113 (76)	209 (84)	102 (95)	1219 (82)
Characteristics									
Antibiotic before admission	1486	0	28 (10)	111 (34)	7 (14)	17 (11)	111 (45)	61 (62)	335 (23)
Antimalarial before admission	1476	0	3 (1)	25 (8)	5 (10)	11 (7)	63 (26)	8 (9)	115 (8)
Use of bed nets	1509	2 (1)	15 (5)	291 (90)	0	25 (17)	6 (2)	53 (56)	392 (26)
Animal exposure	1509	30 (9)	50 (16)	74 (23)	4 (8)	34 (23)	55 (22)	24 (26)	271 (18)
Alcohol use	1510	52 (16)	19 (6)	61 (19)	4 (8)	34 (23)	28 (11)	8 (9)	206 (14)
Smoker	1507	69 (21)	14 (5)	43 (13)	8 (15)	38 (26)	7 (3)	7 (8)	186 (12)
Comorbidity									
HIV known from before	1512	0	0	0	0	75 (47)	0	0	75 (5)
Diabetes	1511	0	32 (10)	13 (4)	4 (8)	0	23 (9)	4 (4)	76 (5)
Cardiac disorder	1514	0	3 (1)	0	0	1 (1)	13 (5)	2 (2)	19 (1)
Outcome									
Death in hospital	1521	0	1 (0.3)	15 (5)	6 (12)	0	13 (5)	2 (2)	37 (2.4)

[a]Total number investigated among 1564 patients. Discrepancies due to missing values.

2.55, 95% CI 1.34 to 4.85), abnormal breathing (aOR 6.81, 95% CI 1.76 to 26.40) and abdominal tenderness (aOR 5.76, 95% CI 1.27 to 26.10) (Table 4).

Reduced oxygen saturation, increased pulse rate, icterus, neck stiffness, edema, spontaneous bleeding, pallor and conjunctival congestion at admission were significant risk factors for death in the univariable analyses (p<0.0001), but were not significant when included in the multivariable analysis. An eschar was found in 8% (3/37) of those who died compared with 3% (38/1473) of survivors, but the difference was not statistically significant. Leucocytosis and thrombocytopenia were associated with risk of death in the multivariable analysis (Table 5).

Increased total bilirubin (p=0.047) and blood urea (p=0.005) at admission were risk factors in the univariable analyses, but were not included in the multivariable analysis due to a high number of missing values.

A diagnosis of malaria (19%, 265/1394), scrub typhus (11%, 156/1410), dengue (16%, 240/1501), leptospirosis (8%, 113/1410), bacteremia (11%, 124/1113) or chikungunya (7%, 96/1460) was not associated with death, either in univariable or multivariable analyses (Table 5).

The etiology of AUF was confirmed in 49% (18/37) of those who died: *Plasmodium falciparum* mono-infection (n=2), *P. falciparum* and leptospirosis (n=2), *Plasmodium vivax* (N = 3), scrub typhus mono-infection (n=3), scrub typhus and dengue (n = 2), scrub typhus and leptospirosis (n=1), bacteremia with *Escherichia coli* or *Staphylococcus aureus* (n=2), leptospirosis mono-infection (n = 1) and dengue mono-infection (n=2) (Table 6).

Patients who died had a significantly shorter duration of hospitalization compared with patients who survived (p=0.001). As many as 28% (9/32) died during the first day and 19% (6/32) during the second day of hospitalization (Table 6).

Treatment

All patients with malaria who died (n=7) had received treatment with intravenous artesunate or quinine, or intramuscular artemether (Table 6). Among all patients, 16% (245/1564) received antimalarials; 76% (73/96) of malaria smear positive cases and 15% (172/1167) of smear negative cases.

All patients with scrub typhus who died (n=6) had received doxycycline. Among all patients, 40% (609/1521) received doxycycline; 39% (586/1484) of those who survived and 62% (23/37) of those who died.

Table 2. Characteristics and comorbidity among survivors and non-survivors (N=1521)

				Univariable[b]			Multivariable[c]		
	N[a]	Survival N (%)	Death N (%)	OR	95% CI	p	aOR	95% CI	p
Total, N	1521	1484	37						
Gender	1517				0.35 to 1.28	NS	1.546	0.797 to 2.996	NS
Men	887	869 (59)	18 (49)	0.67					
Women	630	611 (41)	19 (51)	1.00					
Age, median (IQR), y	1412	31 (20–45)	34 (22–55)	1.01	0.99 to 1.03	NS	0.995	0.977 to 1.014	NS
≤14	198	195 (14)	3 (8)						
>14	1214	1180 (86)	34 (92)						
Characteristics									
Bed nets use	1499	375 (26)	14 (38)	1.76	0.90 to 3.46	NS			
Animal exposure	1499	260 (18)	11 (30)	1.96	0.95 to 4.01	NS			
Alcohol use	1500	198 (14)	7 (19)	1.49	0.65 to 3.44	NS			
Antibiotics prior	1477	320 (22)	12 (33)	1.75	0.87 to 3.54	NS			
Antimalarial prior	1467	111 (8)	3 (8)	1.08	0.33 to 3.58	NS			
Smoking	1497	182 (13)	2 (5)	0.40	0.10 to 1.68	NS			
Recent intake raw milk	1505	23 (2)	1 (3)	0.57	0.08 to 4.36	NS			
Recent travel outside district	1505	134 (9)	1 (3)	0.28	0.04 to 2.03	NS			
Comorbidity									
Heart disorder	1504	16 (1)	3 (8)	8.00	2.23 to 28.8	0.001	5.85	1.46 to 23.48	0.013
Condition with steroid treatment	1503	6 (0.4)	2 (5)	13.9	2.71 to 71.3	0.002	9.25	1.65 to 51.82	0.011
Diabetes	1501	74 (5)	2 (5)	1.07	0.25 to 4.55	NS			
Hypertension	1502	88 (6)	4 (11)	1.90	0.66 to 5.47	NS			
Seizure disorder	1503	9 (1)	1 (3)	4.50	0.56 to 36.4	NS			
Respiratory disease	1503	32 (2)	2 (6)	2.64	0.60 to 11.46	NS			
Kidney disease	1505	12 (1)	1 (3)	3.37	0.48 to 26.6	NS			
Liver disease	1500	15 (1)	1 (3)	2.68	0.35 to 20.85	NS			
Stroke	1504	5 (0.3)	0			-			
HIV	1502	74 (5)	0			-			
TB	1434	11 (1)	0			-			
Cancer	1504	4	0			-			
Splenectomized	1504	0	0			-			
Chemotherapy	1504	1	0			-			

Abbreviations: aOR, adjusted OR; NS, not significant.
[a]Total number investigated among 1521 patients. Discrepancies due to missing values.
[b]Univariable logistic regression.
[c]Multivariable logistic regression.

All patients with leptospirosis (n=4) who died had received beta-lactam antibiotics.

Among patients with bacteremia who died (n=2), one patient with *E. coli* bacteremia had not received antibiotics.

The majority of patients who died had received broad-spectrum antimicrobial treatment. A third-generation cephalosporin was given to 64% (971/1521) overall, to 73% (27/37) of those who died and to 64% (944/1484) of survivors. The combination of penicillin and aminoglycoside was given to 5% (71/1521) overall and to 22% (8/32) of those who died, while piperacillin-tazobactam was given to 4% (54/1521) overall and to 14% (5/37) of those who died. A carbapenem was given to six patients only, none of whom died (Table 6). Antimicrobial resistance data were not available in this study.

Discussion

This study showed that as many as 98% of patients with AUF potentially caused by bacterial, viral or parasitic infections survived when treated in hospital.

Fatal cases more often had symptoms and findings at admission that were consistent with systemic infection with severe organ failure, such as altered consciousness, thrombocytopenia, bleeding, respiratory failure and oliguria. Leucocytosis and neutrophilia consistent with severe systemic inflammation were also associated with death. This emphasizes that a delay in seeking healthcare is the main reason for death from AUF, because patients frequently have advanced incurable disease at the time of hospitalization (Tables 3 and 4).

Table 3. History of signs and symptoms associated with death and survival (N=1521)

				Univariable[b]			Multivariable[c]		
	N[a]	Survival N (%)	Death N (%)	OR	95% CI	p	aOR	95% CI	p
Total	1521	1484	37						
Fever duration, median (IQR), d	1509	5 (3–7)	5 (4–7)	0.99	0.91 to 1.07	NS			
Symptom duration, median (IQR), d	1453	4 (3–4)	4 (3–4)	1.19	0.84 to 1.68	NS			
History of signs and symptoms									
Altered consciousness	1515	62 (4)	21 (57)	30.00	14.91 to 60.26	<0.0001	21.68	8.72 to 53.92	<0.0001
Bleeding[d]	1517	32 (2)	7 (19)	10.59	4.33 to 25.89	<0.0001	14.08	4.21 to 47.13	<0.0001
Oliguria	1515	67 (5)	12 (32)	10.11	4.87 to 21.00	<0.0001	3.41	1.21 to 9.61	0.020
Breathlessness	1484	190 (13)	17 (47)	5.92	3.03 to 11.60	<0.0001	2.91	1.24 to 6.87	0.015
Seizures	1514	26 (2)	6 (17)	11.17	4.28 to 29.13	<0.0001	2.13	0.62 to 7.38	NS
Jaundice	1488	91 (6)	9 (24)	4.80	2.20 to 10.48	<0.0001	1.69	0.61 to 4.70	NS
Prostration	1507	343 (23)	16 (46)	2.78	1.41 to 5.45	0.003	0.63	0.26 to 1.55	NS
Vomiting	1492	494 (34)	19 (51)	2.05	1.07 to 3.95	0.031	1.82	0.80 to 4.14	NS
Nausea	1485	514 (36)	18 (49)	1.72	0.90 to 3.31	NS			
Myalgia	1516	493 (33)	18 (49)	1.90	0.99 to 3.64	NS			
Cough	1518	489 (33)	10 (27)	0.75	0.36 to 1.57	NS			
Sputum	1516	181 (12)	5 (14)	0.82	0.34 to 2.32	NS			
Headache	1517	816 (55)	21 (57)	1.07	0.55 to 2.06	NS			
Retro orbital pain	1514	151 (10)	2 (6)	0.52	0.12 to 2.17	NS			
Abdominal pain	1485	292 (20)	6 (17)	0.79	0.33 to 1.92	NS			
Diarrhea	1486	225 (16)	5 (14)	0.88	0.34 to 2.28	NS			
Arthralgia	1515	210 (14)	6 (16)	1.17	0.48 to 2.84	NS			
Rash	1515	33 (2)	1 (3)	1.22	0.16 to 9.14	NS			

Abbreviations: aOR, adjusted odds ratio; NS, not significant.
[a]Total number investigated among 1521 patients. Discrepancies due to missing values.
[b]Univariable logistic regression.
[c]Multivariable logistic regression, age and gender were included.
[d]Merged variables "Abnormal bleeding" (N survival and death=19 and 4) and "Blood in stools" (N=16 and 5).
Missing coded as negative in merged variables for the sake of the analyses.

As many as 47% (15/32) died on day 1 or 2 after hospitalization, consistent with advanced disease at admission and consequent delay in antimicrobial and supportive treatment. Malaria, bacterial sepsis, dengue, leptospirosis or scrub typhus were diagnosed in 49% among patients who died, and these infections may all present with organ failure in severe cases if left untreated. In a study of patients admitted with sepsis in the USA, mortality increased by 14% in those who received antibiotics within 3–12 h compared with within 3 h.[17] Duration of fever was <1 wk in a study of patients with severe malaria with a mortality of 35% in Orissa, India.[18] Scrub typhus is still often under-recognized and at high risk of delayed treatment and thereby severe disease and death.[2,4,9,19,20] The risk of secondary severe dengue presenting as AUF in need for urgent supportive treatment is high in India, where dengue seroprevalence in the healthy population is >50%.[11] In leptospirosis, duration of fever before treatment is associated with an increased risk of death in patients who develop icterus, bleedings and proteinuria (Weil's disease) with high mortality.[21]

The etiology of AUF was not associated with increased risk of death (Table 5). The majority of patients who died had received antimicrobials likely to be effective against malaria, scrub typhus, leptospirosis and bacteremia (Table 6).

Both mono and double infections were identified among those who died. However, a large overlap between diagnoses in this study has been reported previously, and the prevalence of cross reactivity or background positivity of serological tests, and subclinical malaria, is unknown.[3]

A broad-spectrum antibiotic given to patients with suspected severe bacterial infection may have contributed to the low death rate from bacteremia. A third-generation cephalosporin was given to 64% (971/1521), and among these, 97% (944/971) survived (Table 6).

The use of empiric cephalosporin rather than penicillin in combination with aminoglycoside may reflect a clinical suspicion of typhoid fever taking the high prevalence in India into account. However, the prevalence of extensively drug-resistant bacteria in India, particularly extended-spectrum beta-lactamase and carbapenemase-producing *Enterobacteriaceae*, is associated with increased mortality,[13,22,23] and we cannot rule out that failure of cephalosporin treatment in unidentified bacterial bloodstream infections could be the cause of death in some of the

Table 4. Clinical signs at admittance associated with death and survival (N=1521)

				Univariable[b]			Multivariable[c]		
	Total N[a]	Survival	Death	OR	95% CI	p	aOR	95% CI	p
Total, N	1521	1484	37						
Clinical signs at admittance									
GCS score, median (IQR)	1232	15 (0)	14 (7–15)	0.72	0.65 to 0.78	<0.0001	0.76	0.63 to 0.92	0.005
Abnormal breathing[d]	1513	123 (8)	18 (49)	10.48	5.36 to 20.50	<0.0001	6.81	1.76 to 26.40	0.006
Low urinary output (<750 ml)	1196			3.32	2.35 to 4.69	<0.0001	2.55	1.34 to 4.85	0.004
>750 ml		988 (85)	13 (48)						
500–750 ml		114 (12)	4 (15)						
400–500 ml		23 (2)	3 (11)						
< 400 ml		14 (1)	7 (26)						
Abdominal tenderness[e]	1516	108 (7)	8 (22)	3.52	1.57 to 7.88	0.002	5.76	1.27 to 26.10	0.023
Saturation <95%	1257	264 (22)	15 (50)	3.65	1.76 to 7.56	<0.0001	3.52	0.97 to 12.72	NS
Pulse rate, median (IQR)	1497	92 (84–100)	105 (87–119)	1.02	1.00 to 1.04	0.014	0.98	0.95 to 1.01	NS
Spontaneous bleeding[f]	1508	13 (1)	5 (14)	17.68	5.95 to 52.55	<0.0001	0.47	0.02 to 14.12	NS
Icterus	1514	106 (7)	13 (35)	7.01	3.47 to 14.15	<0.0001	3.63	0.72 to 18.25	NS
Neck stiffness[g]	1514	26 (2)	3 (8)	4.92	1.42 to 17.06	0.012	NA	NA	NA
Edema[h]	1515	89 (6)	11 (30)	6.63	3.17 to 13.86	<0.0001	0.94	0.16 to 5.45	NS
Pallor	1515	320 (22)	18 (50)	3.62	1.86 to 7.04	<0.0001	3.75	0.79 to 17.74	NS
Conjunctival congestion	1500	71 (5)	6 (17)	4.06	1.63 to 10.10	0.003	0.36	0.02 to 6.17	NS
Eschar	1476	38 (3)	3 (8)	3.35	0.99 to 11.41	NS			
Temp F, median (IQR)	1425	101 (99–102)	99 (99–100)	1.00	0.98 to 1.02	NS			
BP systolic, median (IQR)	1470	110 (100–120)	110 (94–120)	1.00	0.98 to 1.02	NS			
Respiratory rate, median (IQR)	1487	24 (22–26)	24 (20–30)	1.04	0.99 to 1.09	NS			
Joint tenderness	1520	46 (3)	3 (8)	2.76	0.82 to 9.30	NS			
Joint swelling	1519	23 (2)	1 (3)	1.75	0.23 to 13.4	NS			
Rash	1502	40 (3)	1 (3)	0.99	0.13 to 7.40	NS			
Coated tongue	1504	126 (9)	4 (11)	1.38	0.48 to 3.96	NS			
Lymphadenopathy	1499	85 (6)	2 (6)	0.02	0.24 to 4.31	NS			
Spleen palpable	1490	110 (8)	2 (6)	0.72	0.17 to 3.03	NS			
Liver palpable	1487	149 (10)	5 (14)	1.41	0.54 to 3.68	NS			
Liver tenderness	1321	39	1	1.07	0.14 to 8.04	NS			
Renal angel tenderness	1509	5	0			NS			
Ascites	1514	10 (1)	0			NS			
Cardiac murmur	1514	5 (0.3)	0			NS			

Abbreviations: aOR, adjusted odds ratio; GCS, Glasgow coma scale, score 1–15 and 15 optimal cerebral function; NA, not applicable.
[a]Total number investigated among 1521 patients. Discrepancies due to missing values.
[b]Univariable logistic regression.
[c]Multivariable logistic regression, age and gender included.
[d]Merged variables "Abnormal breathing pattern" (N=26 and 10), "Adventitious sounds" (N=77 and 13) and "Air entry unequal" (N=51 and 8).
[e]Merged variables "Abdominal tenderness" (N=103 and 8), "Abdominal guarding" (N=14 and 2) and "Abdominal rigidity" (N=3 and 1).
[f]Merged variables "Spontaneous bleeding" (N=8 and 3), "Bleeding from injection sites" (N=5 and 3) and "Torniquet positive" (N=3 and 0)
[g]Results in multivariate analysis not applicable due to sparse data.
[h]Merged variables "Facial puffiness" (N=57 and 8) and "Pedal edema" (N=51 and 7).
Missing coded as negative in merged variables for the sake of the analyses.

13 patients who died without a definitive etiological diagnosis. Regarding leptospirosis, both streptomycin, gentamicin, penicillin, cephalosporins and macrolides are effective,[24] and most patients in the study received effective antibiotics against leptospirosis. Empirical treatment against scrub typhus in the form of doxycycline was given to as many as 40% (609/1521) of all patients, and to all who died from scrub typhus (n=6). Doxycycline was given to 62% (23/37) among patients who died, indicating a high level of suspicion against scrub typhus in severely ill patients.

Fewer patients (19%, 245/1263) overall, but 76% (73/96) of those with laboratory-confirmed malaria, received empirical treatment against malaria. However, all who died from malaria

Table 5. Microbiological and biochemical findings at admission associated with death and survival (n=1521)

				Univariable[b]			Multivariable[c]		
	Cases N[a]	Survival N (%)	Death N (%)	OR	95% CI	p	aOR	95% CI	p
Total	1521	1484	37						
Biochemical tests									
Leucocytes, median (IQR)	1265	7,6 (5,7–11.0)	15,4 (8.3–22.7)	1.06	1.03 to 1.09	<0.0001	1.07	1.04 to 1.10	<0.0001
Neutrophils, median (IQR)	1307	71 (60–80)	84 (76–89)	1.07	1.04 to 1.11	<0.0001			
Platelets, median (IQR)	1367	160 (93–242)	100 (27–182)	0.992	0.988 to 0.997	0.001	0.992	0.987 to 0.997	0.001
Bilirubin total, median (IQR)	476	1.0 (0.6–2.2)	2.3 (0.83–11.3)	1.03	1.00 to 1.06	0.047			
Blood urea (median (IQR)	267	25.0 (17.6–39.5)	64.1 (2.7–139.8)	1.01	1.00 to 1.02	0.005			
Hemoglobin, median (IQR)	1413	11.4 (9.9–12.8)	10.4 (8.5–12.1)	0.91	0.80 to 1.00	NS			
ALT, median (IQR)	707	44 (24–71)	86 (50–167)	1.00	0.99 to 1.00	NS			
Creatinine, median (IQR)	873	1.0 (0.8–1.3)	1.8 (1.2–3.1)	1.01	0.97 to 1.06	NS			
Microbiological diagnoses[d]									
Malaria	1394	258[e] (17)	7[f] (19)	1.12	0.48 to 2.55	NS			
Scrub typhus	1410	151 (10)	5 (14)	1.38	0.53 to 3.59	NS			
Dengue	1501	236 (16)	4 (11)	0.64	0.23 to 1.83	NS			
Leptospirosis	1410	109 (7)	4 (11)	1.53	0.53 to 4.40	NS			
Bacteremia	1113	122 (8)	2[g] (5)	0.64	0.15 to 2.68	NS			
Chikungunya	1460	94 (6)	2 (5)	0.85	0.20 to 3.57	NS			

Abbreviations: ALT, alanine transaminase; aOR, adjusted odds ratio; NS, not significant.
[a]Total number investigated among 1521 patients. Discrepancies due to missing values.
[b]Univariable logistic regression.
[c]Multivariable logistic regression, age and gender included.
Bilirubin and urea were not included in the multivariable analysis due to high number of missing values, and neutrophils was not included due to likely confounding factor.
[d]Case definitions described in text. Some patients fulfilled multiple case definitions.
[e]*P. falciparum*, N=110 (7%); *P. vivax*, N=93 (6%); *P. malariae*, N=9 (1%); *P.f.*+*P.v.*, N=27 (2%); *P.f.*+*P.m.*, N=2; *P.v.*+*P.m.*, N=1.
[f]*P. vivax* (n=3) and *P. falciparum* (n=4).
[g]*S. aureus* (n=1) and *E. coli* (n=1).

(n=7) had received effective antimalarial treatment, indicating that they already were critically ill at admission. Three patients who died had *P. vivax* malaria, in line with findings from other studies supporting that the mortality of vivax-malaria is higher than previously thought.[25–28] Only 15% (172/1167) of smear negative cases had received antimalarial treatment compared with 76% of smear positive cases. This reflects that targeted antimicrobial treatment depends on available diagnostic facilities such as malaria microscopy, blood culture and resistance testing facilities and rapid diagnostic tests, and underlines the obvious need for accurate point of care tests in order to save lives and avoid overuse of broad-spectrum antimicrobials.[29] A recent study of antibiotic use in AUF from India reported a significant association between testing for malaria and dengue, and faster antibiotic discontinuation.[30]

The study adds to the sparse literature on AUF in rural India, providing data on morbidity, mortality and attributable causes, as well as differences in the burden of AUF across the regions. The data can guide treatment guidelines and facilitate the clinical work of doctors in the most resource-limited settings. The strength of this study is a prospective observational design, thorough clinical investigations and etiology data with gold standard diagnostic methods from a large cohort in rural settings across six different states of India. An etiological diagnosis was not confirmed in half of the patients, which reflects that many infectious and non-infectious causes of AUF remain undiagnosed because a broad range of diagnostic tests are not routinely available in rural hospitals in India.

The time since recruitment is a limitation, but it is not likely, unfortunately, that presentation and outcome of severe AUF has changed much during the last decade in resource-poor settings. Immunosuppression is a risk factor for severe infection, and steroid use was a significant risk factor for death (Table 2), while HIV infection was not. Data to explore level of immunosuppression, CD4 count or HIV treatment in these patients were not available in this study. HIV infections were reported only from Anantapur in Andhra Pradesh, which probably reflects that this center had an active anti-retroviral therapy program during the period, and the fact that no one died could be due to effective HIV treatment.

Table 6. Duration of hospitalization and antimicrobial treatment associated with microbiological diagnoses among patients who died (n=37)

			Died										
	Total N[a]	Survived	Total died	*P. f.*	*P. v.*	*P. f* + lepto-spirosis	Lepto-spirosis	Bac-teremia[b]	Scrub typhus	Scrub and lepto-spirosis	Scrub and dengue	Dengue	No microbiol. diagnosis
Total, N	1521	1484	37	2	3	2	1	2	3[c]	1	2	2	19
Duration in hospital, median (IQR), d[d]	1270	4 (3–5)	3 (1–4)										
Antimalarials, n (%)													
Artemisinine and/or quinine				2	3	2							
Artesunate	233	215 (92)	18 (8)		3	1			1		1	1	11
Artemether	31	26 (84)	5 (16)	2		1							2
Quinine	21	15 (71)	6 (29)	2		1							3
Chloroquine	93	87 (94)	6 (7)	2		1							3
Primaquine	50	49 (98)	1 (2)	1									
Mefloquine	6	4 (67)	2 (33)										2
Sulphadox/pyrimeth	4	3 (75)	1 (25)	1					1			1	1
Antibiotics, n (%)													
3. gen cephalosporin	971	944 (97)	27 (3)			2	1	1	2	1	1	1	17
2. gen cephalosporin	38	37 (97)	1 (3)									1	
1. gen cephalosporin	27	26 (96)	1 (4)		1								
Carbapenem	6	6 (100)	0										
Penicillin	117	105 (90)	12 (10)	2	1	1	1						7
Aminoglycoside	71	63 (89)	8 (11)	2		1			1				4
Piperacillin/tazobactam	54	49 (91)	5 (9)						1			2	2
Quinolone	62	60 (97)	2 (3)									1	1
Macrolide	123	122 (99)	1 (1)					1					
Tetracycline	609	586 (92)	23 (4)		2	1	1	1	3	1	2		12
Clindamycin	3	2	1						1				

[a]Total number investigated among 1521 patients. Discrepancies due to missing values.
[b]*S. aureus* case had received three antibiotics and *E. coli* case no antibiotics.
[c] One patient was Scrub ELISA positive and IFA negative, but diagnosis confirmed by eschar.
[d]9/32 (28%) died day 1, 6/32 day 2 and 7/32 day 3. Mann Whitney U test p=0.001.

This study provides knowledge about the fatal consequences of delay in the hospitalization and treatment of AUF in India, and calls for strengthening of microbiological diagnostic facilities in order to provide targeted antimicrobial treatment.

Conclusion

In this study, we investigated clinical features and treatment associated with death from AUF in rural community hospitals in six states in India. Overall mortality from AUF was 2%. Although most patients received appropriate empirical treatment, death was associated with signs of advanced disease at admission with altered consciousness, oliguria, bleeding, abnormal breathing, thrombocytopenia and leucocytosis. The majority of patients received broad-spectrum antibiotics, while antimalarials were given mainly to malaria microscopy positive cases. The study indicates that early hospitalization and timely treatment could improve survival from AUF in rural hospitals in India.

Authors' contributions: DM, KM, AM, NL and BB conceived the study; DM, KM, AM, NL, BB, AS and GVA designed the study protocol; AS, CK, SP, AH, NC, GAU and JN carried out the clinical assessment and data collection; AM, SC, CGH, GVA and SK carried out the microbiological investigations; KM and BB carried out the analysis and interpretation of the data. KM drafted the manuscript; KM, BB, AM, SC, AS, CK, SP, AH, NC, GAU, JN, CGH, SK, GVA, NL and DM critically revised the manuscript for intellectual content. All the authors read and approved the final manuscript. KM and DM are guarantors of the paper.

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Ethical approval: The study was approved by the Institutional Research Board at CMC, Vellore, in Tamil Nadu, India (No. 7242 dated 11 August 2010) and by the Regional Ethics Committee of Norway (2010/2271–5). The participating sites, B.K.L. Walawalkar Hospital, Ratnagiri, Maharashtra, India and Rural Development Trust Hospital, Anantapur, Andhra Pradesh, India, had the study approved through their ethics committees. The other participating sites were secondary mission hospitals affiliated to CMC, Vellore, and therefore the ethics committee of CMC Vellore approved the study at these sites. Written informed consent was obtained from the patients or a legally acceptable representative; in cases of children from the parent or guardian. All methods were carried out in accordance with the relevant guidelines and regulations.

Data availability: The data underlying this article will be shared upon reasonable request to the corresponding author.

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