Trial of Furosemide to Prevent Acute Kidney Injury in Critically Ill Children: A Double-Blind, Randomized, Controlled Trial

Shilpa Abraham, Ramachandran Rameshkumar, Muthu Chidambaram, Rajendran Soundravally, Seenivasan Subramani, Rohit Bhowmick, Abraar Sheriff, Kaushik Maulik, Subramanian Mahadevan

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Abstract

Objective To study whether furosemide infusion in early-onset acute kidney injury (AKI) in critically ill children would be associated with a reduced proportion of patients progressing to the higher stage (Injury or Failure) as compared to placebo.

Method A double-blind, placebo-controlled, randomized pilot trial was conducted. The authors enrolled children aged 1-mo (corrected) to 12-y, who were diagnosed with AKI (“risk” stage) using pediatric-Risk, Injury, Failure, Loss, End stage kidney disease (p-RIFLE) criteria, and achieved immediate resuscitation goals within 24 h of admission. Participants received either furosemide (0.05 to 0.4 mg/kg/h) or placebo (5%-dextrose) infusion. The primary outcome was the proportion of patients progressing to a higher stage (injury or failure). Secondary outcomes were (i) need for renal replacement therapy, (ii) the effect on neutrophil gelatinase-associated lipocalin (urine and blood), (iii) fluid balance, (iv) adverse effects, (v) time to achieve renal recovery, (vi) duration of hospital stay and mechanical ventilation, and (vii) all-cause 28-d mortality.

Results The trial was stopped for futility, and data were analyzed on an intention-to-treat basis (furosemide-group: n = 38; placebo-group: n = 37). No significant difference was noted in the progression of AKI to a higher stage between furosemide and placebo groups (10.5% vs. 21.6%; relative risk = 0.49, 95% CI 0.16 to 1.48) (p = 0.22). There were no differences in the secondary outcomes between the study groups. All-cause 28-d mortality was similar between the groups (10.5% vs. 10.8%). No trial-related severe adverse events occurred.

Conclusions Furosemide infusion in early-onset AKI did not reduce the progression to a higher stage of AKI. A future trial with large sample size is warranted.

Keywords Children · Acute kidney injury · Furosemide · Intensive care unit

Introduction

Acute kidney injury (AKI) is a common problem in the pediatric intensive care unit (PICU) with an incidence of up to 51.2% [1, 2]; however, 82% of AKI occurred within the first 7 d of admission [3]. Patients with AKI have higher morbidity-mortality and health resource use than those without AKI [4]. The management of AKI is a predominantly conservative approach. There are few if any, interventions that proved to have an impact on the clinical course and outcome of AKI [5]. Hence the question—what is the role of furosemide in the management of AKI?

Furosemide is the most commonly used diuretic in critically ill children [6]. It acts on the thick ascending limb of the loop of Henle and inhibits the Na-K-Cl pump on the luminal surface of the tubular epithelium, and can theoretically reduce renal tubular oxygen demand [7]. Low-dose furosemide may reduce the ischemia/reperfusion-induced apoptosis and associated gene transcription in AKI [8]. Furosemide infusion had varied effects on daily urine output in critically ill adult and pediatric patients; however, there were no benefits in renal function and mortality. Systematic reviews recommend the need for controlled trials to fill up this knowledge gap [9, 10]. Pediatric clinical management reviews did not arrive at
a meaningful conclusion for use of furosemide in AKI due to the limited number of controlled studies [11, 12]. It was hypothesized that furosemide infusion in early-onset AKI [by pediatric-Risk, Injury, Failure, Loss, End stage kidney disease (p-RIFLE) criteria] in critically ill children would be associated with a reduced proportion of patients progressing to the higher stage (injury or failure) as compared to placebo.

**Material and Methods**

This double-blind, placebo-controlled, randomized pilot trial was conducted in the PICU of a tertiary-care institution from 1st October 2016 to 31st December 2018. The institutional ethics committee approved the study and, a written informed consent was obtained from parents/legal guardians. Children aged 1-mo (corrected) to 12-y, who were diagnosed with early-onset AKI (risk stage), and achieved immediate resuscitation goals were enrolled within 24 h of admission. AKI was defined by p-RIFLE criteria (either urine output or serum creatinine criterion or both) [3]. The immediate resuscitation goals were defined as directed by the treating physician, which included one or more of the following: fluid resuscitation and/or vasoactive therapy to achieve (i) capillary refill of ≤ 2 s, (ii) > 5th percentile mean arterial blood pressure (MABP), (iii) or vasoactive therapy to achieve (i) capillary refill of more than proportion of patients progressing to the higher stage (injury or failure) as compared to placebo.

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changes, and/or administration of at least one dose of potassium binder and/or intravenous insulin and/or intravenous bicarbonate.

The trial drug infusion was continued for a minimum of 24 h, and discontinued if any one of the following events occurred: (i) patient was initiated on RRT, or as per the decision of the treating team, (ii) patient was discharged from the PICU, (iii) attained operational definition of renal recovery, or (iv) patient died. The operational definition of renal recovery was defined by the return of serum creatinine to 25% of baseline levels and spontaneous urine output $\geq 1.0 \text{mL/kg/h}$ for a minimum of 24 h independent of RRT [16]. Serum creatinine was estimated by the modified Jaffe method using an autoanalyzer (Olympus® AU 680, Beckman Coulter, California, USA). Creatinine clearance was calculated using the modified Schwartz formula ($= \frac{\text{Length in cm} \times 0.413 + \text{Serum creatinine in mg/dL}}{\text{Fluid input in liter} - \left( \text{Output in liter} \div \text{Admission weight in kg} \times 100 \right)$) [17]. The acid-base disturbance was defined using standard criteria [18]. Sepsis and multiorgan dysfunction were defined as per the International Pediatric Sepsis Consensus Conference definition [19]. For neutrophil gelatinase-associated lipocalin (NGAL) assay, 1 mL of plasma and 1 mL of urine were collected at admission, 6, 12, and 24 h and daily. All the blood investigations were collected up to 7-d, and patients were followed up till 28-d. The NGAL samples were stored at $\pm 20 \degree \text{C}$ for batched analysis by enzyme-linked immunosorbent assay method (ELISA; Human NGAL-ELISA kit-E1719Hu by Bioassay Technology Laboratory, China).

The primary outcome was the proportion of patients with the “risk” stage progressing to injury or failure. Secondary outcomes were the proportion of patients requiring RRT, the effect on NGAL (plasma and urine), fluid balance, adverse effects of furosemide, time to achieve the operational definition of renal recovery, and length of hospital stay (including PICU), and mechanical ventilation, and all-cause hospital and 28-d mortality.

Statistical analysis The sample size was calculated based on the assumption that furosemide infusion reduces the progression to a higher stage from 35% to 15% (author center unpublished data, January 2016 to March 2016, [3]). Assuming an attrition rate of 10%, it was estimated that 110 patients would need to be enrolled in each group with an alpha level of 5% and 90% power and an allocation ratio of 1:1 (nQuery advisor 4.0). The trial progress was reviewed yearly by the institute’s ethics and data and safety monitoring committees, including an independent statistician who was also a physician.

Data were analyzed on an intention-to-treat basis. The normality of data was checked with Kolmogorov–Smirnov $z$ test. Continuous variables were compared by Student’s $t$ test if normally distributed or Mann–Whitney $U$ test, if data were non-normally distributed. The proportion was compared by Chi-square test (Fisher exact test when cell frequencies were $<5$). Kaplan–Meier and log-rank test followed by Cox proportional model adjusted for age, gender, and severity, were used for time to event data. Relative risk/hazard ratio with 95% confidence interval was calculated wherever appropriate. All tests were two-tailed, and a $p$ value of $<0.05$ was considered statistically significant. Data analysis was performed using IBM-SPSS, version 20.0 (SPSS Inc. Chicago, Illinois) and Epi Info™ 7 (7.0.9.7, CDC).

Results

The trial was stopped after the planned interim analysis (at two years of study review) contended that it was futile to study further and was decided to present as a pilot trial. The trial flow is depicted in Fig. 1. Seventy-five patients were enrolled (furosemide-group, $n = 38$, and placebo-group, $n = 37$). All patients met the ‘risk’ stage according to the creatinine criteria, and 11/38 (29%) patients in the furosemide-group and 8/37 (21%) in the placebo-group met both creatinine and urine output criteria. The baseline serum creatinine was available in 12 (16%) patients. There was no protocol violation noted. No mechanical problem was encountered during the infusion of trial drugs. No patient required urgent administration of furosemide after enrollment. Baseline characteristics were comparable, between the two groups, except hyperchloremia and blood urea (Table 1). The proportion of patients requiring maximum trial drug infusion was similar in both groups (21.1% vs. 22.2%). The mean (SD) duration of trial drug infusion was similar in both groups (29.7 ± 17 vs. 25.5 ± 14.5 h; $p = 0.25$). The proportion of patients who required suspension of the trial drug at least a single point of time was similar in both groups (47.4%, $n = 18/38$ vs. 37.8%, $n = 14/37$; $p = 0.40$). The mean (SD) duration of suspension of the trial drug was similar in both groups (3.3 ± 1.1 vs. 4.0 ± 1.3 h; $p = 0.12$).

No significant difference was noted in the progression of AKI from the “risk” to “injury” or “failure” stage in furosemide and placebo groups (10.5% vs. 21.6%; relative risk = 0.49, 95% CI 0.16 to 1.48; $p = 0.22$) (Table 2). No significant difference was noted on the hazard of progression to a higher stage in both groups (adjusted hazard ratio = 0.32, 95% CI
0.10 to 1.47; \( p = 0.14 \) (Fig. 2). Two patients in the placebo group received continuous renal replacement therapy (CRRT) (for fluid overload due to persistent oliguria and associated metabolic abnormalities) and none in the Furosemide group. No significant difference was noted in other secondary outcomes (Table 2). No serious trial-related adverse effects were noted.

Discussion

In this controlled pilot study, no significant difference was noted in the progression of AKI to a higher stage in furosemide (10.5%) and placebo groups (21.6%). There were no differences in the other secondary outcomes. Pediatric AKI is different from adults in many ways. Ongoing growth, with greater renal reserve and regeneration capacity in children compared to adults, might affect pediatric AKI outcomes [20]. Hence, the response to furosemide can also be expected to be different in pediatric AKI. In adults with AKI, furosemide bolus followed by infusion was associated with increased urine output in oliguric postoperative patients. Nevertheless, it did not reduce the progression of AKI, the need for RRT, and renal recovery [21–23]. The method, settings, and study results were similar to the present study except that in the present study only furosemide infusion was used to avoid bolus-associated complications.

Furosemide had varied responses on urine output depending upon the method of delivery. A meta-analysis found that continuous infusion of furosemide was associated with a significant increase in daily urine output, a net decrease in body weight, and lower adverse effects than the bolus group. However, this effect was not seen in pediatric studies [10]. A recent systematic review also confirmed the greater diuretic effect associated with continuous infusion of furosemide than bolus dose. Nevertheless, it was associated with an extended hospital stay, and there was no difference in mortality or change in renal function [9]. However, analysis was limited by high heterogeneity among the included studies [9].

Fluid overload is a significant problem in PICU. A controlled study on furosemide vs. peritoneal dialysis in infants with postcardiac surgery found no difference in negative fluid balance on the first postoperative day, hospital stay, and mortality. Furosemide group had a longer duration of inotropic use, higher electrolyte abnormality score, prolonged ventilator use, and more likely to have 10% fluid overload than peritoneal dialysis [24]. In the present study, no significant difference were found in urine output, changes of creatinine, electrolyte abnormality, renal recovery and PICU and hospital stay, duration of ventilation, and mortality between study participants.

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**Fig. 1: Trial flow. AKI Acute kidney injury; CKD Chronic kidney disease; GFR Glomerular filtration rate; RRT Renal replacement therapy**

| Assessed for eligibility (n = 489) |
|-----------------------------------|
| Excluded (n = 400)                |
|  - No AKI (n = 126)              |
|  - AKI: Other than ‘risk’ stage/developed after 24 h of admission (n = 140) |
|  - Goals of resuscitation not achieved (n = 25) |
|  - Received furosemide (n = 29) |
|  - Obstructive etiology (n = 5) |
|  - Received RRT (n = 8)          |
|  - Others [missed = 18, CKD = 12, Missing creatinine value at admission = 26, wrong calculation of GFR = 11] |
| Eligible (n = 89)                 |
| Refused consent (n = 14)          |
| Randomized (n = 75)              |
| Assigned to furosemide (n = 38)  |
| Received allocated intervention (n = 38) |
| Analyzed (n = 38)                |
| Assigned to placebo (n = 37)     |
| Received allocated intervention (n = 37) |
| Analyzed (n = 37)                |
Table 1 Baseline characteristics of two study groups at the time of enrollment

| Parameter                                      | Furosemide group (n=38) | Placebo group (n=37) | p value |
|------------------------------------------------|-------------------------|----------------------|---------|
| *Age, mo*                                      | 21 (7.2–48)             | 11 (6–42)            | 0.45a   |
| Male : Female, n                               | 26 : 12                 | 26 : 11              | 0.86b   |
| *Weight, kg*                                   | 8.2 (6.2–11)            | 7 (5–14)             | 0.29a   |
| *Body surface area*                            | 0.43 (0.32–0.59)        | 0.34 (0.26–0.49)     | 0.12a   |
| *Pediatric risk of mortality – III score*      | 8 (4–10)                | 7 (2–13)             | 0.98a   |
| †Systemwise diagnosis, n (%)                   |                         |                      | 0.51b   |
| Respiratory                                   | 23 (60.5)               | 21 (56.7)            |         |
| Cardiac                                       | 3 (8)                   | -                    |         |
| Central nervous system                        | 5 (13.2)                | 9 (24.3)             |         |
| Gastro intestinal system                      | 1 (2.5)                 | 1 (2.7)              |         |
| Envenomation                                  | 3 (8)                   | 1 (2.7)              |         |
| Metabolic                                     | 2 (5.3)                 | 2 (5.4)              |         |
| Others                                        | 1 (2.5)                 | 3 (8.1)              |         |
| †Exposure to, n (%)                            |                         |                      |         |
| Aminoglycoside                                | 17 (44.7)               | 16 (43.2)            | 0.89b   |
| Vancomycin                                    | 4 (10.5)                | -                    |         |
| †Sepsis, n (%)                                | 14 (36.8)               | 7 (19)               | 0.08b   |
| †Multiorgan dysfunction, n (%)                | 2 (5.3)                 | 2 (5.4)              | 1.00b   |
| Baseline creatinine‡, mg/dL                   | 0.34 ± 0.10             | 0.33±0.11            | 0.71d   |
| Variables at enrollment                       |                         |                      |         |
| Serum creatinine, mg/dL                       | 0.67 ± 0.22             | 0.63 ± 0.26          | 0.52d   |
| Estimated-glomerular filtration rate          | 64.4 ± 8.6              | 65.2 ± 8.8           | 0.67d   |
| Blood urea, mg/dL                             | 29 ± 15.3               | 21.4 ± 9.3           | 0.01d   |
| Blood lactate, mmol/L                         | 2.2 ± 1.9               | 2.1 ± 1.2            | 0.85d   |
| Serum sodium, mEq/L                           | 136 ± 5.7               | 135 ± 4.3            | 0.58d   |
| Serum potassium, mEq/L                        | 4.5 ± 0.7               | 4.4 ± 0.6            | 0.43d   |
| Serum chloride, mEq/L                         | 102 ± 8                 | 104 ± 8              | 0.29d   |
| Serum magnesium, mg/dL                        | 2.2 ± 0.5               | 2.0 ± 0.3            | 0.20d   |
| †Hyperchloremia§, n (%)                       | 12 (31.6)               | 21 (56.7)            | 0.03b   |
| pH                                            | 7.33 ± 0.09             | 7.30 ± 0.10          | 0.07d   |
| Bicarbonate, mEq/L                            | 21.3 ± 5                | 21.5 ± 4.4           | 0.91d   |
| Urine output, mL/kg/h                         | 1.0 ± 0.8               | 1.0 ± 0.7            | 0.99d   |
| Urine NGAL, ng/mL                             | 85 ± 27                 | 81.6 ± 31            | 0.62d   |
| Plasma NGAL, ng/mL                            | 173.7 ± 136             | 157 ± 108            | 0.56d   |
| Fluid balance (percentage)                    |                         |                      |         |
| 6 h prior¶                                    | 1.6 ± 1.4               | 1.5 ± 1.4            | 0.78    |
| Admission to enrollment¶                      | 2.8 ± 2.9               | 2.5 ± 2.9            | 0.70    |

All values are in mean (SD) except *Median (IQR) or †Number (%). †Including the reverse calculation by modified Schwartz’s formula (= 0.413 × height in cm/serum creatinine in mg/dL) in whom baseline creatinine was assumed to 100 mL/min/1.73 m² as it was not known. †Hyperchloremia defined as a serum chloride concentration > 75% of the serum sodium concentration. ‡6 h prior to enrollment. §Fluid balance from admission to enrollment

IQR Interquartile range; NGAL Neutrophil gelatinase-associated lipocalin; SD Standard deviation

aMann–Whitney U test
bChi-square test
cFisher’s exact test
dStudent t test
| Parameter                                                                 | Furosemide group (n=38) | Placebo group (n=37) | p value |
|--------------------------------------------------------------------------|--------------------------|----------------------|---------|
| **Primary Outcome**                                                      |                          |                      |         |
| Risk stage to injury or failure, n (%)                                    | 4 (10.5)                 | 8 (21.6)             | 0.22a   |
| (Relative risk 0.49, 95% CI 0.16 to 1.48)                                |                          |                      |         |
| Worst acute kidney injury stage attained, n (%)                           | 3 (75)                   | 6 (75)               | 1.00a   |
| Injury                                                                   | 2.2                      | 3.2                  | 0.93b   |
| (1.7–7.9)                                                                | (1.8–3.7)                |                      |         |
| Failure                                                                  | 1 (25)                   | 2 (25)               |         |
| *Urine output in those who had primary outcome, mL/kg/h                  | 2.2 (1.7–7.9)            | 3.2 (1.8–3.7)        | 0.93b   |
| *Serum creatinine in those who had primary outcome, mg/dL                | 0.67 (0.64–1.13)         | 0.64 (0.51–1.16)     | 0.46b   |
| *e-GFR in those who had primary outcome, mL/min/1.72 m²                  | 33.14 (22.37–36.15)      | 38.03 (30.66–43.33)  | 0.37b   |
| **Secondary Outcome**                                                    |                          |                      |         |
| Renal replacement therapy, n (%)                                         | –                        | 2 (5.4)              |         |
| *Urine neutrophil gelatinase-associated lipocalin, ng/mL, over 96 h      | 91 (7.5)                 | 80 (7.5)             | 0.28c   |
| *Plasma neutrophil gelatinase-associated lipocalin, ng/mL, over 96 h     | 177.2 (21.3)             | 181.1 (21.6)         | 0.22c   |
| Fluid balance (percentage)                                               |                          |                      |         |
| At 48 h                                                                  | 0.83 ± 1.20              | 0.82 ± 1.13          | 0.96d   |
| At 72 h                                                                  | 0.80 ± 1.23              | 0.79 ± 1.09          | 0.95d   |
| Cumulative balance                                                       | 0.80 ± 1.23              | 0.78 ± 1.09          | 0.93d   |
| *Urine output during study period, mL/kg/h                               | 2.1 (1.9–2.7)            | 1.9 (1.4–3.0)        | 0.50b   |
| Electrolyte disturbance, n (%)                                           |                          |                      |         |
| Hypokalemia (< 3.5 mEq/dL)                                               | 6 (16)                   | 7 (19)               | 0.72e   |
| Hyponatremia (< 130 mEq/dL)                                              | 3 (8)                    | 6 (16.2)             | 0.31a   |
| Metabolic acidosis                                                       | 16 (42)                  | 12 (32.4)            | 0.39e   |
| Metabolic alkalosis                                                      | 16 (42)                  | 12 (32.4)            | 0.39e   |
| Hypocalcemia                                                            | 6 (16)                   | 7 (19)               | 0.72e   |
| Hypomagnesemia (< 1.46 mg/dL)                                            | 6 (16)                   | 7 (19)               | 0.72e   |
| Renal Recovery attained, n (%)                                           | 24 (63.2)                | 22 (59.5)            | 0.74e   |
| (Relative risk 1.1, 95% CI 0.74 to 1.52)                                 |                          |                      |         |
| *Renal recovery (operational), h                                          |                          |                      |         |
| Serum creatinine within 25% of baseline value                            | 6 (6–12)                 | 6 (6–18)             | 1.00b   |
| Serum creatinine and urine output ≥ 1 mL/kg/h for 24 h                   | 30 (30–36)               | 30 (30–42)           | 1.00b   |
| Length of PICU stay, d                                                   | 4 (3–7)                  | 4 (3–9)              | 0.88f   |
| Length of hospital stay, d                                                | 7 (5–22)                 | 8 (5–15)             | 0.42f   |
| Mechanical ventilation, n (%)                                            | 26 (68.4)                | 21 (56.8)            | 0.29g   |
| Length of mechanical ventilation, days                                    | 4 (2–12)                 | 6 (4–8)              | 0.75f   |
| All-cause hospital mortality, n (%)                                      | 3 (8)                    | 3 (8.1)              | 1.00a   |
| All-cause 28-d mortality, n (%)                                          | 4 (10.5)                 | 4 (10.8)             | 1.00a   |

All values in number (%) except *Median (IQR) or †Mean (SE) or ‡Mean (SD)

*Hypocalcemia defined as ionized calcium less than one mmol/L or total serum calcium less than 8.5 mg/dL. Given patient may had one or more electrolyte disturbance at the given point of the time. †Worst value achieved. ‡Among all cases of acute kidney injury (Risk, Injury, Failure stage) 95% CI 95% Confidence interval; e-GFR estimated Glomerular filtration rate; IQR Interquartile range; PICU Pediatric intensive care unit; SD Standard deviation; SE Standard error of mean

aFisher's exact test  
bMann–Whitney U test  
cRM-ANOVA  
dStudent t test  
eChi-square test  
fLog rank test
groups. The adaptation of restrictive fluid strategy in the present study, which was evident at the time of enrollment, and fluid responsive renal injury, could be the potential reasons. Avoiding fluid overload in AKI patients was associated with favorable outcomes [25, 26].

Plasma and urine NGAL levels for early diagnosis of AKI were also compared. Moreover, NGAL can also predict AKI progression. There was no significant change in urine and plasma NGAL in this study. This is in contrast to the previous studies, which showed elevation of NGAL in pediatric AKI [27, 28]. However, the study population predominantly constituted by the post-cardiac surgery and inborn errors of metabolism groups, compared to the present study where the infection or sepsis was predominantly observed. Similar to the present study, Hamishehkar et al. reported that NGAL was not found to reflect any effects of furosemide in adults with AKI [29].

The present study is the first placebo-controlled pilot study with a robust methodology involving critically ill children with AKI. The authors also followed the children up to 28-d and studied the NGAL in AKI of various etiologies, in contrast to previously published studies [22, 27, 28]. There are few limitations. It is a single-center study. The majority (84%) of the patient’s baseline serum creatinine was assumed as 100 mL/min/1.73 m². Measuring acute renal function change is challenging in infants, requiring interpretation of serum creatinine increments referenced to low baseline levels. The ototoxicity was also not assessed. A multicentric study with larger sample size is warranted in the future.

Conclusion

The study concludes that furosemide infusion did not reduce the progression of AKI to a higher stage. Further, furosemide infusion was not associated with the difference in the need for RRT, fluid balance, length of stay in hospital and ventilation, biomarker (NGAL), electrolyte disturbances, and mortality.

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Authors’ Contribution RR: Conceptualization of the study, review of literature, and critical review of the manuscript. SA, SS, RB, MC, AS, KM: Data collection, review of literature, and manuscript writing. RS: Protocol writing, supervision of biological sample analysis, and manuscript writing. SM: Protocol development, review of literature and manuscript writing. All authors were involved in the management of patients and approved the final version of the manuscript. RR is the guarantor of the paper.

Declarations

Conflict of Interest None.

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Protocol accessible Clinical Trial Registry of India (CTR) www.ctri.in. (Trial Registered Prospectively and Registration No. CTRI/2016/09/007321) (Title: “Effect of furosemide on progression of early onset of acute kidney injury in critically ill children: A randomized double blinded, placebo controlled trial.”).

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