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ORIGINAL ARTICLE

Association between Type of Fluid Received Prior to Enrollment, Type of Admission, and Effect of Balanced Crystalloid in Critically Ill Adults

A Secondary Exploratory Analysis of the BaSICS Clinical Trial

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Abstract

Rationale: The effects of balanced crystalloid versus saline on clinical outcomes for ICU patients may be modified by the type of fluid that patients received for initial resuscitation and by the type of admission.

Objectives: To assess whether the results of a randomized controlled trial could be affected by fluid use before enrollment and admission type.

Methods: Secondary *post hoc* analysis of the BaSICS (Balanced Solution in Intensive Care Study) trial, which compared a balanced solution (Plasma-Lyte 148) with 0.9% saline in the ICU. Patients were categorized according to fluid use in the 24 hours before enrollment in four groups (balanced solutions only, 0.9% saline only, a mix of both, and no fluid before enrollment) and according to admission type (planned, unplanned with sepsis, and unplanned without sepsis). The association between 90-day mortality and the randomization group was assessed using a hierarchical logistic Bayesian model.

Measurements and Main Results: A total of 10,520 patients were included. There was a low probability that the balanced solution was associated with improved 90-day mortality in the whole trial population (odds ratio [OR], 0.95; 89% credible interval [CrI], 0.66–10.51; probability of benefit, 0.58); however, probability of benefit was high for patients who received only balanced solutions before enrollment (regardless of admission type, OR, 0.78; 89% CrI, 0.56–1.03; probability of benefit, 0.92), mostly because of a benefit in unplanned admissions due to sepsis (OR, 0.70; 89% CrI, 0.50–0.97; probability of benefit, 0.96) and planned admissions (OR, 0.79; 89% CrI, 0.65–0.97; probability of benefit, 0.97).

Conclusions: There is a high probability that balanced solution use in the ICU reduces 90-day mortality in patients who exclusively received balanced fluids before trial enrollment.

Clinical trial registered with www.clinicaltrials.gov (NCT 02875873).

Keywords: balanced solutions; critical care; fluid challenge

(Received in original form November 3, 2021; accepted in final form March 29, 2022)

Am J Respir Crit Care Med Vol 205, Iss 12, pp 1419–1428, Jun 15, 2022
Copyright © 2022 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.202111-2484OC on March 29, 2022
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Balanced solutions may be associated with better outcomes in critically ill patients. It has been suggested that potential benefits of balanced solutions may be more significant if they are used before ICU admission and are maintained as the preferred fluid during the ICU stay. Randomized controlled trials that allocated patients to receive either 0.9% saline or balanced solutions represent an opportunity to test this hypothesis.

What This Study Adds to the Field: In this secondary analysis of the BaSICS (Balanced Solutions in Intensive Care Study) trial, we found that the type of fluid patients received for initial resuscitation before enrollment appeared to mediate the potential benefits of balanced solution use in the ICU. There was a high probability that balanced solution use was associated with lower 90-day mortality in patients who exclusively received balanced solutions before study enrollment. This benefit was more apparent in patients with unplanned admission due to sepsis (probability of benefit, 0.96).

The optimal composition of crystalloid solution for intravenous administration to ICU patients remains uncertain. In the BaSICS (Balanced Solutions in Intensive Care Study) trial, ICU patients were randomized to receive either 0.9% saline or Plasma-Lyte 148 (balanced solution) as the preferred fluid for maintenance, resuscitation, and dilutions during their ICU stay, but trial protocol controlled neither the volume nor the type of fluid administered before enrollment, which occurred after ICU admission (1). This trial rendered neutral results for its primary endpoint (90-day survival). In contrast, another large cluster-randomized trial suggested a possible benefit of balanced solutions using a composite endpoint (2), which was more pronounced in the subgroup of patients with sepsis, especially if balanced solutions were used before ICU admission (3, 4). It is, therefore, conceivable that the effect of balanced solutions could be moderated by admission type and fluid use before enrollment.

In this secondary *post hoc* analysis of the BaSICS trial, we explored the association between fluid use before enrollment, admission type, and the effect of balanced solution versus 0.9% saline in critically ill patients. We hypothesized that balanced solutions would be associated with lower mortality at 90 days in the subgroup of patients who received only balanced solutions before enrollment and that these effects would differ according to admission types; in particular, we hypothesized that potential benefits of balanced solutions would be greater in the subgroup of patients with sepsis who previously received only balanced solutions (4); these effects could be related to chloride toxicity or different rates of occurrence of hyperchloremia, which were also secondarily explored.

Methods

Study Design

The study was a *post hoc* secondary analysis of a multicenter, randomized clinical trial comparing a balanced solution (Plasma-Lyte 148) with 0.9% saline in critically ill patients (BaSICS).

Population

BaSICS included patients admitted into ICUs who required at least one fluid expansion; who were not expected to be discharged the next day; and who had at least one additional risk factor (age >65 years, hypotension, presence of sepsis, need for mechanical ventilation or noninvasive mechanical ventilation, abnormal measured serum creatinine concentration on presentation, or a diagnosis of liver cirrhosis or acute liver failure). Detailed information on inclusion and exclusion criteria can be found in the original report (1, 5).

Fluid use in the 24 hours before enrollment was collected in the case report form as two sequential variables: whether there was any prescription of fluid therapy (not for dilution or maintenance) in the past 24 hours on medical records (electronic of physical charts, transfer notes, surgical records, etc.) and, if yes, the volume of fluid of both 0.9% saline and balanced solutions (defined as lactated Ringer's solution and/or Plasma-Lyte 148) used. These variables were obligatory in the case report form and were checked for completion during site monitoring. Patients were then categorized according to intravenous crystalloid fluid use in the 24 hours before enrollment in four groups: *1*) patients who did not receive any saline and received exclusively balanced solutions, in any volume; *2*) patients who received exclusively 0.9% saline before enrollment, in any volume; *3*) patients who received a mix of balanced solutions and 0.9% saline ("mixed fluid"); and *4*) patients who did not receive intravenous crystalloid fluid before enrollment ("no fluid"). Admission types were categorized as

Supported by the Brazilian Ministério da Saúde through the "Programa de Desenvolvimento Institucional do Sistema Único de Saúde"; a research scholarship from CNPq – Brazil (National Research Council, no. 302214/2018-6) to A.B.C.; and Baxter Hospitalar. Baxter Hospitalar had no role in the design and conduct of the study. The Brazilian Ministry of Health approved the study but was not involved in design, analysis, interpretation, or decision to publish the results.

Author Contributions: F.G.Z. and A.B.C. had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: F.G.Z., A.B.C., L.P.D., T.D.C., L.C.P.A., F.R.M., M.S.C.A., and N.B.d.S.; acquisition of data: all authors; drafting of the manuscript: F.G.Z. and L.P.D.; critical revision of the manuscript for important intellectual content: all authors; and statistical analysis: L.P.D. and F.G.Z. The steering committee was responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

unplanned admission due to sepsis (defined as suspicion of infection plus organ failure), unplanned admission without sepsis, and planned admission.

Interventions

Patients enrolled in BaSICS were randomized to receive 0.9% saline or balanced solution as the fluid of choice for all fluid challenges, maintenance, and drug dilutions (>100 ml) during their ICU stay and up to 90 days after enrollment. Physicians, patients, and individuals who assessed the outcomes were blinded to the assigned treatment. Patient management, including the decision to perform fluid challenges, was left to the discretion of the attending physician in the trial. Fluid use before enrollment was noted in the case report form as volume of either 0.9% saline or balanced solution (including lactated Ringer's solution or Plasma-Lyte 148) in the 24 hours before enrollment. *See* References (1) and (5) for details.

Endpoints

The primary endpoint for this secondary analysis was 90-day mortality. The secondary endpoint was number of days alive and free of kidney replacement therapy (KRT) up to 28 days after randomization.

Statistical Analysis

Primary endpoint. Univariate analyses are presented as table and exploratory figures. The association between the primary endpoint and the randomization group was assessed using a hierarchical logistic Bayesian model adjusted by group of fluid use before enrollment, admission type, the intervention, and enrolling site as random intercept. An interaction between fluid use before enrollment, admission type, and intervention arm was added. Three sets of priors were applied for the log odds ratio (log[OR]) of the intervention (6), all assuming a normal distribution of the log(OR): one moderate-strength skeptical prior (mean = 0; SD = 0.355); one moderate-strength optimistic prior (mean = −0.182, SD = 0.175, compatible with an OR of 1/1.20 for benefit and allowing 0.15 probability of harm); and one moderate-strength pessimistic prior (mean = 0.182, SD = 0.175; compatible with an OR of 1.2 for harm and allowing 0.15 probability of benefit). For a description of the reasons for these priors, *see* Table E1 in the online supplement. Other priors, including priors for interactions, were set as normal mean zero (SD = 1). Because of the presence of interactions, results were obtained by sampling 4,000 conditional posterior probabilities and providing the following metrics in different possible combination scenarios: *1*) the median OR with 89% credible interval (CrI); *2*) probability of benefit of the intervention (P[OR] < 1); *3*) probability OR ranging from 1/1.1 to 1.1 (1/1.1 < P[OR] < 1.1); *4*) probability OR below 1/1.25 (P[OR] < 1/1.25); and *5*) absolute differences of predicted probabilities for possible scenarios. We also display the 95% CrIs for the primary endpoint in the main analysis.

Secondary analyses. A secondary analysis was performed according to the admission type and evaluated the effect of total volume of fluid used in the 24 hours before enrollment, the percentage of fluid infused as 0.9% saline, and the randomization arm. This analysis was designed to assess whether a "contamination" effect occurred; that is, whether a continuous assessment of the percentage of fluid used as saline could moderate the effect of randomization arm on the primary endpoint (for details, *see* the online supplement). Results are reported graphically as the conditional predicted probabilities in potential scenarios (volume of fluid used and percentage given as 0.9% saline before enrollment).

Sensitivity analysis. One sensitivity analysis for the primary endpoint was performed after excluding patients with traumatic brain injury, a population that may have been harmed by balanced solutions in the main trial (1); this analysis was performed for both the primary main analysis and the secondary analysis (continuous analysis). We also performed a sensitivity analysis based on frequentist methods (details are shown in the online supplement) and another based on flat priors for all predictors for the primary endpoint.

Secondary endpoint. Number of days alive and free of KRT up to 28 days were assessed using a Bayesian beta binomial model with the same adjustment as for the main model. For a discussion of the methods, *see* the online supplement.

Simulation analysis. Because of the use of a complex three-way interaction model for the primary outcome, we performed a simulation study to estimate the frequency of random probabilities of benefit occurring under an absence of effect of balanced solutions after enrollment for the primary endpoint ("type 1 events"). For details, *see* the online supplement.

Missing value policies. We used the same data set used for the main trial analysis, which included imputed values for missing primary outcome for 11 patients, and admission type imputation for 17 patients, as described elsewhere (1). Seventy-two (<1%) patients had unknown information on KRT; we imputed this as absence of use of KRT. There were no missing values on whether fluid was used before enrollment.

All analyses were performed using R, version 4.1.1 (7), using packages *brms* (8) and *tidybayes* (9). For codes for the primary analysis and simulation, *see* the online supplement.

Results

A total of 10,520 patients were included in the analysis. Of all included patients, 3,202 received only balanced fluids before enrollment, 2,096 received only saline, 1,862 received a mix of balanced solutions and saline, and 3,360 did not receive crystalloids. Overall patient features according to subgroups defined by fluid used before enrollment and randomization arm are described in Table 1 (for aggregated values stratified only according to fluid use before enrollment, *see* Table E2). A boxplot shows fluid use according to admission type and fluid use group (Figure E1). There was a weak association between volume of 0.9% saline before enrollment and baseline chloride concentrations (Figure E2). For the trends in serum chloride concentrations for patients who had their serum chloride values measured, *see* Figures E3–E5; and for the percentage of patients with measured chloride who developed hyperchloremia (defined as serum chloride >110 mEq/L), *see* Figures E6–E8. Patients who exclusively received balanced solutions before enrollment or who received a mix of balanced solutions and 0.9% saline were more frequently admitted after elective surgeries, less frequently had sepsis, had lower illness severity scores, and had lower mortality (Table E2). In univariate analysis, patients who received balanced solutions or a mix of balanced solutions and 0.9% saline before enrollment had a numerically lower mortality than those who received no fluids

Table 1. Patient Characteristics according to Fluid Use before Enrollment and Randomization Arm

Characteristic	Balanced Only		Mix		No Fluids		Saline Only	
	0.9% Saline (*n* = 1,638)	Balanced Solution (*n* = 1,564)	0.9% Saline (*n* = 923)	Balanced Solution (*n* = 939)	0.9% Saline (*n* = 1,681)	Balanced Solution (*n* = 1,679)	0.9% Saline (*n* = 1,048)	Balanced Solution (*n* = 1,048)
Age, mean (range)	64 (53–74)	63 (51–73)	63 (51–71)	63 (52–72)	64 (50–75)	64 (50–75)	63 (50–73)	61 (47–73)
Sex, *n* (%)								
Male	898 (55)	868 (55)	542 (59)	550 (59)	922 (55)	913 (54)	599 (57)	589 (56)
Female	740 (45)	696 (45)	381 (41)	389 (41)	759 (45)	766 (46)	449 (43)	459 (44)
Admission type, *n* (%)								
Planned	1,156 (71)	1,092 (70)	683 (74)	686 (73)	354 (21)	341 (20)	399 (38)	381 (36)
Unplanned, no sepsis	309 (19)	313 (20)	151 (16)	164 (17)	876 (52)	913 (54)	390 (37)	412 (39)
Unplanned, sepsis	173 (11)	159 (10)	89 (9.6)	89 (9.5)	451 (27)	425 (25)	259 (25)	255 (24)
SOFA, mean points (range)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.00 (3.00–6.00)	4.00 (3.00–6.00)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	5.0 (3.0–7.0)	5.0 (2.0–7.0)
Vasopressor use, *n* (%)	632 (39)	607 (39)	472 (51)	491 (52)	539 (32)	526 (31)	403 (38)	410 (39)
Creatinine, mg/dL (range)	0.98 (0.75–1.29)	0.97 (0.75–1.27)	0.90 (0.70–1.21)	0.94 (0.70–1.22)	1.09 (0.80–1.63)	1.00 (0.78–1.50)	1.00 (0.76–1.50)	1.00 (0.71–1.50)
Balanced solution before admission, ml (range)	2,000 (1,000–3,000)	2,000 (1,000–3,000)	1,500 (1,000–2,500)	1,500 (1,000–2,500)	—	—	—	—
0.9% Saline before admission, ml (range)	—	—	1,000 (600–1,750)	1,000 (500–1,500)	—	—	1,375 (828–2,000)	1,000 (681–2,000)
Number of days alive and free of KRT at 28 days, mean (SD)	24 (10)	25 (9)	25 (9)	24 (9)	20 (13)	20 (13)	21 (12)	21 (12)
Mortality, *n* (%)	320 (20)	253 (16)	142 (15)	157 (17)	642 (38)	618 (37)	334 (32)	352 (34)

Definition of abbreviations: KRT = kidney replacement therapy; mix = mixed fluid; SOFA = sequential organ failure assessment score.

or exclusively 0.9%, regardless of admission type (Figure E3).

Results for the primary endpoint are shown in Table 2 and Figure 1, 2, and E10–E15. The results of the Bayesian reanalysis considering the skeptical neutral prior are shown in Table 2 (for the results of optimistic, pessimistic, and flat priors, *see* Tables E2, E3, and E4, respectively). Results are presented in Table 2 for all patients and according to all possible combinations of admission type and fluid use before enrollment. The probability that being randomized to balanced solutions was associated with improved outcome in the whole population was 0.58 (difference in mortality, 0; 89% CrI, −0.08 to 0.09; OR, 0.95; 89% CrI, 0.66 to 1.51). These results are also shown separately, according to fluid use before enrollment and admission type in Figures E10 and E11, respectively, and then sequentially according to combinations of groups of fluid use before enrollment and admission type (Figures E12–E15).

Figure 1 shows the ORs and their 89% and 95% CrIs for all possible scenarios arising from the hierarchical Bayesian model shown in Table 2. The conditional distributions of the ORs for balanced solutions versus saline in the 12 possible combinations are shown in Figure 2. For patients who received only balanced solutions before enrollment, the probability of benefit regarding mortality was high (0.92; Table 2 and Figure E10, panel *A*), being very high in planned admissions (0.97) and in unplanned ICU admission with sepsis (0.96), and less pronounced in patients with unplanned admissions not due to sepsis (0.84; Figure E11). In no admission type was the overall probability that balanced solutions were associated with reduction in 90-day mortality above 0.90 (Table 2 and Figure E12). In a sensitivity analysis excluding patients with traumatic brain injury, there was an increase in overall probability of benefit of balanced solutions in the trial (0.58 to 0.63), driven by an increase in the probability of benefit in patients with unplanned admissions without sepsis who only received balanced solutions before enrollment (0.84 to 0.94; Table E4). Results were slightly affected by different priors (Tables E2 and E3). For the optimistic prior, all results were similar, with no difference in interpretation of results. The pessimistic prior also yielded similar results, with the exception of the

Table 2. Results for the Primary Endpoint in the Bayesian Model following the Neutral Moderate-Strength Skeptical Prior

Admission Type and Fluid Group before Enrollment	Difference in 90-Day Mortality (Balanced − Saline); Median (89% CrI) [95% CrI]	Odds Ratio for 90-Day Mortality, Median (89% CrI) [95% CrI]	P(OR < 1)	P(OR < 1/1.25) [P(OR < 0.8)]	P(1/1.1 < OR < 1.1)
All admission types					
All	−0.01 (−0.08 to 0.09) [−0.11 to 0.12]	0.95 (0.66 to 1.51) [0.60 to 1.75]	0.58	0.22	0.31
Balanced only*	−0.04 (−0.13 to 0.00) [−0.15 to 0.02]	0.78 (0.56 to 1.03) [0.51 to 1.10]	0.92	0.55	0.16
Mix	0.02 (−0.04 to 0.15) [−0.05 to 0.18]	1.15 (0.77 to 1.94) [0.72 to 2.19]	0.31	0.07	0.25
No fluids	−0.01 (−0.07 to 0.03) [−0.08 to 0.04]	0.93 (0.72 to 1.17) [0.67 to 1.25]	0.69	0.17	0.45
Saline only	0.01 (−0.04 to 0.08) [−0.06 to 0.09]	1.06 (0.75 to 1.42) [0.70 to 1.51]	0.39	0.09	0.35
Unplanned, sepsis					
All	−0.01 (−0.12 to 0.13) [−0.15 to 0.16]	0.96 (0.59 to 1.75) [0.53 to 2.04]	0.55	0.26	0.24
Balanced only†	−0.08 (−0.16 to −0.01) [−0.18,0.01]	0.70 (0.50 to 0.97) [0.46 to 1.05]	0.96	0.74	0.09
Mix	0.07 (−0.04 to 0.18) [−0.06 to 0.21]	1.38 (0.85 to 2.23) [0.76 to 2.49]	0.15	0.03	0.14
No fluids	−0.03 (−0.08 to 0.02) [−0.09 to 0.03]	0.88 (0.71 to 1.10) [0.67 to 1.15]	0.81	0.23	0.36
Saline only	0.02 (−0.04 to 0.09) [−0.06 to 0.11]	1.11 (0.84 to 1.49) [0.78 to 1.59]	0.28	0.03	0.35
Unplanned, no sepsis					
All	0.00 (−0.06 to 0.08) [−0.08 to 0.11]	1.02 (0.73 to 1.52) [0.68 to 1.71]	0.46	0.11	0.38
Balanced only	−0.03 (−0.09 to 0.02) [−0.11 to 0.03]	0.84 (0.64 to 1.11) [0.61 to 1.18]	0.84	0.38	0.27
Mix	0.03 (−0.04 to 0.12) [−0.06 to 0.11]	1.23 (0.82 to 1.85) [0.75 to 2.04]	0.21	0.04	0.21
No fluids	0.00 (−0.04 to 0.03) [−0.05 to 0.04]	0.98 (0.84 to 1.15) [0.81 to 1.19]	0.57	0.02	0.65
Saline only	0.02 (−0.03 to 0.08) [−0.04 to 0.09]	1.12 (0.88 to 1.43) [0.84 to 1.51]	0.22	0.01	0.37
Planned					
All	−0.01 (−0.06 to 0.03) [−0.07 to 0.04]	0.89 (0.67 to 1.23) [0.64 to 1.32]	0.73	0.29	0.30
Balanced only	−0.03 (−0.06 to 0.00) [−0.08 to 0.00]	0.79 (0.65 to 0.96) [0.62 to 1.00]	0.97	0.53	0.13
Mix	0.00 (−0.04 to 0.03) [−0.05 to 0.04]	0.96 (0.73 to 1.27) [0.68 to 1.36]	0.59	0.15	0.40
No fluids	−0.01 (−0.07 to 0.04) [−0.08 to 0.05]	0.92 (0.67 to 1.26) [0.62 to 1.35]	0.68	0.25	0.34
Saline only	−0.01 (−0.06 to 0.03) [−0.07 to 0.04]	0.92 (0.68 to 1.25) [0.64 to 1.34]	0.67	0.23	0.34

Definition of abbreviations: CrI = credible interval; mix = mixed fluid; P(OR) = probability odds ratio.
*Primary group of interest.
†Primary subgroup of interest.

posterior for balanced solutions on elective admissions that received exclusively balanced solutions before ICU admission where a reduction in probability of benefit was observed (0.97 to 0.85; Table E3). The flat prior, as expected, provided less conservative results than the neutral prior.

Results for the continuous analysis are shown in Figure 3 (also *see* Figures E16–E18). Overall, conditional predicted mortality was lower for balanced solutions in patients who received a lower percentage of fluid before enrollment as 0.9% saline. This effect was apparent across conditional total volumes of fluid used, being more evident for larger volume in planned admissions. For unplanned admissions without sepsis, an invert association occurred for higher volumes of fluid infused before enrollment, with higher mortality for balanced solutions; this trend was reduced after excluding patients with traumatic brain injury (who were mostly coded as unplanned admissions without sepsis; *see* Figure E19).

For frequentist analysis results, *see* the online supplement (Figure E20 and Tables E5 and E6). The only scenario in which *P* values for the association between being randomized to receive balanced solution and 0.9% saline were less than 0.05 was that of the subgroup of patients with sepsis who only received balanced solutions before enrollment (OR, 0.613; 95% confidence interval, 0.330–0.895). Average effects under frequentist framework are similar to Bayesian analysis with flat priors, both being less conservative than the neutral prior used on the main analysis.

For results regarding number of days alive and free of KRT at 28 days, *see* Table E7. In no scenario did we find that the probability that balanced solutions were associated with at least one more day alive and free of KRT at 28 days was above 0.90. The higher probability of benefit found occurred in patients with unplanned admission due to sepsis, where the probability of having one more day alive and free of KRT for the balanced solution group was 0.71.

Results of the simulations for assessing the potential frequency of type 1 events are shown in the online supplement. Probabilities of obtaining results as extreme as those found under the assumption of absence of effect for *1*) all patients who received balanced solutions before

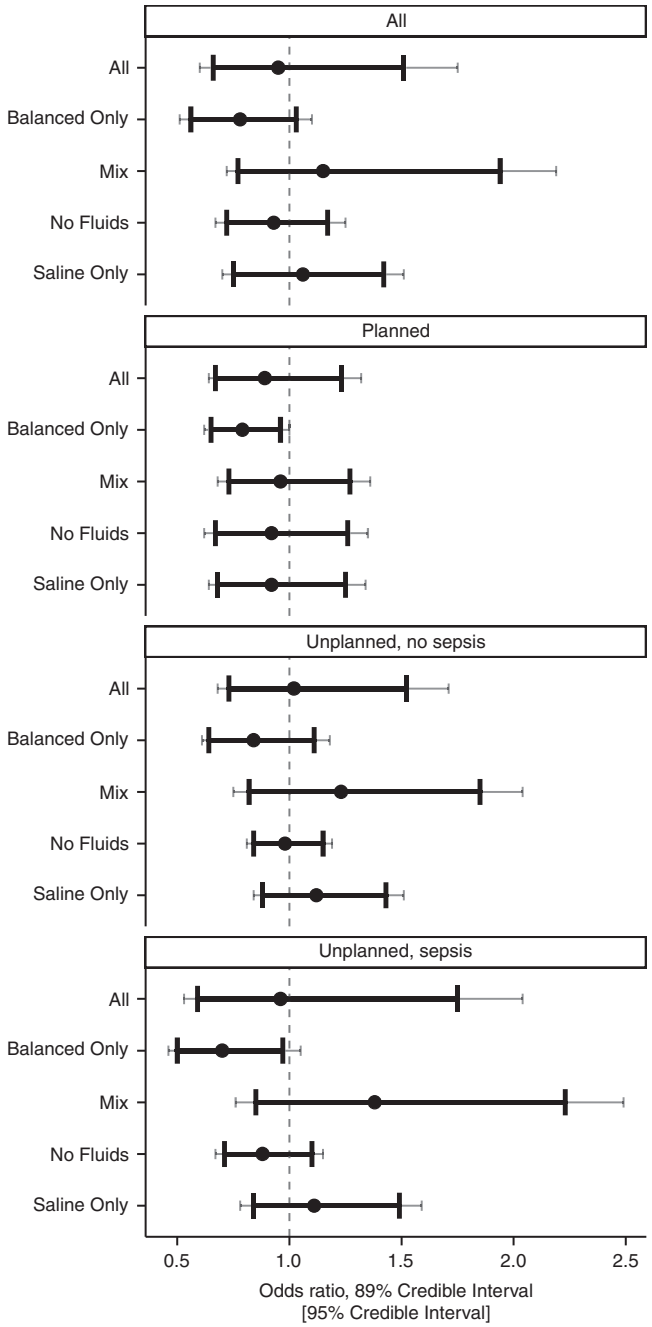

Figure 1. Forest plot of the odds ratios of balanced solution versus 0.9% saline for mortality and their respective 89% and 95% credible intervals (CrIs): 89% CrIs are indicated with bold lines, and 95% CrIs are indicated with light gray lines. All results shown are for the neutral prior. All results were obtained from the main model. Mix = mixed fluid.

enrollment, *2*) patients with unplanned admission due to sepsis who only received balanced solutions before enrollment, and *3*) patients with planned admissions who only received balanced solutions before enrollment were 0.065, 0.003, and 0.028, respectively. For details, *see* the online supplement.

Discussion

In this secondary *post hoc* analysis of a randomized controlled trial comparing a balanced solution versus 0.9% saline in patients admitted to the ICU, overall benefit of balanced solutions appeared to be moderated by fluid use before enrollment and admission type. The overall probability of benefit in the whole population was unremarkable, compatible with the original publication (4). However, important differences regarding the effect of the intervention according to fluid use before enrollment and admission type were observed. There was a high probability of benefit in patients randomized to balanced solutions in the subgroup of patients who received exclusively balanced solutions before enrollment, independent of admission type (0.92); this benefit appeared to be mostly driven by a reduction in 90-day mortality in patients with unplanned admission due to sepsis and in those with planned admissions, both of whom had a probability of benefit above 0.95. In a continuous analysis, a "contamination" effect was present in most scenarios, with increasing percentage of fluid being given as 0.9% saline before enrollment being associated with lower possible benefits of receiving balanced solutions during ICU stay. In no scenario was there was a probability higher than 0.90 that balanced solutions were associated with at least one more day alive and free of KRT at 28 days.

The present analysis expands the results of BaSICS by investigating potential sources of heterogeneity in treatment effect using relevant effect modifiers that were not fully considered in the trial main analyses. One key factor is baseline fluid use before enrollment in the trial; more than 60% of all patients in BaSICS used fluid at baseline that was not protocolized and varied across sites. It is conceivable that both fluid use and admission type may interact and modulate the response to different types of fluid in the ICU. Our results can, therefore, be interpreted as follows: The most promising signal for potential benefit appeared in patients who exclusively received balanced solutions before enrollment; when further dividing this group according to admission type, the effect seemed to be mostly associated with unplanned admission due to sepsis, being the results in other admission types sensitive to priors or to sensitivity analyses. Results in the sepsis subgroup that exclusively received balanced solutions before enrollment were insensitive to different priors; in fact, even when a pessimistic prior that simulated a low (0.15) probability of benefit for the intervention was considered, the posterior probability of benefit of balanced solutions was more than 0.95. This is in contrast with the signal for

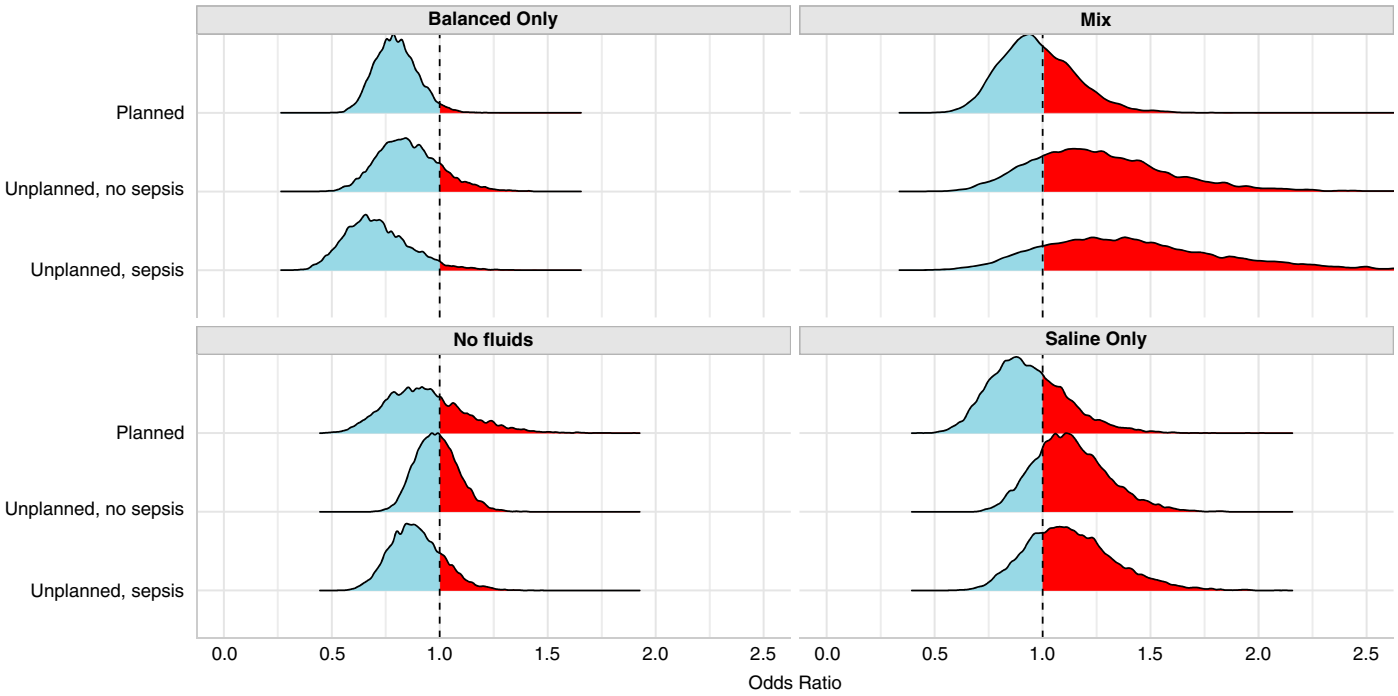

Figure 2. Conditional distributions of the odds ratio for balanced solutions versus saline according to fluid use group before enrollment (panels) and admission types (lines within panels). The probabilities of benefit (odds ratio < 1) are highlighted in blue, and the probability of harm is indicated in red.

benefit in patients with planned admission, where results were more sensitive to different priors (probability of benefit decayed from 0.99 for the optimistic prior to 0.85 for pessimistic prior), suggesting that high uncertainty remains (10). In all subgroups, increasing the percentage of fluid infused as 0.9% saline before enrollment appeared to modulate the results, with higher percentages blunting benefits of balanced solutions, especially on planned admissions and in patients with sepsis.

Our results appear to be consistent with a previous secondary analysis of patients with sepsis in a prior trial that found that fluid therapy before ICU admission modified the effect of the fluid type assigned by the trial on clinical outcomes (4), which motivated a suggestion for use of balanced solutions in patients with sepsis issued by the most recent Surviving Sepsis Guidelines (11). The precise explanation for our findings remains not completely elucidated. Chloride and hyperchloremia are usually considered to be on the mediation pathway for the effect of balanced solutions. However, 0.9% saline use is not the only culprit for hyperchloremia in critical illness and in the postoperative period (11, 12). In fact, the association between chloride infusion and changes in strong ion difference in critically ill patients, although significant, may be of small magnitude (13) (Figure E3). It is unclear how use of 0.9% saline may blunt potential benefits of balanced solutions, although one can hypothesize that abrupt increases on chloride causing fast reductions in strong ion difference and (even if transitory) acidosis might be involved. A single serum chloride measurement may not reflect all changes in electrolyte values that occur after fluid expansion because of redistribution. The acid–base profile in sepsis is usually characterized by an important decrease in albumin and increase in chloride (14). Because of severe inflammation and reduction in albumin synthesis (14), it could be hypothesized that patients with sepsis might be more sensitive to external chloride load, for example. This association was not clear from the baseline data available (Figure E2); however, frequency of hyperchloremia (serum chloride at >110 mEq/L) in the subgroup of patients that had chloride data available was high and sustained (if not increased) during the first 3 days of the trial in the subgroup of septic patients receiving 0.9% saline, whereas the frequency decreased in the group receiving balanced solutions (Figure E6). The group of planned admissions who received balanced solution before enrollment and were randomized to receive balanced solutions also had a low frequency of measured hyperchloremia. Although these findings might corroborate with the chloride hypothesis, they are limited to only some of the included patients and were not incorporated in a formal mediation analysis. Overall, one of the most important conclusions from our data is that confining a trial's intervention to a specific location (in our case, the ICU) may increase the chance of yielding neutral results when intervention is time sensitive and occurs irrespectively of patient's locale (as is the case of fluids, antibiotics, or many other interventions in acutely ill patients).

Bayesian investigations of heterogeneity in treatment effects are a promising tool and should ideally be planned before trial initiation (6). Investigating heterogeneity of treatment effect, especially in the context of a neutral trial, is challenging (15, 16). If overall results are neutral and there is sign of benefit in a specific subgroup, this suggests harm has occurred in another subgroup (or other

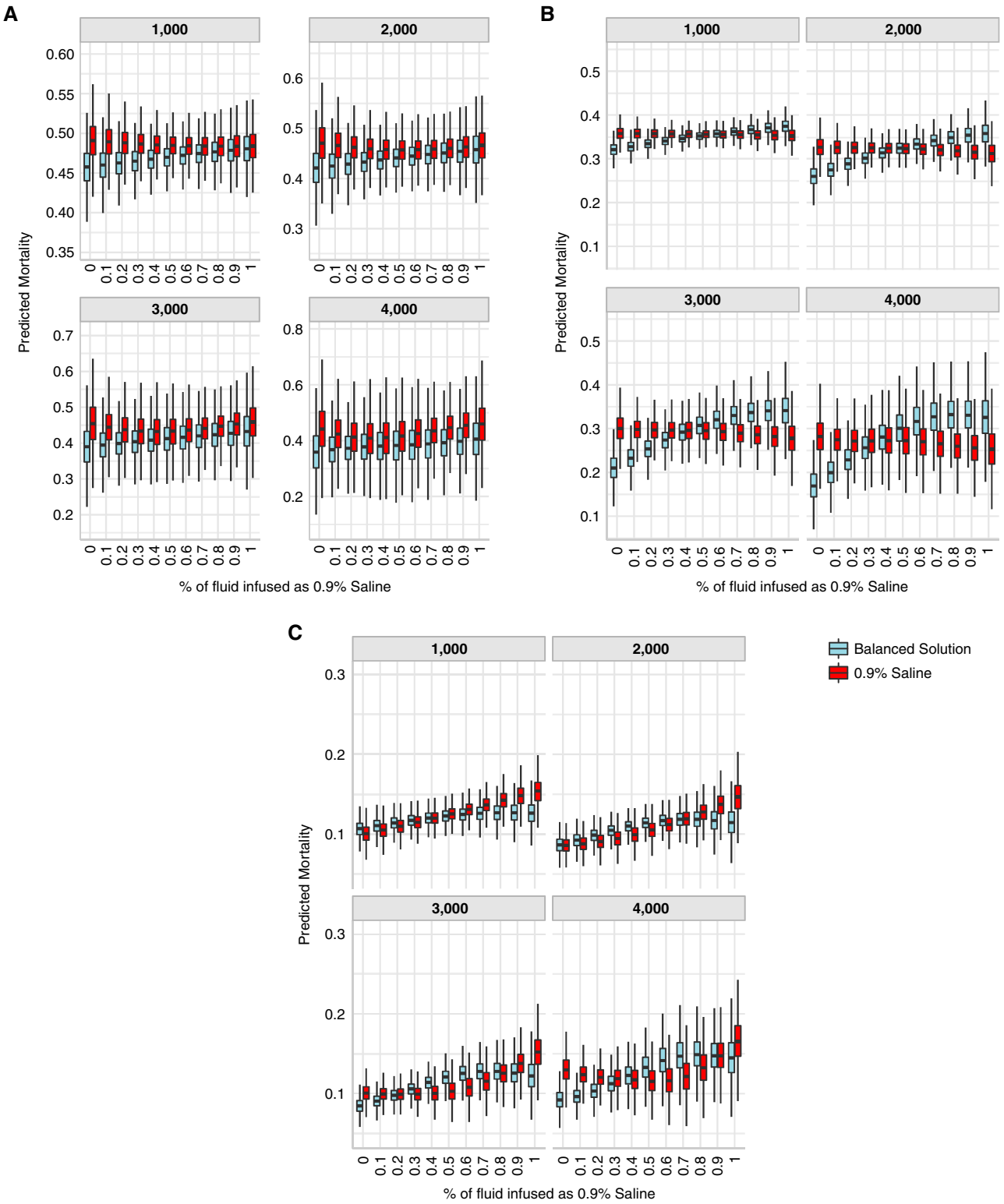

Figure 3. Results for the continuous assessment of fluid use before enrollment according to percentage infused as 0.9% saline for three admission types: (*A*) unplanned admissions with sepsis, (*B*) unplanned admissions without sepsis, and (*C*) planned admissions. Each facet panel represents a hypothetical total volume of fluid received before enrollment (1,000, 2,000, 3,000, and 4,000 ml), and the *x*-axis represents the percentage of fluid volume infused as saline (from 0 to 1, at 0.1 steps). The boxplots represent the model's conditional predicted mortality probability at that specific combination of total volume of fluid before enrollment and the percentage that was infused as 0.9% saline. The benefit of balanced solution seems to be more pronounced when the percentage of fluid infused as 0.9% saline before enrollment was low,

subgroups) of patients. None of our subgroups had undeniable harm of balanced solutions. However, exclusion of patients with traumatic brain injury increased the overall trial probability of benefit, which may explain at least part of the global neutral results in the presence of subgroups of patients who may have benefited from balanced solutions. This was also noticeable on the continuous assessment of percentage use of fluid infused as 0.9% saline analysis, where exclusion of patients with traumatic brain injury hampered the signal of harm for balanced solutions seen at unplanned admissions without sepsis (Figure E18). Future endeavors, including an ongoing individual patient meta-analysis between the SPLIT (The 0.9% Saline vs Plasma-Lyte 148 [PL-148] for ICU fluid Therapy) trial (17), the SMART (Isotonic Solutions and Major Adverse Renal Events Trial) trial (2), BaSICS (1), and the PLUS (Plasma-Lyte 148 versus Saline) trial (18) (PROSPERO CRD42022299282) will provide further information for different subgroups and confirm or refute our findings.

This study has several limitations. First, it is a secondary *post hoc* analysis of a large randomized controlled trial and should, therefore, be seen as exploratory, although it is aligned with other subgroup reports from the SMART trial. Second, the main analysis was performed by arbitrarily classifying patients into four groups according to the use (or not) of each type of fluid before enrollment while considering groups of admission types that were largely heterogeneous; however, a continuous analysis suggested that there was a continuous "contamination" effect of increasing the percentage of fluid infused as saline before enrollment and a reduction in the potential benefits of receiving balanced solutions in the ICU. Use of fluid before enrollment was a core variable in the BaSICS case report form; however, because of the pragmatic nature of the trial, we did not monitor source documents for all enrolled patients, and it is conceivable that some misclassification may have occurred. Approximately 60% of all patients had documented fluid use before enrollment, which is compatible with data from the SMART trial (2). Third, as with all Bayesian analyses, priors were used in the analyses; although we have the used priors previously suggested, prior selection can always be considered subjective (6). Fourth, we made no distinction regarding the type of balanced solution before enrollment. Finally, the Bayesian model created was heavily sampled. Bayesian models may be, however, less sensitive to multiple comparison (19, 20), and our simulations suggest that, even in the context of multiple comparisons, the probability of obtaining a high probability of benefit (arbitrarily set as above 0.90) was very low for the main group of interest.

Conclusions

There is a high probability that balanced solution use in the ICU reduces 90-day mortality in patients who exclusively received balanced fluids before trial enrollment, especially in the subgroup of those with sepsis. These findings require confirmation by future studies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgments: The authors thank Baxter Hospitalar for supplying fluids and logistics.

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Figure 3. (*Continued*). especially up to 0.20 for unplanned admissions. For unplanned admissions without sepsis, there was a trend toward higher mortality in patients randomized to balanced solutions (*B*), which was importantly reduced when patients with traumatic brain injury were excluded (*see* Figure E6 in the online supplement). For patients with planned admission, differences were more pronounced only at higher volumes of fluid used before enrollment (*C*, bottom left panel).

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