

Clinical spectrum and outcome of critically ill hospitalized patients with acute febrile illness and new-onset organ dysfunction presenting during monsoon season

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Summary

Acute febrile illness (AFI) is one of the commonest indications for hospitalization and can present with varying severity including single or multiple organ dysfunction syndrome (MODS). During monsoon season, there is a spurt of AFI often caused by vector borne diseases leading to substantial morbidity and mortality. Our aim was to determine distribution of etiological causes, differential organ involvement and predictors of mortality in critically ill patients with AFI. It was a hospital based observational study which included patients with AFI with dysfunction of at least one organ system. The study was conducted over 4 months during monsoon season. Admitted patients were included who had been subjected to a standard battery of tests and managed with standard hospital based management protocol. 145 patients were included and etiology of fever was ascertained in 81.4% of patients with the most common single infection being chikungunya (20.7%) followed by dengue (20%) fever. Thrombocytopenia and deranged liver biochemistry each were seen in nearly 75% of the patients. Renal (50.3%) and nervous system (46.2%) dysfunction were the predominant organ failures. 49 patients died (33.8%) which correlated with predicted mortality by APACHE (acute physiological assessment and chronic health evaluation) II score. Independent predictors for mortality were older age (> 55 years) ($p = 0.01$), acidemia ($p = 0.01$), altered sensorium ($p = 0.02$) and coagulopathy ($p = 0.048$). Sub-group analysis revealed that amongst patients with MODS, hypotension could help differentiate between bacterial and non-bacterial causes ($p = 0.01$). Critically ill patients with AFI suffer from significant morbidity and mortality. Features like the presence of hypotension in MODS may differentiate between a bacterial cause vis-à-vis viral or protozoal etiology.

Keywords: Acute febrile illness, MODS, chikungunya, hypotension

1. Introduction

Fever is one of the most common indications for seeking medical attention. The severity of an acute febrile illness (AFI) may vary from a simple self-limiting viral infection to a life threatening multi-organ dysfunction syndrome. The causes of AFI are diverse and frequently the associated symptoms are non-specific. In a resource-limited setting or at the time of an outbreak or epidemic, a severe shortage of local data

and epidemiology is often perceived. Investigations need to be rationalized and often, empirical therapy has to be initiated based on clinical findings and assumptions.

The causes of acute febrile illness have been studied in different backdrops. In 2013, a systematic review revealed that only 17.9% cases had been diagnosed with a specific cause. Blood stream infection was the most common diagnosis with bacterial and fungal cultures being positive in 10.3% of patients (1). The above mentioned review included two studies from India, the largest of which was from South India – which may not be representative of the entire country because of its unique landscape and characteristic endemicity of pathogens (2). Other studies on acute febrile illness have been done where only about 40% cases could

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be given a definitive diagnosis (3,4). A study from Dehradun, India showed that dengue followed by enteric fever was the most common etiology (5). There are some studies which have focused on individual disease and their pattern but limited data is available about the epidemiology of acute febrile illnesses during monsoon season in the northern parts of India. The mortality of patients with acute febrile illness when complicated by organ dysfunction can be as high as 20% (6-8). Febrile illness severe enough to cause dysfunction of an organ or multiple organs leads to significant morbidity and mortality in tropical countries (8). Most studies on AFI from India have focused only on etiology with little information on the other important aspects like predictors of poor prognosis and mortality. In 2016, we initiated a hospital based prospective observational study of severe acute febrile illness with organ dysfunction with focus on these hitherto unexplored aspects. We describe the demographic, clinical, and laboratory features, etiology, predictors of mortality, pattern of organ involvement in various diseases as also certain pointers helpful in making a provisional syndromic diagnosis.

2. Materials and Methods

2.1. Study design

The study was conducted in a tertiary care centre catering to the national capital as well as the adjoining National Capital region (NCR). It is an apex tertiary care centre which serves as a referral centre for a large part of Northern India. Geographically New Delhi is an inland and surrounded by land on all sides and the population is largely urban.

This is a prospective hospital-based observational study conducted over 4 months (from July 2016 to October 2016 which covered the entire monsoon season). Ethics clearance was obtained from the Institute Ethics Committee prior to start of the study. All patients with history of fever were screened and were included in the study after applying the inclusion and exclusion criteria. We included only admitted patients who had presented with fever of ≤ 7 days at time of presentation, presence of at least one organ dysfunction (according to criteria mentioned below) and age > 13 years. Patients with history of hospitalization in last 3 months or refusal to give written informed consent were excluded from the study.

Organ dysfunction was defined as below (any of the following): 1) Acute kidney injury (AKI): according to acute kidney injury network (AKIN) definition (absolute increase in creatinine ≥ 0.3 mg/dL over 24 hours or a 50% increase in creatinine from baseline or urine output ≤ 0.5 mL/kg/hour for at least 6 hours) (9). 2) Acute respiratory distress syndrome (ARDS): as per the Berlin definition, $\text{PaO}_2/\text{FiO}_2$ ratio of ≤ 300 with a

CPAP of 5 cm water (10). 3) Central nervous system: as per Glasgow coma scale when score is less than 15. 4) Coagulopathy: prothrombin time (PT) more than 16 seconds or INR > 1.5 . 5) Liver: a serum bilirubin of > 2 mg/dL or patients having encephalopathy with deranged INR. 6) Thrombocytopenia: platelets $< 150,000/\text{cu. mm}$ with abnormal bleeding not explained by other causes. 7) Cardiovascular: systolic blood pressure < 90 mm Hg or a drop in SBP > 40 mm Hg from baseline or mean arterial pressure < 65 mm Hg.

After inclusion into the study, demographic and clinical details were recorded at admission in a pre-designed pro forma. The patients were followed up till discharge or death; details of stay in hospital as well as ICU stay (if present) were recorded along with results of laboratory investigations.

2.2. Laboratory evaluation

All patients underwent hematological investigations including complete blood count (CBC), liver function tests (LFT), kidney function tests (KFT), arterial/venous blood gas analysis (as required), prothrombin time/INR and blood culture. A urine routine microscopy, urine culture and chest-X ray were done for all patients. Basic work-up for etiology included rapid test (a point of care test based on lactate dehydrogenase and histidine rich protein 2) and peripheral smear for malaria, NS-1 antigen (Panbio Dengue Early ELISA, Standard diagnostics Inc., Republic of Korea) and IgM antibody detection for dengue virus (NIV DEN Immunoglobulin (IgM) Capture ELISA, National Institute of Virology, Pune, India) and IgM antibody against chikungunya virus (NIV Chikungunya IgM ELISA, National Institute of Virology, Pune, India). For dengue, NS-1 antigen was tested if the patient presented in the first 5 days of illness and the IgM test if later than that. When clinically suspected, tests were done for Leptospira (Panbio Leptospira IgM ELISA, Standard Diagnostics, Republic of Korea) and scrub typhus (InBios International scrub typhus IgM indirect ELISA, Seattle, WA). Other investigations were done as required on a case to case basis. The study team collected data independent from the clinical team in-charge and no changes were made to the management of the patient by the study group though relevant investigations reports were timely conveyed to the treating team. The patients with multi organ dysfunction i.e. two or more organ failures, were further divided into sub-groups for analysis. Those with dengue fever, chikungunya, malaria, scrub typhus and confirmed viral illness were put in the sub group of "viral and viral like illness". Those with confirmed or likely bacterial infection and enteric fever were included in "bacterial and presumed bacterial". "Likely bacterial infection" was kept as the diagnosis in patients who had a raised total leukocyte count with polymorphonuclear leukocyte predominance

and any of the following: an area of consolidation on chest x ray or urine routine microscopy showing more than 10 WBC/high power field (hpf) (only valid for newly catheterized or uncatheterized patients) or meningitis with cerebrospinal fluid showing low sugar, high protein with neutrophils is CSF. "Confirmed bacterial infection" was diagnosed when culture grew pathogenic bacteria species.

2.3. Statistical analysis

Data was recorded in a predesigned pro forma and subsequently on an excel spreadsheet. Categorical variables were summarized as frequency (percentage) and analyzed using χ^2 (Chi squared) or Fischer's exact test. Continuous variables were summarized as mean and standard deviation (SD) or median and range (when SD was > 50% of mean) and analyzed using

Table 1. Demographic profile, co morbidities and clinical spectrum of patients with acute febrile illness (n = 145)*

Parameter	Overall (n = 145)
Gender	
Males	92 (63.4%)
Females	53 (36.6%)
Age (years)	30 (24.75)
Co morbidities	
Diabetes	21 (14.5%)
Hypertension	27 (18.6%)
Chronic kidney disease	8 (5.5%)
Coronary artery disease	6 (4.2%)
Cerebrovascular disease	7 (4.8%)
Chronic liver disease	6 (4.1%)
Clinical features	
Body ache	65 (44.8%)
Altered sensorium	62 (42.7%)
SOB	52 (35.9%)
Joint pain	48 (33.1%)
Bleeding	41 (28.3%)
Decreased urine output	35 (24.1%)
Cough	24 (16.5%)
Jaundice	15 (10.3%)
Seizure	19 (13.2%)
Tachycardia	89 (61.3%)
Tachypnea	73 (50.3%)
Hypotension	48 (33.0%)
Hepatomegaly	26 (17.9%)
Splenomegaly	20 (13.8%)
Rash	27 (18.6%)
Organ failures	
Renal	73 (50.3%)
Altered sensorium	67 (46.2%)
Pulmonary	49 (33.8%)
Liver	48 (33.1%)
Cardiovascular	42 (29%)
Thrombocytopenia with bleeding	38 (26.2%)
Coagulopathy	33 (22.7%)
MODS	93 (64.1%)
Hospital stay (median)(Days)	6 (6)
ICU stay	29 (20%)
Mortality	49 (33.7%)

*Categorical variables are summarized as n (%). Continuous variables are represented as mean \pm SD or median (Interquartile range) if SD > 50% of mean.

parametric tests (*t*-test or one way analysis of variance). When analyzing for predictors of mortality, those with *p* value of < 0.10 in univariable analysis were included for multivariable analysis. A *p*-value of < 0.05 was considered as significant. Statistical analysis was performed using the Stata 12 software (StataCorp [2011], College station, TX).

3. Results

A total of 145 patients were included in the study. They were all followed up for the entire duration of the hospital stay. The median age of participants was 30 years and 63.4% were male. The mean duration of illness at time of presentation was 5.1 ± 2.3 days. Median duration of hospital stay was 6 days. Etiology for fever could be ascertained in 118 patients (81.4%) while 27 remained undifferentiated. Most common specific diagnosis was found to be chikungunya in 30 patients (20.7%) closely followed by dengue (*n* = 29) (20%). Of the group comprising bacterial infection (*n* = 30), 12 (40%) had pneumonia related sepsis, 8 (26.7%) had urosepsis, 4 (13.3%) had tuberculosis, 3 (10%) had leptospirosis, 2 (6.7%) had enteric fever and 1 (3.3%) patient had pyogenic meningitis. Ten patients (6.9%) had a mixed infection with most common co-infection being chikungunya and dengue fever (*n* = 5).

There was significant variation in symptomatology of patients (Table 1). Myalgia was the most common symptom followed by altered mentation. Tachycardia and tachypnea were the most frequently elicited signs. Hypotension requiring inotropic support was seen in around one third of the patients. Baseline laboratory parameters of the participants are listed in the Table 2. Thrombocytopenia was the most common lab finding followed by elevated liver enzymes both of which were seen in three quarters of the patients.

The incidence of different organ system dysfunction in the participants is shown in Table 3. Few diseases

Table 2. Laboratory parameters of patients with acute febrile illness (n = 145)*

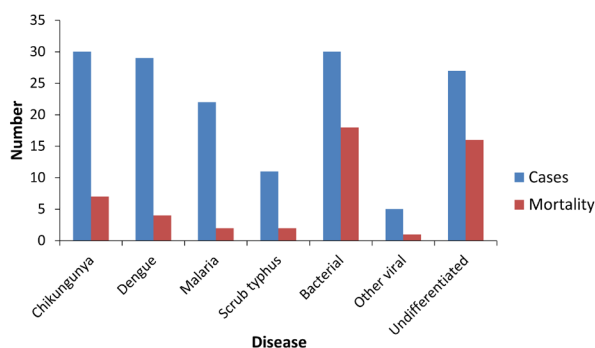
Laboratory Parameters	Overall (n = 145)
Hemoglobin(g/dL)	11.0 \pm 2.7
Anemia	86 (59.3%)
TLC (/mm ³)	9,100 (11,600)
Leucopenia (< 4,000/mm ³)	24 (16.5%)
Leucocytosis (>11,000/mm ³)	59 (40.6%)
Platelets(/mm ³)	53,000 (105,250)
Thrombocytopenia	114 (78.6%)
Urea(mg/dL)	56.5 (70.5)
Creatinine(mg/dL)	1.2 (2.5)
Bilirubin(mg/dL)	0.9 (2.6)
AST(IU/L)	114 (155.5)
ALT(IU/L)	80 (152.5)
Elevated transaminases	104 (71.7%)

*Categorical variables are summarized as n (%). Continuous variables are represented as mean \pm SD or median (Interquartile range) if SD > 50% of mean.

Table 3. Pattern of organ dysfunction with different diagnoses

Organ Dysfunction	Total n (%)	Liver (%)	Lung (ARDS) (%)	Renal (AKI) (%)	Cardiovascular (Hypotension) (%)	Central nervous system (%)	Thrombocytopenia with Bleeding (%)
Chikungunya	23 (15.9)	26.1	17.3	39.1	34.8	34.7	30.4
Dengue	21 (14.5)	38.1	0	28.6	14.3	14.3	52.4
Malaria	21 (14.5)	52.4	23.8	38.1	28.6	28.6	28.6
Scrub typhus	10 (6.9)	40	40	60	20	20	0
Leptospira	3 (2.1)	33.3	33.3	100	100	100	33.3
Other bacterial	25 (17.2)	32	44	80	48	72	28
Other viral infections	5 (3.5)	40	60	40	20	100	0
Undifferentiated	27 (18.6)	25.6	48.1	62.3	44.4	25.6	3.7
Co infection Chikungunya & Dengue	5 (3.4)	60	40	20	0	40	60
Other co infections*	5 (3.4)	20	0	20	20	40	40
Total n (%)	145 (100)	48 (33)	49 (33.8)	73 (50.3)	42 (29)	67 (46.2)	38 (26.2)

*Other co infections include co infection of dengue with scrub typhus, enteric fever and malaria in one case each; and co infection of chikungunya with Japanese encephalitis, enteric fever in one case each.

**Figure 1. Proportional prevalence of disease and associated mortality.**

had predilection for particular systems. Renal dysfunction was more common in leptospirosis, confirmed bacterial infection and scrub typhus as compared to the others. ARDS was most common in the group which remained undifferentiated, followed by bacterial infections and scrub typhus. Hypotension was common in leptospirosis, bacterial and undifferentiated groups. Altered sensorium and acute kidney injury were the most common organ dysfunction seen and occurred in around half of the patients. Dengue, leptospirosis, malaria and chikungunya had a predilection for thrombocytopenia and bleeding. These pointers are not exclusive but may provide a clue to diagnosis in the setting of monsoon season in a tropical country when all these ailments are at their peak incidence. Individual diseases have different patterns of organ dysfunction and this has been depicted in Table 3. Mean APACHE (acute physiological assessment and chronic health evaluation) II score for participants at admission was 21.5 and SOFA (sequential organ failure assessment) score at day 0 was 7.4.

The overall mortality rate was 33.8% ($n = 49$). This was close to the adjusted death rate (39%) calculated as per the mean APACHE score (21.5) at the time of presentation. Disease wise mortality is depicted in

Figure 1. Predictors of mortality were identified by stepwise logistic regression. Previously known diabetes, higher age (> 55 years), smoking, tachycardia, tachypnea, abnormal Glasgow coma score (GCS) (< 15), lower SpO_2/FiO_2 ratio (< 315), leucocytosis (TLC $> 11,000/cu. mm$), acidosis on ABG ($pH < 7.35$), urea > 40 mg/dL, serum creatinine > 1.2 mg/dL, coagulopathy (INR > 1.5) were identified as significant predictors of mortality while diagnosis of dengue and malaria were associated with relatively lower mortality on univariate analysis. Amongst these, higher age, abnormal GCS, acidosis and coagulopathy were found to be independent predictors (Table 4). Lower SpO_2/FiO_2 ratio as an independent predictor of mortality showed a trend towards statistical significance. APACHE II and SOFA score were also good predictors of mortality. APACHE II score in the range of 10 to 35 was having an odds ratio (OR) of 20 while > 35 had an odds ratio of 117.3 and a p value of < 0.01 . SOFA score of 5-10 had an OR of 7.25 and SOFA > 11 had an OR of 49.3 with an overall p value < 0.01 .

The sub-groups of patients with "bacterial, presumed bacterial and likely bacterial" was compared with group of patients with "viral or viral like" for possible clinical predictors which could differentiate the patients at the time of presentation. Patients with multi-organ dysfunction (MODS) were selected and compared. It was found that if a patient was having MODS with hypotension, then the diagnosis was more likely to be bacterial than viral or viral like. This difference was statistically significant ($p = 0.01$) (Table 5).

4. Discussion

Every monsoon season there is a spate of vector borne diseases in India. Many of the patients are critically ill and require hospital admission with significant morbidity and mortality. While some diseases like malaria have point-of-care tests, similar tests for others

Table 4. Predictors of mortality, Univariable and Multivariable Logistic regression analysis

Variable	Outcome		Unadjusted OR (95% CI); <i>p</i> value	Adjusted OR (95% CI); <i>p</i> value
	Alive (<i>n</i> = 96), <i>n</i> (%)	Dead (<i>n</i> = 49), <i>n</i> (%)		
Age > 55	12 (12.5)	14 (28.6)	4 (1.4-11.3); < 0.01	8.1 (1.6-40.5); 0.01
Diabetes	10 (10.4)	11 (22.4)	2.49 (0.9-6.35); 0.06	
Smoking	5 (5.2)	10 (20.4)	4.6 (1.5-14.3); 0.01	
Tachycardia	52 (54.2)	37 (75.5)	2.6 (1.2-5.6); 0.01	
Tachypnea	40 (41.7)	33 (67.3)	2.9 (1.4-5.9); < 0.01	
Abnormal GCS	32 (33.3)	35 (71.3)	5 (2.3-10.6); < 0.01	3.1 (1.2-4.4); 0.02
spO ₂ /FiO ₂ < 315	20 (20.8)	29 (59.2)	5.5 (2.6-11.7); < 0.01	2.94 (0.9-9.2); 0.06
Leucocytosis	28 (29.2)	31 (63.2)	2.8 (1.4-5.7); < 0.01	
Acidosis (pH < 7.35)	18 (18.8)	31 (63.2)	5.7 (2.4-13.3); < 0.01	4.3 (1.3-14.1); 0.01
Urea (> 40 mg/dL)	47 (49)	38 (77.5)	4.6 (1.9-10.8); < 0.01	
Creatinine (> 1.2 mg/dL)	32 (33.3)	35 (71.4)	5 (2.4-10.6); < 0.01	
INR (> 1.5)	30 (31.2)	25 (51)	2.4 (1.1-4.6); 0.02	3.7 (1.0-13.4); 0.048
Dengue	25 (26)	4 (8.2)	0.2 (0.1-0.7); 0.02	
Malaria	22 (22.9)	2 (4.1)	0.1 (0.03-0.64); 0.01	

Table 5. Association of hypotension with multi-organ dysfunction (MODS) with diagnosis

Number of patients	MODS with hypotension	MODS without hypotension	
Bacterial and presumed bacterial	11	4	<i>p</i> = 0.01
Viral and viral like illness	18	33	Odds ratio – 4.89, (1.35-17.61)

like scrub typhus are not readily available. Also, in resource limited settings the availability of these tests may be limited. In such a backdrop it is important to suspect these diseases and to timely treat them with appropriate agents.

In our study population, the most common diagnosis was chikungunya followed by presumed bacterial infection. The combination of non-bacterial diseases far outnumbered the bacterial cases. It is known that vector borne diseases like dengue peak during the monsoon season (11). The incidence of Chikungunya had increased in recent times and numerous outbreaks have been declared in the recent past in various parts of India (12-14). One study had described the etiologies of acute febrile illnesses in northern India during the monsoon season of 2013 and had found dengue to be the commonest cause of fever (15). It was a retrospective study designed to include cases positive for dengue, malaria, typhoid and scrub typhus. However, the clinical presentations and organ involvement were not recorded by the authors. A paper from south India had reported on the etiology of fever and the associated case fatality admitted in a period of one month in 2007 (16). In the hundred patients studied, 66% had fever of more than 7 days. In such a group of patients, tuberculosis (19%) was reported as the most common cause and the incidence of malaria, scrub typhus and typhoid were 5%, 5%, and 4%, respectively. The deaths observed in the above group were 7%, with bacterial causes responsible for the majority. However, in our study all the patients had acute febrile illnesses with duration of fever ≤ 7 days presenting during the monsoon season (July to October).

In our study, amongst organ involvement neurological and renal involvements were the most common manifestations. Amongst the organ dysfunction no statistically significant predilection was noted for any specific etiology. However acute kidney injury, bleeding and hepatic dysfunction were most common in chikungunya, dengue and malaria respectively.

The most important predictors of mortality were higher age, low GCS, acidemia and coagulopathy. Age and low GCS are a part of simplified acute physiology score II (SAPS II), while coagulopathy is a part of sequential organ failure score (SOFA) in intensive care unit patients (15,17). These findings reiterate the importance of these parameters in critically ill patients with acute febrile illness. Amongst the patients with chikungunya, there were 7 deaths. Six (86%) of them had another associated co morbid illness and 5 (71%) were above the age of 55 years.

One of the most important highlights of this study was that in the presence of MODS, hypotension suggested the diagnosis of bacterial cause vis-à-vis non-bacterial cause. This is important as it suggests that MODS without the presence of shock is more common in patients without bacterial etiology. The exact cause of this can be hypothesized in the following way. Bacterial sepsis from a focal infection occurs when the release of proinflammatory mediators breaches the boundaries of the local environment leading to malignant intravascular inflammation (18). The reason why localized responses sometimes spread beyond the local boundaries causing sepsis is likely to be multifactorial and may include characteristics of invading microbes, massive release of cytokines,

complement activation or genetic susceptibility of the individuals (19). The overflowing cytokines reach distant organs causing cellular injury and resultant multiple organ dysfunction. On the other hand, for non-bacterial infections, the cellular injury is thought to be brought about by the agency of tissue ischaemia, cytopathic injury and apoptosis (20-22). Malaria might have a different pathophysiological basis than cytokine overflow for the development of multiple organ dysfunction. Brain dysfunction in malaria occurs due to parasitized erythrocytes in the cerebral vasculature (23). In malaria renal dysfunction may result from immune-complex deposition and infected RBC adhesion to renal vasculature (24). Rickettsial infections may not lead to exotoxin production but bring about damage to small blood vessels (25). Rickettsial organisms may induce rearrangement of cellular actin and engulfment by the cell *via* endocytosis. There is subsequent passage of the organism into neighbouring cells *via* filopodia resulting in spread throughout the body *via* bloodstream or lymphatics (26). In non-bacterial infections, organ dysfunction may occur without concomitant shock due to possibly different pathophysiological characteristics as outlined above unlike cytokine overflow in bacterial infections which leads to circulatory shock along with organ dysfunction. Though, cytokine release and amplification may very well be a part of non-bacterial as well as bacterial infection, however the difference in composition and quantum of the same as well as their effects on the host have not been studied. The results from such studies may further throw light on the pathophysiology of organ dysfunctions in the settings discussed above.

This is the first study from India where critically ill patients with acute febrile illness during the monsoon season have been studied extensively with details about the clinical profile, organ dysfunction, morbidity and mortality. This study also highlights the importance of presence/absence of hypotension in such group of patients with multi-organ dysfunction in suggesting a probable cause. A limitation of the study was the small sample size. Also the differentiation between bacterial and non-bacterial causes was at times empirical in the absence of culture positivity for bacteria.

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