Haemodynamic and biochemical responses to fluid bolus therapy with human albumin solution, 4% versus 20%, in critically ill adults

Jonathan Bannard-Smith, Paschal Alexander, Neil Glassford, Matthew J Chan, Matthew Lee, Ben T Wong, Grant Crawford, Michael Bailey and Rinaldo Bellomo

ABSTRACT

Background: Fluid bolus therapy (FBT) is common in critically ill patients. With the exception of use in patients with traumatic brain injury, FBT with human albumin solution (HAS) appears safe and perhaps superior in severe sepsis.

Objective: To determine the physiological effects of FBT with 4% v 20% HAS.

Design, setting and participants: A retrospective observational study of 202 critically ill patients receiving FBT with HAS in a tertiary intensive care unit between April 2012 and March 2013.

Methods: FBT was instituted with 4% or 20% HAS, according to clinician preference.

Main outcome measures: We compared biochemical and haemodynamic data between groups at baseline and at 1, 2 and 4 hours after FBT.

Results: Patients who had received 20% HAS had more liver disease, a greater need for renal replacement therapy and higher Acute Physiology and Chronic Health Evaluation III scores on admission. Patients who had received 4% HAS received a median volume of 500 mL (interquartile range [IQR], 350–500 mL), compared with 100 mL (IQR, 100–200 mL) in the 20% HAS group ($P < 0.0001$); a median of 70 mmol v 10 mmol of sodium ($P < 0.0001$); and a median of 64 mmol v 2 mmol of chloride ($P < 0.0001$). There was a trend toward higher mean arterial pressures in the 20% group after FBT (78.2 mmHg v 76.4 mmHg, $P = 0.03$). There were no significant differences in the absolute or percentage change for any haemodynamic parameters. Serum biochemical test results were comparable with a non-significant signal of higher serum chloride and more negative base excess in patients receiving 4% HAS.

Conclusions: Haemodynamically, FBT with 100 mL of 20% HAS performs in an equivalent way to 500 mL of 4% HAS but delivers much less fluid, sodium and chloride.

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Intravenous fluid bolus therapy (FBT) is ubiquitous in critically ill patients. Despite the lack of evidence of a survival benefit, the use of artificial and/or natural colloid solutions remains common for FBT.[1,2] However, artificial colloids containing hydroxyethyl starch have been associated with a higher incidence of severe acute kidney injury (AKI) in intensive care patients[3,4] and increased mortality in sepsis.[5] In addition, gelatin solutions may also be associated with higher rates of AKI.[6,7] On the other hand, with the notable exception of patients with traumatic brain injury, natural colloids (human albumin solutions [HAS]) appear safe in intensive care patients[8] and possibly beneficial in severe sepsis or septic shock.[9,10]

In addition to fluid type, the sodium and chloride content of any fluid used for FBT and the contribution to a positive fluid balance induced by FBT are also of concern.[11-13] For example, chloride-rich fluids, such as 0.9% saline, can induce metabolic acidosis[14,15] and decrease renal cortical perfusion in healthy volunteers when compared with balanced solutions.[16] They may also contribute to the development of AKI.[17] Moreover, a positive cumulative fluid balance is associated with higher mortality in patients with septic shock[18] and AKI,[19] and a neutral-to-negative fluid balance shortens the duration of mechanical ventilation in patients with acute lung injury.[20] Thus, using a natural colloid solution that minimises chloride and volume administration would logically be an attractive choice for FBT.

In Australia and New Zealand, HAS is available as two preparations. The 4% solution (Albumex 4 [CSL Behring]) contains sodium 140 mmol/L and chloride 128 mmol/L and is presented as 20 g albumin in 500 mL.[21] The 20% solution (Albumex 20 [CSL Behring]) contains sodium 50–100 mmol/L and chloride 20 mmol/L and is presented as 20 g in 100 mL.[22] Both can be used for FBT but no studies have compared these two fluids when used for such purposes. We conducted a retrospective cohort study of critically ill patients receiving 4% or 20% HAS for FBT according to clinician preference. We hypothesised that 4% HAS would lead to a greater mean arterial pressure (MAP) response than 20% albumin in the 4 hours after its administration,

but that 4% HAS would also lead to a greater degree of hyperchloraemia.

Methods

Ethics approval and registration

Our study was approved by the Austin Health Human Research Ethics Committee (Project LNR/14/Austin/313) and is also registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000744651).

Patients

At our institution, we routinely record the details of all patients receiving HAS in a specific database held by the blood bank. We used this database to compile a temporally paired list of patients receiving 4% and 20% HAS between April 2012 and March 2013. Overall, 20% HAS was used less commonly for FBT compared with 4% HAS, so every patient receiving 20% HAS was paired with the nearest chronologically treated patient receiving 4% HAS. This temporally populated our sample while minimising any bias caused by variances in clinician practice. Patients were excluded from the study if they had received both 4% and 20% HAS within 24 hours of baseline, or if they had previously received any HAS during their intensive care unit stay.

Data collection

We routinely prospectively record data for patient demographics, admission details and outcomes in our unit database, and we extracted that information for every patient included in our study. We used observation charts and electronic pathology records to acquire data for haemodynamic and biochemical parameters. Biochemical data were deemed appropriate for use in relation to a given time point if the sample had been drawn within 30 minutes before FBT (for baseline measurements) or within 30 minutes either side of any subsequent observation points (1, 2 and 4 hours after FBT).

Table 1. Baseline patient characteristics before albumin fluid bolus therapy

		Albumin level		
Characteristic	All patients ($n = 202$)	4% ($n = 101$)	20% ($n = 101$)	*P*
Mean age (SD)	60.8 (16.6)	62.0 (16.5)	59.6 (16.8)	0.3
Male (%)	127 (62.9%)	70 (69.3%)	57 (56.4%)	0.05
Comorbidities (%)				
Cardiovascular disease	2 (1%)	0 (0)	2 (2%)	0.5
Respiratory disease	1 (0.5%)	1 (1%)	0 (0)	1.0
Renal disease	4 (2%)	2 (2%)	2 (2%)	1.0
Liver disease	29 (14%)	7 (7%)	22 (22%)	0.003
Insulin-dependent diabetes	0 (0)	0 (0)	0 (0)	1.0
Cancer	7 (3.5%)	3 (3%)	4 (4%)	1.0
Immunosuppressive therapy	5 (2.5%)	0 (0)	5 (5%)	0.06
Mechanically ventilated (%)	103 (51%)	56 (55%)	47 (47%)	0.21
Receiving renal replacement therapy (%)	17 (8.4%)	3 (3%)	14 (14%)	0.005
Receiving vasoactive drugs before bolus (%)				
Noradrenaline	70 (35%)	38 (37.6%)	32 (31.7%)	0.37
Adrenaline	9 (4.5%)	7 (6.9%)	2 (2%)	0.08
Mean APACHE III score on ICU admission (SD)	64.9 (26.8)	58.7 (23.6)	71.2 (28.4)	0.0007
Risk of death on ICU admission (95% CI)	0.11 (0.03–0.32)	0.05 (0.02–0.19)	0.22 (0.07–0.47)	< 0.0001
Admission source (%)				
Emergency department	32 (15.8%)	13 (12.9%)	19 (18.8%)	0.24
Operating theatre	95 (47.1%)	65 (64.4%)	30 (29.7%)	< 0.0001
Ward	42 (20.8%)	8 (7.9%)	34 (33.7%)	< 0.0001
Another hospital	27 (13.3%)	14 (13.8%)	13 (12.9%)	0.83
Another hospital ICU	6 (3.0%)	1 (1.0%)	5 (4.9%)	0.09
Parent speciality (%)				
Medical	63 (31.2%)	17 (16.8%)	46 (45.5%)	< 0.0001
Surgical	139 (68.8%)	84 (83.2%)	55 (54.5%)	< 0.0001

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit.

Table 2. Physiological and serum biochemistry values before albumin fluid bolus therapy

Parameter	All patients	Albumin level		*P*
		4%	20%	
Mean heart rate, beats/min (SD)	90.2 (18)	88.7 (17.7)	91.7 (18.4)	0.24
Mean systolic blood pressure, mmHg (SD)	112 (21)	112 (23)	111 (19)	0.59
Mean diastolic blood pressure, mmHg (SD)	57.4 (13.1)	58.0 (15.2)	56.7 (10.6)	0.47
Mean arterial pressure, mmHg (SD)	75.9 (14.6)	76.7 (17.0)	75.2 (11.9)	0.48
Mean central venous pressure, mmHg (SD) ($n = 134$)	10.1 (4.0)	9.9 (4.0)	10.4 (4.0)	0.47
Median cardiac index, L/min/m^2 (IQR) ($n = 44$)	2.7 (2.2–3.3)	2.7 (2.2–3.4)	2.7 (2.3–3.1)	0.79
Median urine output, mL/hr (IQR) ($n = 194$)	45 (20–100)	60 (28–100)	35 (10–85)	0.022
Mean temperature, °C (SD) ($n = 157$)	36.8 (1.0)	36.7 (0.9)	36.8 (1.1)	0.28
Mean Pa/FiO_2 ratio, mmHg (SD) ($n = 134$)	304 (187)	309 (155)	299 (222)	0.78
Serum biochemistry ($n = 142$)				
Mean sodium, mmol/L (SD)	138 (13)	138 (4)	136 (18)	0.34
Median chloride, mmol/L (IQR)	107 (103–110)	108 (105–110)	105 (101–110)	0.043
Median calcium, mmol/L (IQR)	1.11 (1.06–1.18)	1.10 (1.03–1.16)	1.15 (1.09–1.19)	0.001
Median base excess, mmol/L (IQR)	0 (– 2.8 to 3.0)	0 (– 2.9 to 2.0)	1.3 (– 2.5 to 5.0)	0.06
Median lactate, mmol/L (IQR)	1.8 (1.1–3.0)	1.7 (1.0–2.7)	1.9 (1.3–3.3)	0.16
Median creatinine, μmol/L (IQR)	97 (68–159)	82 (64–114)	132 (75–193)	0.001
Mean haemoglobin, g/L (SD)	76.2 (41.8)	78.7 (42.7)	73.2 (40.9)	0.43

IQR = interquartile range.

Data analysis

We calculated that we would require at least 93 patients in each group to achieve 80% power to detect a 7 mmHg (SD, 17 mmHg) difference in MAP between 4% and 20% HAS, with an alpha error of 5% ($P = 0.05$).[23] We aimed to collect data from at least 100 patients for each group to compensate for potential missing biochemical or haemodynamic data.

We compared continuous parametric and non-parametric data for each group using the student *t* test (reporting results as means and SDs) or the Mann–Whitney test (reporting results as medians and interquartile ranges [IQRs]). Categorical data were compared using the χ^2 test for equal proportion. Haemodynamic and biochemical trends from baseline to 4 hours after the fluid bolus were analysed using repeated-measures analysis of variance fitting main effects for group, time and an interaction between group and time to determine if the groups behave differently over time. When outcome variables were different at baseline, analysis was performed as differences from baseline. To further account for the baseline imbalance in illness severity between groups, additional sensitivity analysis was performed adjusting for patient risk of death as a covariate. The relationship between ICU mortality and treatment was determined using logistic regression adjusting for illness severity with results reported as odds ratios (ORs) with 95% CIs. In view of the retrospective nature of our study and the multiple outcomes, a two-sided *P* of < 0.01 was used to indicate statistical significance.

Table 3. Characteristics of fluid bolus

Characteristic	4% albumin ($n = 101$)	20% albumin ($n = 101$)	*P*
Median volume, mL (IQR)	500 (350–500)	100 (100–200)	< 0.0001
Median calculated sodium dose, mmol/L (IQR)	70 (25–70)	10 (10–20)	< 0.0001
Median calculated chloride dose, mmol/L (IQR)	64 (20–64)	2 (2–4)	< 0.0001
Median delivery speed, hours (IQR)	1 (1–2)	1 (1–1)	0.04
Patients receiving further bolus within 24 hours (%)	59/101 (58%)	45/101 (45%)	0.05

IQR = interquartile range.

Results

Patient comparison

We extracted data for 202 consecutive patients receiving 4% HAS ($n = 101$) and

20% HAS ($n = 101$) between April 2012 and March 2013. The characteristics of patients before the fluid bolus are shown in Table 1. Patients receiving 20% HAS had a higher incidence of pre-existing liver disease, a greater need for renal replacement therapy (RRT) and had significantly higher Acute Physiology and Chronic Health Evaluation (APACHE) III scores and predicted risk of death on admission to the ICU. Most patients were admitted under surgical specialities and there were significantly more surgical patients in the 4% HAS group.

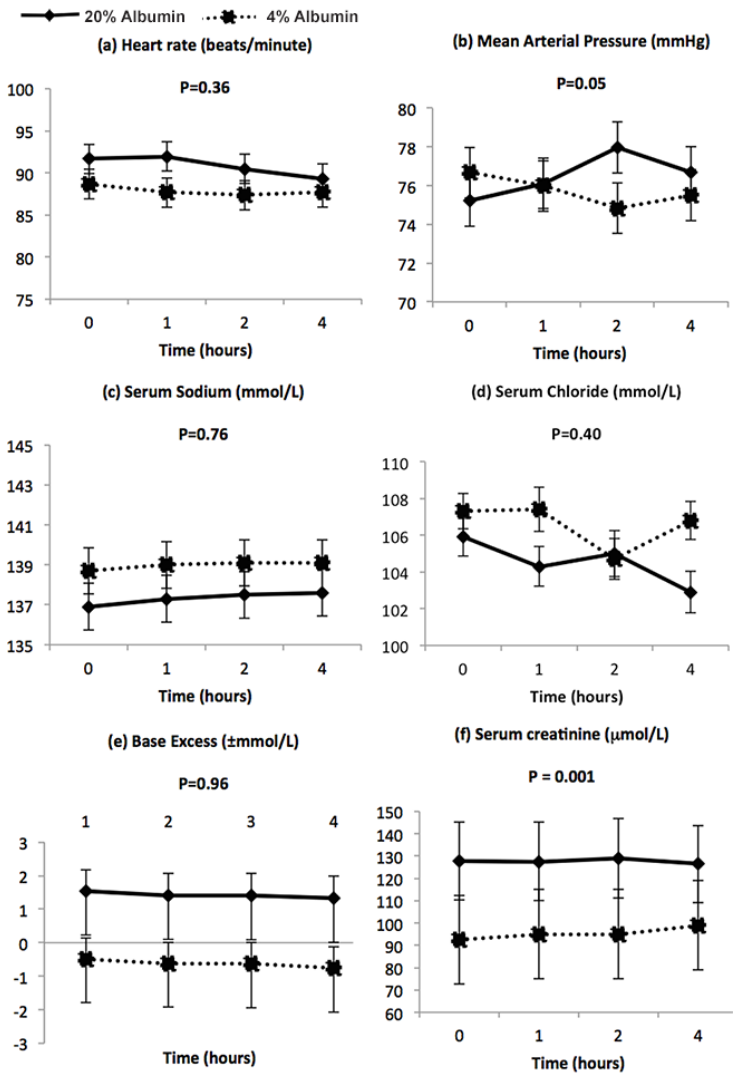
Baseline haemodynamic and biochemical indices

Haemodynamic measurements and serum biochemical values at baseline are shown in Table 2. All values were similar between groups, except for serum creatinine and ionised calcium levels, which were significantly higher in patients receiving 20% HAS.

Characteristics of albumin FBT

During each episode of FBT, patients in the 4% HAS group received a median volume of 500 mL albumin (IQR, 350–500 mL) compared with 100 mL albumin (IQR, 100–200 mL) in the 20% HAS group ($P < 0.0001$). Patients in the 4% HAS group received 70 mmol of sodium compared with 10 mmol in the 20% HAS group ($P < 0.0001$), and 64 mmol of chloride compared with 2 mmol of chloride ($P < 0.0001$). FBT was delivered within 1 hour in 68 patients (67%) receiving 4% HAS compared with 79 patients (78%) receiving 20% HAS ($P = 0.039$). In the 4% HAS group, 59 patients (58%), and 45 patients (45%) in the 20% HAS group, received further FBT after 4 hours but within 24 hours of baseline ($P = 0.049$) (see Table 3).

Figure 1. Mean physiological and biochemical values over time after fluid bolus therapy, including baseline values at 0 hours*



* P is comparison of change over time from baseline (human albumin solution 4% v 20%); vertical I-lines are 95% CIs.

Physiological changes associated with albumin FBT

Figure 1a and Figure 1b show the changes in MAP and heart rate over time after FBT with the two solutions. When considering the difference from baseline and adjusting for illness severity, patients receiving 20% HAS had higher MAPs after the fluid bolus (1.62 mmHg v −1.25 mmHg; $P = 0.03$). Values for central venous pressure and cardiac index were not significantly different at baseline (see Table 2) and the dataset for these variables was not complete enough to formally compare in the hours after FBT. There were no significant differences in absolute or percentage change of any physiological parameters over the 4 hours after the fluid bolus.

Biochemical changes associated with albumin FBT

Figure 1c to Figure 1f show sequential serum biochemical measurements at baseline and 1, 2 and 4 hours after FBT. Patients receiving 4% HAS tended to have higher serum chloride levels and more negative base excess over the study period. Baseline values for serum creatinine were significantly higher in patients receiving 20% HAS (132 μmol/L v 82 μmol/L; $P = 0.001$). All other biochemical variables were not significantly different at baseline, nor did they behave differently over time when comparing the two FBT groups.

Patient-orientated outcomes

ICU mortality was 6.9% (7/101) in the 4% HAS group compared with 18.8% (19/101) in the 20% HAS group ($P = 0.01$). However, this effect was not significant after adjustment for APACHE III risk of death (OR, [20% v 4%], 1.21; 95% CI, 0.69–5.21; $P = 0.22$].

Discussion

Key findings

We conducted a retrospective comparative study of 202 intensive care patients who had received FBT with either 4% or 20% HAS according to clinical judgement. Patients who had received 20% HAS were more acutely ill at ICU admission and were more likely to have liver disease and to be on RRT at the time of treatment. Contrary to our hypothesis, we found that, despite the fact the patients treated with 20% HAS were more severely ill, there were no significant differences in their MAP in the first 4 hours and there was instead a trend toward a greater effect with 20% HAS compared with baseline values. We also found that, for each episode of FBT, patients given 20% HAS received five times less volume, seven times less sodium and about 30 times less chloride than those in the 4% HAS group. In keeping with their patient characteristics and the above differences in electrolyte administration, patients receiving 4% HAS displayed non-significantly higher serum sodium and chloride values and a more negative base excess during the study period.

Relationship to previous studies

To our knowledge, ours is the first study to compare haemodynamic and biochemical changes after FBT with 4% v 20% HAS in critically ill patients (or any patients). However, extensive data are available on the use of 4% HAS for FBT from the Saline versus Albumin Fluid Evaluation (SAFE) study.[8] The baseline haemodynamic status of our patients compared with that of patients in the SAFE study showed that mean values for heart rate, arterial pressure and central venous pressure were similar, which supports the external validity of our findings.

There are only limited data on the use of 20% HAS as FBT in the ICU. However, patients in the recent Albumin Italian Outcome Sepsis (ALBIOS) study received 20% albumin supplementation.[9] The study reported no significant difference in mortality at 90 days, but significantly higher MAPs and a lower net fluid balance for patients in the 20% HAS group. Our patients were younger than those in the ALBIOS study and had a higher incidence of liver disease but were less likely to be mechanically ventilated when receiving FBT. A comparison of mean baseline values for heart rate, arterial pressure and central venous pressure in our patients shows that they were similar to those in the ALBIOS trial, further supporting the broad generalisability of our observations.

We saw a small increase in MAP for patients receiving 20% HAS. Bihari and colleagues reported similar findings in an observational study of patients receiving FBT for severe sepsis.[24] In their study, patients receiving 4% HAS showed a 1 mmHg increase in MAP ($P = 0.01$), but also a significant increase in vasopressor requirements. In our cohort, there was no significant change in the use of vasoactive drugs after FBT with either 4% or 20% HAS.

In patients with acute lung injury, Martin and colleagues used 25% HAS to improve diuresis in association with furosemide.[20] The addition of an 8-hourly 25% HAS solution to the furosemide infusion resulted in more patients achieving a negative fluid balance compared with controls. As in our study, Martin and colleagues found no difference in heart rate, blood pressure or serum electrolytes, but also that patients receiving hyperoncotic HAS received significantly less fluid compared with controls during the 3-day study period.

In patients with liver disease and spontaneous bacterial peritonitis, Sort and colleagues found that administering 20% HAS prevented renal failure and reduced mortality.[25] The authors used 20% HAS to initially deliver 1.5 g/kg/day of albumin supplementation. Such data, as well as information on the use of 20–25% HAS in the management of patients with liver disease and paracentesis, explain the preferential use of 20% HAS in patients with pre-existing liver disease in our cohort. When comparing the baseline haemodynamic status of our patients to that of patients in the study of Sort and colleagues, mean values for heart rate, arterial pressure and central venous pressure were all similar, which suggests that our practice may reflect practice in the care of patients with liver disease elsewhere.

The above studies showed that 20% HAS can be used safely in critically ill patients, but do not provide any information on the differential haemodynamic and biochemical effects of 20% v 4% HAS in such patients. No such comparative studies have been performed.

Implications of study findings

In our study, we showed that FBT with 20% HAS did not lead to the administration of more than one bottle, thus reducing chloride administration. FBT with chloride-rich fluids has been associated with metabolic acidosis[26,27] and AKI.[17] We also found that FBT with 20% HAS reduced sodium administration. Recent observations suggest that sodium accumulation may be undesirable and contributes to worse gas exchange in critically ill patients.[11,13] Finally, the widespread use of FBT in critically ill patients often results in patients accumulating a significant positive fluid balance,

which has been associated with dependency on mechanical ventilation in severe lung injury and increased mortality in patients with septic shock.[18,28] Given the fact that only one bottle was typically used, 20% HAS FBT was associated with an 80% reduction in administered volume.

Strengths and limitations

To our knowledge, ours is the first comparative study of two widely available colloidal solutions which are currently in use for FBT worldwide. The data used for this study were prospectively collected and documented and are electronically stored in the unit database, scanned medical records and central pathology database. Therefore, they are not subject to selection bias or open to interpretation bias. The differences in volume, sodium and chloride administered are clear. Similarly, there is no evidence of superiority for 4% HAS in any of the variables being studied. The observation that 20% HAS achieves the same haemodynamic effect at 80% less volume, seven times less sodium and about 30 times less chloride suggests that it may be a more physiologically rational choice for FBT if a colloidal solution is chosen. We note that 20% HAS is hypotonic and should not be used in patients with traumatic brain injury, and that 20% HAS is also hyperoncotic and may affect renal function adversely, but we found no evidence of such an effect in our study.

The main limitations of our study relate to its retrospective observational design and the fact that, due to lack of randomisation, there was a strong selection bias in favour of giving 20% HAS to patients with greater illness severity, more underlying liver disease and undergoing more frequent RRT. However, given such selection bias, one would expect FBT with 20% HAS to deliver inferior haemodynamic or biochemical outcomes. In fact, the trends were in the opposite direction and supported the safety and likely haemodynamic equivalence of FBT with 20% HAS. Measurement of cardiac index was available only in a minority of patients, thus we cannot comment on the differential effects of the two fluids on this important variable. We note that no large trials of FBT so far have reported data on the effect of FBT on cardiac index. Finally, comparative observational studies such as ours represent the first step to justify subsequent pilot randomised controlled trials (RCTs).

Conclusion

The haemodynamic and biochemical effects of 20% and 4% HAS appeared comparable when used for FBT in critically ill adults. However, 20% albumin delivered 80% less volume, seven times less sodium and about 30 times less chloride, making it a more rational physiological choice for FBT in most ICU patients. Given the results of our study, an RCT now appears justified.

Competing interests

None declared.

Author details

Jonathan Bannard-Smith, Clinical Research Fellow[1]
Paschal Alexander, Medical Registrar[1]
Neil Glassford, Clinical Research Fellow,[1] and PhD Candidate[2]
Matthew J Chan, Medical Student[1]
Matthew Lee, Critical Care Registrar[1]
Ben T Wong, Critical Care Registrar[1]
Grant Crawford, Critical Care Resident[1]
Michael Bailey, Statistician[2]
Rinaldo Bellomo, Director of Research,[1] and Co-Director[2]

1 Department of Intensive Care, Austin Health, Melbourne, VIC, Australia.

2 Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventative Medicine, Monash University, Alfred Hospital, Melbourne, VIC, Australia.

Correspondence: rinaldo.bellomo@austin.org.au

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