Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness

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A full list of Role of Active Deresuscitation After Resuscitation (RADAR) Investigators is listed in **Appendix 1**.

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Objectives: To characterize current practice in fluid administration and deresuscitation (removal of fluid using diuretics or renal replacement therapy), the relationship between fluid balance, deresuscitative measures, and outcomes and to identify risk factors for positive fluid balance in critical illness.

Design: Retrospective cohort study.

Setting: Ten ICUs in the United Kingdom and Canada.

Patients: Adults receiving invasive mechanical ventilation for a minimum of 24 hours.

Interventions: None.

Measurements and Main Results: Four-hundred patients were included. Positive cumulative fluid balance (fluid input greater than output) occurred in 87.3%: the largest contributions to fluid input were from medications and maintenance fluids rather than resuscitative IV fluids. In a multivariate logistic regression model, fluid balance on day 3 was an independent risk factor for 30-day mortality (odds ratio 1.26/L [95% CI, 1.07–1.46]), whereas negative fluid balance achieved in the context of deresuscitative measures was associated with lower mortality. Independent predictors of greater fluid balance included treatment in a Canadian site.

Conclusions: Fluid balance is a practice-dependent and potentially modifiable risk factor for adverse outcomes in critical illness. Negative fluid balance achieved with deresuscitation on day 3 of ICU stay is associated with improved patient outcomes. Minimization of day 3 fluid balance by limiting maintenance fluid intake and drug diluents, and using deresuscitative measures, represents a potentially beneficial therapeutic strategy which merits investigation in randomized trials. (*Crit Care Med* 2018; XX:00–00)

Key Words: critical illness; diuretics; fluid therapy; furosemide; water-electrolyte balance

Fluid therapy is widely used to optimize tissue perfusion in sepsis and other critical illness states, supported by international guidelines (1, 2). In addition to resuscitation fluid boluses, significant volumes of fluid are administered as nutrition, maintenance fluid, and a diluent for medications. In the context of endocrine influences and acute kidney injury (AKI) predisposing to fluid retention, critically ill patients commonly accumulate a positive fluid balance (2–5).

The association between positive fluid balance and mortality in a range of critical illness states is now well established (2–8). Although fluid accumulation is most evident clinically as peripheral and pulmonary edema, other negative physiologic consequences such as renal congestion have been postulated (9).

Two complementary strategies have evolved to prevent or mitigate fluid accumulation: restrictive fluid administration (10, 11) or active removal of accumulated fluid using diuretics or renal replacement therapy (RRT) when clinically stable (deresuscitation) (12). Our recent systematic review and meta-analysis found low-quality evidence in favor of a conservative or deresuscitative fluid strategy compared with liberal fluid administration or usual care (13), but considerable heterogeneity was evident with regard to interventions: these ranged from restriction of resuscitation fluid alone (10) to deresuscitation using diuretics and "hyperoncotic" albumin (14). Further work is needed to define the optimum fluid strategy to be tested in future large-scale randomized trials.

We undertook a multicenter cohort study of critically ill patients in Canada and the United Kingdom, aiming to increase our understanding of variability in current practice in fluid administration and deresuscitation, to characterize the relationship between fluid balance, deresuscitation, and patient outcomes and to identify risk factors for positive fluid balance with a view to informing the design of future trials. We hypothesized that a more positive fluid balance would be associated with mortality, that drivers of positive fluid balance would include practice-dependent variables, and that the use of deresuscitative measures to achieve a negative fluid balance would be associated with better outcomes.

METHODS

Design and Setting

Participating centers were selected on the basis of expressed interest in the study and were asked to provide data retrospectively for up to 50 consecutive patients admitted between June 2012 and June 2014 who met prespecified inclusion and exclusion criteria. A formal sample size calculation was not performed. Research ethics approval was obtained, but the requirement for individual patient consent was waived.

Participants

We included patients over 16 years old who received invasive mechanical ventilation in a participating ICU for a minimum of 24 hours. Exclusion criteria were failure to survive for more than 24 hours; lack of a commitment to full active care at ICU admission; drug overdose (fluid management unlikely to be relevant to outcome); transfer from another ICU or ICU case records unavailable; and those with a diagnosis of subarachnoid hemorrhage or diabetic ketoacidosis, conditions where specific considerations are relevant to fluid management.

Data Collection and Definitions

Data collected included demographic factors, diagnosis, severity of illness, furosemide and RRT use, and fluid input and output. Data were collected by trained study personnel using a standard data dictionary. The primary outcome was 30-day mortality. Secondary outcomes included duration of ICU stay in survivors, censored at day 30, and duration of mechanical ventilation in survivors, defined as the number of ICU days from intubation until successful extubation (> 24 hr without invasive ventilatory support).

Study day 1 was from ICU admission until 07:00 or 8:00 AM depending on unit practice, whereas subsequent study days were consecutive 24-hour periods, or part thereof on the day of ICU discharge. Daily fluid balance was the total delivered input (IV fluids, nutrition, medications) minus total measured output (e.g., urine, ultrafiltrate, output from surgical drains, etc) as recorded in case records. Cumulative fluid balance for a given day was the total fluid input minus the total output from ICU admission at the end of that day. Deresuscitative measures were defined as any use of furosemide or fluid removal using RRT.

We calculated Multiple Organ Dysfunction Scores (MODS) (15) daily. We estimated missing central venous pressure values as 8 mm Hg, as previously described (16). Daily delta-MODS was defined as the change in MODS between that day and the subsequent day. We estimated AKI severity using the Kidney Disease: Improving Global Outcomes (KDIGO) consensus criteria for the definition and classification of AKI (17) daily.

Statistical Analysis

Between-group comparisons were made using univariate logistic regression, Kruskal-Wallis test, or chi-square as appropriate. We constructed multivariate logistic regression models for 30-day mortality. Negative binomial regression was used for the outcomes of duration of ICU stay and duration of mechanical ventilation. A generalized estimating equation model was used to account for time and clustering within patients when investigating a possible association between daily fluid balance and the outcome of daily delta-MODS, using an identity link and exchangeable correlation structure. Multivariate linear regression modeling was used for exploration of a possible association between day 3 fluid balance and potential predictor variables.

Four criteria were used to select variables for inclusion in multivariate models: relevance to underlying hypothesis, clinical plausibility, previously reported associations in the literature, and univariate associations with a p value of less than 0.2. Where candidate variables were correlated at a level greater than 0.5, the most clinically plausible was selected.

Sensitivity analyses were conducted using several fluid balance time points to identify that most strongly associated with the primary outcome. We also separated cumulative fluid balance into "early" (days 1–2) and "later" time points, on the basis that early fluid balance may be more reflective of resuscitation fluid administration and thus potentially more confounded by severity of illness. Other sensitivity analyses were used to explore the relationship between deresuscitative measures and mortality.

Statistical analyses were performed using Stata Version 14 (StataCorp LLC, College Station, TX). Two-sided p values of less than 0.05 were considered to represent statistical significance.

RESULTS

Patient Characteristics

Data were collected on 400 patients from 10 ICUs (three in Canada and the remaining seven in the United Kingdom); the minimum number of patients per site was 21. During the study period, a total of 2,473 patients were admitted to participating ICUs. Baseline characteristics are shown in **Table 1**.

Mortality at day 30 following ICU admission was 31.0% (124/400), with a median length of ICU stay of 7 days (interquartile range [IQR], 4–13 d) for survivors. Nonsurvivors differed from survivors with respect to age, source and type of admission, baseline creatinine, Acute Physiology and Chronic Health Evaluation II scores, MODS, and KDIGO scores and in vasopressor use, blood pressure, and oxygenation (Table 1).

Fluid Balance Over Time

Mean daily fluid balances and mean cumulative fluid balances from day 1 to day 7 are shown in **Figure 1**. Mean daily fluid balance was significantly greater for nonsurvivors than survivors on days 1–5 and 7 (maximum difference in means, 0.98 L [95% CI, 0.57–1.37 L] on day 3). Mean cumulative fluid balance was significantly higher in nonsurvivors for days 1–7 (maximum difference in means, 2.38 L [95% CI, 0.98–3.78 L] on day 5). Most patients still in ICU at day 7 were in a positive fluid balance (148/237; 62.45%).

Sources of Fluid Input

The largest component of fluid input over days 1–3 was from medications (1,148.0 of a total 3,325.5 L; 34.5%), whereas maintenance and bolus IV fluids comprised 26.5% and 24.4%, respectively. There was considerable variability between sites in both total volume of fluid input and in sources of that input (**Fig. 2** and **Table E1**, Supplement Digital Content 1, http://links.lww.com/CCM/D719). Over days 1–7, proportionately lower contributions were from bolus and maintenance IV fluid. Striking numerical differences were present between study sites in fluid bolus volumes (ranging from median 0.75 L (IQR, 0.25–1.75 L) to 3.50 L (IQR, 1.0–9.0 L) and in maintenance fluids administered (ranging from one site where no maintenance fluid was given to a median 5.77 L [IQR, 4.66–6.37 L] in another) (Fig. 2 and Table E1, Supplement Digital Content 1, http://links.lww.com/CCM/D719).

Use of Deresuscitative Measures

Deresuscitative measures were used on at least 1 day while in ICU in 209 patients (52.3%), most commonly for the first time on days 2 or 3. Deresuscitative measures were used in 125 of 400 patients (31.3%) on days 1–3 and in 140 of 320 patients (43.8%) on days 4–5. This varied considerably between sites from 16.7% to 50.0% of patients on days 1–3 (Fig. 2) and from 18.2% to 60.6% on days 4–5.

Fluid Balance and Mortality

In univariate analysis, 30-day mortality was associated with greater fluid balance on days 1–7. The strength of the association decreased over days 1–7 and increased when "early" fluid balance (days 1 and 2) was excluded, so that the association between fluid balance and 30-day mortality was strongest for fluid balance on day 3 alone (odds ratio [OR], 1.32; 95% CI, 1.17–1.50 per liter) (**Table E2**, Supplement Digital Content 1, http://links.lww.com/CCM/D719). The dose-response relationship between day 3 fluid balance and unadjusted 30-day mortality is shown in **Figure E1** (Supplement Digital Content 1, http://links.lww.com/CCM/D719).

In a multivariate logistic regression model for 30-day mortality, we found daily fluid balance on day 3 to be independently associated with 30-day mortality (**Table E3**, Supplement Digital Content 1, http://links.lww.com/CCM/D719). Sensitivity analyses confirmed that the association was strongest for daily fluid balance on day 3 alone rather than other fluid balance time points (e.g., days 1–3, days 1–5).

In a sensitivity analysis, we treated day 3 fluid balance as a ternary variable, defined as positive balance (> 500 mL), even balance (between 500 mL negative and 500 mL positive), or negative balance (> 500 mL). Both an "even balance" (adjusted OR, 0.40; 95% CI, 0.21–0.80) and "negative balance" (adjusted OR, 0.17; 95% CI, 0.07–0.40) were strongly protective compared with positive balance (**Table E4**, Supplement Digital Content 1, http://links.lww.com/CCM/D719).

Deresuscitative Measures and Mortality

Of the 123 patients in whom fluid balance on day 3 was negative, a negative balance developed spontaneously (without diuretics or RRT) in 70 (56.9%). Patients who achieved a spontaneous negative fluid balance on day 3 of ICU stay were less severely ill than either those with a positive fluid balance or those who achieved negative fluid balance using deresuscitative measures (**Table E5**, Supplement Digital Content 1, http://links.lww.com/CCM/D719); however, crude mortality was lower whether a negative fluid balance occurred in the context of deresuscitative measures ($p = 0.02$) or spontaneously ($p < 0.01$) compared with patients who had a positive fluid balance on day 3. However, patients who had a positive fluid balance in

TABLE 1. Comparison of Patient Characteristics Between Survivors and Nonsurvivors, and Candidate Predictor Variables for 30-Day Mortality

Demographics	All (*n* = 400)	Survivors (*n* = 276)	Nonsurvivors (*n* = 124)	*p* (Univariate)
Age, yr, median (IQR)	63 (51–74)	60 (48–71)	69 (57–79)	< 0.01
Male sex, *n* (%)	243 (60.8)	73 (58.9)	170 (61.6)	0.61
Admission source, *n* (%)				0.01
Emergency department	117 (29.3)	89 (32.3)	28 (22.6)	
Operating room/recovery	75 (18.8)	64 (23.2)	11 (8.9)	
Ward (same hospital)	139 (34.8)	79 (28.6)	60 (48.4)	
Other hospital (not ICU)	66 (16.5)	41 (14.9)	25 (20.2)	
Other	3 (0.8)	3 (1.1)	0 (0.0)	
Admission type, *n* (%)				0.01
Elective surgical	31 (7.8)	28 (10.1)	3 (2.4)	
Emergency surgical	81 (20.3)	65 (23.6)	16 (12.9)	
Medical	267 (66.8)	162 (58.7)	105 (84.7)	
Trauma	21 (5.3)	21 (7.6)	0 (0.0)	
Baseline creatinine, µmol/L, median (IQR), (*n* = 230)	77 (60–100)	75 (58–96)	77 (67–113)	0.05
Admission diagnosis, *n* (%)				0.22
Cardiovascular	64 (16.0)	37 (13.4)	27 (21.8)	
Respiratory	132 (33.0)	91 (33.0)	41 (33.1)	
Gastrointestinal	85 (21.3)	62 (22.5)	23 (18.6)	
Neurologic	36 (9.0)	28 (10.1)	8 (6.5)	
Other	83 (20.8)	58 (21.0)	25 (20.2)	
Acute Physiology And Chronic Health Evaluation II score, mean (SD)	18.5 (7.2)	16.8 (6.6)	22.4 (6.9)	0.01
Congestive cardiac failure, *n* (%)	37 (9.3)	21 (7.6)	16 (12.9)	0.09
End-stage renal disease, *n* (%)	12 (3.0)	8 (2.9)	4 (3.2)	0.86
Highest MOD score (days 1–2), mean (SD)	4.6 (2.5)	4.1 (2.3)	5.8 (2.6)	< 0.01
Highest Kidney Disease: Improving Global Outcomes stage (days 1–2), *n* (%)				< 0.01
0	182 (45.5)	148 (53.6)	34 (27.4)	
1	99 (24.8)	67 (24.3)	32 (25.8)	
2	11 (2.8)	7 (2.5)	4 (3.2)	
3	108 (27)	54 (19.6)	54 (43.6)	
Lowest Pao_2/Fio_2 ratio (days 1–2) (*n* = 397), median (IQR)	174.5 (118–258)	193 (128–271)	137 (91–227)	< 0.01
Lowest mean arterial pressure, days 1–2 (mm Hg), mean (SD)	73.7 (13.3)	75.0 (12.8)	70.9 (13.9)	< 0.01
Vasopressors, days 1–2, *n* (%)	250 (62.5)	158 (57.2)	92 (74.2)	< 0.01
Highest serum lactate, days 1–2 (mmol/L), mean (SD)	3.8 (3.2)	3.3 (2.6)	4.9 (4.0)	< 0.01
RRT, days 1–2 (*n* = 399), *n* (%)	40 (10)	24 (8.7)	16 (12.9)	0.20
RRT with fluid removal, days 1–3, *n* (%)	40 (10.0)	24 (8.7)	16 (12.9)	0.20
Use of furosemide, days 1–3, *n* (%)	111 (27.8)	76 (27.5)	35 (28.2)	0.89
Total furosemide dose, days 1–3 (mg), median (IQR)	0 (0–20)	0 (0–20)	0 (0–20)	0.81

IQR = interquartile range, RRT = renal replacement therapy.

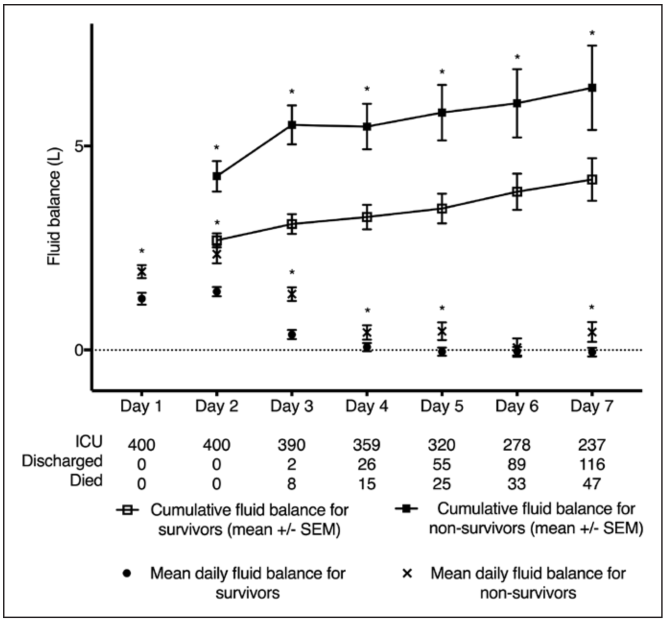

Figure 1. Cumulative and daily fluid balances over time for survivors and nonsurvivors. *$p < 0.05$.

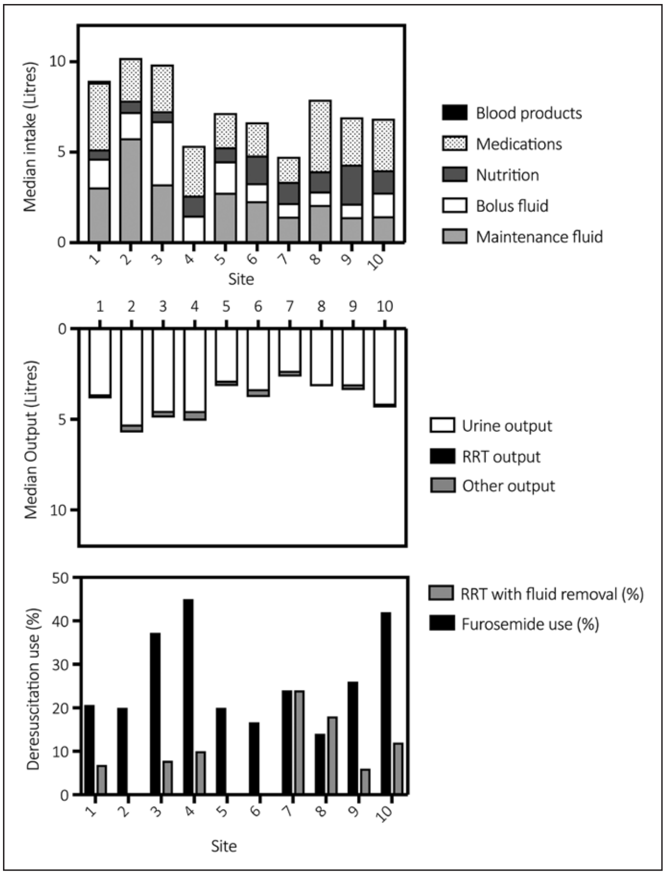

Figure 2. Median fluid input and output and use of deresuscitative measures for days 1–3 by study site. RRT = renal replacement therapy.

the context of deresuscitative measures had the highest crude mortality (**Fig. E2**, Supplement Digital Content 1, http://links.lww.com/CCM/D719).

In a multivariate model, the association between day 3 fluid balance and mortality was robust after dichotomization of patients with a negative fluid balance, in that both spontaneous negative fluid balance (adjusted OR, 0.21; 95% CI, 0.08–0.56) and negative fluid balance with deresuscitative measures (adjusted OR, 0.29; 95% CI, 0.12–0.69) were independently associated with lower mortality relative to a positive fluid balance (**Table 2**).

In a further sensitivity analysis limited to patients who were in a positive fluid balance on day 3, neither furosemide use nor RRT with fluid removal was associated with increased 30-day mortality (**Table E6**, Supplement Digital Content 1, http://links.lww.com/CCM/D719).

Fluid Balance and Organ Function Scores

Missing central venous pressure values were imputed as 8 mm Hg for 971 of 1,869 measurements (52.0%) for the purpose of calculating MODS. A greater fluid balance on day 3 was associated with worsening organ dysfunction reflected in an increasing MOD score over the subsequent 2 days, after adjustment for change in MOD score over days 1–3 (coefficient 0.2/L; 95% CI, 0.1–0.3). This association was not identified in any specific organ system subscore.

We found a weakly positive association between delta MOD score over any 1-day period and daily fluid balance over the same period (number of days = 2,115; coefficient = 0.06/L [95% CI, 0.03–0.08]). This association was similar whether the fluid balance occurred in the context of deresuscitative measures or not.

Fluid Balance and Other Outcomes

In multivariate models, greater fluid balance on day 3 was associated with longer duration of ICU stay (**Table E7**, Supplement Digital Content 1, http://links.lww.com/CCM/D719) and with increased duration of invasive mechanical ventilation in survivors (**Table E8**, Supplement Digital Content 1, http://links.lww.com/CCM/D719). Negative fluid balance in the context of deresuscitation was associated with shorter duration of mechanical ventilation and a shorter length of ICU stay in survivors. Fluid balance on day 3 was not associated with change in KDIGO AKI stage over the following 2 days (days 3–5) of ICU admission.

Predictors of Positive Fluid Balance

Independent predictors of a positive fluid balance on day 3 of ICU admission were vasopressor use, serum creatinine, blood product transfusion, and treatment in a Canadian site, while furosemide use predicted a less positive fluid balance (**Table 3**).

DISCUSSION

In this binational study of a broad cohort of critically ill patients, we found that a negative fluid balance on day 3 of ICU stay is associated with lower 30-day mortality whether occurring spontaneously or achieved with deresuscitative measures; that medication diluents, rather than IV fluids, represent the single largest component of fluid input; and that

TABLE 2. Multivariable Logistic Regression Model for Outcome of 30-Day Mortality, Fluid Balance on Day 3 Trichotomized as Positive (Reference Group), Spontaneously Negative, or Negative With Deresuscitative Measures

Variables	OR (95% CI)	*p*
Age (/yr)	1.04 (1.02–1.06)	< 0.01
Acute Physiology and Chronic Health Evaluation II score (per point)	1.04 (0.99–1.09)	0.09
Congestive cardiac failure	0.86 (0.34–2.21)	0.76
Multiple Organ Dysfunction Scores (highest on days 1 and 2, per point)	1.16 (1.02–1.31)	0.02
Kidney Disease: Improving Global Outcomes stage (highest on days 1 and 2, per stage)	1.10 (0.88–1.39)	0.40
Maximum serum lactate (days 1 and 2, per mmol/L)	1.08 (0.99–1.18)	0.08
Days of vasopressors (days 1–3)	1.14 (0.89–1.44)	0.30
Admission source		
Ward	Reference	
Emergency department	0.32 (0.16–0.65)	< 0.01
Operating room/recovery room	0.69 (0.23–2.02)	0.50
Other hospital	0.72 (0.34–1.55)	0.41
Surgical admission type	0.22 (0.09–0.53)	< 0.01
Early fluid balance (up to 2 d, per liter)	1.08 (0.99–1.17)	0.07
Positive fluid balance on day 3	Reference	
Spontaneous negative fluid balance on day 3	0.21 (0.08–0.56)	< 0.01
Negative fluid balance with deresuscitative measures on day 3	0.29 (0.12–0.69)	< 0.01

OR = odds ratio.
$n = 377$, Pseudo $r^2 = 0.28$. Pearson goodness of fit, $p = 0.88$.

TABLE 3. Multivariate Linear Regression Model for the Outcome of Day 3 Fluid Balance

Variables	Coefficient (95% CI)	*p*
Acute Physiology And Chronic Health Evaluation II score (per point)	0.01 (–0.02 to 0.04)	0.37
Canadian site	0.91 (0.39–1.42)	< 0.05
Change in Multiple Organ Dysfunction Scores, days 1– 3 (per point)	0.06 (–0.03 to 0.14)	0.30
Transfusion of blood products, day 3	0.65 (0.06–1.24)	0.13
Maximum lactate, day 3 (per mmol/L)	0.13 (–0.00 to 0.27)	0.35
Vasopressors, day 3	0.53 (0.14–0.92)	0.03
Pao_2/Fio_2 ratio, day 3 (per 10 mm Hg)	–0.01 (–0.03 to 0.01)	0.27
Creatinine, day 3 (per µmol/L)	0.02 (0.00–0.04)	0.03
Cumulative fluid balance, days 1–2	0.14 (0.07–0.20)	< 0.01
Total furosemide dose, day 3 (per 10 mg)	–0.13 (–0.18 to –0.08)	< 0.01
Renal replacement therapy, day 3	–0.08 (–0.72 to 0.56)	0.70

marked practice variability exists in the use of fluid therapy and deresuscitative measures.

There are two possible interpretations of our findings. First, positive fluid balance may be a biomarker of greater severity, complexity, or duration of critical illness, in which case attempts to modify fluid balance using diuretics or ultrafiltration may be unhelpful or even harmful. Alternatively, several considerations support our hypothesis that fluid balance represents an iatrogenic factor in critical illness which may be modified by deresuscitative measures. First, rigorous attempts were made to minimize confounding by illness severity, comorbidities, and early illness course and to adjust for early fluid balance which is most likely to be impacted by resuscitation fluid volumes. Second, negative fluid balance was independently associated with lower mortality even when occurring in the context of deresuscitative measures and not spontaneously. Third, we found a positive association between daily fluid balance and other outcomes such as delta MOD score, and this association was present whether deresuscitative measures were used or not. Finally, much of the variation in fluid input derives from potentially modifiable practice factors, particularly the use of maintenance fluids, rather than from bolus fluids which are likely to reflect perceived clinical need. It is reassuring that even in those patients in whom deresuscitative measures were "unsuccessful," in that fluid balance remained positive, there was no evidence of worse outcomes after adjustment for potential confounders.

We attempted to identify the time point at which fluid balance was most closely associated with outcome. Reasoning that much of the fluid administered early in the ICU stay may constitute fluid boluses for resuscitation, we separated these into "early" and "late" fluid balance variables. We found the strongest associations with outcome to be with fluid balance on day 3 alone, after adjustment for early (days 1–2) fluid balance. This was also the most common point at which spontaneous negative fluid balance occurred, and the first use of deresuscitative measures was most commonly on day 2 or 3. Although patients are unlikely to all follow the same time trajectory, it is possible that day 3 of ICU stay represents a pivotal point at which many patients begin to demonstrate spontaneous negative fluid balance or are perceived to be suitable for deresuscitative measures. Independent predictors of a positive fluid balance on day 3 included markers of hemodynamic instability and renal dysfunction. The strongest risk factor, however, after adjustment for patient and disease characteristics was treatment in one of the three Canadian ICUs in the cohort. Marked variability in practice patterns between sites highlights the potentially modifiable nature of fluid accumulation.

Our study has limitations. The sample size is modest, and practice variability is evaluated in only 10 separate sites: the results may not therefore be representative, and practice variability may be underrecognized. The retrospective nature of our study made it impossible to determine indications or clinician intent for practice variables. Our definition of deresuscitative measures, therefore, was pragmatic, representing "presumed attempted deresuscitation" as we captured only the use of furosemide and no other diuretics or RRT with any removal of fluid. We lacked hourly urine output data, limiting our ability to distinguish KDIGO stages 2 and 3 using urine output criteria. In the absence of prospective screening, we lacked data on excluded patients, and in addition, we lacked data on pre-ICU fluid balance. Finally, despite adjustment for illness severity, we cannot exclude the possibility that the association between positive fluid balance and poor outcomes represents residual confounding by indication.

In conclusion, we demonstrate that negative fluid balance, whether occurring spontaneously or achieved through deresuscitative measures, is associated with lower mortality. We found considerable practice variation in the use of IV fluids and in the use of deresuscitative measures and demonstrated that the largest source of fluid intake is from maintenance fluids, leading us to infer that fluid balance is a practice driven and therefore modifiable variable. We identified day 3 as potentially a pivotal time point for intervention.

An approach involving limited maintenance fluid intake, and deresuscitative measures if required to minimize fluid balance on day 3 of ICU stay onwards, therefore, represents a promising therapeutic strategy which merits investigation in randomized controlled trials.

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REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017; 43:304–377
2. Marik PE, Linde-Zwirble WT, Bittner EA, et al: Fluid administration in severe sepsis and septic shock, patterns and outcomes: An analysis of a large national database. *Intensive Care Med* 2017; 43:625–632
3. Payen D, de Pont AC, Sakr Y, et al; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; 12:R74
4. Rosenberg AL, Dechert RE, Park PK, et al; NIH NHLBI ARDS Network: Review of a large clinical series: Association of cumulative fluid balance on outcome in acute lung injury: A retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; 24:35–46
5. Acheampong A, Vincent JL: A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 2015; 19:251
6. Boyd JH, Forbes J, Nakada TA, et al: Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39:259–265
7. Vaara ST, Korhonen AM, Kaukonen KM, et al; FINNAKI Study Group: Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: Data from the prospective FINNAKI study. *Crit Care* 2012; 16:R197
8. Silversides JA, Pinto R, Kuint R, et al: Fluid balance, intradialytic hypotension, and outcomes in critically ill patients undergoing renal replacement therapy: A cohort study. *Crit Care* 2014; 18:624
9. Prowle JR, Echeverri JE, Ligabo EV, et al: Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010; 6:107–115
10. Hjortrup PB, Haase N, Bundgaard H, et al; CLASSIC Trial Group; Scandinavian Critical Care Trials Group: Restricting volumes of resuscitation fluid in adults with septic shock after initial management: The CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016; 42:1695–1705
11. Chen C, Kollef MH: Targeted fluid minimization following initial resuscitation in septic shock: A pilot study. *Chest* 2015; 148:1462–1469
12. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
13. Silversides JA, Major E, Ferguson AJ, et al: Conservative fluid management or deresuscitation for patients with sepsis or acute respira-

tory distress syndrome following the resuscitation phase of critical illness: A systematic review and meta-analysis. *Intensive Care Med* 2017; 43:155–170

14. Martin GS, Moss M, Wheeler AP, et al: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; 33:1681–1687
15. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
16. Marshall JC: Measuring organ dysfunction in the intensive care unit: Why and how? *Can J Anaesth* 2005; 52:224–230
17. Kwaja A: KDIGO clinical practice guideline for acute kidney injury. *Nephron Clin Pract* 2012; 120:179–184

APPENDIX 1. ROLE OF ACTIVE DERESUSCITATION AFTER RESUSCITATION (RADAR) INVESTIGATORS

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