

# Clinical Profile and Predictors of Intensive Care Unit Admission in Pediatric Scrub Typhus: A Retrospective Observational Study from North India

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## ABSTRACT

**Introduction:** Children with scrub typhus may present with one or more organ failures. Identifying the predictors of severe disease and need for pediatric intensive care unit (PICU) admission would help clinicians during outbreak seasons.

**Materials and methods:** This observational study included 160 children admitted to the emergency department (ED) with scrub typhus confirmed by polymerase chain reaction (PCR) between January 2013 and December 2015. Demographic, clinical, and laboratory data were collected and predictors for PICU admission were identified.

**Results:** There was a seasonal trend with peak presentation in post-monsoon months between August and October. Mean (SD) age at presentation was 6.8 (3.2) years. Fever was present in all with a median (IQR) duration of 9 (6–11) days. Respiratory distress (42%), altered sensorium (24%), hepatomegaly (93%), splenomegaly (57%), and lymphadenopathy (54%) were other features. Rash and eschar were noted in 24% each. Thrombocytopenia (83%), hypoalbuminemia (63%), and hyponatremia (62%) were common laboratory abnormalities. Meningoencephalitic presentation was noted in 29%; acute kidney injury (AKI) (16%), acute respiratory distress syndrome (ARDS) (11%), and myocarditis (3%) were other organ dysfunctions. Sixty-six (41%) children required PICU admission. Intensive care needs include invasive ventilation ( $n = 27$ , 17%), vasoactive drugs therapy for hemodynamic support ( $n = 43$ , 27%), osmotherapy to treat raised intracranial pressure ( $n = 27$ , 17%), and renal replacement therapy ( $n = 3$ , 2%). Mortality was 8.8%. On multivariable analysis, lymphadenopathy, respiratory distress, shock, elevated lactate, and meningoencephalitis predicted the requirement of PICU admission.

**Conclusion:** Scrub typhus presents with organ dysfunction during post-monsoon months. We identified predictors of intensive care in children with scrub typhus admitted to ED.

**Clinical significance:** Our results would help clinicians identify severe cases and prioritize resources.

**Keywords:** Children, India, Intensive care, Pediatric intensive care unit, Scrub typhus.

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## INTRODUCTION

Scrub typhus has emerged as an important etiology of acute undifferentiated fever in Southeast Asia, particularly in India.<sup>1–3</sup> Increasing number of pediatric cases have been reported from several endemic regions of the country in the last decade.<sup>4–12</sup> Children with scrub typhus usually present in a season that is common to most other tropical fevers such as dengue, malaria, acute viral hepatitis, and viral encephalitis.<sup>3,13</sup> A significant proportion of them have severe manifestations requiring emergency department (ED) or pediatric intensive care unit (PICU) admission. The presence of one or more organ failures with overlapping clinical features at the outset poses a challenge in clinical differentiation of severe scrub typhus from other tropical infections.<sup>13</sup> Likewise, the laboratory confirmation may be difficult owing to nonavailability or inaccurate serology in the first few days and questionable reliability of a single-point serological titer in endemic settings.<sup>14</sup> Diagnostic challenges aside, severe scrub typhus imposes a significant burden on healthcare resources. In a multicenter study from Indian ICUs where scrub typhus was the second most common tropical fever, 16% of ICU days and 21% of total ventilation days were utilized for treating these infections.<sup>13</sup> With this background, we believe that periodically updating the epidemiology

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of confirmed scrub typhus patients may help physicians understand the clinical presentation better during the epidemic seasons. Identifying the predictors of severe disease and need for intensive care would help plan resource allocation in low-middle-income countries

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in addition to improving clinical care. Therefore, we conducted this study to determine the clinical-laboratory profile and predictors of PICU admission in children with scrub typhus presenting to a tertiary care center in north India.

## MATERIALS AND METHODS

This retrospective observational study was conducted in children admitted to ED and PICU of a tertiary care teaching and referral hospital in north India. Our ED is a stand-alone unit that has short-stay beds for acute admissions. Critically ill children requiring ongoing organ supportive care are transferred from ED to PICU after stabilization. Records of children aged 12 years or younger presenting between January 2013 and December 2015 with an acute febrile illness defined as onset in the previous 14 days with fever of at least 48 hours' duration or a documented axillary temperature  $\geq 38^{\circ}\text{C}$  recorded within 24 hours of admission were screened for eligibility. All cases with clinically compatible presentation, positive IgM ELISA, and confirmatory PCR positive result for scrub typhus were included in the study.

Demographic, clinical, and laboratory data were retrieved from medical case records and entered into a predesigned case record form. Clinical variables included presenting symptoms and their duration and physical examination findings that included eschar, edema, rash, icterus, pallor, lymphadenopathy, and organomegaly. Laboratory tests included complete blood count, serum electrolytes, renal and liver function tests, coagulation parameters, lactate, and quantitative C-reactive protein (CRP). The ELISA for scrub typhus IgM antibody was performed using Scrub Typhus Detect IgM ELISA (InBios International Inc., Seattle, WA). Nested PCR was performed using the DNA extracted from the whole blood and was amplified to detect scrub typhus according to the nested PCR protocol.<sup>15,16</sup> We used the oligonucleotide primers that were based on the nucleotide sequences of a gene encoding for the 56 kDa antigen of a Gilliam strain of *Orientia tsutsugamushi*. The specific PCR products of size 484 base pairs were sequenced to confirm the diagnosis. Treatment-related variables, details of organ supportive therapies, length of PICU stay, and hospital outcome were recorded. The criteria of organ system dysfunction, acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI) were defined according to standard guidelines.<sup>17-19</sup>

Descriptive statistics including frequency, mean, median, interquartile range (IQR), and standard deviation (SD) were calculated for the demographic data and laboratory parameters. The univariate analysis followed by the multivariable logistic regression analysis were done to identify independent predictors of PICU admission. For all tests, a two-sided  $p$  value of  $<0.05$  was considered statistically significant. All statistical analyzes were performed using the SPSS software version 22.0 (SPSS Inc., Chicago, IL). The study was approved by the Institute Ethics Committee.

## RESULTS

During the 3-year study period, 160 children were diagnosed with scrub typhus. There was a clear seasonal trend with peaks during post-monsoon months—October ( $n = 48, 30\%$ ), September ( $n = 44, 28\%$ ), and August ( $n = 37, 23\%$ ). Mean (SD) age at presentation was 6.8 (3.2) years and about half ( $n = 87, 54\%$ ) were boys. Children presented from the adjoining districts of Haryana ( $n = 59, 37\%$ ), Punjab ( $n = 41, 26\%$ ), and Himachal Pradesh ( $n = 32, 20\%$ ) representing geographically both hilly Himalayan regions and

sub-Himalayan plains. Fever was present in all with a median (IQR) duration of 9 (6, 11) days. Other prominent symptoms included respiratory distress ( $n = 67, 42\%$ ), vomiting ( $n = 55, 34\%$ ), seizures ( $n = 41, 26\%$ ), and altered sensorium ( $n = 39, 24\%$ ). Most patients presented with hepatomegaly (93%), while about half presented with splenomegaly (57%), lymphadenopathy (54%), and edema (47%). Erythematous maculopapular rash was seen in 39 (24%) cases while eschar was noted in 40 (25%) cases (Table 1).

The laboratory parameters are shown in Table 2. Most children ( $n = 132, 82\%$ ) developed thrombocytopenia, and almost half ( $n = 72, 45\%$ ) had evidence of severe thrombocytopenia ( $<50,000$  cells/ $\text{mm}^3$ ). The mean (SD) hemoglobin was 9.7 (1.6) g/dL. Significant hypoalbuminemia ( $<2.5$  g/dL) was seen in 101 (63%) children. Hyponatremia ( $<135$  mmol/L) was noted in 99 (62%) cases.

Of all syndromic manifestations, meningoencephalitic presentation ( $n = 46, 29\%$ ) was the most common. Acute respiratory distress syndrome was diagnosed in 17 (11%) children. Myocarditis evidenced by left ventricular ejection fraction (LVEF)  $<40\%$  in echocardiography and elevated cardiac enzymes was present in 5 (3%) children. Acute kidney injury was noted in 26 (16%) children. Sixty-six (41%) patients required PICU admission. Organ-supportive therapies in intensive care included positive pressure ventilation ( $n = 27, 17\%$ ), fluid boluses and/or vasoactive drug for hemodynamic support ( $n = 43, 27\%$ ), osmotherapy to treat raised intracranial pressure ( $n = 27, 17\%$ ), and renal replacement therapy ( $n = 3, 2\%$ ) (Table 3).

**Table 1:** Baseline characteristics of children with scrub typhus

A	Patient characteristics	$n = 160$
	Age in years (mean $\pm$ SD)	$\pm 3.2$
	Male [ $n$ (%)]	87 (54)
	Duration of symptoms in days [median (IQR)]	9 (6, 11)
B	Symptoms	$n$ (%)
	Fever	160 (100)
	Respiratory distress	67 (42)
	Nausea/vomiting	55 (34)
	Seizures	41 (26)
	Altered sensorium	39 (24)
	Abdominal pain	37 (23)
	Headache	24 (15)
	Bleeding	17 (11)
	Myalgia	13 (8)
	Diarrhea	13 (8)
	Oliguria	4 (2.5)
C	Signs	$n$ (%)
	Hepatomegaly	149 (93)
	Splenomegaly	92 (58)
	Lymphadenopathy	87 (54)
	Edema (facial/pedal)	75 (47)
	Eschar	40 (25)
	Rash	39 (24)
	Conjunctival hyperemia	20 (13)
	Petechiae	15 (9)
	Icterus	14 (9)
	Low GCS ( $<8$ )	13 (8)

GCS, glasgow coma scale; SD, standard deviation; IQR, interquartile range

**Table 2:** Laboratory findings at the time of admission

Laboratory markers <sup>a</sup>	n = 160
Hemoglobin g/dL	9.7 ± 1.7
Leukocyte count per mm <sup>3</sup>	11,800 (7,825, 16,725)
Platelet count per mm <sup>3</sup>	61,000 (26,000, 126,750)
Thrombocytopenia <150,000 per mm <sup>3</sup> [n (%)]	132 (82.5)
Severe thrombocytopenia <50,000 per mm <sup>3</sup> [n (%)]	72 (45)
AST U/L	136 (74, 243)
ALT U/L	81 (52, 139)
Albumin g/dL	2.4 ± 0.6
Hypoalbuminemia (<2.5 g/dL) [n (%)]	101 (63)
Urea mg/dL	44.8 ± 36
Creatinine mg/dL	0.57 ± 0.32
CRP mg/L	87.7 (32.4, 145)
Coagulopathy (INR > 1.5) [n (%)]	26 (20.8)
Sodium mEq/L	133.5 ± 6.3
Hyponatremia (<135) [n (%)]	99 (62)
Glucose mg/dL	108 ± 40.3
Hypoglycemia (<60 mg/dL) [n (%)]	7 (4.4)
Lactate mmol/L	2.75 ± 1.9

<sup>a</sup>Values expressed are mean ± SD or median (interquartile range)

**Table 3:** Organ dysfunction, supportive therapies, and outcomes

A	Organ dysfunction	n (%)
	Meningoencephalitis	46 (29)
	Shock at admission	
	Hypotensive	21 (13)
	Compensated	6 (4)
	ARDS	17 (11)
	AKI	26 (16)
	Acute liver failure	7 (4)
	Myocarditis	5 (3)
	Organ supportive care in PICU	n (%)
	Need for fluid boluses/vasoactive drug therapy during PICU stay	43 (27)
	Need for positive pressure ventilation during PICU stay	27 (17)
	No. of patients requiring osmotherapy (mannitol and/or 3% saline)	27 (17)
	No. of patients requiring renal replacement therapy	3 (2)
B	Outcome measures	Median (IQR)
	Duration of hospital stay, days	7 (4, 9)
	Duration of PICU stay, days	4 (3, 7)
	Time to defervescence, days	3 (2, 4)
	Duration of ventilation, hours	108 (48, 174)
	Deaths [n (%)]	14 (8.8)

ARDS, acute respiratory distress syndrome

Doxycycline was used in 143 (89.4%) and azithromycin in 13 (8.2%) patients. The median (IQR) duration of defervescence after starting antimicrobial therapy was 3 (2, 4) days. Evidence for coinfection or recent exposure to other tropical infections were identified in 20

cases. These included seropositivity for dengue (n = 6), enteric fever (n = 5), leptospirosis (n = 3), hepatitis A (n = 2), and HIV in one case. Malarial smears were positive in three cases. A total of 146 patients had survived to discharge with case fatality rate of 8.8%. The median (IQR) length of PICU and hospital stay were 4 (3, 7) and 7 (4, 9) days. We performed univariate analysis comparing demographic, clinical, and laboratory variables to identify the factors associated with PICU admission. On further multivariable analysis of all significant factors using the backward conditional method, presence of lymphadenopathy, respiratory distress, shock, elevated lactate, and meningoencephalitic presentation emerged as independent predictors for the need of intensive care (Table 4).

## DISCUSSION

Scrub typhus has become a pan-Indian phenomenon in the last decade with several published reports from diverse geographical regions of the subcontinent highlighting its varied clinical presentations. Early diagnosis of scrub typhus is challenging given the seasonal predilection and overlapping clinical features with many other tropical fevers. Majority of our children were above 5 years and tended to present during the 2nd week of illness. We observed a definite clustering during the post-monsoon months similar to previously reported trends.<sup>4-9</sup> Growth of secondary vegetation (scrubs) with the rain, prevalence of vectors, and increased outdoor activities by older children during this season increase the risk. The median duration of illness was 9 days, which is similar to a previous study from central India.<sup>10</sup> In a study from south India, 44% children had fever for 8–14 days, and 13% children had fever for more than 14 days.<sup>9</sup> In another study, about 96% of all patients presented after 5 days of fever; 48% (n = 25) presented in the second half of 1st week; while a further 38% (n = 20) presented in the first half of 2nd week and there were no clear localizing symptoms in the vast majority.<sup>7</sup> Presence of an eschar, considered a valuable clue for scrub typhus was present only in 25% of our cases and hence may not be a reliable surrogate for the illness. The reported incidence for eschar varied from 11 to 80% in most case series.<sup>5-7,9,20,21</sup> Variation in cutaneous immunity has been suggested as one of the reasons for an absent eschar in some cases; however, it can be easily missed if children are not carefully examined.<sup>10</sup>

We used IgM ELISA and PCR to diagnose scrub typhus. The immunofluorescence test is classically considered as the gold standard; however, IgM ELISA is used by many laboratories as it is cheap, simple, and has sensitivity >90%. The IgM ELISA used in our study has shown comparable results to the microimmunofluorescence test in previous studies.<sup>22,23</sup> The nested PCR protocol has a specificity of 100%.<sup>23</sup> In this study, all PCR products were sequenced and verified to be *O. tsutsugamushi*. The laboratory abnormalities observed in our cohort are in concordance with previously published reports in adults and children. Thrombocytopenia (82%) at admission was very common and in about half it was profound with counts below 50,000 cells/mm<sup>3</sup>. In previous studies, the incidence of thrombocytopenia has ranged from 22 to 78%.<sup>4-6,10</sup> Hypoalbuminemia was another frequent abnormality that has been reported as a marker of severity and mortality in adults with scrub typhus. Low serum albumin was associated with increased incidence of pulmonary edema, nonoliguric acute renal failure, longer hospital stay, and higher hospital cost.<sup>24</sup>

Organ dysfunctions are common in the early phase of the disease and improve well with the intensive care support. A recent

**Table 4:** Predictors of PICU admission (logistic regression model)

Variable	Intensive care admission		Univariate analysis <i>p</i> value	Multivariable analysis	
	No ( <i>n</i> = 94)	Yes ( <i>n</i> = 66)		<i>p</i> value	OR (95% CI)
Age in years median (IQR)	6 (4, 9)	8 (5, 10)	<b>0.03</b>	0.17	1.1 (0.9–1.3)
Male sex	58 (62)	29 (44)	<b>0.02</b>	0.30	0.5 (0.2–1.7)
Duration of symptoms in days, median (IQR)	10 (6, 12)	8.5 (6, 10)	0.25		
Respiratory distress	22 (23)	45 (68)	<b>0.0001</b>	<b>0.0001</b>	9 (3.4–24.3)
Altered sensorium	15 (16)	24 (36)	<b>0.003</b>	0.18	2.5 (0.6–9.9)
Seizures	22 (23)	19 (29)	0.44		
Edema	36 (38)	39 (59)	<b>0.01</b>	0.34	1.7 (0.5–5.7)
Rash	25 (27)	14 (21)	0.43		
Eschar	17 (18)	23 (35)	<b>0.02</b>	0.26	0.5 (0.2–1.7)
Lymphadenopathy	44 (47)	43 (65)	<b>0.02</b>	<b>0.016</b>	3.3 (1.3–8.6)
Hepatomegaly	87 (93)	62 (94)	0.49		
Splenomegaly	53 (56)	39 (59)	0.73		
Anemia (Hb < 9 g/dL)	29 (31)	28 (42)	0.13		
Leukocytosis (>11,000/mm <sup>3</sup> )	46 (49)	40 (61)	0.14		
Severe thrombocytopenia (<50,000/mm <sup>3</sup> )	36 (38)	36 (54)	<b>0.04</b>	0.8	1.2 (0.3–3.5)
Hyponatremia (<135 mEq/L)	62 (66)	37 (56)	0.20		
Severe hypoalbuminemia (<2.5 g/dL)	50 (53)	51 (77)	<b>0.002</b>	0.95	0.9 (0.3–3.2)
AST >100 U/L	49 (56)	49 (77)	<b>0.01</b>	0.56	1.4 (0.4–5.2)
ALT >100 U/L	26 (31)	33 (52)	<b>0.007</b>	0.57	0.7 (0.2–2.2)
Lactate > 2 mmol/L	17 (18)	30 (45)	<b>0.0001</b>	<b>0.01</b>	3.4 (1.3–8.9)
ARDS	2 (2)	15 (23)	<b>0.0001</b>	0.09	3.2 (0.9–5.5)
Meningoencephalitis	19 (20)	27 (41)	<b>0.004</b>	<b>0.005</b>	4.5 (1.6–12.7)
AKI	13 (14)	13 (20)	0.32		
Shock	6 (6)	21 (32)	<b>0.0001</b>	<b>0.002</b>	10.8 (2.4–48.6)
Myocarditis	1 (1)	4 (6)	0.16		

Bold font denotes statistically significant *p* values in univariate and multivariable analysis respectively

multicenter study reported that scrub typhus was among the leading causes of tropical fever admissions to Indian ICUs in both adults and children.<sup>13</sup> We observed 66 (41%) children with scrub typhus with one or more organ failures requiring PICU admission. Presence of lymphadenopathy, respiratory distress, shock, elevated lactate, and meningoencephalitis determined the requirement of intensive care. With scarcity of intensive care beds in resource-limited settings, our findings could help prioritize PICU resources for the most severe cases. The onset of respiratory distress may herald the onset of ARDS, the most frequently described organ dysfunction. The ARDS in scrub typhus results from interstitial pneumonitis and noncardiogenic pulmonary edema possibly driven by vasculitis. This feature helps discriminate scrub typhus from other undifferentiated fevers.<sup>1,25</sup> Central nervous system (CNS) dysfunction is not uncommon in severe scrub typhus infection.<sup>4,6,16</sup> It can be multifactorial with reasons ranging from direct CNS infection (meningitis or encephalitis) to other systemic factors such as hypoxia, renal failure, and hepatic dysfunction. Encephalitic presentations have been increasingly recognized in the recent literature with the reported incidence ranging from 5 to 30.3%. In this study too, meningoencephalitic presentation accounted for 29% of the cases and predicted the need for PICU admission. Myocarditis was seen in only 3% of our cases in contrast to studies from southern India reporting up to a third of cases.<sup>4,9</sup> Acute kidney injury was noted in 16% of our cases, the range varied from 10 to 20% in previous studies.<sup>4–6</sup> Acute kidney injury is usually caused by impaired renal perfusion due to volume depletion or

increased vascular permeability but acute tubular necrosis due to direct invasion by the *O. tsutsuamushi* has also been described.<sup>26</sup> Renal involvement in scrub typhus is increasingly recognized as a part of multisystem disease while oliguric AKI and need for renal replacement therapy are less common. Table 5 compares various complications reported in previous pediatric studies with those observed in our study.

Scrub typhus is a potentially treatable disease with an excellent therapeutic response. Most of our patients received doxycycline and the median period of defervescence was 3 days, a trend similar to other studies.<sup>4,5</sup> About 10% children had serological evidence of other tropical infections, though it was difficult to ascertain them as concurrent infections. Coinfections during seasons are not uncommon; hence, several guidelines recommend testing for treatable infections and covering them empirically at the outset.<sup>3</sup> The case fatality rate in the present study was 8.8%. Mortality from pediatric scrub typhus has ranged from 2.8 to 20% in different series. Several outcome predictors have been studied including duration of fever, absence of eschar, thrombocytopenia, ARDS, oliguric AKI, CNS dysfunction, etc., but none have been consistently reported.<sup>27,28</sup> Despite the severity of illness and high prevalence of multiorgan dysfunction, early treatment with doxycycline and good supportive care had shown favorable outcome in adults.<sup>29</sup> We believe that our study focusing on pediatric scrub typhus requiring intensive care would be a valuable addition to the recent descriptive literature addressing seasonal tropical fevers in India. The strength of this study is that it is the first study in children to

**Table 5:** Complications noted in various Indian studies on pediatric scrub typhus<sup>a</sup>

Complications	Kumar et al. (Puducherry) <sup>4</sup>	Bhat et al. (Dehradun) <sup>6</sup>	Palanivel et al. (Chennai) <sup>5</sup>	Kalal et al. (Bengaluru) <sup>8</sup>	Narayanasamy et al. (Puducherry) <sup>9</sup>	Masand et al. (Jaipur) <sup>10</sup>	Krishna et al. (Chennai) <sup>7</sup>	Ganesh et al. (Chennai) <sup>12</sup>	Present study (Chandigarh)
Year	2010–2011	2011–2012	2010–2011	2010–2012	2014–2015	2013	2010–2011	2012–2015	2013–2015
Number of patients	35	66	67	53	117	30	52	358	160
Age range	1.5–12 years	8 months–18 years	<12 years	<18 years	6 months–12 years	3–16 years	7 months–16 years	<18 years	3 months–12 years
Design	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Prospective	Retrospective
Cardiac dysfunction/ myocarditis	34%	9.1%			24%			0.5%	3%
Hepatitis	31%	13.6%	64.17%	81.1%	8%	60%	62%		
ALF			10.4%						4%
Thrombocytopenia (<1.5 lakh/mm <sup>3</sup> )	61%	27.2% (<50,000)	77.6% (<1 lakh)	66.7%	41%	26% (<1 lakh)	25% (<1 lakh)	23.2% (<1 lakh)	82.5%
AKI	20%	16.7%	10.4%		12%	3.3%	10%		16%
Meningoencephalitis	6%	30.3%	5.97%	17%	8%		7.7%	1.9%	29%
Pneumonia	3%	10.6%	14.9%		16%				
Respiratory failure/ ARDS	9%	12.1%	4.47%		8%	6.6%		3%	11%
DIC	9%	1.5%	1.5%		46%			0.2%	13%
Shock		25.8%	44.7%	10%				3.9%	17%
Mortality	2.8%	7.5%	11.9%	0	6.6%	0	0	0.8%	8.8%

ALF, acute liver failure; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation

<sup>a</sup>Published between 2011 and 2018 and a minimum of 30 cases

have looked into the predictors of PICU admission. Though the retrospective study design is a notable limitation, we analyzed a sizeable sample collected over three seasons that were confirmed by robust laboratory methods.

## CONCLUSION

Scrub typhus is an important childhood fever presenting with organ dysfunction in post-monsoon months to ED. Presence of lymphadenopathy, respiratory distress, circulatory shock, elevated lactate, and meningoencephalitic presentation predicted the need for intensive care.

## CLINICAL SIGNIFICANCE

Antimicrobial therapy with doxycycline and supportive care are the mainstay in treatment of scrub typhus. Our findings would guide clinicians identify severe cases that might benefit from intensive care and help prioritize resources during seasonal outbreaks.

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