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Hematological, Hepatic and Renal Profiles in Patients with Scrub Typhus at a Tertiary Centre in Upper Assam

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ABSTRACT

Background: Scrub typhus is a zoonotic, vector-borne disease transmitted by larval stage (chiggers) of trombiculid mites. It presents usually as acute febrile illness with potential multiple organ systems involvement, particularly affecting hematological, hepatic and renal functions. Data on the clinical and biochemical profiles of scrub typhus from Upper Assam were limited.
Aims and objective: To evaluate the hematological, hepatic and renal profile abnormalities in scrub typhus patients.
Material and method: This cross-sectional hospital-based study was conducted among 55 consecutive patients with scrub typhus attending a tertiary care hospital in upper Assam. All patients underwent detailed clinical evaluation and laboratory investigations, with emphasis on hematological parameters, liver and kidney functions tests. Data were analyzed descriptively.
Results and observations: Scrub typhus predominantly affected young and middle -aged adults (21-51 years). Anemia was observed in 50.9%, leukocytosis in 34.5%, thrombocytopenia in 40% and thrombocytosis in 3.6% cases. Hyperbilirubinemia (>3gm/dl) was observed in 18.2%. Elevated transaminases were common with raised SGOT and SGPT were noted in 83.2% and 69.09% of cases respectively. marked elevation (>3 times the upper limit of normal) was observed in 29.09% for SGOT and 16.36% for SGPT. Serum dysfunction was evident, with Serum creatinine >1.6 mg/dl in 21.81% of cases; 9.1% had levels between 1.7-2.9 mg/dl,5.5 % had between 3-4.9 mg/dl and 7.3% had values >5 mg/dl.
Conclusion: Scrub typhus is frequently associated with significant hematological, hepatic and renal dysfunction reflecting multi system involvement. Awareness of these abnormalities is crucial for early diagnosis, appropriate management and improved prognosis in endemic regions.
Keywords: Scrub typhus, hepatic and renal profile, thrombocytopenia, Orientia tsutsugamushi, upper assam

INTRODUCTION

Scrub typhus is an important re-emerging disease caused by Orientia tsutsugamushi, an obligate gram-negative bacterium. Earlier, the prevalence was believed to be confined to Japan and eastern Russia in north, northern Australia in south to Afghanistan in West, known as

tsutsugamushi triangle.[1] However, in recent years, many Epidemic out breaks have been reported from various part of India including Meghalaya, Odisha ,Rajasthan, Maharashtra ,West Bengal and southern part of the country.[1] Most of the cases are reported from rural areas, where people mostly engaged in agricultural activities particularly during rainy season. Scrub typhus is a zoonotic disease and humans accidently gets infection. It is a vector borne disease, transmitted by larvae or chiggers of trombiculid mite.

Scrub typhus is a zoonotic, vector-borne disease transmitted by larval stage (chiggers) of trombiculid mites. During outdoor or agricultural activities, the larvae get attached to the human body and acquire the infection. An inflammatory reaction occurs at the site of mite attachment, which later progress to necrotic area with black crust formation with surrounded by erythematous lesion, known as eschar. The eschar is a pathognomonic sign for acute febrile illness caused by scrub typhus; however, its prevalence (7-80%) varies depending on geographical location, individual cellular immunity and endemicity of the disease [2]

After an Incubation period of 1-2 weeks, Patients with scrub typhus usually present with fever associated with chills, headache, vomiting, myalgia, jaundice and other systemic symptoms.[3] The clinical spectrum of disease ranges from mild and self-limiting illness to severe life-threatening disease with a fatal outcome.

Scrub typhus can affect multiple organ system, leading to acute renal failure, hepatitis, meningoencephalitis, pneumonia, gastrointestinal involvement, and multiple organ system dysfunction syndrome.

Similar clinical manifestations are also observed in many co-endemic infectious disease like malaria, typhoid, dengue and leptospirosis etc. Therefore, a strong clinical suspicion is essential for the diagnosis of scrub typhus as there are very few distinguishing features.

Hepatic and renal dysfunction are common in scrub typhus. [1-3] Leukocytosis and neutrophilia are explained by bacterial infection. [4] There is paucity of systemic study data on scrub typhus and hematological, hepatic and renal parameter abnormalities in this region. Therefore, we carried out this study to address the lacunae in a tertiary care Centre in upper Assam.

Aims and objective-To evaluate the hematological, hepatic and renal profile abnormalities in scrub typhus patients attending the hospital.

MATERIALS & METHODS

Study Design:

This was a cross-sectional observational study carried out at tertiary care hospital in upper Assam over a period of twelve months, from July 2020 to June 2021.

Inclusion Criteria:

All patient with serologically confirmed scrub typhus attending department of Medicine of a tertiary care center and aged above 12 years were included in this study

Exclusion Criteria:

Patients with co-infected with other endemic infectious disease like malaria, typhoid, dengue, leptospirosis were excluded from the study after appropriate laboratory investigations.

Patient with comorbidities such as known liver dysfunction, acute or chronic infective hepatitis, alcoholic liver disease hematological disorders, chronic renal failure, malignancy were excluded from this study.

Patient with declined consent also excluded from the study.

Ethics:

The study was approved by institutional ethics committee (Human). Written informed consent was obtained from all participants or their legal guardians prior to enrolment in the study.

Data collection:

A detailed clinical history regarding fever, headache myalgia, vomiting, pain abdomen, urine output, seizures, altered sensorium, jaundice dyspnea cough, generalized weakness were recorded from the patents or legal guardians.

A comprehensive general and systemic examination was performed and finding were recorded.

All necessary investigation were performed including complete blood count, liver function test, renal function test, chest X-ray, ultrasonography of abdomen, CT scan of brain when indicated.

Possible alternative diagnoses such as malaria, leptospirosis, dengue fever, enteric fever, viral hepatitis etc. were excluded based on clinical evaluation and appropriate laboratory investigations. The diagnosis of scrub typhus was confirmed by IgM serology using the scrub typhus Detect^{TM} IgM ELISA kit (In Bios International Inc, USA). All patients diagnosed to have scrub typhus were treated with oral or intravenous doxycycline depending on their clinical condition. Additional supportive measures, such as hemodialysis, mechanical ventilation, were provided as indicated.

Statistical Analysis

The data recorded on predesigned and pretested proforma was tabulated and master chart was prepared. The statistical analysis of data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 21.0 Chicago, SPSS inc.) and Microsoft Excel 2010. Continuous data were presented in terms of Mean ± SD, and discrete or categorical data were presented in terms of frequency and percentage.

RESULT

A total of 55 cases of scrub typhus, all above 12 years of age, diagnosed by positive IgM antibody ELISA against *Orientia tsutsugamushi* were included in the study on the basis of inclusion and exclusion criteria.

Table 1: Socio-demographic Profile of the patients

Variables	Number *(n = 55)*	Percentage *(%)*
Age group *(in years)*		
▪ 13–20	6	10.9
▪ 21–30	20	36.4
▪ 31–40	11	20
▪ 41–50	8	14.5
▪ 51–60	3	5.5
▪ 61–70	4	7.3
▪ >70	3	5.5
Gender		
▪ Male	33	60
▪ Female	22	40
Locality		
▪ Rural	47	85.5
▪ Urban	8	14.5

Table 1 shows the socio-demographic profile of the 55 patients diagnosed with scrub typhus. The mean age was 35.27 ± 14.53 years, with range of 12 to 75 years, with the highest proportion in the 21-30 years age group (36.4%), followed 31-40 years (20%).

Males constituted 60%(n=33) and females 40% (n=20). The majority were from rural areas (85%, n=47), while 14.5%(n=8) were from urban areas. The highest number cases were observed in month of August (18,2%) followed by June (16.4%) and July (14.5%).

Among the study population, farmers constituted the highest occupational group (43.3%) followed by housewives (21.8%), students (14.5%), tea garden laborers (7.3%), businessmen (5.5%), government

employees (3.6%), Fishermen (1.8%) and daily wage earners (1.8%).

Regarding clinical features of the study population, fever (98.2%), headache (67.3%) were the most common presenting symptoms followed by cough (30.9%), vomiting (36.4%), abdominal pain (27.3%), myalgia (21.8%), eschar (18.2%), breathlessness (16.4%), lymphadenopathy (16.4%), hepatomegaly (20%), decrease urine output (14.5%), jaundice (14.5%), splenomegaly (12.7%), diarrhea (9.1%), altered sensorium (9.1%), rash (3.6%), neck rigidity (5.5%) and seizure (1.8%).

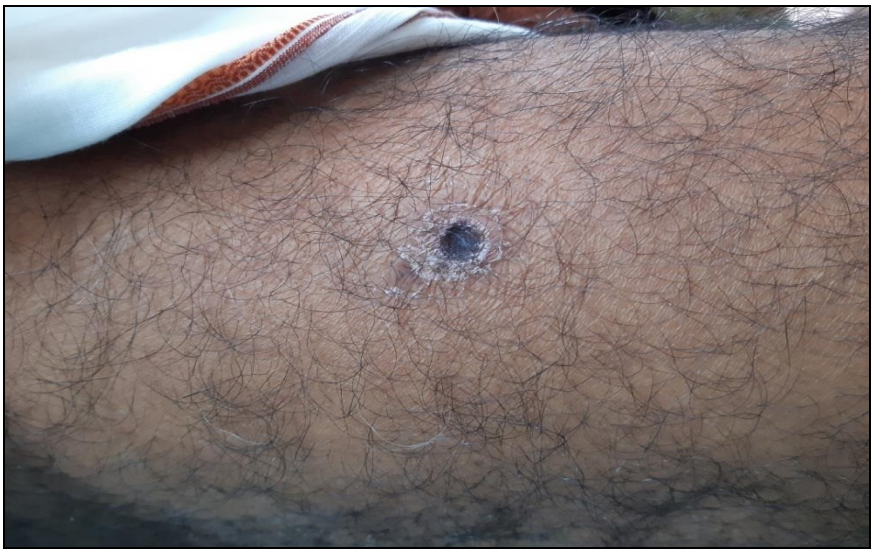

Figure 1: An Eschar over the thigh

Figure 1 shows an eschar in a patient over the thigh with scrub typhus, characterized by central black necrotic crust. Eschar was present in 10 patients (18.2%) of total cases. Among these, 4 patients (40%) had eschar in the inguinal region followed by 2(20%) in abdomen 2 (20%) in axillary region, 1(10%) in chest and 1(10%) in thigh.

Table 2: Hematological parameters of the cases

Hematological Parameters	**Number *(n* = 55*)***	**Percentage *(%)***
Hb (gm/dl)		
▪ <11	28	50.9
▪ ≥11	27	49.1
Mean ± S.D.	10.88 ± 2.76 *gm/dl*	
WBC Count (*cells/cu. mm)*:		
▪ <4000	2	3.6
▪ 4000–11000	34	61.8
▪ >11000	19	34.5
Mean ± S.D.	11024.49 ± 7140.83 *cells/cu. mm*	
Platelet Count (*lakh/cu.mm*:)		
▪ <1.50	22	40
▪ 1.50–4.00	31	56.4
▪ >4.00	2	3.6
Mean ± S.D.	1.68 ± 0.79 *lakh/cu.mm*	

Table 2 shows the hematological parameters among the study populations(n=55). Anemia (hemoglobin of less than 11 gm/dl) was observed in 50.9% (n=28) of patients. Leukocytosis (WBC>11,000) was observed is 34.5 % of patients, while leukopenia was seen in 3.6%. Regarding platelet count thrombocytopenia was observed in 40% of patients and thrombocytosis was noted in 3.6%.

Table 3: Liver function test values of the cases

Liver function test	Number *(n = 55)*	Percentage *(%)*
Bilirubin *(mg/dl)*		
▪ <1.5	25	45.5
▪ 1.5–3	20	36.36
▪ >3	10	18.2
Mean ± S.D.	2.6 ± 3.79 *mg/dl*	
SGOT *(U/L)*		
▪ <50	9	16.36
▪ 50–100	15	27.27
▪ 101–150	15	27.27
▪ >150	16	29.09
Mean ± S.D.	135.41 ± 108.25*U/L*	
SGPT *(U/L)*		
▪ <50	17	30.91
▪ 50–100	22	40
▪ 101–150	7	12.73
▪ >150	9	16.36
Mean ± S.D.	88.57 ± 67.96 *U/L*	

Table 3 shows the liver function test values of the study populations. Serum bilirubin levels < 1.5mg/dl, were observed in 27 patients (55.10%), while bilirubin level >3mg/dl were noted in 18.2% cases(n=10)
SGOT elevation was observed in 83.63% of cases and SGPT elevation in 69.09%. Elevation of SGOT and SGPT more than 3 times of normal upper limit (more than 150 IU/ml) was observed in 16 patients (29.09%) and 9 patients (16.36%) respectively.

Table 4: Serum creatinine values of the cases

Serum Creatinine *(mg/dl)*	Number *(n = 55)*	Percentage *(%)*
≤1.6	43	78.2
1.7–2.9	5	9,1
3.0–4.9	3	5.5
>5.0	4	7.3

Table 4 shows distribution of serum creatinine levels among study population. Elevated serum creatinine level above 1.6mg/dl was noted in 12 patients (21.81%). Out of these, 5 patients (9.1%) had values between 1.7 to 2.9 mg/dl, 3 patients (5.5%) had creatinine values between 3.0 to 4.9 mg/dl and 4 patients (7.3%) had serum creatinine values more than 5.0 mg/dl.
Hyponatremia was observed in 16 patients (29.09%), while 36 patients (65.45%) had normal sodium values. Hypernatremia was noted in 3 patients (5.45%). Hypokalemia was seen in 12 patients (21.82%) patients whereas hyperkalemia was seen in 3 patients (5.45%).
In the present study, complications of the cases were recorded during hospital stay. The most common complication was acute kidney injury (AKI) in 12 patients (21.82%) followed by Hepatitis in 11 patients (20%), Pneumonia in 7 patients (12.73%), acute respiratory distress syndrome (ARDS) in 4 patients (7.27%) and Meningoencephalitis in 3 patients (5.45%). Additionally, 4 patients (7.27%) developed multiple organ dysfunction syndrome (MODS).
Out of 55 patients, 53 patients (96.36%) recovered, while 2 patients succumbed to the multiple organ dysfunction syndrome, with the mortality rate of 3.64%.

DISCUSSION

Scrub typhus is a vector-borne, zoonotic disease transmitted by chigger larva of trombiculid mite. It commonly occurs during rainy season when people mostly engaged in agricultural activities in rural areas. Patients typically present with fever, myalgia, headache cough diarrhea, along

with lymphadenopathy, hepatomegaly, splenomegaly and jaundice. The presence of an eschar is considered as pathognomonic lesion of scrub typhus infection; although its prevalence varies with geographic regions. Severe cases may present with complications such as AKI, ARDS, hepatitis, pneumonia, meningoencephalitis, and MODS.

In Scrub typhus, the pathogen invades the endothelial cells and proliferates within them. Subsequently, infected endothelia cell releases various proinflammatory cytokines leading to endothelial injury and inflammation.[4] The pathogenesis is believed to involve disseminated vasculitis along with inflammation of perivascular region, resulting in significant plasma leakage, progressive end organ dysfunction and ultimately multiple organ failure. Several laboratory abnormalities may be observed including hyperbilirubinemia, increased transaminases, thrombocytopenia, anemia, leukocytosis, hyponatremia and hypokalemia and elevated serum creatinine level. [1,3,4]

The present study demonstrates that scrub typhus predominantly affects the young and middle-aged adults, with majority of cases occurring individuals aged 21-51 years. A male predominance was observed in the present study which aligns with reports from other regions of India. This may be attributed to greater participation of outdoor activities, firming and field work increasing risk of exposure to chiggers. [2,5,6] In the present study, a majority of patients were from rural areas, accounting for 78.5% of cases. Seasonal analysis revealed that cases occurred throughout the year with marked increasing during the monsoon, maximum number of cases observed between July and August

In a similar study from Vellore, Tamil Nadu nearly equal distribution between males and females was observed .[7] Similar rural dominance and seasonal clustering have been observed in previous Indian studies from Odisha, Meghalaya and south India, with most patients engaged in agricultural activities.[6,8-10] Fever was the most common presentation followed by headache, consistent with previous studies from southern West Bengal, Tamil Nadu, Rajasthan and West Bengal.[2,7,11,12] Eschar, considered as pathognomonic of scrub typhus, was identified in 18.2% cases in the present study, comparable to earlier reports.[2,3] The inguinal region was most common site followed by abdomen.

Systemic complications are common in scrub typhus and usually develop after 1 weeks of infection.[2] In the present study, most common complication was AKI followed by Hepatitis, Pneumonia, ARDS, Meningoencephalitis and MODS. Hematological parameter abnormalities were observed in substantial proportion of cases. Being a bacterial infection leukocytosis and neutrophilia was commonly noted.[4]

Anemia (Hb<11gm/dl) was observed in 50.9% of patients. comparable findings have been reported from west Bengal and north Andhra, where anemia was present in 52% and 46.66% of cases respectively. [5,12] A study from southern West Bengal reported anemia in 57.1% of cases.[2]

Leukocytosis (WBC count > 11000/ *cu mm*) was observed in 34.5% patients, whereas leukopenia (WBC count <4000/ *cu mm*) was seen in 3.6 %. Similar patterns have been described in studies from West Bengal and Odisha. A study conducted by Sarkar K et al. leukocytosis was seen in 37% of cases and leukopenia in 5% of cases, findings consistent with our study.[12] A similar study from Odisha, leukocytosis was seen in 45% cases and leukopenia in 6.3 % of cases.[6] Across other regions, leukocytosis has been reported in 13.5% - 40.7% of cases. [2,8,16]

In similar studies, Zhang M et al. and Jamil M et al. and Mohanty L et al., from China (Shandong), North Eastern India and Odisha reported leukopenia in 4.1%,5.1% and 6.3% of cases respectively, findings that are comparable to the present study.[6,8,15] In contrast, Bhowmik KK et al. from southern West Bengal reported leukopenia in 63.6%

cases which was significantly higher than our findings and inconsistent with the present results.[2]

Thrombocytopenia (platelet count <1.5lakh/ cu mm) was observed in 40% of patients. Thrombocytosis (platelet count > 4 lakh/ cu. mm) was noted in 3.6% of cases. In a similar study by Singh SP *et al.* from Uttarakhand, thrombocytopenia was seen in 46.8% of cases, comparable to our findings.[13] Likewise, a study from southern West Bengal, reported thrombocytopenia in 48.15% cases.[2] Thrombocytosis was observed in 14.2% cases in a study by Sinha P *et al*. [14]

In similar studies conducted by Zhang M et al. and Hamaguchi et al. reported thrombocytopenia in 25.4% and 45% of cases respectively while Jamil M et al. reported a prevalence of 32%. [8,15,16] Another regional study from Odisha have documented in 20% of cases.[6]

Clinical Jaundice was seen in 18.2% of patients in the present study. Comparable findings were reported from southern West Bengal, where jaundice was documented in 26% of cases and by Jamil M *et al.* from North Eastern India where prevalence was 15.25% of cases. [2,8]. Another regional study documented clinical jaundice in 25.88% of cases.[3]

In the present study, hepatomegaly was noted in 20% and splenomegaly in 12.7% cases. Similar findings were observed by Bhowmik KK et al. (20.1% and 15.6%) and by Philomena J *et al.* (24% and 18%). [2,7] Mohanty L et al. documented slightly higher rates (31.7 and 19.2%).[6] In contrast, a study from Chandigarh reported hepatomegaly in 61% cases which was significantly higher than that observed in the present study.[17]

Hepatic dysfunction is a common presentation in scrub typhus infection and usually presents with mild hepatitis, elevated transaminases, hyperbilirubinemia, coagulopathy and fulminant hepatic failure in rare occasion.[3] Hepatic injury due to scrub typhus is difficult to differentiate from other infection such as falciparum malaria, dengue, leptospirosis and acute viral hepatitis. [1]

The present study documented substantial burden of hepatic involvement, with hepatitis identified in 21.73% of cases. These findings are consistent with earlier studies from different regions of India including Southern Rajasthan, South India and North Eastern India, although reported prevalence varies widely (15.25%-35.82%), likely reflecting regional variations in disease severity, timing of hospital presentation. [8,9,11]

Hyperbilirubinemia was observed in 54.54 % of patients; however, serum bilirubin exceeding 3 mg/dl were documented in 18.2% of cases. Derangement of hepatic transaminases was common, with elevated SGOT and SGPT levels were noted in 83.63% and 69.09% of cases respectively, and values exceeding three times the upper limit of normal in 29.09% and 16.36% of cases. Hypoalbuminemia (serum albumin <3.5 gm/dl) was seen in 83.63% patients reflecting significant hepatic and systemic involvement. Notably, a 62 years old male patient presented with markedly elevated SGOT (350 IU/L) and SGPT (250 IU/L) levels in absence of clinical jaundice and significant hyperbilirubinemia (serum bilirubin-1.35mg/dl).

Comparable findings have been reported in previous studies; Hamaguchi et al. and Mohanty L et al., observed serum bilirubin >3 mg/dl in 7.7% and 11.3% cases respectively whereas, Jamil M et al. reported such elevations in 27.1% of cases. [6,8,16]

Comparable findings have been reported in similar studies including Zhang M et al., Jamil MD et al, Mohanty L et al. documented, elevated SGOT (>120 IU/L) more than 3 times in 75%, 47.55%, 24.6% respectively.

Elevated SGPT (>120 IU/L) was reported in similar study by Zhang M et al, in 80.3%, in accordance with the present study.[15] In contrast, Jamil M et al and Mohanty L et al reported significantly lower rates (20.3% and 18.3% respectively) likely reflecting

regional clinical heterogeneity.[6,8] Additionally, Bhowmik KK et al. from southern West Bengal reported liver enzymes such as SGOT and SGPT were raised in 84.4% and 81.8% cases respectively, that findings closely aligned with results of the present study.[2] These variation across studies may be attributable to differences in diseases severity, timing of presentations and regional epidemiological factors.

AKI is in scrub typhus is multifactorial resulting from acute tubular necrosis, glomerulonephritis, hypovolemia and shock. Among these factors, acute tubular necrosis is the predominant factor.[1]

In the present study, decreased renal function with the serum creatinine level above 1.6mg/dl was noted in 21.81% of cases; among these, 9.1% had serum creatinine values between 1.7 to 2.9 mg/dl, 5.5% had levels between 3 to 4.9 mg/dl and 7.3% had values exceeding 5mg/dl. Comparable findings have been reported by Sharma M et al. and Jamil M et al., who documented elevated serum creatinine level in 20% cases and 27.1% cases respectively. [3,8] Similarly, Philomena J *et al*, observed serum creatinine more than 1.6 mg/ dl in 22% cases, closely aligning with our study. [7]

In contrast, studies from China (Shandong), Vietnam (Hanoi)and India (Odisha) reported a lower prevalence of elevated serum creatinine level (>1.5 mg/dl), ranging from 3.7% to 11.5%, which was significantly lower than that observed in the present study. [6,15,16] Conversely, Bhowmik KK et al. reported a substantially higher proportion of patients (57.1%) with serum creatinine levels >1.5mg/dl which was significantly higher than our findings.[2]

Electrolyte abnormalities were frequently observed in the present study. Hyponatremia (serum sodium <135 mmol/l) was the most common abnormality, observed in 29.09% of cases. Hypernatremia (sodium value >145 mmol/l) was noted in 5.45% cases. These findings are comparable to those reported by Sharma N et al., who documented hyponatremia and hypernatremia in 16% and 5% of cases respectively. [17]

Hypokalemia (serum potassium < 3.5 mmol/l) was observed in 16.33% of cases, while hyperkalemia (serum potassium >5.5 mmol/ l) in 6.12% cases. In a study conducted by Grover R et al. hypokalemia was found in 10% of cases and 11% of cases had hyperkalemia. [18] Electrolyte abnormalities and variations may reflect differences in disease severity, renal involvement, gastrointestinal losses and treatment initiations across study populations.

In the present study two patients died due to of acute kidney injury and multiple organ dysfunction.

Limitation of the study: This was a single-center study with a relatively small sample size, limiting generalizability. Laboratory parameters were assessed at a single time point only and dynamic changes during the course of illness were not evaluated.

CONCLUSION

Scrub typhus is frequently associated with significant hematological, hepatic and renal dysfunction; important clues for clinical diagnosis and prognosis, underscoring its potential for multisystem involvement. The presence of leucocytosis, thrombocytopenia hyperbilirubinemia and elevated transaminases should heighten clinical suspicion, while acute kidney injury remains a critical determinant of severity and outcome. Given the risk of rapid deterioration, early recognition and prompt initiation of appropriate antibiotic, coupled with vigilant supportive management are imperative to reduce mortality and morbidity- particularly in resource - constrained rural setting where delayed diagnosis is common

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