# **Original Article**

# Comprehensive Analysis of Clinical, Laboratory, Radiological Profile and Prognostic Factors in Patients with Scrub Typhus in the South-east Region of Rajasthan: A Single Center Observational Cross-sectional Study

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#### Abstract

**Background :** To study demographic profile, clinical manifestations, laboratory profile, Radiological profile, and complications in patients diagnosed with scrub typhus admitted to a Tertiary Health Centre in South-east Rajasthan.

**Materials and Methods :** This is an observation cross-sectional study that included 112 patients with Scrub Typhus. After obtaining informed consent, a detailed history was taken and through physical examination was done. All routine investigations such as CBC, Renal Function Tests, Liver Function Tests, Creatine Kinase, ECG, and Chest X-ray were done. If required, higher imaging such as HRCT thorax and 2D-Echo was done. Patients were observed for systemic complications and followed-up till recovery/mortality.

**Results :** 112 patients were enrolled in our study. The mean age of the patients was 44.93 ± 16.84 years with slight female preponderance. Around half of the patients had farming background. 98.2% of patients had fever as the most common presentation followed by myalgia, shortness of breath, nausea and vomiting. On physical examination, Eschar was found in 40 patients. Other findings on physical examination were crepitations, splenomegaly, neck rigidity, and splenomegaly. Around half of total patients had abnormal Chest X-ray. The renal system was most affected organ with involvement in 46.4% of the total patients. Other systems involvement include hepatitis, meningitis, thrombocytopenia, Acute Respiratory Distress Syndrome (ARDS) and myocarditis. Around two-thirds of patients had multiorgan dysfunction. We observed four mortalities in our study (3.6%). Leucocytosis, neutrophilia, raised creatinine, raised creatine kinase, hyperbilirubinemia and raised alkaline phosphatase levels are associated with severity of Scrub Typhus infection.

**Conclusion :** Diagnosis of Scrub Typhus is often missed due to its wide clinical spectrum. Most of the symptoms of scrub are similar to the clinical presentation of other common tropical diseases. Fever with multiple organ dysfunction, acute kidney injury, hepatitis and ARDS should raise suspicion of scrub typhus. Early diagnosis and appropriate treatment can reduce complications associated with scrub and improve outcomes in a positive way.

Key words : Scrub Typhus, Multiorgan Dysfunction, Acute Respiratory Distress Syndrome (ARDS).

Scrub Typhus is an arthropod-borne rickettsial disease caused by Orientia tsutsugamushi, an alphaproteobacterium. There are 1 million estimated cases of scrub typhus throughout the Asia-pacific region annually. Bite of the larva (chigger) of trombiculid mites species is responsible for human infection<sup>1</sup>. This is why, the epidemiology of scrub typhus is closely related to epidemiological patterns of trombiculid mites<sup>1</sup>. Habitats of the vector may range from subtropical regions to subarctic regions, semidesert

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#### Editor's Comment :

Scrub Typhus presents with a wide range of clinical features that often mimic other tropical illnesses, making timely diagnosis challenging. In endemic areas, patients presenting with fever and multiorgan dysfunction – especially renal involvement, hepatitis, or ARDS – should prompt consideration of Scrub Typhus. Early recognition and appropriate management are crucial to reduce complications and mortality.

areas, locations with woody vegetation, deep jungles, and rice paddies. Often seasonal variation is seen in scrub typhus with most cases occurring with monsoon and heavy rains<sup>1</sup>. in India, Assam and Bengal witnessed an early epidemic of scrub during the world war but recently many states are affected by the disease including Himachal Pradesh, Jammu and Kashmir, Rajasthan, Tamil Nadu, Kerala, Maharashtra, Bihar, Karnataka and West Bengal<sup>2,3</sup>.

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Clinical manifestations of scrub are fever, chills, headache, cough, nausea, vomiting, body ache and skin rash. These symptoms are nonspecific and may be confused for viral infections or malaria. Scrub usually involves multiple systems and is associated with systemic complications such as Myocarditis, Pneumonia, Acute Renal Failure, Meningitis, Meningoencephalitis, Gastrointestinal (GI) Bleeding, And Multi-organ Dysfunction Syndrome (MODS)<sup>3</sup>. Therefore Without prompt treatment, the case fatality rate varies up to as high as 30% to 45%<sup>4</sup>. timely diagnosis and early treatment may reduce these complications and improve survival in these patients.

Scrub typhus is associated with various laboratory parameters abnormalities such as thrombocytopenia, hyperbilirubinemia with raised liver enzymes<sup>5,6</sup>, renal failure as evidenced by elevated serum creatinine and oliguria<sup>5,6</sup>, deranged lipid profile with hyper-triglyceridemia<sup>7</sup>.

Treatment of scrub typhus is antimicrobial agents such as Doxycycline and Azithromycin. less preferred antibiotics are Chloramphenicol and Rifampicin. Doxycycline is given in dosing of 100 mg twice a day either orally or intravenous. Azithromycin can be used as an alternative or in case of resistance to Doxycycline<sup>8</sup>.

This study is done in patients of Scrub Typhus in South-east Rajasthan with the aims of studying the epidemiological profile, clinical profile, laboratory features, radiological profile and clinical outcomes of this disease.

# MATERIALS AND METHODS

## Study Design :

This is a Cross sectional Observational study.

# Setting :

This study was conducted in Department of General Medicine, Government Medical College, Kota and Group of associated hospitals, Kota. Study was conducted in the year 2022-23.

#### Participants : Inclusion and Exclusion criteria

All the admitted with acute febrile illness cases were potentially eligible for study. Serum IgM ELISA for Scrub Typhus positive patients were final study candidates. Patients less than 12 years were excluded from this study.

#### **Ethical Approval :**

Ethical clearance was taken from Institutional Ethical Committee of Medical College. All the patients were explained in detail about this study and written informed consent was obtained for each patient before their enrollment in the study.

## Methodology :

All the patients of Scrub Typhus after satisfying inclusion and exclusion criteria were investigated for various laboratory parameters such as complete blood count, liver function tests, renal function tests, Creatine Kinase-MB (CK-MB), triglycerides and electrolytes. Detailed history of each patient was taken for demographic data, clinical history and past history. All patients gone through general physical examination and systemic examination. Other investigations such as ECG, Chest X-ray, ABG, NCCT head were done if indicated. Clinical course of all the patients was monitored for respiratory failure, circulatory failure or any other complications. All the patients were followed till the end point like recovery/ death.

#### **Statistical Analysis :**

Data were entered in Microsoft Excel 2017 and analyzed using IBM SPSS statistics version 26. Among the nominal variables, the number and percentage were presented. The data were analyzed by descriptive statistics. Tests such as Chi square test, Mann-Whitney tests were used for statistical analysis.

# RESULTS

Total of 168 patients above the age of 12 years were admitted in our ward and ICU with acute febrile illness. Out of these, 122 patients were found IgM ELISA positive for scrub typhus. 10 patients refused for consent. Finally, 112 patients were included in our study (Fig 1).

# **Demographics :**

Our study comprised 112 patients with Scrub Typhus, the median age was 44 years with a mean age of  $44.93 \pm 16.84$  years. Females were slightly higher in proportion with 60 females out of 112 (53.6%). Most subjects were housewives 48.2 %, followed by farmers (46.4 %) and others (5.4%). Four patients were hypertensive (3.6%), two were diabetic (1.8%), 2 had history of coronary artery disease (1.8%) and

# Total admitted patients with acute febrile illness (n=336)



Non eligible candidates (n=214) (Patients with negative IgM ELISA for scrub)

#### Reviewed for exclusion criteria (n=122)



Total excluded patients (n=10) Refused for consent (n=10)

# Final study size (n=112)

#### Fig 1 — Study flowchart

2 were known case of chronic kidney disease (1.8%)(Table 1).

#### **Clinical Profile :**

Most common presenting symptom was fever and was present in 100% patients followed by myalgia (55.4%), shortness of breath(44.6%), nausea and vomiting (42.9%), headache (37.5%), pain abdomen (25%), cough (25%), altered sensorium (10.8%), oedema (8.9%), vertigo (3.6%), and seizures (3.6%). An eschar was observed in 40 cases with scrub typhus (35.7%), in this study. During physical examination, 30.7 % patients had crepitations on auscultation, 26.8% had splenomegaly and two patients had lymphadenopathy. two patients (1.8%) with altered sensorium had neck rigidity too.

#### Lab parameters :

In our study, the mean hemoglobin was 11.145 gm. Patients in this study had a mild elevation in their total leukocyte counts with a mean of 10176 cells/mm<sup>3</sup>. Thrombocytopenia was seen in 72.8 % of patients with a mean platelet count of 90285 cells/mm<sup>3</sup>. 46.4% had derangement in renal function (creatinine more than 1.2) with a mean creatinine of 1.42 mg%. The liver function test showed an elevation of serum bilirubin levels in 39.2% of patients (bilirubin >1.2mg/ dl). Mean bilirubin was also elevated with a mean value of 1.9 mg/dl. There was a mild elevation in liver enzymes; both SGOT and SGPT were elevated, with a mean of 148.2 IU/L and 105.5 IU/L respectively. This shows an increase in SGOT was more than the SGPT. Hypertriglyceridemia was seen in our study with mean triglycerides level of 305.33 mg/dl

## **Radiological Profile :**

In the present study, most patients had pleural effusion

on chest imaging (26.8%). Other findings include bilateral pneumonia (21.4%), unilateral pneumonia (3.6%), and Ground-glass opacity (19.6%). 24 patients (21.4%) had Acute Respiratory Distress Syndrome (ARDS). 17.8% of patients had Hilar lymphadenopathy and mediastinal lymphadenopathy. Cardiomegaly was seen in 3.6% of patients (Table 2).

On USG abdomen examination, 30.3% of patients had splenomegaly followed by hepatomegaly in 26.8% of patients and ascites in 5.4% of patients.

14 patients were taken for 2D-Echocardiogram (2D-Echo), out of which 12 (10.8% of total) patients had myocardial dysfunction.

#### **Organ System Involvements :**

SOFA score was used for the assessment of organ dysfunction and failure. On the basis of SOFA score, organ involvement was classified as organ

Table 1 — Baseline characteristics of the study population				
Characteristics	n	Percentage		
Age :				
<25	18	16.1%		
26-40	32	28.6%		
41-55	26	23.2%		
>55	36	32.1%		
Gender :				
Male	52	46.4%		
Female	60	53.6%		
Occupation :				
Farmers	54	48.2		
Housewives	52	46.4		
Others	6	5.4		
Co-morbidity :				
Hypertension	4	3.6%		
Diabetes	2	1.8%		
Coronary artery disease	2	1.8%		
Chronic kidney disease	2	1.8%		

Table 2 — Radiological features observed in Scrub Typhus				
Radiological Investigations	n	Percentage		
Chest X-ray and HRCT Thorax :				
Unilateral pneumonia	4	3.6%		
Bilateral pneumonia	24	21.4%		
Pleural effusion	30	26.8%		
Acute Respiratory Distress Syndrome	24	21.4%		
Hilar lymphadenopathy	20	17.8%		
Mediastinal lymphadenopathy	20	17.8%		
Ground-glass opacity	22	19.6%		
Cardiomegaly	4	3.6%		
Ultrasonography (USG)				
Splenomegaly	30	26.8%		
Hepatomegaly	34	30.3%		
Ascites	6	5.4%		
2D-Echocardiogram				
Myocardial dysfunction	12	10.8%		

dysfunction and organ failure. A SOFA score of 1 or 2 was considered organ dysfunction while a score of 3 or 4 was considered as organ failure. SOFA score was calculated for each patient. Hematological organ involvement was most prominent with 78.6 % followed by renal involvement (46.4%) and hepatic involvement (39.3%). Cardiovascular system and respiratory involvement were seen in 25 % of patients each. The central nervous system involvement was least commonly affected in (10.7%)(Table 3).

In our study, none of the patients had all six-organ involvement, 7.1% had involvement of five organ systems simultaneously and 64.3% of them had 2 or more organ involvement.

#### **ECG Profile :**

All patients had routine ECG examinations. 32.1% of patients had sinus tachycardia and 5.4% had T inversions in ECG. 3 patients had tachyarrhythmias too, comprising of 2 with atrial fibrillation (3.6%) and one with supraventricular tachycardia (1.8%).

#### **Complications :**

About two third of total patients (64.3%) had MODS in the present study. Hepatitis was seen in 33.9% of patients. 23.2% of patients with shock required vasopressor support. Around 21.4% of cases had ARDS requiring ventilation support. Other complications were Meningitis (1.8%), and AKI with creatinine >1.5 mg/dl in

Table 3— Organ failure assessment based on sequential organ failure assessment score (SOFA score)(n=100)				
Organ Involvement – SOFA score of at least 1				
Organ Involvement	n	Percentage		
Renal system :				
Renal Involvement		52	46.4	
Liver :				
Liver Involvement		44	39.3	
Cardiovascular System (CVS)				
CVS Involvement	28	25		
Respiratory System	00	05		
Respiratory involvement	28	25		
	00	79.6		
Central Nervous System			70.0	
CNS Involvement		12	10.7	
		12	10.7	
Number of organs involved	N	Cumula	tive percentage	
No organ involved	10		100	
One	30		91.1	
Тwo	30		64.3	
Three	28		37.5	
Four	6		12.5	
Five	8		7.1	
Six	0		0	

30.4% of the patients. In 12 patients (10.8%), myocarditis was also present (Table 4).

The average duration of hospital stay was  $6.64 \pm 3.25$  with a median duration of 6 days. Around 48.2% of patients required ICU admission. Ventilatory support was required in one-fourth of patients. Among these, 10.7% of cases required non-invasive ventilation, and 14.3% required invasive ventilation. None of the patients in our study required hemodialysis as all patients with acute renal failure were managed conservatively. There were four mortalities in our study.

# **Prognostic Factors :**

Patients were categorized into three groups based on disease severity, ie, severe (patients with involvement of three or more organs), moderate (patients with involvement of two or fewer organs) and mild (patients without any organ involvement) (Table 5).

There was no statistically significant difference in severity based on gender of patients but it was observed that patients falling in a higher age group had more chances of severe infection(p-value <0.001). Chronic co-morbidities did not have a statistically significant impact on the prognosis of patients. Various laboratory parameters such as total leucocyte counts, platelets, creatinine, creatine kinase, bilirubin and alkaline phosphatase levels had statistically significant co-relation with the severity of scrub infection.

# DISCUSSION

Scrub typhus is one of the common causes of acute febrile illness during rainy and monsoon seasons in our institute associated with multiple organ

Table 4 — Complications associated with scrub typhus				
Outcomes	n	Percentage		
Myocarditis	12	10.8%		
Meningitis	2	1.8%		
Acute Respiratory Distress Syndrom	e 24	21.4%		
Acute Kidney Injury	34	30.4%		
Shock	26	23.2%		
Hepatitis	38	33.9%		
Multiple Organ Dysfunction Syndrom	e 72	64.3%		
Intensive Care Unit (ICU) Requireme	ent 54	48.2%		
Vasopressors Requirement	26	23.2%		
Ventilation Requirement	28	25%		
Non-invasive Ventilation	12	10.7%		
Invasive Ventilation	16	14.3%		
Hemodialysis Requirement	0	0%		
Duration of Hospital Stay (in Days)	6.64 ± 3.25			
Mortality	4	3.6%		

Table 5 — Various prognostic factors for Scrub Typhus					
Parameters		Severity Groups			p-value
	-	Mild (n=10)	Moderate (n=60)	Severe (n=42)	
Gender					
Male		5	27	20	0.9397
Female		5	33	22	
Age					
<25		6	11	1	<0.001
26-40		2	25	5	
41-55		1	15	10	
>55		1	9	26	
Co-morbidities					
Present		1	3	6	0.2678
Absent		9	57	36	
Lab Parameter (Mean ± SD)					
Hemoglobin (Hb)	(gram/dl)	11.2 ± 2.4	11.3 ± 2.4	10.9 ± 2.3	0.743
Total Leucocyte Count (T	LC) (cells per mm <sup>3</sup> )	9745.02 ± 4683.70	10149.71 ± 4893.2	12623.09 ± 5782.3	<0.001
Neutrophils	(%)	67.08 ± 15.02	72.7 ± 13.5	79.4 ± 12.4	0.037
Platelets	(Cells per mm <sup>3</sup> )	119523.77 ± 107363	97509 ± 82019.37	56009.34 ± 54812.81	<0.001
Creatinine	(mg/dl)	1.19 ± 0.67	1.54 ± 0.65	$2.9 \pm 0.95$	<0.001
Creatine Kinase	(mg%)	179.40 ± 239.8	231.57 ± 312.43	438.77 ± 612.4	<0.001
Bilirubin	(mg/dl)	1.47 ± 1.59	3.47 ± 4.12	5.24 ± 6.92	<0.001
SGOT	(IU/L)	125.2 ± 156.2	213.6 ± 189.4	197.57 ± 210.8	0.576
SGPT	(IU/L)	115.4 ± 139.7	183.7 ± 181.8	167.25 ± 249.1	0.602
Alkaline Phosphatase	(IU/L)	127.6 ± 174.9	162.1 ± 199.3	201.9 ± 246.3	<0.001
Triglycerides	(mg/dl)	325.91 ± 276.1	341.76 ± 299.1	301.3 ± 247.9	0.823
Duration of hospital stay in days (Mean ± SD)					
Days		5.34 ± 2.9	$5.98 \pm 3.4$	7.44 ± 4.21	0.012

dysfunction. In our study, most of the patients were in the age group of 26 to 40 years (28.6%) with a slight female preponderance (53.6%). Around one-half of the patients were farmers by occupation. This can be explained as in this region, farming is carried by young adults with an increasing number of women working in the fields.

The mean age of patients was  $44.93 \pm 16.84$  years with a median age of 44 years. This is slightly higher than a study done by Chrispal, *et al*<sup>6</sup> in which the mean age of presentation was 45.4 years. Male: Female ratio in our study was 26:30. This female predominance is similar to other studies by Varghese GM, *et al*<sup>9</sup> and Kim DM, *et al*<sup>3</sup>. There was a higher female proportion in study by Griffith M, *et al*<sup>10</sup> too. Around 48.2 % of total patients were farmers and 46.4% were housewives. This trend is slightly in contrast with study by Chrispal, *et al*<sup>6</sup> in which farmers comprised of 38.8% of total patients and 42.9 % were housewives.

In present study, fever was the most common presentation (100%) along with myalgia (55.4%) and breathlessness (44.6%). Other clinical manifestations were nausea and vomiting (42.9%) followed by headache (37.5%), pain abdomen (25%) and cough

(25%). Less common presentations were generalized body swelling (8.9%), vertigo (3.6%) and seizures (3.6%). Twelve patients were in altered sensorium at the time of admission (10.8%).

On clinical examination, Eschar mark on the skin was present in around one-third of patients. Presence of eschar varies widely in different studies ranging from around 37 to 60 percent<sup>6,9,11</sup>. Eschar is a typical feature of Scrub Typhus which indicates the initial site of inoculation by the chigger through which the organism enters the lymphatic system and it can be used as a reliable diagnostic feature. The eschar detection rate may vary according to geographic location and demographics. For example, countries in south-east Asian regions have high eschar detection rates due to differences in skin color helping the identification of eschar marks<sup>12</sup>.

Other findings on clinical examination are crepitations (30.7%), splenomegaly (26.8%), and lymphadenopathy (1.8%). One, two patient had neck rigidity.

Scrub Typhus is associated with multiorgan involvement which can lead to an increase in mortality and morbidity if early treatment is not initiated. In the current study, around 64% of patients had involvement of two or more organ dysfunction.

In our study around one-fourth of total patients had respiratory system dysfunction. Respiratory dysfunction is most probably due to pneumonia (25%) and ARDS (21.4%). Charoensak A, et al<sup>13</sup> in their study suggested respiratory involvement in 20-72% of patients. Cough and breathlessness, with or without chest infiltrates, are seen in Scrub Typhus which is seen in our study. Respiratory involvement varies in severity from pleural effusion and pneumonitis to severe ARDS warranting mechanical ventilation. Pathogenesis leading to respiratory involvement is the presence of interstitial pneumonia with or without vasculitis<sup>14,15</sup>. Our study showed the presence of ARDS in 21.4% of total patients which is significantly higher compared with previously done studies. Past studies showed an incidence of ARDS ranging from 10 to 15%<sup>16,17</sup>. Around two third of patients had abnormal chest skiagram and HRCT scan of Thorax. Abnormality in chest radiography was reported in 59-72% of cases based on studies done by Charoensak A, et al<sup>13</sup> and Choi YH, et al<sup>18</sup>. In our study, one-fourth of patients required ventilatory support. 10.7% of patients required non-invasive ventilation and 14.3% needed invasive ventilation.

CNS involvement is seen in the form of meningitis, meningoencephalitis, encephalomyelitis or focal neurological deficits. Study by Chrispal A, *et al*<sup>6</sup> suggests that altered sensorium is most common neurological feature of Scrub Typhus present in around 20 to 30% of patients which is higher than the incidence of altered sensorium in our study (10.8%). In our study, 12 patients (10.8%) had CNS involvement based on SOFA score. Only two patient (1.8%) had meningitis in our study. None of the patients had focal neurological deficits in our study.

Hepatic involvement is seen in the form of raised liver enzymes. it is a consistent finding (60-90%) in various studies<sup>5,6</sup>. In the present study, hepatic dysfunction was slightly lower compared with previous studies involving two-thirds of total patients. In our study, there was hyperbilirubinemia in 39.3% of patients with a mean bilirubin level of 1.93 mg/dl. Both SGOT and SGPT were elevated with mean values of 148 IU/L and 105 IU/L respectively. Raised bilirubin levels were associated with severe scrub infection.

Renal involvement was seen in around half of the patients suggested by deranged renal function tests with a mean creatinine value of 1.42 mg/dl. This proportion is a little bit higher than the results from

previous studies<sup>9,11,19</sup> suggesting renal involvement in 30 to 40% of patients. However, no patient needed hemodialysis support. We observed that severe scrub infections were associated with raised creatinine values.

Thrombocytopenia is a characteristic laboratory feature of Scrub Typhus and was present in 78.6% of total patients, localized and generalized vasculitis can be considered as a potential cause of thrombocytopenia<sup>9,11</sup>. In the current study, the hematological system was most commonly involved with around four-fifth of patients having thrombocytopenia. However, none of the patients required platelet transfusion. Tsay and Chang, et al<sup>17</sup> found decreased platelet counts in severe Scrub Infections. Our study reported a significant association of thrombocytopenia with the severity of Scrub Typhus infection. In our region, Dengue fever also has similar hematological manifestations as scrub typhus along with many similar clinical features. Acute febrile illness presenting with MODS should raise suspicion of scrub typhus.

Previous studies<sup>2,3</sup> have suggested that Scrub Typhus is associated with elevated white blood cell counts and our study also found that raised WBC counts were associated with severe scrub infection. In the current study, it was also observed that neutrophilia is associated with severe Scrub Typhus infection.

In a study by Kalita J, *et al*<sup>21</sup>, it was observed that severe scrub infection was associated with raised creatine kinase levels. Our study also had similar results showing higher values of creatine kinase in severe infections.

Based on the SOFA score, 25% of patients had cardiovascular system involvement. Around 23.2% of cases required vasopressor support. The majority of patients requiring vasopressor support were started on Nor-epinephrine and few of them on dobutamine support. Out of 112 patients, most of them (57.1%) had normal ECG. Most common ECG abnormality was sinus tachycardia followed by T inversion (5.4%), atrial fibrillation (3.6%) and supraventricular tachycardia (1.8%). The cardiac profile in Scrub Typhus has not been well studied. In our study, 10.8% of patients had myocarditis which is comparable to a study done by Jung YC, *et al*<sup>20</sup>, in which they found myocarditis in 14% of patients.

In our study, 86% of patients had hypertriglyceridemia with a mean triglyceride level of 305 mg/dl. This result is almost similar to study done Sharda M,  $etal^{\vec{r}}$ , which shows raised triglyceride levels in around 92% patients.

The mean and median duration of hospital stay was 6.64 days and 6 days consecutively. Almost half of the patients required ICU support. We observed four mortalities (3.6%) in our study; all 4 of these patients had 5 organ dysfunctions based on SOFA scoring. Both of these patients were intubated for ventilation. Both were having pleural effusion on imaging and two had coronary artery disease as morbidity. Both patient with coronary artery disease were having atrial fibrillation on ECG.

Scrub typhus is a serious infective illness requiring early diagnosis and appropriate treatment. Prompt and timely treatment can reduce life-threatening complications and thus mortality.

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