Acta Med. Okayama, 2015
Vol. 69, No. 4, pp. 197–204

Acta Medica Okayama

http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Hemodynamic Effects of Intravenous Calcium Administration on Septic Shock Patients: A Retrospective Study

Naoki Ishibashi[a], Koji Miyasho[a], Tetsuhisa Kitamura[b], Takaaki Ookuma[a], Nobuhiro Kashitani[a], Nobuhiko Beika[a], Takahiro Yamashita[a], and Yoshihito Ujike[c]*

[a]Fukuyama City Hospital Emergency Medical Center, Fukuyama, Hiroshima 721–8511, Japan,
[b]Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Osaka 565–0871, Japan, and
[c]Department of Emergency & Critical Care Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan

We evaluated the hemodynamics and outcomes of septic shock (SS) patients who did not respond to fluid resuscitation, after treatment with or without intravenous calcium. We retrospectively collected information on 154 eligible SS patients who were admitted to Fukuyama City Hospital Emergency Medical Center and did not respond to fluid resuscitation. To compare their degree of hemodynamic impairment, we compared the changes in the vasoactive-inotropic score (VIS) in the calcium-treated group (n = 112) and the noncalcium-treated group (n = 42). We compared the length of stay in the intensive care unit (ICU) and hospital, in-hospital deaths, 28-day deaths, and changes in the Sequential Organ Failure Assessment score within 72 h of ICU admission between the 2 groups. Changes in the VIS at 1 h after the baseline time were significantly greater in the calcium-treated group than in the noncalcium-treated group (1.41 vs. −1.25, respectively; $p < 0.001$). However, the changes in the VIS at 3, 6, 24, 48, and 72 h did not differ between the 2 groups. The secondary outcomes also did not differ between the groups. Our findings indicate that calcium administered to SS patients might reduce their hemodynamic stabilization, but only for a short time after its administration.

Key words: hemodynamics, calcium, shock, sepsis

Severe sepsis and septic shock cause high mortality in intensive care units (ICUs) [1, 2]. Although potent antibiotics and procedures have been developed for these diseases, the mortality rate is currently 30–50% in patients with severe sepsis and can exceed 50% in septic shock (SS) patients [3]. The incidence of patients with severe sepsis is also increasing [4, 5]. Guidelines for the management of severe sepsis and septic shock have not been well established, and the development of effective strategies for the treatment of SS patients is an important issue worldwide [6].

It has been reported that the concentration of ionized calcium is reduced in septic patients and that this reduction is associated with the severity of sepsis and patient mortality [7, 8]. A paper has also suggested that the administration of calcium reduces the doses of inotropic and vasopressor agents required by critically ill patients with ionized hypocalcemia, by increasing

Received September 25, 2014; accepted January 30, 2015.
*Corresponding author. Phone: +81–86–235–7426; Fax: +81–86–235–6601
E-mail: ujike@cc.okayama-u.ac.jp (Y. Ujike)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

the myocardial contractility and vascular tonus [9]. In animal model studies, the administration of calcium increased the mortality of septic rats [10], whereas it improved sepsis-related myocardial suppression with no deleterious events [11]. Human studies have shown no benefits of calcium administration to septic patients [12, 13]. The effectiveness of calcium administration to septic patients thus remains unclear.

In the Emergency Medical Center of Fukuyama City Hospital, intravenous calcium is sometimes administered to SS patients with ionized hypocalcemia who are receiving inotropic and/or vasopressor agents. This retrospective study assessed the hemodynamics and outcomes of SS patients treated with or without intravenous calcium.

Subjects and Methods

Study subjects. This was a retrospective, single-center study. We enrolled SS patients who had been admitted to the Emergency Medical Center of Fukuyama City Hospital and were administered intravenous catecholamine. The catecholamine, predominantly dopamine or noradrenaline, was administered to those SS patients who did not respond to fluid resuscitation. The observational period was from April 1, 2005 to March 31, 2013. The study protocol was approved by the Institutional Review Board of Fukuyama City Hospital.

Setting and data collection. Fukuyama City Hospital, located in the eastern area of Hiroshima Prefecture, Japan, has 506 beds and 7 regular intensivists in its Emergency Medical Center (24 beds in the ICU). In the ICU, the attending doctors from each department are responsible for the treatment of their patients in collaboration with the intensivists. Approximately 1,400 patients are admitted to this center every year, and 60 of them had sepsis during the study period. Intravenous calcium was administered to the SS patients receiving a catecholamine based on the judgment of the attending physicians and/or intensivists.

In accordance with the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [14, 15], we defined sepsis as a systemic inflammatory response to infection; we defined severe sepsis as sepsis associated with organ dysfunction, hypoperfusion, or hypotension, and we defined septic shock as severe sepsis with persistent hypotension (systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg from baseline), associated with organ perfusion abnormalities that were not improved by fluid resuscitation, or with normotension sustained by inotropic or vasopressor agents. The SS patients were treated according to the guidelines for the management of severe sepsis and septic shock [6, 16, 17].

The exclusion criteria for this study were: children aged < 18 years, pregnant women, patients with burns, terminally ill patients (do-not-attempt-resuscitation), and patients with postcardiac arrest, neutropenia caused by chemotherapy, a history of organ transplantation, or nonseptic shock (*e.g.*, anaphylactic shock) within 72 h of admission. Patients without data on the dose of catecholamine within 72 h after admission were also excluded.

Information on the characteristics and outcomes of the SS patients was extracted retrospectively from their medical records, including age, sex, the Acute Physiology and Chronic Health Evaluation (APACHE) II score [18], the Sequential Organ Failure Assessment (SOFA) score [19], the type and dose of inotropic and vasopressor agents given, mean arterial pressure, intravenous calcium administered, laboratory data at ICU admission (white blood cell count, concentrations of ionized calcium, sodium, potassium, and creatinine), 24-h urine volume, renal replacement therapy, transfusion of red cell concentrate, fresh frozen plasma, or platelet concentrate, corticosteroid therapy, treatment for disseminated intravascular coagulation, the time interval from admission to calcium administration, the lengths of ICU and hospital stays, in-hospital death, and 28-day death.

Among the SS patients who received a catecholamine, we defined those who were administered intravenous calcium within 24 h of admission as the "calcium-treated group," and those who were not administered intravenous calcium within 24 h of admission as the "noncalcium-treated group."

Study endpoints. The primary endpoint was the change in the vasoactive-inotropic score (VIS) [20], an index of the required amount of hemodynamic support, which can be used as a surrogate for the degree of hemodynamic impairment. A higher VIS indicates a greater vasopressor requirement. We were therefore able to assess the hemodynamic differences

among the SS patients treated with or without intravenous calcium by comparing the changes in their VISs. The formulae for the VIS and inotropic score are:

VIS = inotropic score + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × noradrenaline dose (μg/kg/min) [20]

Inotropic score = dopamine dose + dobutamine dose + 100 × adrenaline dose (all doses in μg/kg/min) [21]

The secondary endpoints were the lengths of ICU and hospital stays, in-hospital deaths, 28-day deaths, and the change in the SOFA score 72 h after ICU admission.

Statistical analysis. The patient characteristics and outcomes of the 2 groups (*i.e.*, the groups with and without intravenous calcium) were compared. Continuous variables are presented as means and 95% confidence intervals (CIs), and differences were analyzed with the Mann-Whitney U-test; categorical variables are expressed in percentages (n/N), and differences were analyzed with the χ^2 test or Fischer's exact test. We compared changes in the VIS values of the 2 groups at 1, 3, 6, 24, 48, and 72 h from baseline. We defined the baseline as the time at which intravenous calcium was administered for the first time (the calcium-treated group) or when the patient was admitted to the ICU (the noncalcium-treated group), because the patient's hemodynamic condition would be most unstable at the baseline. All data were analyzed with SPSS Statistics software, version 21.0J (IBM Corp. Armonk, NY, USA). Two-sided p-values < 0.05 were considered significant, and we also used the Bonferroni correction method to correct the problem of multiple comparisons for changes in the VIS values of the 2 groups.

Results

Between April 2005 and March 2013, 452 septic patients were admitted to the Emergency Medical Center of Fukuyama City Hospital (Fig. 1). We excluded 181 patients who were not in shock, 65 who did not receive a catecholamine within 72 h of ICU admission, 42 who did not meet our inclusion criteria, and 10 who had no available data on the dose of catecholamine. Therefore, 154 SS patients who were

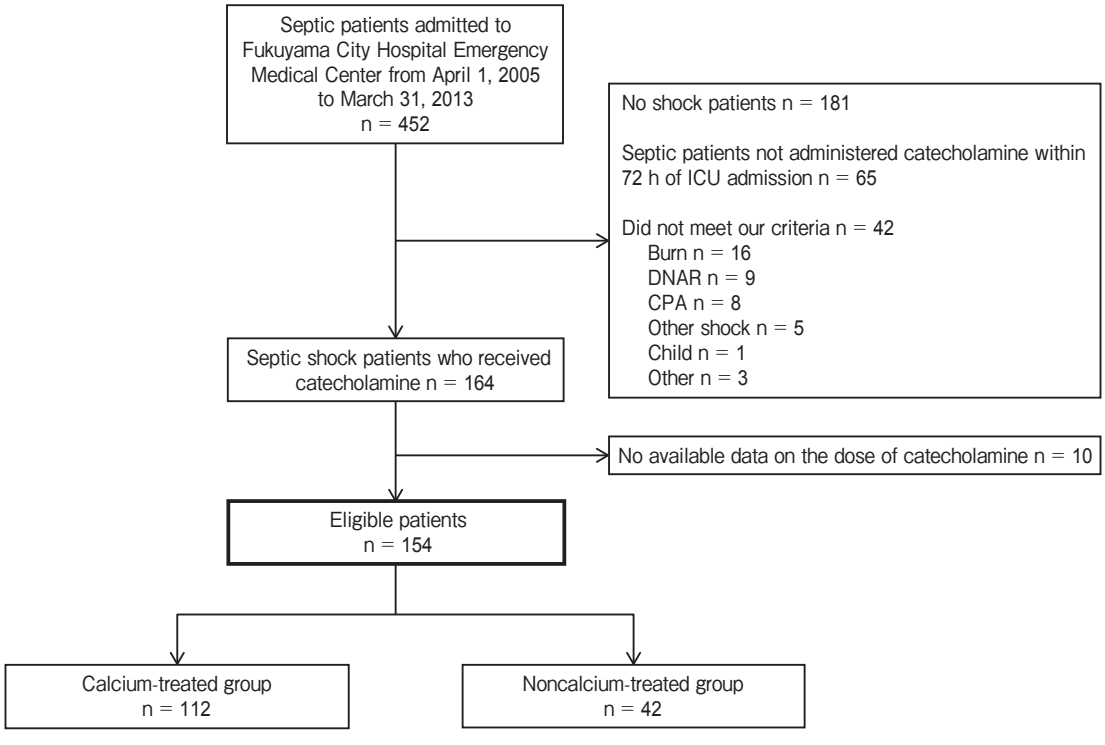

Fig. 1 Patient flow. ICU, intensive care unit; DNAR, do-not-attempt-resuscitation; CPA, cardiopulmonary arrest.

administered a catecholamine (112 in the calcium-treated group and 42 in the noncalcium-treated group) were eligible for our analysis.

Table 1 shows the characteristics of the SS patients who received a catecholamine, with or without intravenous calcium, at ICU admission. There were no significant differences in the age or sex of the 2 groups. The dose of vasopressin (0.008 vs. 0.003 units/min, respectively; $p = 0.032$), the requirement for fresh frozen plasma (11.0 vs. 7.3 units, respectively; $p = 0.013$), and platelet concentrate (8.8 vs. 3.4 units, respectively; $p = 0.032$) were significantly higher in the calcium-treated group than in the noncalcium-treated group, and the number of white blood cells was significantly lower in the calcium-treated group (11,900 vs. 15,400/μL, respectively; $p = 0.012$). However, all other factors were almost identical between the 2 groups. In the calcium-treated group, the mean time interval from ICU admission to calcium administration was 3.3 h.

To compare the degree of hemodynamic impairment in the 2 groups, we compared the changes in VIS at 1, 3, 6, 24, 48, and 72 h from baseline (Table 2). The VIS values at baseline were similar in the calcium- and noncalcium-treated groups (7.10 vs. 7.08, respectively; $p = 0.872$). The change in the VIS at 1 h from baseline was significantly greater in the calcium-treated group than in the noncalcium group (1.41 vs. -1.25, respectively; $p < 0.001$). This p-value was still significant when the Bonferroni correction tested

Table 1 Characteristics of septic shock patients treated with a catecholamine with or without intravenous calcium administration at ICU admission

	Calcium-treated group (n = 112)		Noncalcium-treated group (n = 42)		*P* value
Age, y	72	(70–74)	74	(71–78)	0.320
Men, no. (%)	73	65.2	24	57.1	0.358
APACHE II score	33.5	(32.1–34.9)	30.5	(28.0–32.9)	0.068
SOFA score*	11.5	(10.8–12.1)	10.4	(9.3–11.4)	0.094
Mean arterial pressure, mmHg†	68.1	(64.9–71.3)	74.3	(67.8–80.9)	0.234
Noradrenaline, μg/kg/min†	0.017	(0.007–0.027)	0.014	(0.001–0.027)	0.792
Dopamin, μg/kg/min†	3.7	(3.0–4.5)	4.7	(3.0–6.4)	0.433
Vasopressin, units/min†	0.008	(0.005–0.010)	0.003	(0.000–0.006)	0.032
Inotropic score†	3.91	(3.16–4.66)	5.12	(3.36–6.88)	0.326
Laboratory data					
White blood cell count, 1,000/μL	11.9	(10.0–13.9)	15.0	(12.1–17.8)	0.024
Ionized calcium, mmol/L	1.12	(1.11–1.14)	1.15	(1.12–1.17)	0.181
Sodium, mmol/L	133	(132–134)	133	(131–135)	0.889
Potassium, mmol/L	3.8	(3.7–4.0)	3.9	(3.7–4.0)	0.748
Creatinine, mg/dL	2.2	(1.9–2.5)	2.1	(1.1–3.2)	0.083
Diuresis, mL/24 h	3,473	(2,845–4,101)	3,878	(2,927–4,829)	0.238
Renal replacement therapy, no. (%)	36	32.1	10	23.8	0.314
Transfusion‡					
RCC, units	2.7	(2.0–3.4)	1.7	(0.8–2.5)	0.103
FFP, units	11.0	(8.9–13.1)	5.3	(2.8–7.8)	0.002
PC, units	8.8	(6.1–11.4)	3.4	(1.0–5.8)	0.032
Corticosteroids, no. (%)	43	38.4	14	33.3	0.562
DIC therapy, no. (%)	81	72.3	25	59.5	0.127
Time interval from ICU admission to calcium administration, hours	3.3	(2.5–4.1)	–	–	

ICU denotes Intensive Care Unit; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; RCC, red cell concentrate; FFP, fresh frozen plasma; PC, platelet concentrate; DIC, disseminated intravascular coagulation. Data are means (95% confidence interval).

*The SOFA score was missing for 28 patients in the calcium-treated group and 14 in the noncalcium-treated group.

†These values in the calcium-treated group were obtained when intravenous calcium was administered initially after ICU admission.

‡Total transfusion units within 72 h after ICU admission.

Table 2 Changes in vasoactive-inotropic score (VIS) at 1, 3, 6, 24, 48, and 72 h from baseline among septic shock patients treated with a catecholamine with or without intravenous calcium administration

	Calcium-treated group (n = 112)				Noncalcium-treated group (n = 42)				*P* value*
	Baseline†	After 1 h	Δ 1 h (1 h–baseline)		Baseline†	After 1 h	Δ 1 h (1 h–baseline)		
Vasoacitve-inotropic score (VIS)	7.10 (5.55–8.65)	8.51 (6.88–10.2)	1.41	(0.53–2.30)	7.08 (4.35–9.82)	5.84 (3.03–8.64)	−1.25	(−2.06 to −0.44)	<0.001‡
		After 3 h	Δ 3 h (3 h–baseline)			After 3 h	Δ 3 h (3 h–baseline)		
		8.23 (6.57–9.90)	1.13	(−0.20–2.47)		6.60 (4.03–9.17)	−0.49	(−1.47–0.49)	0.087
		After 6 h	Δ 6 h (6 h–baseline)			After 6 h	Δ 6 h (6 h–baseline)		
		8.32 (6.45–10.20)	1.22	(−0.48–2.92)		6.18 (3.99–8.36)	−0.91	(−2.28–0.46)	0.313
		After 24 h	Δ 24 h (24 h–baseline)			After 24 h	Δ 24 h (24 h–baseline)		
		7.45 (5.07–9.83)	0.35	(−2.16–2.86)		3.97 (2.72–5.21)	−3.12	(−5.88–0.35)	0.178
		After 48 h	Δ 48 h (48 h–baseline)			After 48 h	Δ 48 h (48 h–baseline)		
		3.05 (2.09–4.02)	−4.05	(−5.67 to −2.42)		1.93 (0.99–2.87)	−5.15	(−8.13 to −2.18)	0.638
		After 72 h	Δ 72 h (72 h–baseline)			After 72 h	Δ 72 h (72 h–baseline)		
		1.62 (0.80–2.45)	−5.47	(−6.99 to −3.96)		1.06 (0.47–1.66)	−6.02	(−8.86 to −3.18)	0.871

**P* values assess the differences between the changes in the physiological endpoints at 1, 3, 6, 24, 48, and 72 h from baseline in the calcium-treated and noncalcium-treated groups.
†Baseline time in the calcium-treated group means the time of first calcium administration, and in the noncalcium-treated group means the time of ICU admission.
‡This *P* value was statistically significant when the Bonferroni correction tested each individual hypothesis at $\alpha = 0.05/6 = 0.00833$.
All data are means (95% confidence intervals).

Table 3 Secondary endpoints of septic shock patients treated with a catecholamine with or without intravenous calcium administration

	Calcium-treated group (n = 112)		Noncalcium-treated group (n = 42)		*P* value
ICU stay, day, mean (95% confidence interval)	9	(7–11)	9	(6–11)	0.495
Hospital stay, day, mean (95% confidence interval)	35	(29–41)	45	(30–61)	0.290
In-hospital death, no. (%)	31	27.7	7	16.7	0.158
28-day death, no. (%)	24	21.6	5	11.9	0.178
Change in SOFA score 72 h after ICU admission, mean (95% confidence interval)*	−2.4	(−3.2 to −1.7)	−2.3	(−3.2 to −1.4)	0.932

ICU denotes Intensive Care Unit; SOFA, sequential organ failure assessment.
*The SOFA score was missing for 49 patients in the calcium-treated group and 24 in the noncalcium-treated group.

each individual hypothesis at $\alpha = 0.05/6 = 0.00833$. The changes in the VIS at 3, 6, 24, 48, and 72 h did not differ between the 2 groups.

The secondary outcomes, *i.e.*, the lengths of the ICU and hospital stays, in-hospital deaths, 28-day deaths, and changes in the SOFA score 72 h after ICU admission, did not differ between the 2 groups (Table 3).

Discussion

The results of this retrospective single-center study demonstrated that the changes in VIS among SS patients at 1 h from baseline were significantly greater in the patients treated with calcium compared to the no-calcium group, whereas the changes in the VIS at 3, 6, 24, 48, and 72 h were similar between the 2 groups. These results suggest that the administration of calcium temporarily increases the requirement for inotropic and vasopressor agents in SS patients and has a deleterious effect on their hemodynamic stabilization.

The guidelines for the management of severe sepsis and septic shock do not recommend the routine use of pulmonary artery catheters for SS patients [6], and information on these patients' hemodynamics, including the cardiac index and the systemic vascular resistance index (which are measured directly from the pulmonary catheter) is not available for most SS patients. Therefore, unlike previous studies, we assessed the hemodynamics of SS patients who were treated with or without intravenous calcium by using the VIS, calculated from the patients' requirement for inotropic and vasopressor agents. The VIS was originally developed as an index of cardiovascular support during the perioperative period among infants who underwent congenital heart surgery [20] and was also used to assess the hemodynamics of adult patients receiving cardiac surgery [22].

Vasoactive agents such as vasopressin and milrinone are now available for the management of patients with severe sepsis or septic shock [6, 16, 17, 23], and we therefore assessed the hemodynamics in SS patients by using the VIS, which can reflect the influence of these drugs. We thus believe that the present study's findings provide valuable information for the treatment of SS patients.

Here we evaluated whether the intravenous administration of calcium affects the hemodynamics and outcomes of SS patients. Why is the ionized calcium concentration reduced among septic patients, and is this reduction associated with the severity of their disease and their mortality? Although the definitive mechanism underlying hypocalcemia in septic patients is unclear, their hypocalcemia might be partly explained by hypoparathyroidism, vitamin D deficiency, resistance to parathyroid hormone or activated vitamin D, or calcium influx into the cells and tissues [12]. Cardiovascular dysfunction, caused by the depression of myocardial contractility and the loss of vascular tonus, occasionally occurs in septic patients [24, 25]. The relationship between ionized hypocalcemia and cardiovascular dysfunction is still contentious, but it is speculated that cardiovascular dysfunction in septic patients is caused not by ionized hypocalcemia alone, but by complex processes mediated by many factors (*e.g.*, tumor necrosis factor, interleukin 1, platelet-activating factor, oxygen free radicals, and nitric oxide) [26, 27].

In this study, we found that the changes in the VIS at 1 h from baseline were significantly greater in the calcium-treated group than in the noncalcium-treated group. The results of previous studies that assessed the hemodynamics of septic patients treated with or without calcium are controversial. The continuous administration of intravenous calcium increased the mean arterial pressure in septic rats for only 15 min [10]. Although the mechanism that causes intravenous calcium to affect the cardiovascular systems of septic patients only temporarily remains unclear, the results of that animal study [10] are consistent with ours in terms of the temporal effects of calcium. However, in contrast to our results, the effect on the cardiovascular system was positive.

A human study demonstrated that the administration of calcium was not associated with significant changes in the flow, filling pressures, or systemic or pulmonary vascular resistance in septic patients [28]. In other studies, calcium influx into cells resulted in elevated intracellular calcium concentrations in septic patients, and this elevation was associated with cell dysfunction and death [29–31].

In the present study, the secondary outcomes, including the lengths of ICU and hospital stays, in-hospital deaths, 28-day deaths, and changes in the SOFA score at 72 h from ICU admission did not differ

significantly between the 2 groups. Importantly, the guidelines for the management of severe sepsis and septic shock do not refer to the administration of calcium to SS patients [6, 23]. A recent systematic review concluded that there was no evidence to support the treatment of critically ill patients for hypocalcemia [13]. The results of our study support this conclusion.

Moreover, an observational study of 870 septic patients revealed that calcium administration was associated with an increased risk of death, a significantly increased risk of renal dysfunction, and a significant reduction in ventilator-free days [32]. However, there are still few data on the effects of calcium administration to septic patients, and large observational studies or randomized controlled trials that investigate the effects of calcium administration on SS patients are required to confirm our results.

This study had some inherent limitations. First, it was conducted retrospectively, and there was potential selection bias. For example, intravenous calcium was administered to SS patients based on the judgement of the attending physicians and/or intensivists. In addition, we did not investigate the method of administration or the target concentration of calcium. Second, although the SS patients in this study were treated according to the guidelines for the management of severe sepsis and septic shock [6, 16, 17], there was no standard protocol for administering the catecholamine (*e.g.*, type, timing, and dose). Third, we did not assess the influence of factors associated with calcium homeostasis, such as magnesium depletion, hypoparathyroidism, and vitamin D deficiency [12]. Finally, unmeasured confounding factors might have influenced the association between the administration of calcium and the outcomes measured here.

In this retrospective single-center observational study, we demonstrated that the change in the VIS of SS patients at 1 h from baseline was significantly greater in the calcium-treated patients than in the noncalcium-treated patients, which suggests that the administration of calcium to SS patients has a deleterious effect on their hemodynamic stabilization for a short time after its administration. Large observational studies or randomized controlled trials are essential to verify the effects of calcium administration on SS patients and to test our results.

Acknowledgments. We are deeply indebted to all the staff and physicians at Fukuyama City Hospital.

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