Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Mortality and severity predictors of Scrub typhus in North Eastern states of India

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Received: November 2019
Accepted: November 2019

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ABSTRACT

Background: Scrub typhus is a common tropical infection prevalent in sub Himalayan, southern, coastal and north eastern states. It is associated with sizable mortality and morbidity. The fatality with this disease is variable 1.6% to 45 % in different studies. Fever, headache breathless and reduced urine output at the time of presentation is associated with very high mortality. Late reporting of the cases and late defervescence is a treatable factor associated with the fatality in our study. There are a number of studies published from south India and sub Himalayan region , very few studies are done and published in North eastern states such as Arunachal Pradesh ,Tripura , Nagaland , Assam and Manipur , in this study , we have studied the patients from these region. We have less eschar noted with patients 30%compared to South India (45%) and 78 % in Korea. **Methods:** In this study serially reporting cases of fever with headache, breathlessness with reduced urine output having eschar or found positive on ELISA for IgM against Scrub typhus were included . All the cases were treated with intravenous or oral doxycyclin and were followed up for 6 months. **Results:** The rate of complications including fatalities were calculated. Factors related to complications and fatalities were identified. **Conclusion:** It was concluded that cases reporting early have better prognosis. Hemodynamic dysfucntion, decreased urine output and high fever at presentation was associated with higher fatalities.

Keywords: Scrub Typhus- mortality and complication predictors, mortality in scrub Typhus, severity of scrub typhus.

INTRODUCTION

Scrub typhus is an important disease which occurs when human enters areas where transmission is going on, classic example being military personnel, field adventurists and farmers moving in such areas. The importance of this disease has been highlighted by its epidemic level incidence in armies world over particularly when deployed in jungles and rural areas. In spite of considerable mortality and morbidity associated with the disease, it is kept relatively lower in the differential diagnosis due to non-specificity of its symptoms and signs, low index of suspicion and lack of diagnostic facilities.

Pathologically it presents with focal or disseminated vasculitis as a result of endothelial destruction along with perivascular leucocytic infiltration. It has a huge spectrum of manifestations, on one end it presents with a short febrile illness to a severe fulminant sepsis syndrome with multi organ dysfunction.

In India this disease is known to occur in Tamil Nadu, Himachal Pradesh, Bihar, Maharashtra, Andhra Pradesh, Telangana Kerala.[1-3] With very few data being available from north eastern part of India though the disease has been described first in the North Eastern states in Military medicine dispatches of 1 st and 2nd world war. In this study we tried to delineate profile of patients in this region in addition to analyze various factors at presentation affecting the course of illness.

Aims

In this study we tried to profile patients, who had presented to a secondary level health care facility in north eastern part of India and who were diagnosed to be suffering from scrub typhus.

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MATERIALS AND METHODS

The study was a prospective observational study which was conducted over a period of 18 months (Jan 17 to June 18) in a secondary level health care facility during which all patients who were diagnosed to be suffering from scrub typhus on the basis of ELISA (Ig M Scrub Typhus) were enrolled into the study after taking an informed consent. The history, clinical examination findings and laboratory investigations were recorded at presentation. These patients were then followed up after administration of standard treatment (Doxycycline) and were looked for the time taken for defervescence along with development of adverse outcomes (Complications and if any Fatality).

Inclusion criteria-

- Patients >18yrs of age.
- Patients who presented with acute febrile illness and had a confirmed diagnosis of scrub typhus on basis of ELISA (Ig M Scrub Typhus)

Exclusion criteria-

- Immuno-suppression (HIV, Immunosuppressive drugs, malignancies, connective tissue disorders and diagnosed Auto immune disorders)
- Co-infection with other pathogens (Malaria, Typhoid, Dengue, Leptospirosis, Hanta virus, HBV, HCV, or other viruses noted as activated lymphocytes)
- Patients with Chronic kidney disease
- Patient with Chronic liver disease
- Patients with Chronic respiratory disease
- Non consenting patients

Diagnosis of scrub typhus was considered in patients with Acute febrile illness with positive IgM Elisa with/without eschar. Additional tests were done to rule out co-infections with Malaria (PBS-MP, Paracheck), Dengue (NS1, IgM/IgG), Typhoid (Typhi dot), Leptospirosis (Ig M), Hanta virus (IgG/IgM) and spotted fever Gp (IgG/IgM).

Definitions-

a) Anemia- Defined hemoglobin levels less than 13g/dl in male and less than 12 g/dl in females
b) Leucopenia- Defined Total Leucocyte count levels less than 4000/µl.
c) Leucocytosis- Defined Total Leukocyte count levels more than 11000/µl.
d) Acute Kidney Injury – Defined as serum creatinine >1.5mg/dl with no known background of renal disease prior.
e) Hepatitis- Defined as AST/ALT >3 times normal
f) Pneumonia- Defined as consolidation on chest x ray with corroborating clinical findings.
g) ARDS- Defined as PaO2/FiO2 <800
h) Brain dysfunction- Defined as MMSE<25 or development of focal neurological deficits on clinical examination.
i) Patients who received antimicrobial other than Doxycycline.

After completion of study statistical analysis was done comparing following groups

a) Those who developed complications Vs those didn't developed.
b) Survivors Vs Fatalities

These groups were compared with reference to baseline historical, clinical, lab findings and the response to therapy, using students t test for quantitative variables and linear regression for qualitative variables.

Those patients who did not respond to initial therapy with Doxycycline were managed with other drugs however their data was not included in the study.

RESULTS

At the culmination of the study, data of total of 184 patients was collected however only 108 patients matched both inclusion and exclusion criteria hence their data was analyzed using statistical tools (Mean, Standard deviation, Students T test and linear regression). Comparisons were made between complicated cases Vs Uncomplicated cases and Survivors Vs Fatalities. Analysis revealed the most common symptoms in patients were Fever (96.29%, 100% of complicated ones had fever Vs 95% of uncomplicated ones, 100% of fatalities vs 96.15% of survivors), Headache (75%, 89.28% of complicated ones had it Vs 70% 0f uncomplicated ones, 75% of fatalities and survivors), Nausea/Vomiting (35.18%, 64.28% in complicated ones Vs 25% in uncomplicated ones, 34.61 in survivors Vs 50% in fatalities), Breathlessness (26.85%,82.14% in complicated ones Vs 7.5% in uncomplicated ones, 26.92% in survivors vs 25% in fatalities) and Cough (23.14%, 25% in complicated ones vs 22.5% in uncomplicated ones, 21.15% in survivors Vs 75% in fatalities). The most common clinical findings being Hepatomegaly (65.74%, 96.42% in complicated ones Vs 55% in uncomplicated ones, 65.38% in survivors Vs 75% in fatalities), Conjunctival congestion (37.03%, 34.61% of Survivors Vs 100% of fatalities, 64.28% in complicated Vs 27.5% in uncomplicated), Maculopapular rash [Figure 1] (36.11%, 39.28% in complicated ones Vs 35% in uncomplicated ones,) (Only those cases which had rash on examination at initial presentation were considered), Inoculation eschar [Figure 1] (30.55%, 39.28% in complicated Vs 27.5% in uncomplicated ones, 30.76% in survivors Vs 25% in fatalities), pedal edema (25.92%, 92.85% in complicated Vs 2.5% in uncomplicated ones,25% in survivors Vs 50% in fatalities), abnormal chest findings (crackles)were seen in 13.88% of total cases (53.57% complicated ones Vs nil in uncomplicated ones, 11.53% in survivors Vs 75% in fatalities).

Hemoconcentrations was noted in complicated cases and fatality. There was statistically significant higher transaminitis , bilirubinemia and renal failure in fatal cases Biochemical evaluations revealed mean Urea

levels of 41mg/dl +/- 7.87, 40.7g/dl in survivors Vs 55.5g/dl in fatalities, 48.5g/dl in complicated Vs 38.8g/dl in uncomplicated ones. Mean serum creatinine of 1.4mg/dl, 1.29mg/dl in survivors Vs 4.27mg/dl in fatalities, 2.75mg/dl in complicated Vs 0.9mg/dl in uncomplicated ones. Mean sodium levels were 136.92mEq/l +/- 5.92, 137.5mEq/l in survivors Vs 120.5mEq/L in fatalities, 131.5mEq/L in complicated cases Vs 138.8mEq/L in uncomplicated ones. Mean age of presentation was 36.99years +/- 11.4 (36.78yr for survivors Vs 42.25yr for fatalities, 39.75yr for complicated cases Vs 36.02yrfor uncomplicated ones).

Mean presentation after symptom onset was 6.05 days +/- 3.080 (5.84days for survivors Vs 11. 5days for fatalities, 10.21 days for complicated Vs 4.6days for uncomplicated). On an average treatment was initiated on 7.29 day +/- 3.073 of disease (7day in survivors Vs 12.5day in fatalities, 11.35day in complicated cases Vs 5.8day in uncomplicated).

On an average defervescence was achieved by 8.98day +/- 3.609 (8.9day in survivors, 13.91day in complicated cases and 7.5 day in uncomplicated cases), Complications developed by 10.64 day +/- 2.344 (Survivors by 10.5day Vs fatalities by 11.5 day). 14.8% patients had abnormal urinary findings and 11.11% having abnormal chest X-ray findings. 3.7% of the total cases succumbed to their illness and 96.29% survived. 25.92% of the total cases developed complications in form of AKI (Defined as serum creatinine >1.5mg/dl), hepatitis (Defined as AST/ ALT >3 times normal), pneumonitis/ARDS and impairment of brain function. Among those who developed complications 85.71% patients achieved complete recovery at discharge from hospital. [Table 1 & 2]

This was followed by a comparison between patients who developed complications and those who did not with an aim to identify any differences between their profiles which revealed that those who developed complications had statistically significant differences with reference to fever, headache, pain abdomen, diarrhea, breathlessness, inoculation eschar, conjunctival congestion, pallor, icterus, generalized lymphadenopathy, oedema, hepatomegaly, splenomegaly, neurological dysfunction, chest findings, urinary abnormalities, abnormal chest X-ray and ECG. Similarly those developing complications presented late, had decreased mean arterial pressure, oxygen saturation, sodium, potassium and hemoglobin. They had increased heart rate, blood urea, serum creatinine, serum bilirubin, serum aminotransferases, alkaline phosphate and lactate dehydrogenase with difference being statistically significant. Those developing complications had their treatment initiated later than those who did not. On an average complications developed by day 10.6 of illness. [Table 3&5]

A similar comparison done between those who survived and those who succumbed to their disease presence of headache, breathlessness, maculopapular rash, abnormal neurological/chest/urinary findings, abnormal chest X-ray and ECG were associated with poor prognosis. Those who died presented late, had low mean arterial pressure, oxygen saturation, hemoglobin, Total Leukocyte count, platelets and sodium levels. They had higher blood urea, serum creatinine, serum bilirubin, serum aminotransferases, serum alkaline phosphatase and serum lactate dehydrogenase with statistical significance. Those who survived had their treatment started earlier which again was statistically significant. [Table 4 &6]

Table 1: Variables in different subgroups (Qualitative)

Parameters	Total (108)		Survivors (104)		Fatality (4)		Complications (28)		Uncomplicated (80)	
	No	%	No	%	No	%	No	%	No	%
Headache	81	75%	78	75%	3	75%	25	89.28%	56	70%
Nausea/Vomiting	38	35.18%	36	34.61%	2	50%	18	64.28%	20	25%
Pain abdo	18	16.66%	16	15.38%	2	50%	12	42.85%	6	7.5%
Diarrhoea	13	12.03%	12	11.53%	1	25%	7	25%	6	7.5%
Cough	25	23.14%	22	21.15%	3	75%	7	25%	18	22.5%
Breathlessness	29	25.92%	28	26.92%	1	25%	23	82.14%	6	7.5%
Fever	104	96.29%	100	96.15%	4	100%	28	100%	76	95%
Inoculation eschar	33	30.55%	32	30.76%	1	25%	11	39.28%	22	27.5%
Conjunctival congestion	40	37.03%	36	34.61	4	100%	18	64.28%	22	27.5%
Maculopapullar rash	39	36.11%	38	36.53%	1	25%	11	39.28%	28	35%
Pallor	20	18.51%	18	17.30%	2	50%	18	64.28%	2	2.5%
Icterus	7	6.48%	6	5.76%	1	25%	7	25%	0	0
Generalized LN	13	12.03%	12	11.53%	1	25%	3	10.71%	10	12.5%
Oedema	28	25.92%	26	25%	2	50%	26	92.85%	2	2.5%
Hepatomegaly	71	65.74%	68	65.38%	3	75%	27	96.42%	44	55%
Splenomegaly	16	14.81%	14	13.46%	2	50%	12	42.85%	4	5%
Neurological findings	4	3.70%	2	1.92%	2	50%	4	14.28%	0	0
Chest findings	15	13.88%	12	11.53%	3	75%	15	53.57%	0	0
Urine RE ME	16	14.81%	12	11.53%	4	100%	14	50%	2	2.5%
ECG	1	0.9%	0	0	1	25%	1	3.57%	0	0
CXR	12	11.11%	8	7.69%	4	100%	12	42.85%	0	0
Survival	104	96.29%	104	100%			24	85.71%		
Recovery complications	23	21.29%	23				24	85.71%	80	100%

Table 2: Variables in different subgroups (Quantitative)

Parameters	Total (108)		Survivors (104)		Fatality (4)		Complications (28)		Uncomplicated (80)	
	Average	SD	Average	SD	Average	SD	Average	SD	Average	SD
Age Yr	36.99	11.456	36.78	11.24	42.25	17.31	39.75	13.33	36.02	10.65
Day of presentation	6.05	3.080	5.84	2.92	11.5	1.91	10.21	2.69	4.6	1.45
Heart rate (bpm)	95.86	9.586	95.52	9.06	104.5	18.65	102.6	11.95	93.43	7.25
MAP (mm Hg)	81.22	9.03	81.74	8.62	68	10.46	76.14	10.78	83.05	7.6
SpO2(%)	94.84	5.119	95.4	4.27	80.5	4.12	89.14	6.96	96.89	1.62
Hb (g/dL)	12.7	1.198	12.75	1.12	11.5	1.73	11.78	1.29	13.02	0.94
Total Leukocyte count (No/µl)	12617.5	2701.94	12744.22	2585.12	9325	3991.14	12339.2	2024.72	12715	2906.87
Platelet (No/µl)	275065.8	84823.43	278961.5	81936.97	173750	109118.8	260607.1	124738.1	280125	65782.22
Urea (mg/dl)	41.31	7.873	40.76	7.33	55.5	9.15	48.5	8.51	38.8	5.87
Creatinine (mg/dl)	1.4	0.954	1.29	0.75	4.27	1.253	2.75	0.961	0.93	0.215
Sodium (mEq/l)	136.92	5.922	137.5	4.85	120.5	8.23	131.5	7.94	138.82	3.45
Potassium (mEq/l)	3.9	0.477	3.92	0.44	3.45	1.038	3.67	0.616	3.98	0.392
Bilirubin (mg/dl)	1.12	0.894	1.03	0.7	3.45	1.969	2.07	1.323	0.78	0.216
AST (IU/L)	126.5	135.5	116.42	117.06	388.5	298.89	259.35	218.04	80	13.21
ALT (IU/L)	158.29	178.27	143.9	149.71	532.5	412.43	342.6	278.5	93.77	16.64
ALP (U/L)	160.44	76.332	155.36	68.14	292.5	155.61	228.8	115.72	136.5	32.8
LDH (U/L)	369.62	154.64	350.17	110.5	875.5	281.81	466.7	252.3	335.6	78.24
Day of treatment start	7.29	3.073	7	2.94	12.5	1.29	11.35	2.87	5.8	1.44
Day of defervescence	8.98	3.609	8.9	3.6			13.91	3.35	7.5	2.03
Day of complication	10.64	2.344	10.5	2.41	11.5	1.91	10.64			

Table 3: Students t test comparison between Subgroup with complications and without complications.

Parameters	Complications (28)	SD	SEM	Uncomplicated (80)	SD	SEM	T	SED	95% CI	P
Age (yrs)	39.75	13.33	2.52	36.02	10.65	1.19	1.4892	2.501	-1.23 to 8.68	0.1394
Day of Presentation	10.21	2.69	0.51	4.6	1.45	0.16	13.8375	0.406	4.81 to 6.42	0.0001
Heart rate (bpm)	102.6	11.95	2.26	93.43	7.25	0.82	4.794	1.921	5.40 to 13.02	0.0001
MAP (mm Hg)	76.14	10.78	2.04	83.05	7.6	0.86	3.6733	1.881	-10.64 to -3.18	0.0004
SpO2 (%)	89.14	6.96	1.32	96.89	1.62	0.18	9.2296	0.840	-9.42 to -6.09	0.0001
Hb (g/dl)	11.78	1.29	0.24	13.02	0.94	0.11	5.4265	0.228	-1.69 to -0.79	0.0001
Total Leukocyte count (No/µl)	12339.2	2024.72	382.64	12715	2906.87	325	0.6315	594.961	-1555.28 to 803.85	0.5291
Platelets (No/µl)	260607.1	124738.1	23573.28	280125	65782.22	7354.68	1.0484	18616.694	-56427.28 to 17391.57	0.2968
Urea (mg/dl)	48.5	8.51	1.61	38.8	5.87	0.66	6.6471	1.459	6.81 to 12.59	0.0001
Creatinine (mg/dl)	2.75	0.961	0.182	0.93	0.215	0.024	15.9891	0.114	1.597 to 2.050	0.0001
Sodium (mEq/L)	131.5	7.94	1.5	138.82	3.45	0.39	6.6838	1.096	-9.50 to -5.15	0.0001
Potassium	3.67	0.616	0.116	3.98	0.392	0.044	3.1066	0.101	-0.514	0.002

(mEq/L)									to -0.113	4
Bilirubin (mg/dl)	2.07	1.323	0.25	0.78	0.216	0.024	8.4941	0.152	0.992 to 1.596	0.0001
AST (IU/L)	259.35	218.04	41.21	80	13.21	1.48	7.3831	24.293	131.19 to 227.52	0.0001
ALT (IU/L)	342.6	278.5	52.63	93.77	16.64	1.86	8.0217	31.024	187.36 to 310.38	0.0001
ALP (U/L)	228.8	115.72	21.87	136.5	32.8	3.67	6.4805	14.252	64.10 to 120.61	0.0001
LDH (U/L)	466.7	252.3	47.68	335.6	78.24	8.75	4.1442	31.649	68.41 to 193.91	0.0001
Start treatment	11.35	2.87	0.54	5.8	1.44	0.16	13.0635	0.42	4.65 to 6.31	0.0001
Defervescence	13.91	3.35	0.68	7.5	2.03	0.23	11.5437	0.556	5.31 to 7.52	0.0001

Table 4: Students t test comparison between Subgroup of survivors and fatalities.

Parameters	Survivors (104)	SD	SEM	Fatality (4)	SD	SEM	T	SED	95% CI	P
Age (yrs)	36.78	11.25	1.1	42.25	17.31	8.65	0.9351	5.841	-17.04 to 6.12	0.3519
Day of Presentation	5.84	2.93	0.29	11.5	1.91	0.96	3.824	1.479	-8.59 to -2.72	0.0002
Heart rate (bpm)	95.52	9.06	0.9	104.5	18.65	9.32	1.8571	4.83	-18.55 to 0.61	0.0661
MAP (mm Hg)	81.74	8.62	0.85	68	10.46	5.23	3.1068	4.424	4.97 to 22.52	0.0024
SpO2 (%)	95.4	4.27	0.42	80.5	4.12	2.06	6.8523	2.176	10.60 to 19.23	0.0001
Hb (g/dl)	12.75	1.13	0.11	11.5	1.73	0.87	2.1309	0.587	0.09 to 2.41	0.0354
Total Leukocyte count (No/µl)	12744.22	2585.13	253.49	9325	3991.14	1995.57	2.5465	1342.727	757.14 to 6081.32	0.0123
Platelets (No/µl)	278961.5	81936.98	8034.58	173750	109118.8	54559.41	2.493	42203.43	21539.10 to 188883.98	0.0142
Urea (mg/dl)	40.76	7.34	0.72	55.5	9.15	4.57	3.9093	3.768	-22.20 to -7.26	0.0002
Creatinine (mg/dl)	1.29	0.754	0.074	4.27	1.253	0.626	7.5751	0.394	-3.763 to -2.202	0.0001
Sodium (mEq/L)	137.5	4.86	0.48	120.5	8.23	4.11	6.7176	2.539	12.02 to 22.09	0.0001
Potassium (mEq/L)	3.92	0.445	0.044	3.45	1.038	0.519	1.9604	0.240	-0.005 to 0.948	0.0526
Bil (mg/dl)	1.03	0.707	0.069	3.45	1.969	0.984	6.1514	0.393	-3.199 to -1.640	0.0001
AST (IU/L)	116.42	117.06	11.48	388.5	298.89	149.45	4.2421	64.137	-399.23 to -144.92	0.0001
ALT (IU/L)	143.9	149.72	14.68	532.5	412.43	206.21	4.6767	83.092	-553.34 to -223.86	0.0001
ALP (U/L)	155.36	68.15	6.68	292.5	155.61	77.8	3.733	36.736	-209.97 to -64.30	0.0003
LDH (U/L)	350.17	110.51	10.84	875.5	281.81	140.9	8.6786	60.531	-645.34 to -405.32	0.0001
Start treatment	7	2.94	0.29	12.5	281.81	0.65	3.6437	1.483	-8.34 to -2.46	0.0004
Complications	10.5	2.41	0.49	11.5	1.29	0.96	0.7841	1.275	-3.62 to 1.62	0.4401

Table 5: Linear regression of variables with reference to complications.

Y Variable	X Variable	Regression coefficient	p value	SD	R2
COMPLICATIONS	Fever	0.519238	0.243307	0.094867	0.012821
	Headache	0.469136	0.014544	0.217516	0.055022
	Nausea/Vomiting	0.609023	0.000381	0.239887	0.112782
	Pain abdo	1	3.34E-06	0.187208	0.185185
	Diarrhoea	0.65587	0.010141	0.163456	0.060729
	Cough	0.078072	0.696023	0.211873	0.001446
	Breathlessness	1.390659	5.99E-18	0.222627	0.506475

	Inoculation eschar	-0.152727	0.403273	0.231395	0.006599
	Conjunctival congestion	0.555882	0.001096	0.242578	0.096078
	Maculopapullar rash	0.020067	0.908984	0.241281	0.000124
	Pallor	1.472727	7.35E-15	0.195129	0.436364
	Icterus	1.60396	7.08E-07	0.123673	0.207921
	Generalized LN	-0.043725	0.865987	0.163456	0.00027
	Oedema	1.735714	9.37E-36	0.220136	0.771429
	Hepatomegaly	0.67834	7.46E-05	0.238395	0.13818
	Splenomegaly	1.027174	5.6E-06	0.178451	0.177536
	Neurological findings	1.557692	0.000322	0.094867	0.115385
	Chest findings	1.587097	1.81E-13	0.173721	0.401673
	Urine RE ME	1.467391	5.57E-12	0.178451	0.362319
	ECG	1.514019	0.083251	0.048113	0.028037
	CXR	1.6875	1.89E-12	0.157867	0.375

Table 6: Linear regression of variables with reference to fatalities.

Y Variable	X Variable	Regression coefficient	p value	SD	R2
Survival	Fever	0.07692308	0.692696	0.094867	0.00147929
	Headache	-8.22387	1	0.217516	8.07047E-16
	Nausea/Vomiting	0.0481203	0.531646	0.239887	0.003701562
	Pain abdo	0.17777778	0.069397	0.187208	0.030769231
	Diarrhoea	0.09068826	0.421562	0.163456	0.006104017
	Cough	0.21590361	0.011951	0.211873	0.058127896
	Breathlessness	-0.00698385	0.93292	0.222627	6.71524E-05
	Inoculation eschar	0.01939394	0.808023	0.231395	0.000559441
	Conjunctival congestion	0.2	0.007563	0.242578	0.065384615
	Maculopapullar rash	-0.03567447	0.641059	0.241281	0.002058143
	Pallor	0.15454546	0.100382	0.195129	0.025262238
	Icterus	0.22630835	0.127628	0.123673	0.021760418
	Generalized LN	0.09068826	0.421562	0.287129	0.006104017
	Oedema	0.09285714	0.26707	0.220136	0.011607143
	Hepatomegaly	0.03045299	0.6942	0.238395	0.001464086
	Splenomegaly	0.20652174	0.043972	0.178451	0.037729933
	Neurological findings	0.96153846	1.39E-07	0.094867	0.231139053
	Chest findings	0.37849462	0.000239	0.173721	0.120099256
	Urine RE ME	0.5	2.82E-07	0.178451	0.221153846
	ECG	1.94392523	5.97E-08	0.048113	0.242990654
	CXR	0.66666667	4.69E-10	0.157867	0.307692308

DISCUSSION

Scrub typhus is an important cause of acute febrile illness in remote sparsely populated areas. It is cause by O.Tsutsugamushi, which is a gram negative obligate intracellular parasite. Its transmission to vertebrates occur when larval form of trombiculid mite bites.[5-7] It was documented in India during Word war-II in North eastern regions, since then this disease has shown its re-emergence in almost all regions of India from time to time.[3,8,9] Scrub typhus is an important but less considered cause of Acute febrile illness due to non-specificity of symptoms and clinical signs. Around a million cases occur yearly with people at risk being much more.[10] It is the most commonly reported rickettssiosis in Indian subcontinent.[11] The availability of facilities to correctly identify the pathogen is limited to a few centres particularly in remote areas. This leads to delay in diagnosis and initiation of drug therapy resulting in poor outcomes for patients. The setting of this study was in a secondary level health care facility which was covering for military troops deployed in remote areas of North-eastern part of India particularly Arunachal Pradesh, Nagaland and Assam. In this terrain any patient needs up to 2 week to reach an adequately equipped healthcare facility.

Data regarding this disease, with reference to this region is sparse. Few smaller studies in this region done at centre located in drainage areas of this region have revealed that case in this region presented as Fever (100%), ARF (44.4%), Abdominal pain (33.3%), Headache(27.7%), Nausea(27.7%), Splenomegaly (16.6%), Hepatomegaly (11.1%), Coma (11.1%), Eschar (11.1%) and seizures (5.5%).[4]

In our study we found that myriad of presenting features like Fever (96.29%) and Headache (75%) which are relatively nonspecific for most of the tropical infections were there. Inoculation eschar was found in 30.55% of patients however in studies from the Himalayas 9.5% patients, South India 43.5% and Jeju Island in South Korea 75.8% of cases had it.[12-14] This variation can be ascribed to skin colour and variability in immune reactivity.[15] Maculopapular rash was seen in 36.11% of cases however in studies from South India it was there in 22% cases and from Himalayas it was 20%.[13,16] Nausea/Vomiting (35.18%) and diarrhea (12.03%) was found compared to nausea in 23% and diarrhea in 10% cases in earlier studies, again a common manifestations of tropical infections.[16,17] Conjunctival congestion was seen in 37.03% of cases, Breathlessness in 26.85% and Cough in

23.14% of cases. Commonest clinical findings being Hepatomegaly (65.74%), generalized lymphadenopathy (12.03%) similar to 61% and 11% seen in similar studies,[18] pedal oedema (25.92%), pallor (18.51%), abnormal chest findings (13.88%) and splenomegaly (14.81%) when compared to 45% seen in other study,[18] Commonest complications being AKI (25.93) and Hepatitis (20.37%). In our study patients presented to medical facility at day 6 after onset of symptoms on an average. Therapy (Oral Doxycycline) was initiated by 7-8th day. Defervescence was achieved on 8-9th day and complications developed usually by 10-11th day. Inspite of quick initiation of therapy 25% cases developed complications in form of AKI, hepatitis (Defined as AST/ ALT >3 times normal), pneumonitis and impairment of brain function usually by 10th day of illness. 3.7% cases succumbed to their illness.

These differences in presentation were probably related to earlier presentation of patients in a military setup where quick evacuation facilities to higher centers from periphery is readily available when compared to general population.

Case fatality rates from other Indian studies have varied from 1.2% to 46.3%.[19-22] A comparison between different subgroups (Survivors and Fatalities) of study revealed statistically significant differences between parameters- Day of presentation (5.84 Vs 11.4), MAP (81.7 Vs 68mm Hg), SpO2 (95.4 Vs 80.5%), Creatinine (1.29 Vs 4.27 mg/dl), Na+(137.5 Vs 120.5 mEq/L), AST/ALT (103/116 Vs 345/388 IU/L), ALP (143 Vs 532 U/L) and initiation of therapy (7 Vs 12.5 day). Differences in some variables were statistically significant however the difference were not significant clinically - Hb (12.7 Vs 11.5 g/dl), Total Leukocyte count (12744 Vs 9325 /µl), platelets (278961.5 Vs 173750 /µl), urea (40.7 Vs 55.5mg/dl), K+ (3.92 Vs 3.45 mEq/L) and LDH (155 Vs 292 U/L). A linear regression analysis revealed following factors which were associated fatal outcomes- Breathlessness, abnormal neurological findings, abnormal CXR and ECG. We therefore conclude that early presentation, early initiation of therapy, preserved cardiac, respiratory, electrolytes and renal function at onset was associated with survival.

A similar comparison between Complicated Vs Uncomplicated cases revealed statistically significant differences between parameters- Day of presentation (10.2 Vs 4.6 day), MAP (76.1 Vs 83 mmHg), SpO2 (89.1 Vs 96.8%), Creatinine (2.75 Vs 0.93 mg/dl), Na+(131 Vs 138 mEq/L), AST/ALT (207/259 Vs 78/80 IU/L), ALP (342 Vs 93 U/L), defervescence (13.9 Vs 7.5 day) and initiation of therapy (11.3 Vs 5.8 day). Differences in some variables were statistically significant however the difference were not significant clinically - Hb (11.7 Vs 13 g/dl), urea (48.5 Vs 38.8 mg/dl), K+ (3.67 Vs 3.98 mEq/L) and LDH (228 Vs 136 U/L). A linear regression analysis revealed following factors which were associated complicated course- Breathlessness, pallor, oedema, abnormal chest findings, abnormal urine, CXR and ECG. We therefore conclude that early presentation, early initiation of therapy, preserved cardiac, respiratory, electrolytes, renal function and early defervescence at onset was associated with uncomplicated course.

CONCLUSION

Hence on the above basis we conclude that early initiation of therapy had a positive impact in preventing complications as well as mortality. During the whole study period no significant incidence of Doxycycline related toxicity was found. Though we had limitations in our study as our study population was young healthy males who were not residents of the area where study was done and we were unable to get genotype analysis of pathogen done, so results probably cannot be generalized for routine practice however they have significant implications for military personnel/tourists/travelers operating in this area.

On the basis of above findings we recommend empirical initiation of Doxycycline therapy in patients (except females of childbearing age) who present from an area where transmission of scrub typhus is known and who have presented with acute febrile illness of more than 4 days duration accompanied with headache, conjunctival congestion, maculopapular rash and nausea/vomiting till final confirmation of diagnosis is done as it may reduce development of complications which is very high (25.9%) after day 10 of illness if untreated.

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How to cite this article: Kanwar A, Ojha A, Upreti V, Marwaha V, Kakani LS, Bhardwaj UB, Gopinath M, Neki NS. Mortality and severity predictors of Scrub typhus in North Eastern states of India. Ann. Int. Med. Den. Res. 2020; 6(1):ME01-ME08.

Source of Support: Nil, **Conflict of Interest:** None declared