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RESEARCH ARTICLE
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RESEARCH TITLE: " STUDY OF FACTORS INFLUENCING MORBIDITY AND ROLE OF DEXAMETHASONE IN LABORATORY-CONFIRMED DENGUE PATIENTS: A SINGLE CENTRE RETROSPECTIVE ANALYSIS"

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Abstract

Background: Dengue is a significant global health concern, particularly in tropical and subtropical regions. Understanding the factors influencing morbidity and the potential benefits of treatments like Dexamethasone is crucial for improving patient outcomes. This study focuses on the clinical and laboratory parameters that predict ICU admission and evaluates the role of Dexamethasone in managing severe Dengue cases.

Objectives: The study aims to determine the incidence of Dengue patients requiring critical care and extended hospital stays, identify clinical and laboratory risk factors associated with ICU admission, and investigate the effect of steroids, specifically Dexamethasone, in reducing hospital stay and complications in laboratory-confirmed Dengue patients.

Methodology: This observational, retrospective study used medical records of laboratory-confirmed Dengue patients at Vedant Hospital, Pimpri, Pune. Data collected included demographic information, clinical presentation, laboratory parameters, severity indicators, steroid usage, total length of stay, and ICU duration.

Results: Among 200 patients, 58% were male and 42% female, with a majority (94%) residing in urban areas. ICU admissions showed no significant associations with gender, address, or age. Decreased appetite (69% ICU vs. 39.4% non-ICU, $p<0.0001$) and chest pain (3.4% ICU vs. 0% non-ICU, $p=0.026$) were more common in ICU patients, while myalgia was more frequent in non-ICU patients (31% vs. 6.9%, $p<0.0001$).

ICU patients had lower platelet counts (61,310 ± 72,229 vs. 127,355 ± 87,736, $p<0.0001$) and higher bilirubin (0.88 ± 0.67 vs. 0.73 ± 0.30, $p=0.036$) and ALT levels (130.21 ± 129.03 vs. 92.98 ± 90.93, $p=0.022$). Neutrophil counts were higher in ICU patients (63.34 ± 15.71 vs. 57.13 ± 20.57, $p=0.04$). Hemoglobin levels were higher in ICU patients (14.21 ± 1.87 vs. 13.54 ± 1.70, $p=0.015$). Oxygen supplementation was required by 6.9% of ICU patients ($p<0.0001$).

Steroid use was more prevalent in ICU patients (93.1% vs. 84.5%). SDP transfusions were more common in ICU patients (72.4% vs. 1.4%, $p<0.0001$).

Patients treated with Dexamethasone (N=174) had longer illness durations (5.29 ± 1.41 days vs. 4.54 ± 1.10 days, $p=0.01$) and lower platelet counts (98.7 ± 86.4 x 10^3 vs. 171.8 ± 77.5 x 10^3, $p<0.001$), indicating Dexamethasone use in severe cases.

Conclusion: Significant clinical and laboratory differences exist between ICU and non-ICU Dengue

patients. Dexamethasone was used in more severe cases, suggesting its potential role in managing severe Dengue symptoms and complications. Further research is needed to determine the benefits of steroid use in Dengue treatment

INTRODUCTION

Dengue is a vector-borne disease that is a major public health threat globally. It is caused by the dengue virus (DENV, 1–4 serotypes), which is one of the most important arboviruses in tropical and subtropical regions(1). It results in a significant public health and economic burden in the endemic regions particularly in the WHO South-East Asia and Western Pacific Regions, accounting for nearly 75% of the current global dengue disease burden(2). High dengue disease burden and frequent outbreaks result in a serious drain on the country's economy and stress on the health systems. In India, case detection, case management, and vector control are the main strategies for prevention and control of dengue virus transmission(3).

As per the WHO 1997 classification, symptomatic dengue virus infection has been classified into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

(4)The symptoms of dengue fever individuals range from no signs, mild fever, high fever, pain behind eyes, headache, vomiting, and muscle pains. Severe cases can be massive bleeding, shock, and death(5).

Dengue is typically diagnosed by non-structural protein-1 (NS1) antigen capture assays, detectable up to nine days after symptom onset in primary infection(6).Climate variability/changes have a significant impact on vector populations. Factors, such as temperature, precipitation and humidity can influence vector development/survival rates, behavior and habitats(5).

Patients with dengue infection may present in the critical phase of their disease exhibited by severe plasma leakage (causing dengue shock and/or pulmonary edema with respiratory distress), severe hemorrhage, or severe organ impairment. Organ impairment may manifest as hepatic or renal impairment, respiratory failure, myocarditis, encephalopathy, or encephalitis. Such patients require intensive monitoring and care in an ICU setup. The outcome of such patients largely depends on early recognition and aggressive management of shock and organ failure. With good supportive care (primarily judicious use of parenteral fluid therapy for plasma volume losses due to leakage), mortality rates of less than 1% are possible even among severe cases. However, in rural regions with lack of facilities, the mortality rate may be higher(2).

The outbreak of Dengue fever is reported in many regions within India either seasonal or cyclic patterns since the last two decades. The actual cost of treatment of suspected Dengue fever or fever from other causes during the outbreak is not exactly known in Indian situations and availability of such literature are rare(7).

World Health Organization (WHO) has published guidelines for the management of dengue fever. This management prevents hemoconcentration during the early phase and fluid overload in the late phase of the illness and halts severe complications such as dengue shock syndrome (DSS) and multiple organ failure. Improved fluid management protocols have resulted in a large decrease in mortality in dengue infection. However, this approach does not consider any immune suppressive therapy to prevent immunological damage in dengue hemorrhagic fever

(DHF), DSS and other complications in dengue such as carditis, ascites, liver and renal damage, encephalitis and bleeding(8).

Co-morbidities in dengue patients result in complications leading to deaths. A study from Singapore reported that out of every 27 deaths due to dengue, 21 had comorbidities. Another study reported that dengue patients with allergies or diabetes are 2.5 times more at risk of developing dengue hemorrhagic fever. Likewise higher frequency of complications is reported in dengue patients suffering from hepatitis(9).

Corticosteroids are potent immune modulators and are used therapeutically for a broad spectrum of diseases including autoimmune, allergic and inflammatory diseases. However, the evidence from trials using corticosteroids in dengue is inconclusive and the quality of evidence is low to very low.

However, when immune-mediated mechanisms, cross-reacting antibodies, cytokines and chemokines are considered, the immune pathology of dengue has many similarities to other autoimmune diseases which have been treated effectively by corticosteroids for several decades.

Trials conducted by Kularatne et al (2009) and Shashidhara et al (2013) on use of different oral corticosteroids or intravenous dexamethasone in different doses(10-11). They used low dose dexamethasone (4 mg dexamethasone, followed by 2 mg doses every 8 hourly for 24 hours) whereas Shashidhara et al. (2013)examined the use of high dose dexamethasone (8 mg initially, followed by 4 mg every 8 hourly thereafter for 4 days) in adult dengue patients found that it was not effective in achieving a higher rise in the platelet count in the acute stage of dengue fever.Tam et al. (2012) who conducted a randomized controlled trial reported hyperglycemia in the steroid recipients but no association between use of Prednisolone and the predefined clinical, hematological, or virological endpoints.(12)

The present study focuses on factors influencing morbidity and the role of dexamethasone in laboratory-confirmed dengue patients contributes to our understanding of potential interventions and treatment strategies. By addressing these critical aspects, we aim to improve the care and outcomes of dengue patients, ultimately reducing the disease's impact on public health.

2. Objectives

The main objectives of the study are as follows:

- To determine the incidence of laboratory-confirmed Dengue patients requiring critical care and longer duration of hospital stay.
- To identify clinical and laboratory risk factors associated with ICU admission.
- To investigate the effect of steroids in reducing length of stay and other complications among laboratory-confirmed Dengue patients.

3. Methodology

This study was an observational, retrospective analysis utilizing data extracted from the medical records of patients with laboratory-confirmed Dengue. The study population encompassed both pediatric and adult patients diagnosed with Dengue and admitted to Vedant Hospital, Pimpri, Pune, during the year 2023.

Data collection involved a comprehensive review of medical records and hospital databases. The recorded variables included demographic information (age, sex, location, and month of admission), clinical presentation (symptoms, signs, and duration of illness), and laboratory parameters (complete blood count, liver function tests, renal function tests, coagulation profile, IL-6, serum LDH, and serum ferritin).

Severity indicators were meticulously documented and comprised the presence of severe bleeding manifestations, acute respiratory failure (necessitating oxygen support, non-invasive ventilation (NIV), or mechanical ventilation), acute kidney injury (elevated serum creatinine and blood urea nitrogen (BUN)), acute liver failure (elevated bilirubin, SGOT, and SGPT), and other relevant organ failures. Additionally, information regarding steroid administration during hospitalization, including dosage and frequency, was recorded, alongside the total length of hospital stay and duration of ICU stay.

Statistical analyses were conducted using IBM SPSS Statistics version 25. Descriptive statistics were utilized to summarize demographic and clinical characteristics. Categorical variables were compared using Chi-square tests, while continuous variables were analyzed using independent samples t-tests or Mann-Whitney U tests, as appropriate.

Observations and Results

There was male preponderance with 58% males and 42% females. Majority (94.0%) patients resided in corporation areas while 6.0% were from Rural areas. Total 23% patients were ≤20 years whereas only 4% cases were >60 years. There was no significant difference in distribution of cases between

ICU admitted and non-ICU admitted cases based on gender, address, or age groups.
Among patients admitted to the ICU 69.0% had decreased appetite, compared to only 39.4% in non-ICU admitted cases (p<0.0001) also 3.4% had chest pain compared to none in non-ICU admitted. (p=0.026) . Myalgia was present in significantly higher proportion (31%) in non-ICU admitted cases compared to ICU admitted cases (6.9%) (p<0.0001). Other symptoms were comparable between the two groups.

Table No 1: Demographic characteristics comparison Based on ICU admission.

Demographic Characteristics			Admitted to ICU		Total	P
			No (N=142)	Yes (N=58)		
Sex	Female	Number	64	20	84	0.169
		%	45.10%	34.50%	42.00%	
	Male	Number	78	38	116	
		%	54.90%	65.50%	58.00%	
Address	PUNE and PCMC	Number	136	52	188	0.098
		%	95.80%	89.70%	94.00%	
	Rural	Number	6	6	12	
		%	4.20%	10.30%	6.00%	
Age distribution	Up to 20 Years	Number	38	8	46	0.106
		%	26.80%	13.80%	23.00%	
	21 to 40 years	Number	72	30	102	
		%	50.70%	51.70%	51.00%	
	41 to 60 Years	Number	26	18	44	
		%	18.30%	31.00%	22.00%	
	> 60 years	Number	6	2	8	
		%	4.20%	3.40%	4.00%	

Table No 2: Symptoms Based on ICU admission**.**

Symptoms		Admitted to ICU		Total	P
		No (N=142)	Yes (N=58)		
Headache	Number	108	44	152	0.977
	%	76.1%	75.9%	76.0%	
Myalgia	Number	2	0	2	0.364
	%	1.4%	0.0%	1.0%	
Nausea	Number	94	34	128	0.311
	%	66.2%	58.6%	64.0%	
Rash	Number	6	0	6	0.112
	%	4.2%	0.0%	3.0%	
Abdomen Pain	Number	12	6	18	0.671
	%	8.5%	10.3%	9.0%	
Weakness	Number	116	48	164	0.852
	%	81.7%	82.8%	82.0%	
Dehydration	Number	2	0	2	0.364
	%	1.4%	0.0%	1.0%	
Myalgia	Number	44	4	48	<0.0001**
	%	31.0%	6.9%	24.0%	
Decreased Appetite	Number	56	40	96	<0.0001**
	%	39.4%	69.0%	48.0%	
COUGH	Number	2	0	2	0.364
	%	1.4%	0.0%	1.0%	
Chest Pain	Number	0	2	2	0.026*
	%	0.0%	3.4%	1.0%	
Tounge Bite	Number	2	0	2	0.364
	%	1.4%	0.0%	1.0%	

Table No 3: Comparison of Average Duration of Illness, Fever and Stay in hospital based on ICU admission.

Admitted to ICU		Duration of Illness (Days)	Fever (^{0} F)	Stay in hospital (Days)
No (N=142)	Mean	5.10	100.72	4.15
	SD	1.43	1.78	2.29
Yes (N=58)	Mean	5.41	101.25	4.93
	SD	1.28	1.51	1.37
Total	Mean	5.19	101.10	4.38
	SD	1.39	1.61	2.10
P		0.147	0.034	0.017

Average Duration of Illness was slightly lesser (5.10 ±1.43 days) in cases who were not admitted to ICU compared to 5.41±1.28 in ICU admitted cases. (p>0.05). Average baseline Fever was higher in ICU admitted cases compared to non-ICU admitted cases. (101.25 ± 1.51 vs 100.72 ± 1.78, p=0.034) . Also, average stay in hospital was higher in ICU admitted cases compared to non-ICU admitted cases (4.93±1.37 Vs4.15±2.29, p=0.017)

Table No 4: Lab parameters based on ICU admission.

	Admitted to ICU						
Lab Parameters	No (N=142)		Yes (N=58)		Total		
	Mean	SD	Mean	SD	Mean	SD	P
Hb	13.5	1.7	14.2	1.9	13.7	1.8	0.015*
Lymphocytes	29.8	15.0	26.9	10.7	28.9	14.0	0.196
Neutrophils	57.1	20.6	63.3	15.7	58.9	19.5	0.04*
RBC	4.4	1.4	4.6	1.0	4.5	1.3	0.528
WBC	4518.3	3105.9	5475.9	4155.6	4796.0	3460.0	0.076
Platelets	127354.9	87735.9	61310.3	72228.7	108202.0	88605.9	<0.0001**
ALT (SGOT)	93.0	90.9	130.2	129.0	103.8	104.5	0.022*
AST (SGPT)	66.2	67.3	83.5	72.1	71.2	69.0	0.108
Sr. Bilirubin	0.7	0.3	0.9	0.7	0.8	0.4	0.036*
HS-CRP	2.0	10.2	0.3	1.7	1.5	8.7	0.209
Sr. Creatinine	0.9	0.2	1.0	0.3	0.9	0.3	0.7

The average platelet count in patients who were not admitted to the ICU was 127354.93 ± 87735.88 was significantly higher compared to those who were ICU admitted (61310.34 ± 72228.73) (p<0.0001). Average Sr. Bilirubin level was 0.88 ± 0.67 in ICU-admitted patients as compared to 0.73 ± 0.30 in non-ICU patients showing significant mean difference.(p=0.036) Average ALT (SGOT) levels in in non-ICU patients (92.98 ± 90.93)were significantlu lower compared to ICU admitted patients (130.21 ± 129.03)(p=0.022*). Average Neutrophil counts in non-ICU patients were lower (57.13±20.57) compared to ICU admitted patients (63.34 ± 15.71) (p=0.04*). Patients who were not admitted to the ICU, the average haemoglobin level was 13.54 ± 1.70 compared to 14.21 ± 1.87 in ICU admitted cases. (p=0.015*). Other lab parameters were comparable between the two groups.

Table No 5: Distribution of Treatments given based on *ICU admission.*

			Admitted to ICU		Total	P
			No (N=142)	Yes (N=58)		
O2 supplements	No	Number	142	4	196	
		%	100.0%	6.9%	98.0%	
	Yes	Number	0	54	4	<0.0001
		%	0.0%	93.1%	2.0%	
DEXAMETHASONE given	No	Number	22	4	26	
		%	15.5%	6.9%	13.0%	
	Yes	Number	120	54	174	
		%	84.5%	93.1%	87.0%	0.101
SDP transfusion	No	Number	140	16	156	
		%	98.6%	27.6%	78.0%	
	Yes	Number	2	42	44	<0.0001
		%	1.4%	72.4%	22.0%	

In non-ICU admitted patients, none of the patient required O2 supplementation, while 6.9% of ICU patients required O2 supplement.(p<0.0001)
15.5% of non-ICU admitted patients and 6.9% of ICU patients overall did not receive dexamethasone, respectively. whereas 84.5% of non-ICU admitted patients and 93.1% of ICU patients received injectable doses of dexamethasone.
Only 1.4% of non-ICU hospitalised patients received SDP transfusions whereas 72.4% of ICU patients received SDP transfusion.(p<0.0001)

Table No 6: Assessment of Independent Risk factors for ICU admission**.**

Risk Factor	Number	Number in ICU admission	ODD	95% CI	P
Age >50 years	8	2	1.23	0.24 to 6.30	0.799
Duration of fever ≥ 5 days	148	46	0.665	0.320 to 1.38	0.274
Stay in ICU >3 days	186	54	0.978	0.29 to 3.25	0.971
Platelet count <1 lac	90	12	4.67	2.28 to 9.56	<0.0001**
Platelet count <50,000	140	14	24.75	11.17 to 54.81	<0.0001**
Fever >101 Degree F	32	2	7.5	1.73 to 32.517	0.002**
Decreased appetite	104	18	3.41	1.78 to 6.53	<0.0001**
Sr. Creatinine >1	56	22	1.94	1.008 to 3.74	0.46
Lymphocytopenia	188	56	2.12	0.45 to 9.99	0.331
Lymphocytosis	182	56	3.556	0.79 to 15.988	0.08
SGPT > 40	38	18	2.74	1.32 to 5.69	0.006**
SGOT >40	42	18	2.21	1.08 to 4.49	0.026*
Neutropenia (< 2500)	188	56	2.12	0.45 to 9.99	0.331
N/L Ratio > 5	14	6	1.933	0.64 to 5.84	0.236

Among the total risk factors, Platelet count <1 lac(OR=4.67, 95% CI=0.24 to 6.30,p<0.0001**), Platelet count <50,000(OR=24.75, 95% CI=11.17 to 54.81,p<0.0001**),Decreased appetite(OR=3.41, 95% CI=1.78 to 6.53 ,p<0.0001**) Fever >101 Degree F(OR=7.5, 95% CI=1.73 to 32.517,p=0.002) followed by SGPT > 40(OR=18, 95% CI=1.32 to 5.69,p=0.006**) emerged as highly significant independent risk factor for ICU admission.
Other significant risk factor was SGOT >40 (OR=18, 95% CI=1.08 to 4.49,p=0.026) . Neutropenia (Neutrophils < 2500) (OR=56, 95% CI=0.45 to 9.99, p=0.331), N/L Ratio > 5(OR=6, 95% CI=0.64

to 5.84, p=0.236), Lymphocytosis(OR=56, 95% CI=0.79 to 15.988, p=0.08) and Sr. Creatinine >1(OR=22, 95% CI=1.008 to 3.74, p=0.46) were found to be non-significant risk factors for ICU admission.

Table 7: Comparison Based On Steroids Given

Parameters	Dexamethasone given	N	Mean	SD	P
Age	Yes	174	33.6	15.1	0.61
	No	26	32.1	14.4	
Duration of Illness	Yes	174	5.3	1.4	0.01
	No	26	4.5	1.1	
Platelets	Yes	174	98703.4	86398.4	<0.001
	No	26	171769.2	77511.4	
Duration of ICU in days	Yes	174	1.7	1.2	0.01
	No	26	1.3	0.7	

Patients treated with Dexamethasone (N=174) compared to those who were not (N=26), showed no significant age difference between the groups. However, significant differences were noted in the duration of illness and platelet counts. The Dexamethasone group had a longer mean duration of illness at 5.29 ± 1.41 days compared to 4.54 ± 1.10 days in the non- Dexamethasone group [P=0.01], and a lower baseline mean platelet count (98.7 ± 86.4 x 10^3) versus 171.8 ± 77.5 x 10^3 in the non-treated group [P<0.001]. These results suggest that Dexamethasone was given to more severe cases of dengue having longer duration of illness and lower platelet counts.

DISCUSSION

Dengue infection results in a wide spectrum of clinical severity, from self-limiting dengue fever to severe dengue. Timely appropriate monitoring and clinical management, mainly with fluid interventions of dengue patients is critical to reduce morbidity and mortality (1) In this single centre based study we found that 58 patients (27%) required ICU admission.

Dengue generally affects the younger population, and other Indian studies have also reported a higher incidence in males similar to the present study (2)

Fifty-eight (27%) patients in our study required admission to intensive care units (ICU) which is very low compared to the study by Leo Y-S *et al.*, (2011) who conducted retrospective multicenter trial including 28 adult dengue deaths. Out of which Twenty (71.4%) patients were admitted to intensive care units(7) .

An Indian study by Rajender A. et al reported that the main cause of ICU admission was shock or hypotension due to sepsis (20%), closely followed by severe thrombocytopenia (19.05%) and respiratory failure (18.1%).(6) Among the warning signs, abdominal pain was seen in thirty-nine patients (37.4%). Vomiting (35.2%) and restlessness (34.3%) were other common warning signs associated. 61 (58.1) patients had hemorrhagic manifestations(6)

In considering the significance of individual warning signs in dengue-related fatalities, a retrospective study conducted in Puerto Rico highlighted four major warning signs observed in dengue deaths: abdominal pain, persistent vomiting, abrupt temperature changes, and abnormal mental status (18). Similarly, all twelve fatalities in Cuba exhibited headache, persistent vomiting, malaise, bleeding, and shock (19). Another study in Singapore reported that abdominal pain and nausea/vomiting were prevalent in half of adult dengue-related deaths (20).

In our study, although no mortalities were observed, we assessed the risk for admission to the Intensive Care Unit (ICU). It was noted that 69.0% of admitted cases experienced decreased appetite, significantly higher than the 39.4% observed in non-ICU admitted cases (p<0.0001). Additionally, another notable warning sign for ICU admission was chest pain (p=0.02).

Dengue patients who require admission to the intensive care unit (ICU) often exhibit distinct clinical

and laboratory risk factors. A study conducted in Singapore pinpointed early risk factors for ICU admission, including a hematocrit change of ≥20% concurrent with a platelet count of <50 K, hypoproteinemia, hypotension, and severe organ involvement.(10) Another study underscored that age, comorbidities, the presence of at least one alert sign, a platelet count of <30×10^9/L, a prothrombin time of <60%, AST and/or ALT levels >10N, and a previous dengue infection were major risk factors.(21) Comparing these findings to our present study, several similarities and differences emerge. Similarities include the recognition of a platelet count of <50,000 (OR=24.75, 95% CI=11.17 to 54.81, p<0.0001**) and SGPT > 40 (OR=18, 95% CI=1.32 to 5.69, p=0.006**) as highly significant independent risk factors for ICU admission. Additionally, both studies identified SGOT >40 (OR=18, 95% CI=1.08 to 4.49, p=0.026) as a notable risk factor.

However, differences arise in the specific thresholds and parameters considered. For instance, the earlier studies highlighted a platelet count of <30×10^9/L as a significant risk factor, while our study focused on a threshold of <50,000. The variations in the inclusion of neutropenia, N/L Ratio > 5, lymphocytosis, and Sr. Creatinine >1 as non-significant risk factors for ICU admission further contribute to the nuanced understanding of dengue-related complications across studies.

The role of corticosteroids in dengue treatment has been a subject of extensive research. Since 1998, studies have consistently used prolonged low-dose corticosteroid therapy, and analysis of this subgroup suggests a beneficial drug effect on short-term mortality.(22) This study aligns with the observation that corticosteroids, specifically Dexamethasone, are often administered to patients with severe dengue symptoms, as indicated by a longer duration of illness and lower platelet counts.(23) This is consistent with some studies suggesting potential benefits of corticosteroids in preventing progression to severe dengue if administered early, and in improving survival rates in patients with dengue-related shock. However, the Cochrane review concluded that the evidence supporting corticosteroid use in dengue treatment is inconclusive and of low to very low quality. (24) Moreover, the CDC advises against the use of corticosteroids in dengue management due to potential risks such as gastrointestinal bleeding, hyperglycemia, and immunosuppression.(25). Tam et al reported that use of oral prednisolone during the acute stage of dengue infection was not associated with significant clinical or virological adverse effects, nor with a reduction in the incidence of recognized complications of dengue.(17).

These findings underscore the complexity of dengue treatment and the need for further high- quality, randomized controlled trials to conclusively determine the role of corticosteroids. This study adds valuable insights to this ongoing discussion, highlighting the importance of considering patient severity when administering corticosteroids.

Conclusion

Our study identified significant risk factors for ICU admission in Dengue patients, including low platelet counts, decreased appetite, and elevated liver enzyme levels. The administration of dexamethasone showed comparable efficacy in more severe cases. These findings enhance our understanding of critical care needs in Dengue patients, guiding better management strategies.

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