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# The apache II Score and mortality in relation to hypocalcaemia in critically Ill patients

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**Abstract**
**Aim:** To study the frequency of hypocalcemia in patients admitted to an intensive care unit and whether hypocalcemia has any correlation with disease severity measured by acute physiology and chronic health score APACHE II.
**Materials and methods:** The prospective study was carried out in Chattrapati Shivaji Subharti Hospital, Meerut in the Department of Medicine among 100 critically ill patients who were admitted in the ICU. The patients underwent a detailed history including past, treatment and personal history to identify possible aetiologies and a thorough clinical examination to identify the hypocalcemia. Demographic information, clinical information and the (APACHE) II score was collected and patients were followed up to determine mortality. Ionized calcium (iCa), pH and lactate results was obtained from blood gas analysis on whole arterial blood collected in heparinized syringes.
**Results**: Burn, cardiac, medical, neurology, respiratory and trauma was revealed among the 12%, 6%, 41%, 18%, 12% and 11% of the subjects respectively. Normal calcium level was found among 43% of the subjects while hypocalcemia was reported among 57% of the subjects. It was found that APACHE II score increases with decrease in calcium level. Mortality was revealed among 13.95%, 14.82%, 42.86% and 43.85% of the subjects having normocalcaemic, mild, moderate and severe hypocalcemic level.
**Conclusion**: In this study, severely hypocalcemic patients on admission whose calcium failed to rebound to normal trended towards having a higher mortality and may be a target for intervention.

**Keywords:** calcium, APACHE II, mortality

## Introduction

Electrolytes play a major role in most of the physiological processes, from maintaining electrical properties across the membranes to the release of many hormones and muscle contraction. Small electrolyte imbalances are very harmful to the human systems and have to be monitored very carefully in the patients. The assessment of the serum electrolyte values is of vital importance in caring for the critically ill patients [1, 3].

Calcium is one of the common cations found in Extracellular Fluid (ECF) and of great importance in critical care practice. The ECF concentration of calcium is kept constant by processes that continuously add or remove calcium. Pumping intracellular calcium out of the cytosol in to the sarcoplasmic reticulum or ECF is energy dependent. During shock, intracellular energy is depleted and calcium accumulates within cells which may facilitate cell death5. Kidneys are the major organ responsible for regulating the plasma concentration of calcium. As acute kidney injury, sepsis, shock etc., are very much prevalent in critically ill patients, extracellular calcium is expected to be low in such severely ill patients [4].

Hypocalcemia is defined as a reduction in ionized serum calcium (Ca) concentration. In critically ill patients, it is a relatively common laboratory abnormality [5, 6]. Hypocalcaemia is a common finding in the critically ill patients who are admitted to the adult as well as the paediatric intensive care units (ICU) [7, 8]. and in patients who are admitted with trauma [9, 10]. Critically ill surgical patients and leukaemic patients with infections have been shown to present with hypocalcaemia [11, 12]. The ionized and total calcium levels were also found to be lower in children with meningococcal infections and were found to be well related to the severity of the disease [13]. Several studies have reported increased mortality in critically ill septic patients with hypocalcemia compared with similar patients without hypocalcemia. However, most of these studies restricted their evaluations to medical ICU and a few surgical ICU patients [14, 15].

Acute physiology and chronic health score (APACHE) is one of the most commonly used and validated scoring tool used to assess the severity of illness in critically ill patients. Development of the original APACHE (acute physiology and chronic health evaluation) severity-of-illness classification system began in 1978 with the specific goal of developing a measure for use in describing groups of intensive care unit (ICU) patients and evaluating their care. In the present study, APACHE II will be used which was simpler version of APACHE. It is based on 12 of the most commonly measured physiologic measures included in the original APACHE system [16].

Several factors can alter the proportion of total calcium that is ionized and studies have shown that adjusted calcium formulae do not provide a reliable substitute for ionized calcium in various groups of critically ill patients [17, 19]. Despite this, adjusted calcium continues to be used in many ICUs to guide clinical practice. The present study was envisioned to study the frequency of hypocalcemia in patients admitted to an intensive care unit and whether hypocalcemia has any correlation with disease severity measured by acute physiology and chronic health score APACHE II.

## Materials and methods

The prospective study was carried out in Chattrapati Shivaji Subharti Hospital, Meerut in the Department of Medicine among 100 critically ill patients who were admitted in the ICU. Informed consent was obtained from all patients. The patients underwent a detailed history including past, treatment and personal history to identify possible aetiologies and a thorough clinical examination to identify the hypocalcemia.

All participants were told about the study and informed consent was taken.

### Inclusion Criteria

1. Patients of either sex with age more than >18 years;
2. Who remained hospitalized for at least 24 hours.

### Exclusion Criteria

1. Patient who died before 24 hours of ICU stay;
2. Patients who had received intravenous calcium supplement just before ICU admission.

### Method

a. Demographic information, clinical information and the (APACHE) II score [43] was collected and patients were followed up to determine mortality.
b. Sepsis status was checked on a daily basis according to the 1992 ACCP/SCCM consensus guidelines [44].
c. All blood tests were carried out as part of routine clinical practice and consisted of daily serum chemistry and 4-hourly blood gas analysis unless otherwise dictated by clinical need.
d. Admission serum biochemistry and blood gas results were (defined as the first available results within 24 h of the recorded admission date) recorded alongside the serum biochemistry and blood gas results at 6 am (±2 hours) for the 3 days following admission.
e. Ionized calcium (iCa), pH and lactate results was obtained from blood gas analysis on whole arterial blood collected in heparinized syringes.

### Investigations

Patients were subjected to the routine work up including:

a. Complete blood count
b. Serum creatinine
c. Serum calcium
d. Magnesium
e. Albumin
f. Acute Physiology and Chronic Health Evaluation (APACHE) II score
g. Ionized calcium (iCa),
h. pH
i. Lactate

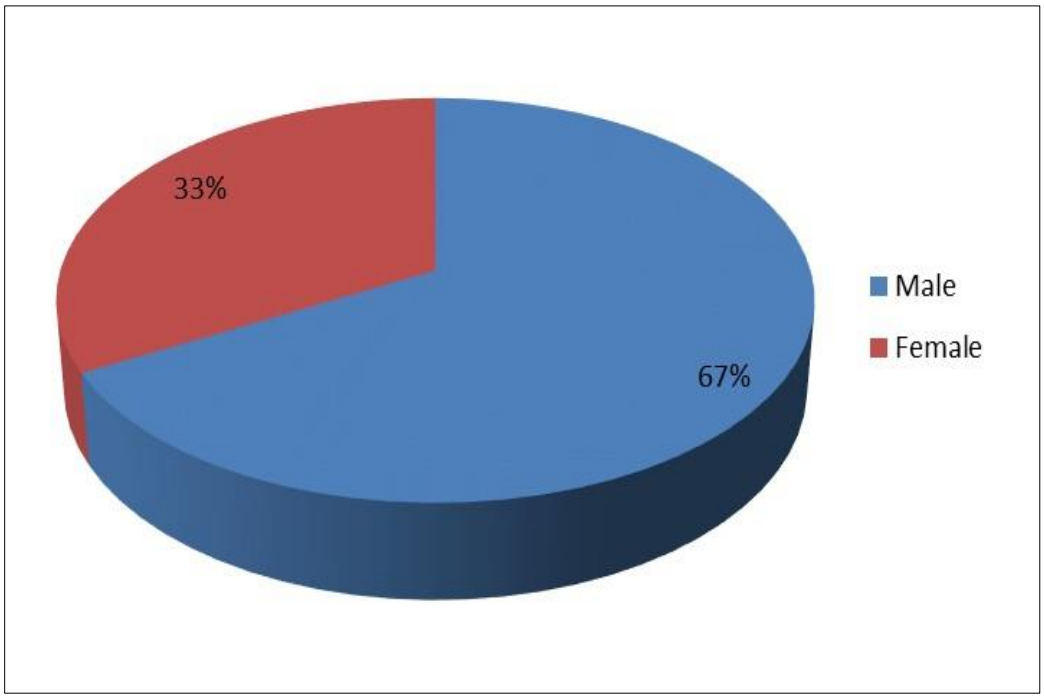
Data was collected and subjected to statistical analysis.

### Statistical analysis

Data were tabulated and examined using the Statistical Package for Social Sciences Version 22.0 (IBM SPSS Statistics for Mac, Armonk, NY: IBM Corp, USA). Descriptive statistical analysis had been carried out in the present study. Results on continuous measurements are presented as Mean±SD. Categorical data has been presented as frequency distribution. The statistical power calculation was based on the assumption that the data were normally distributed. P-value of <0.05 was considered as significant. Difference between two groups was determined using chi square test and student T test for categorical data and continuous data respectively.

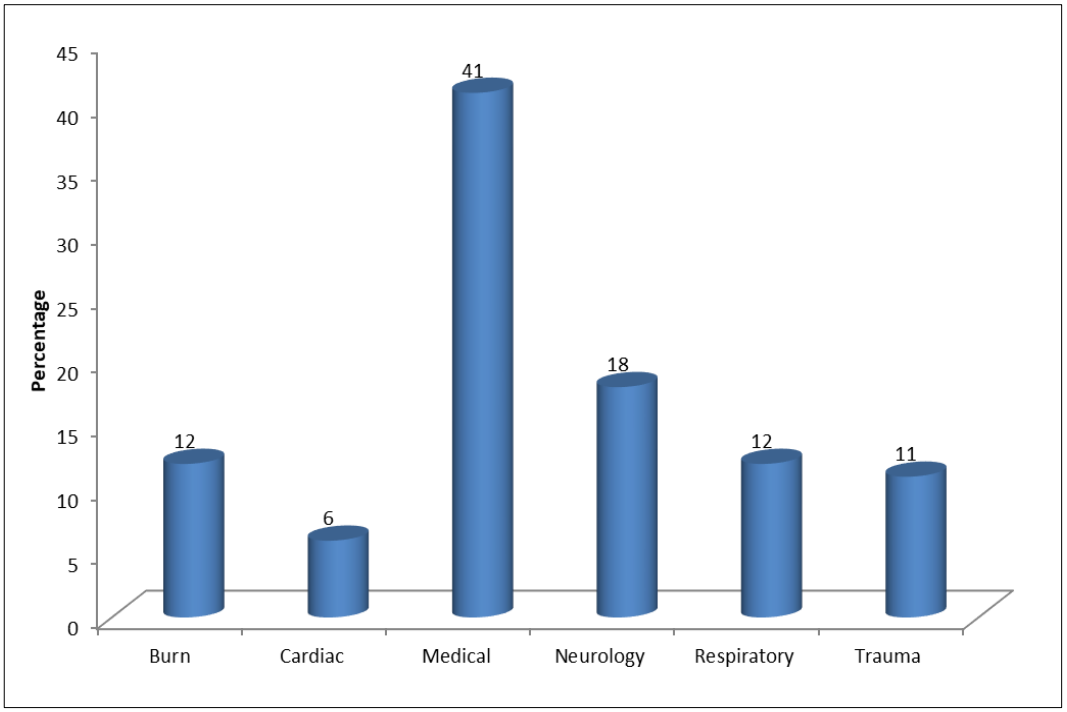
## Results

The present study comprised of 100 subjects, out of which 67 were males and 33 were females. The mean age of the study subjects was 53.81±13.48 years (graph 1). Hypertension, diabetes, COPD and other co-morbidities were reported among 17%, 12%, 14% and 3% of the subjects respectively.



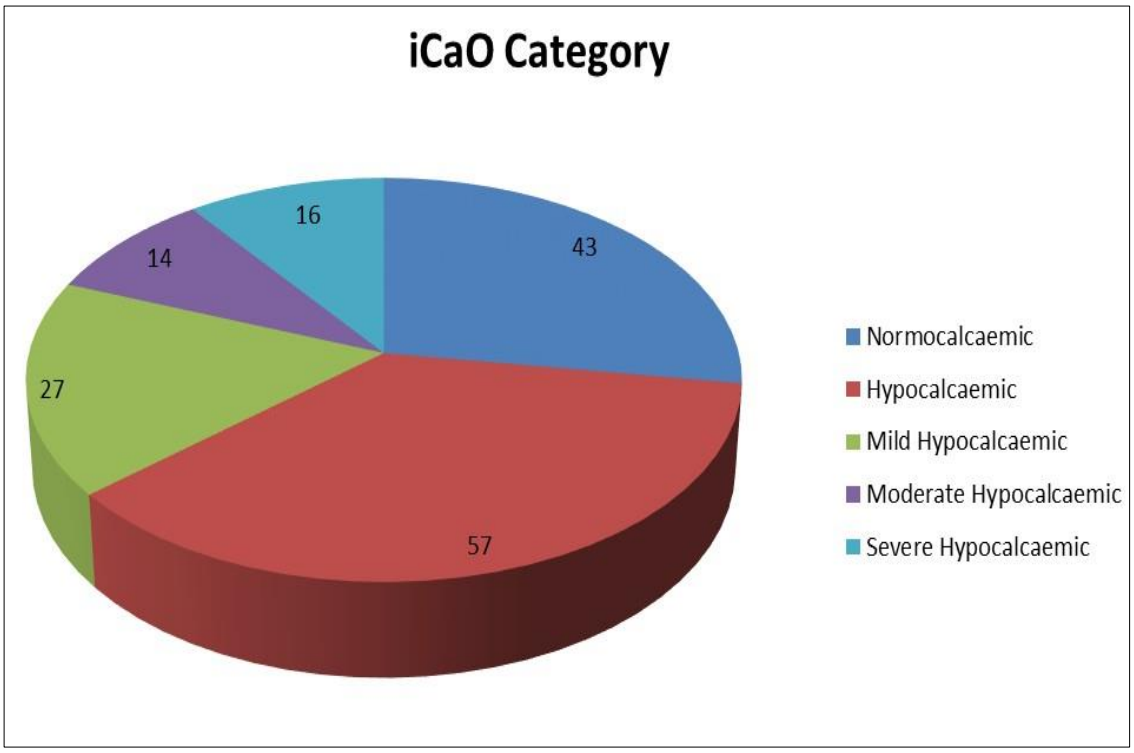

**Graph 1:** Gender distribution among the study subjects

Burn, cardiac, medical, neurology, respiratory and trauma was revealed among the 12%, 6%, 41%, 18%, 12% and 11% of the subjects respectively (graph 2).




**Graph 2:** ICU types among the study population

Normal calcium level was found among 43% of the subjects while hypocalcemia was reported among 57% of the subjects. Out of 57 hypocalcaemic subjects; mild, moderate and severe hypocalcemia was revealed among 27%, 14% and 16% of the subjects respectively (graph 3). APACHE-II score <9, 10-19 and >20 was reported among 8%, 58% and 34% of the subjects respectively.




**Graph 3:** Distribution of patients based on calcium level

It was found that APACHE II score increases with decrease in calcium level. Mean APACHE II score among mild, moderate and severe hypocalcemic was 17.93±7.05, 21.64±5.92 and 22.17±6.19 respectively. When mean

APACHE II score was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically significant as $p<0.05$ (table 1).

**Table 1:** APACHE II of normocalcaemic and hypocalcaemic patients

| iCaO Category | APACHE II | | p value$^{\lambda}$ |
|---|---|---|---|
| | Mean | SD | |
| Normocalcaemic | 15.38 | 6.13 | Reference |
| Mild Hypocalcaemic | 17.93 | 7.05 | 0.23 |
| Moderate Hypocalcaemic | 21.64 | 5.92 | 0.036* |
| Severe Hypocalcaemic | 22.17 | 6.19 | 0.003* |

$^{\lambda}$**:** t test, *: statistically significant

Mean length of stay in ICU among normocalcaemic, mild, moderate and severe hypocalcemic was 5.21±5.79, 5.14±6.11, 7.05±5.89 and 4.88±4.1 respectively. The length of ICU stay in severe hypocalcaemic is less because of mortality. When mean length of stay in ICU was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically insignificant as $p>0.05$ (table 2).

**Table 2:** Length of stay in ICU of normocalcaemic and hypocalcaemic patients

| iCaO Category | Length of ICU Stay (in days) | | p value$^{\lambda}$ |
|---|---|---|---|
| | Mean | SD | |
| Normocalcaemic | 5.21 | 5.79 | Reference |
| Mild Hypocalcaemic | 5.14 | 6.11 | 0.92 |
| Moderate Hypocalcaemic | 7.05 | 5.89 | 0.11 |
| Severe Hypocalcaemic | 4.88 | 4.16 | 0.38 |

$^{\lambda}$**:** t test

Mortality was revealed among 13.95%, 14.82%, 42.86% and 43.85% of the subjects having normocalcaemic, mild, moderate and severe hypocalcemic level. When mortality was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically significant with moderate and severe hypocalcemic level as $p<0.05$ (table 3).

**Table 3:** Mortality among normocalcaemic and hypocalcaemic patients

| iCaO Category | Mortality | | p value$^{\gamma}$ |
|---|---|---|---|
| | N | % | |
| Normocalcaemic | 6 | 13.95 | Reference |
| Mild Hypocalcaemic | 4 | 14.82 | 0.83 |
| Moderate Hypocalcaemic | 6 | 42.86 | 0.021* |
| Severe Hypocalcaemic | 7 | 43.85 | 0.018* |

$^{\gamma}$: Chi Square test, *: statistically significant

Mean APACHE II score among survivors and non-survivors was 16.09±5.87 and 16.09±5.87 respectively. When mean APACHE II score was compared statistically according to outcome, it was found to be statistically insignificant as $p>0.05$ (table 4).

**Table 4:** APACHE II score according to outcome

| Mortality | APACHE II | | p value$^{\gamma}$ |
|---|---|---|---|
| | Mean | SD | |
| Yes | 22.47 | 6.83 | 0.007* |
| No | 16.09 | 5.87 | |

*: statistically significant

## Discussion

Considering the important role of calcium in the human body, the high prevalence of hypocalcaemia in ICU patients and the low number of studies assessing the correlation between calcium indicators with ICU outcome, the present study was undertaken to analyse the frequency of hypocalcemia in patients admitted to an intensive care unit and whether hypocalcemia has any correlation with disease severity measured by acute physiology and chronic health score APACHE II.

The present study comprised of 100 subjects, out of which 67 were males and 33 were females. The mean age of the study subjects was 53.81±13.48 years. Samarjit Dey *et al* [20] in their study found 58 (52.25%) males and 53 (47.75%) females with mean age 47.85±19.29 years. In a study by Tom Steele *et al*21, median age on admission was 61 years (IQR 48-73) and 56.8% of patients were men. These results are approximately similar to the present study. Julie R. Zivin *et al* [22] too similar age and gender distribution.

Hypertension, diabetes, COPD and other co-morbidities were reported among 17%, 12%, 14% and 3% of the subjects respectively in our study. Julie R. Zivin *et al* [22] too reported similar distribution of co-morbidities in their study. Burn, cardiac, medical, neurology, respiratory and trauma was revealed among the 12%, 6%, 41%, 18%, 12% and 11% of the subjects respectively in this study. Julie R. Zivin *et al* 22 reported broad range of admission diagnoses for ICU patients, although the majority of were admitted for either multiple trauma or an acute neurological event (mostly intracranial hemorrhages and seizures).

Normal calcium level was found among 43% of the subjects while hypocalcemia was reported among 57% of the subjects. Out of 57 hypocalcaemic subjects; mild, moderate and severe hypocalcemia was revealed among 27%, 14% and 16% of the subjects respectively. Similarly Tom Steele *et al* [21] reported hypocalcemia among 55% of the subjects. In a study by Samarjit Dey *et al* [20], seventy eight patients (70.27 %) of the cohort were having hypocalcaemia (36.94% mild, 9.91% moderate and 23.42% severe) on admission. The prevalence of 57% was slightly lower than recently reported values, which have ranged to beyond 80%, probably reflecting higher cut off values for hypocalcemia.

It can be well appreciated that APACHE II score increases with decrease in calcium level. Mean APACHE II score among mild, moderate and severe hypocalcemic was 17.93±7.05, 21.64±5.92 and 22.17±6.19 respectively. When mean APACHE II score was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically significant as $p<0.05$. In a study by Samarjit Dey *et al* [20], the mean APACHE-II score of normocalcaemic patients were significantly ($p<0.05$) lower as compared to moderate and severe hypocalcaemic patients (15.57±6.85 versus 21.72±6.37 and 15.57±6.85 versus 22.34±7.53 respectively). The mean iCa0 level in patients with APACHE-II <9 (class a) were significantly higher than patients with APACHE-II >20 (class c) (1.09±0.24 versus 0.88±0.26; $p<0.05$). These findings were similar to our study.

Mortality was reported among 23% of the subjects in our study. Mean APACHE II score among survivors and non-survivors was 16.09±5.87 and 16.09±5.87 respectively. When mean APACHE II score was compared statistically according to outcome, it was found to be statistically insignificant as $p>0.05$. The APACHE II score and the simplified acute physiology score (SAPS) are the most commonly used scoring systems to predict the outcomes in critical illness. Recently, Iqbal M *et al* [11] used the APACHE II score to classify the severity of the illness, they sub grouped the critically ill patients into three groups and reported that hypocalcaemia and disease severity (APACHE II scores) were negatively correlated. Out of the 17 expired cases in the current study, 14 of them (82%) were in group C, having an APACHE II score of >25 and 13 out of the 14 who expired in group C (93%) had hypocalcaemia. These observations indicated that there was increased mortality with increasing APACHE scores and decreasing calcium levels.

In our study; mean length of stay in ICU among normocalcaemic, mild, moderate and severe hypocalcemic was 5.21±5.79, 5.14±6.11, 7.05±5.89 and 4.88±4.1 respectively. The length of ICU stay in severe hypocalcaemic is less because of mortality. When mean length of stay in ICU was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically insignificant as $p>0.05$. Mortality was revealed among 13.95%, 14.82%, 42.86% and 43.85% of the subjects having normocalcaemic, mild, moderate and severe hypocalcemic level. When mortality was compared statistically between normocalcemic and mild, moderate, severe hypocalcemic categories, it was found to be statistically significant with moderate and severe hypocalcemic level as $p<0.05$. Samarjit Dey *et al* [20] too found increased mortality and length of stay in ICU in patients admitted with moderate hypocalcaemia (iCaO of 0.81 – 0.90 mmol/L), but the differences as compared to other on admission hypocalcaemic as well as normocalcaemic patients were not statistically significant. Ravindra Prabhu Attur *et al* in their study revealed similar results too. 3 Several authors have described a significantly higher mortality rate in severely hypocalcemic patients in particular and suggested that it is in this group in which the association is clinically significant [21].

In contrast to our study, Tom Steele *et al* [21] found no significant association between hypocalcemia on admission and mortality. The failure in their study to reach statistical significance was most likely due to the small number of patients who were severely hypocalcemic on admission and in whom calcium levels were available on day 4. It appears that in patients with mild hypocalcemia on admission, normalization of ionized calcium level does not have an influence on mortality. However, in patients with severe hypocalcemia, normalization of calcium concentrations may be less likely to occur and mortality may be higher in this group, suggesting they could be targets for intervention.

The present study finding cannot give a conclusive interpretation of whether increasing hypocalcaemia is associated with increasing severity of illness or not in adult ICU patients. However, it is indicative of the fact that, hypocalcaemia of moderate and severe grade should most probably be considered as similar clinical entity of importance and targeted for treatment and research. The present study was also limited with the fact that the sample size is relatively smaller. Therefore further study with higher sample size is required to draw a stronger conclusion.

## Conclusion

Hypocalcemia is a common finding in patients admitted to a general ICU. In this study, severely hypocalcemic patients on admission whose calcium failed to rebound to normal trended towards having a higher mortality and may be a target for intervention. Findings also indicate that calcium supplementation is not associated with calcium normalization or improved outcome, although this study was observational in nature. A large randomized controlled trial of calcium supplementation in critically ill patients with different degrees of hypocalcemia is required to determine the effectiveness and side effects of this treatment and its role in clinical practice. In conclusion, our study has shown a negative trend of hypocalcaemia with respect to the APACHE II score, and a direct positive correlation between hypocalcaemia and mortality in the critically ill patients. This study may help in checking for hypocalcaemia as an indicator of mortality in the critically ill patients. However, the pathophysiological cause effect mechanism has to be worked out by further consideration.

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