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Association Between Fluid Balance and Outcomes in Critically Ill Children
A Systematic Review and Meta-analysis

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IMPORTANCE After initial resuscitation, critically ill children may accumulate fluid and develop fluid overload. Accruing evidence suggests that fluid overload contributes to greater complexity of care and worse outcomes.

OBJECTIVE To describe the methods to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children.

DATA SOURCES Systematic search of MEDLINE, EMBASE, Cochrane Library, trial registries, and selected gray literature from inception to March 2017.

STUDY SELECTION Studies of children admitted to pediatric intensive care units that described fluid balance or fluid overload and reported outcomes of interest were included. No language restrictions were applied.

DATA EXTRACTION AND SYNTHESIS All stages were conducted independently by 2 reviewers. Data extracted included study characteristics, population, fluid metrics, and outcomes. Risk of bias was assessed using the Newcastle-Ottawa Scale. Narrative description of fluid assessment methods and fluid overload definitions was done. When feasible, pooled analyses were performed using random-effects models.

MAIN OUTCOMES AND MEASURES Mortality was the primary outcome. Secondary outcomes included treatment intensity, organ failure, and resource use.

RESULTS A total of 44 studies (7507 children) were included in this systematic review and meta-analysis. Of those, 27 (61%) were retrospective cohort studies, 13 (30%) were prospective cohort studies, 3 (7%) were case-control studies, and 1 study (2%) was a secondary analysis of a randomized trial. The proportion of children with fluid overload varied by case mix and fluid overload definition (median, 33%; range, 10%-83%). Fluid overload, however defined, was associated with increased in-hospital mortality (17 studies [n = 2853]; odds ratio [OR], 4.34 [95% CI, 3.01-6.26]; I^2 = 61%). Survivors had lower percentage fluid overload than nonsurvivors (22 studies [n = 2848]; mean difference, −5.62 [95% CI, −7.28 to −3.97]; I^2 = 76%). After adjustment for illness severity, there was a 6% increase in odds of mortality for every 1% increase in percentage fluid overload (11 studies [n = 3200]; adjusted OR, 1.06 [95% CI, 1.03-1.10]; I^2 = 66%). Fluid overload was associated with increased risk for prolonged mechanical ventilation (>48 hours) (3 studies [n = 631]; OR, 2.14 [95% CI, 1.25-3.66]; I^2 = 0%) and acute kidney injury (7 studies [n = 1833]; OR, 2.36 [95% CI, 1.27-4.38]; I^2 = 78%).

CONCLUSIONS AND RELEVANCE Fluid overload is common and is associated with substantial morbidity and mortality in critically ill children. Additional research should now ideally focus on interventions aimed to mitigate the potential for harm associated with fluid overload.

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Supplemental content

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Fluid therapy is the cornerstone of resuscitation in critically ill children. Reestablishment of adequate intravascular volume using early aggressive fluid administration can be lifesaving.[1,2] However, beyond fluid therapy directed at resuscitation, critically ill children often receive variable amounts of "obligatory" fluid intake as part of their management (ie, nutrition, medications, and maintenance fluid). This cumulative fluid delivery frequently exceeds fluid loss, leading to a net positive fluid balance. A growing body of circumstantial evidence suggests that fluid accumulation after initial resuscitation may exert hazard for major morbidity and mortality.[3-6] These observations highlight the importance of monitoring fluid status and daily evaluation of critically ill children for avoidable fluid accumulation.

The concept of "fluid overload" has been described in the literature using various definitions.[7-10] Although some of the proposed definitions have shown strong correlation with outcomes, it is unclear how generalizable these findings are considering limitations in study design, size and methods, and variation in case mix. There are concerns about the potential discrepancy in fluid overload estimation contingent on the definition applied.[9] Moreover, there is no clear consensus on how to precisely and reliably define fluid overload.

Our aim was to describe the methods used to assess fluid balance, discuss the definitions for fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children. We contend that a rigorous synthesis of available evidence is needed to harmonize the definitions of fluid metrics and aid in the development of management strategies to prevent or mitigate avoidable fluid overload.

Key Points

Question Is there an association between fluid balance and outcomes in critically ill children admitted to pediatric intensive care?

Findings This systematic review and meta-analysis of 44 studies including 7507 children showed strong and consistent evidence of an association between fluid overload and poor outcomes in critically ill children, including worsening respiratory function, development of acute kidney injury, longer pediatric intensive care stay, and death.

Meaning Fluid overload appears to be an important modifier of outcome in critically ill children, implying that additional research is needed focused on strategies for preventing or mitigating this risk.

Methods

This systematic review and meta-analysis followed an a priori protocol that was registered with the PROSPERO International Prospective Register of Systematic Reviews[11] (CRD42016036209) and previously published.[12] We followed the formats recommended by the Cochrane[13] Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Data Sources and Searches

The search strategy[15] was developed and executed in consultation with an experienced research librarian (R.F.) and was independently peer reviewed by a nonauthor second librarian. We executed our original search in June 2016 and completed an updated search in March 2017. No language or publication date restrictions were applied (eTable 1 in the Supplement).

We searched Ovid MEDLINE (1946 to present), Ovid EMBASE (1974 to present), Cochrane Library via Wiley (inception to present), ProQuest Dissertations & Theses Global (1861 to present), and selected gray literature. In addition, clinicaltrials.gov (http://www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) were searched for ongoing and completed clinical trials. Proceedings of selected relevant pediatric, critical care, and nephrology conferences in the last 3 years were manually searched (eTable 2 in the Supplement). A manual search using reference lists of retrieved citations was conducted for other relevant studies.

Study Selection

Potentially relevant citations were identified through independent screening of search result titles and abstracts by 2 of us (R.A. and E.S.). The selected studies were then retrieved and subjected to a second screening phase for eligibility using standard, predefined eligibility criteria. Disagreements were resolved through discussion, with input from another of us (S.M.B). Eligible studies had the following criteria: (1) investigated a population that was limited to patients younger than 25 years who were admitted to a pediatric intensive care unit (PICU) setting; (2) presented original data from interventional (randomized controlled trials or quasi-randomized controlled trials), cohort, or case-control studies; (3) described a measure of fluid balance, fluid accumulation, or fluid overload; and (4) contained at least one outcome of interest. Studies were excluded if they had one of the following characteristics: (1) included patients 25 years or older; (2) comprised primary neonatal studies inclusive of premature infants or infants younger than 4 weeks; (3) were case reports, case series, review articles, or observational studies without a control or comparator; or (4) represented studies conducted in a non-critical care setting.

Outcome Measures

The primary outcome was all-cause mortality, as defined by the included studies. Secondary outcomes included respiratory outcomes, acute kidney injury (AKI), PICU length of stay, and other reported measures of treatment intensity, organ failure, and health resource use.

Data Extraction

A structured data extraction form was piloted and then used to extract data from the reports of all included studies in duplicate and independently by 2 of us (R.A. and E.S.). Discrepancies in extracted data were resolved through discussion. Both

crude and adjusted statistics were collected. Where relevant, attempts were made to contact authors for missing data.

Quality Assessment

Two of us (R.A. and E.S.) independently assessed the risk of bias using the Newcastle-Ottawa Scale,[16] and any discordant assessments were resolved via discussion. We considered a study to be of good quality if its total score was at least 8, of fair quality if the score was 5 to 7, and of poor quality if the score was 4 or lower.

Data Synthesis and Analysis

The included studies were arranged based on exposure (ie, the main measure used to describe fluid balance) and outcomes of interest. Within each group, studies were further clustered based on whether the exposure was dichotomous or continuous. For dichotomous outcomes, odds ratios (ORs) were used as the common measure of an association, with their 95% CIs. Continuous outcomes were reported as weighted mean differences (WMDs), with their 95% CIs. Where necessary, means (SDs) were estimated from the median and interquartile range using a standard approach.[17] We used random-effects models for pooled analyses because of anticipated heterogeneity. Statistical analyses were performed using Review Manager software (RevMan, version 5.3; The Cochrane Collaboration).[18] When statistical pooling was not possible due to exposure-outcome heterogeneity or an insufficient number of studies for an outcome or exposure, the findings were described in narrative form.

Assessment of Heterogeneity and Reporting Bias

Clinical heterogeneity was addressed by performing subgroup analyses based on populations, exposures, and outcome measurements in all included studies. Statistical heterogeneity was evaluated using I^2 statistics, with estimates of 50% or higher considered as significant heterogeneity.[13] Visual assessment of funnel plots was used to evaluate reporting bias in analyses with a sufficient number of studies (>10).[19] Statistical significance was set at 2-sided $P < .05$.

Results

The literature search identified 7211 potentially relevant studies. Forty-four studies, including 7507 children, fulfilled all eligibility criteria (eFigure 1 in the Supplement). Of those, 27 (61%) were retrospective cohort studies, 13 (30%) were prospective cohort studies, 3 (7%) were case-control studies, and 1 study (2%) was a secondary analysis of a randomized trial. Of the included studies, 15 (34%) were performed in cohorts of patients receiving renal replacement therapy (RRT), 9 (20%) in multisystem PICUs, 6 (14%) after cardiac surgery, 5 (11%) in children with sepsis, 4 (9%) in stem cell transplantation, 3 (7%) in children with acute lung injury, and 2 (5%) in children supported by extracorporeal membrane oxygenation (ECMO) (**Table 1**).[3-10,20-55]

The median risk-of-bias score was 8 (range, 6-9). Fourteen studies (32%) were labeled as being of fair quality, while the remaining 30 studies (68%) were of good quality. The main potential sources of bias were "representativeness of the cohort" and "comparability," which required adjustment for the confounders of age and severity of illness in the analysis (eTable 3 in the Supplement).

Fluid Balance Assessment

Four different fluid metrics were used to describe fluid balance. These metrics included cumulative or peak percentage fluid overload (37 studies), cumulative or peak percentage weight change (4 studies), net fluid balance in relation to weight (5 studies), and net fluid balance in relation to body surface area (1 study) (eTable 4 in the Supplement).

Percentage fluid overload was calculated using the following formula: [(Total Fluid Intake in Liters − Total Fluid Output in Liters) / Admission Weight in Kilograms] × 100. This equation was based on the literature.[4-10,20-35,38-45,47,48,50-52,54]

Percentage weight change was calculated as follows: [(Current Weight − Admission Weight) / Admission Weight] × 100. This equation was taken from relevant studies.[8-10,49]

The PICU admission weight was used as the denominator "admission weight" in 22 studies, hospital admission weight was used in 7 studies, outpatient weight was used in 2 studies, and dry or ideal body weight was used in 2 studies. In 13 studies, the weight used was not specified. These results are summarized in eTable 5 in the Supplement.

Three studies compared the fluid intake-output and weight-based methods. In a small cohort of patients undergoing stem cell transplant, Lombel et al[9] described significant variability in fluid balance calculations, with the fluid intake-output method showing the greatest correlation and effect on outcomes in adjusted analysis. The weight-based method was significantly associated with outcomes only when PICU admission weight was used instead of hospital admission weight or estimated dry weight. Hazle et al[10] reported significant correlation between the 2 methods ($r = 0.65$, $P < .0001$) in infants after cardiac surgery, although percentage fluid overload was an independent predictor of poor outcome in adjusted analysis only when calculated by the weight-based method. Alternatively, in a cohort of patients receiving continuous RRT (CRRT), Selewski et al[8] reported significant correlation and comparable predictive values between these 2 methods.

Fluid Overload Definitions

Twenty-six studies identified the following specific threshold values to define fluid overload: greater than 5% (n = 4), greater than 7% (n = 1), greater than 10% (n = 15), greater than 13% (n = 1), greater than 15% (n = 1), and greater than 20% (n = 10). The assessment period varied from 24 hours after PICU admission to the entire PICU stay (**Table 2**). Depending on the population and fluid overload definition used, the proportion of children identified as having fluid overload (dichotomous exposure) ranged between 10% (in patients after cardiac surgery) and 83% (in ECMO patients receiving RRT), with a pooled median of 32.7%. Three studies described the time to maximum percentage fluid overload (continuous exposure). Arikan et al[20] reported that maximum percentage fluid

Table 1. Characteristics of the Included Studies

Source	Country	Study Type	No.	Age, Mean (SD), y	Population	Main Fluid Measures	Main Outcomes
Abulebda et al,[4] 2014	United States	RC	317	2.0 (3.8) For nonsurvivors 3.5 (4.1) For survivors	Sepsis	%FO	Mortality, composite of complicated course
Arikan et al,[20] 2012	United States	RC	80	4.8 (6.1)	Multisystem (ventilated only)	%FO	Mortality, OI, LMV, PICU LOS
Askenazi et al,[21] 2013	United States	PC	84	1.0 (2.1)	CRRT	%FO	Mortality
Baird and Wald,[22] 2010	United States	RC	39	8.8 (5.7)	CRRT	%FO	Mortality
Bhaskar et al,[5] 2015	United States	CC	114	4.8 (2.8)	Sepsis/shock	%FO	Mortality, LMV, PICU LOS, ECMO
Boschee et al,[23] 2014	Canada	RC	90	2.5 (5.1)	CRRT	%FO	Mortality
Chen et al,[24] 2016	China	RC	202	0.7 (0.9)	Sepsis	%FO	Mortality, LMV, PICU LOS, AKI
Choi et al,[25] 2017	South Korea	RC	123	NA	CRRT	%FO	Mortality
Diaz et al,[26] 2017	United States	PC	224	4.6 (6.8)	Multisystem	%FO	Mortality, LMV, PICU LOS
de Galasso et al,[27] 2016	Italy	RC	131	7.3 (8.1)	CRRT	Fluid balance (mL/m^2), %FO	Mortality
Elbahlawan et al,[28] 2010	United States	RC	30	10.3 (4.5)	CRRT in stem cell transplant	%FO	Mortality, Pao_2/FIo_2 ratio
Flores et al,[29] 2008	United States	PC	51	12.8 (5.8)	CRRT in stem cell transplant	%FO	Mortality
Flori et al,[3] 2011	United States	PC	313	7.1 (13.3)	ALI	Fluid balance (mL/kg/d)	Mortality, VFD
Foland et al,[30] 2004	United States	RC	113	8.8 (8.8)	CRRT	%FO	Mortality
Gillespie et al,[31] 2004	United States	RC	77	5.1 (5.7)	CRRT	%FO	Mortality
Goldstein et al,[7] 2001	United States	RC	21	8.8 (6.3)	CRRT	%FO	Mortality
Goldstein et al,[32] 2005	United States	PC	116	8.5 (6.8)	CRRT in MODS	%FO	Mortality
Gulla et al,[33] 2015	India	RC	27	9.8 (3.7)	CRRT in sepsis	%FO	Mortality
Hassinger et al,[34] 2014	United States	PC	98	1.1 (1.5) For FO 5.8 (8.4) For no FO	After cardiac surgery	Fluid balance (mL/kg), %FO	LMV, PICU LOS, inotropic support, AKI
Hayes et al,[35] 2009	United States	RC	76	7.6 (3.2)	CRRT	%FO	Mortality, LMV, PICU LOS, time to renal recovery
Hazle et al,[10] 2013	United States	PC	49	0.2 (0.2)	After cardiac surgery	%FO, % weight change	Composite of poor outcome
Hoover et al,[36] 2008	United States	CC	52	5.2 (4.0) for ECMO with CRRT 5.4 (4.3) For ECMO without CRRT	CRRT in ECMO	Fluid balance (mL/kg/d)	Mortality
Ingelse et al,[37] 2017	The Netherlands	RC	135	1.8 (1.4)	Multisystem (ventilated only)	Fluid balance (mL/kg)	LMV, OI
Jhang et al,[38] 2014	Korea	RC	87	7.9 (6.4)	CRRT	%FO	Mortality
Kaempfen et al,[39] 2017	United Kingdom	RC	71	0.3 (0.5) For nonsurvivors 0.4 (0.6) For survivors	CRRT	%FO	Mortality
Ketharanathan et al,[40] 2014	South Africa	PC	100	1.4 (2.9)	Multisystem	%FO	Mortality, LMV, OI
Lex et al,[41] 2016	Hungary	PC	1520	0.6 (0.8) For FO 2.4 (3.8) For no FO	After cardiac surgery	Fluid balance (mL/kg), %FO	Mortality, LMV, low cardiac output syndrome
Li et al,[6] 2016	China	PC	370	0.9 (1.3) For FO 1.4 (2.1) For no FO	Multisystem	%FO	Mortality, LMV, PICU LOS, AKI
Lombel et al,[9] 2012	United States	RC	21	4.4 (1.5)	CRRT after stem cell transplant	%FO, % weight change	Mortality
Michael et al,[42] 2004	United States	RC	26	13.0 (5)	Stem cell transplant	%FO	Mortality
Modem et al,[43] 2014	United States	RC	190	10.4 (3.7)	CRRT	%FO	Mortality
Naveda and Naveda,[44] 2016	Venezuela	PC	102	6.6 (3.3)	Sepsis	Fluid balance (mL), %FO	Mortality
Park et al,[45] 2016	South Korea	RC	220	1.2 (1.8) For no AKI 0.3 (0.3) For AKI	After cardiac surgery	%FO	AKI
Randolph et al,[46] 2005	United States	PC	301	NA	Multisystem (ventilated only)	Fluid balance (mL/kg)	LMV, extubation failure

(continued)

Table 1. Characteristics of the Included Studies (continued)

Source	Country	Study Type	No.	Age, Mean (SD), y	Population	Main Fluid Measures	Main Outcomes
Sampaio et al,[47] 2015	Canada	RC	85	3.6 (3.1)	After cardiac surgery	%FO	LMV, OI, extubation failure, PICU LOS
Seguin et al,[48] 2014	Canada	RC	193	2.6 (4.2)	After cardiac surgery	%FO	LMV, OI, PICU LOS, AKI
Selewski et al,[8] 2011	United States	RC	113	5.5 (11.2)	CRRT	%FO, % weight change	Mortality
Selewski et al,[49] 2012	United States	RC	53	0.3 (0.6)	CRRT in ECMO	% Weight change	Mortality
Sinitsky et al,[50] 2015	United Kingdom	RC	636	1.8 (2.8)	Multisystem	%FO	Mortality, LMV, OI, need for RRT
Sutherland et al,[51] 2010	United States	PC	297	8.5 (7.0)	CRRT	%FO	Mortality
Sutawan et al,[52] 2016	Indonesia	CC	120	3.3 (1.9) For nonsurvivors 3.4 For survivors	Multisystem	%FO	Mortality
Valentine et al,[53] 2012	United States	RC	168	4.9 (7.5)	ALI	Fluid balance (mL/kg)	Mortality, VFD
Vidal, et al,[54] 2016	Argentina	RC	163	1.6 (2.1)	Multisystem (ventilated only)	%FO	LMV
Willson et al,[55] 2013	United States	RCT	109	6.1 (5.8)	ALI	Fluid balance (mL/m^2)	Mortality, OI, VFD

Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; CC, case control; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FIO_2, fraction of inspired oxygen; FO, fluid overload; %FO, percentage fluid overload; LMV, length of mechanical ventilation; LOS, length of stay; MODS, multiorgan dysfunction syndrome; NA, not available; OI, oxygenation index; PaO_2, partial pressure of oxygen in arterial blood; PC, prospective cohort; PICU, pediatric intensive care unit; RC, retrospective cohort; RCT, randomized clinical trial; RRT, renal replacement therapy; VFD, ventilation-free days.

overload was achieved on mean (SD) day 5.7 (4.2) after PICU admission in a cohort of general PICU patients receiving mechanical ventilation. In 2 studies[47,48] of patients after cardiac surgery, percentage fluid overload peaked within the first 24 to 48 hours after surgery.

Outcomes

Mortality

Seventeen studies evaluated mortality using fluid overload as a dichotomous exposure. Fluid overload, however defined across studies, was associated with increased in-hospital mortality (OR, 4.34 [95% CI, 3.01-6.26]; I^2 = 61%; n = 2835) (**Figure 1**). This association between fluid overload and mortality was robust in sensitivity analysis that included data from only 6 studies that adjusted for illness severity (adjusted OR, 4.38 [95% CI, 2.64-7.28]; I^2 = 14%; n = 782) (eFigure 2 in the Supplement). Similarly, sensitivity analysis that included non-RRT studies only showed significant association with mortality (OR, 6.20 [95% CI, 2.89-13.28]; I^2 = 80%; n = 1868) (eFigure 3 in the Supplement).

We pooled studies that used similar fluid overload threshold and duration of assessment. This process resulted in 4 different fluid overload definitions, all of which showed significant association with mortality and low statistical heterogeneity (**Figure 2**). Definition 1 was cumulative percentage fluid overload exceeding 5% during the first 24 hours of admission (OR, 9.35 [95% CI, 5.05-17.29]; I^2 = 0%; n = 572). Definition 2 was peak percentage fluid overload exceeding 10% at any point during the entire PICU admission (OR, 15.02 [95% CI, 7.09-31.82]; I^2 = 0%; n = 322). Definition 3 was cumulative percentage fluid overload exceeding 10% at CRRT initiation (OR, 2.82 [95% CI, 1.95-4.10]; I^2 = 0%; n = 451). Definition 4 was cumulative percentage fluid overload exceeding 20% at CRRT initiation (OR, 4.29 [95% CI, 2.78-6.62]; I^2 = 0%; n = 460).

When fluid overload was evaluated as a continuous exposure (22 studies), survivors had lower percentage fluid overload compared with nonsurvivors (WMD, −5.62 [95% CI, −7.28 to −3.97]; I^2 = 76%; n = 2848) (**Figure 3**). There was marked variation in the periods during which percentage fluid overload was assessed (eFigure 4 in the Supplement). Among 11 studies that adjusted for illness severity, pooled analysis found a 6% increased odds of mortality for every 1% increase in percentage fluid overload (adjusted OR, 1.06 [95% CI, 1.03-1.10]; I^2 = 66%; n = 3200) (eFigure 5 in the Supplement). Funnel plots of fluid overload percentage (as a categorical and continuous variable) association with mortality are shown in eFigure 6 and eFigure 7 in the Supplement.

Respiratory Outcomes

Respiratory dysfunction and outcomes, including change in oxygenation index, ventilation-free days, or length of mechanical ventilation, were evaluated in 19 studies. Of these, 15 studies (79%) reported that positive fluid balance or fluid overload was associated with negative outcomes (eTable 6 in the Supplement). Six studies[20,40,47,48,50,55] reported significant correlation between increasing fluid overload and worsening oxygenation index. In addition, 3 studies[20,48,50] showed that greater percentage fluid overload was an independent predictor of worsened oxygenation index. In 3 studies[3,53,55] of children with acute lung injury, positive fluid balance was associated with fewer ventilation-free days. Pooled data from 3 studies[6,34,54] demonstrated that fluid overload was associated with prolonged mechanical ventilation (>48 hours) (OR,

Table 2. Fluid Overload Definitions

%FO Cutoff	Weight Used	Assessment Period		Source
		Start	End	
%FO>5%	Not specified	PICU admission	POD 1	Hassinger et al,[34] 2014
	PICU admission weight	PICU admission	24 h After admission	Chen et al,[24] 2016
	PICU admission weight	PICU admission	24 h After admission	Li et al,[6] 2016
	Hospital admission weight or the most recent PICU weight	Intraoperative	POD 2	Lex et al,[41] 2016
%FO>7%	Not specified	Intraoperative	POD 3	Park et al,[45] 2016
%FO>10%	PICU admission weight	PICU admission	CRRT initiation	Askenazi et al,[21] 2013; Boschee et al,[23] 2014; de Galasso et al,[27] 2016; Gillespie et al,[31] 2004; Selewski et al,[49] 2012; Sutherland et al,[51] 2010
	PICU admission weight	Not specified	CRRT initiation	Modem et al,[43] 2014
	Not specified	24 h Before CRRT	CRRT initiation	Elbahlawan et al,[28] 2010
	Hospital admission weight	Hospital admission	Not specified	Michael et al,[42] 2004
	Hospital admission weight	PICU admission	PICU day 2	Sinitsky et al,[50] 2015
	PICU admission weight	PICU admission	PICU day 3	Bhaskar et al,[5] 2015
	PICU admission weight	Not specified	Not specified	Sutawan et al,[52] 2016
	Preoperative weight	PICU admission	PICU day 7	Hazle et al,[10] 2013
	PICU admission weight	PICU admission	PICU discharge	Ketharanathan et al,[40] 2014
	Not specified	PICU admission	PICU discharge	Naveda et al,[44] 2016
%FO>13%	Not specified	PICU admission	PICU day 2	Vidal et al,[54] 2016
%FO>15%	PICU admission weight	PICU admission	14d	Arikan et al,[20] 2012
%FO>20%	PICU admission weight	PICU admission	PICU discharge	Diaz et al,[26] 2017
	PICU admission weight	PICU admission	CRRT initiation	Askenazi et al,[21] 2013; Goldstein et al,[32] 2005; Jhang et al,[38] 2014; Selewski et al,[49] 2012; Sutherland et al,[51] 2010
	PICU admission weight	Not specified	CRRT initiation	Modem et al,[43] 2014
	Hospital admission weight	PICU admission	CRRT initiation	Hayes et al,[35] 2009
	Hospital admission weight	PICU admission	PICU day 2	Sinitsky et al,[50] 2015
	Preoperative weight	PICU admission	PICU day 7	Hazle et al,[10] 2013

Abbreviations: CRRT, continuous renal replacement therapy; %FO, percentage fluid overload; PICU, pediatric intensive care unit; POD, postoperative day.

2.14 [95% CI, 1.25-3.66]; I^2 = 0%; n = 631) (eFigure 8 in the Supplement). Pooled analyses of the remaining data were not feasible due to marked clinical and statistical heterogeneity in exposure-outcome combinations.

Acute Kidney Injury

Data from 7 studies demonstrated that fluid overload was associated with increased risk of AKI (OR, 2.36 [95% CI, 1.27-4.38]; I^2 = 78%; n = 1833) compared with those without fluid overload (eFigure 9 in the Supplement). In one study,[35] fluid overload was significantly associated with longer time to kidney recovery in a cohort of children receiving CRRT.

PICU Length of Stay

Pooled data from 6 studies showed that fluid overload was associated with longer PICU stay compared with no fluid overload (WMD, −2.51 [95% CI, −4.99 to −0.03]; I^2 = 88%; n = 1001) (eFigure 10 in the Supplement). Three additional studies[20,26,47] reported significant association between fluid overload and increased PICU length of stay; however, data could not be pooled statistically.

Additional Outcomes

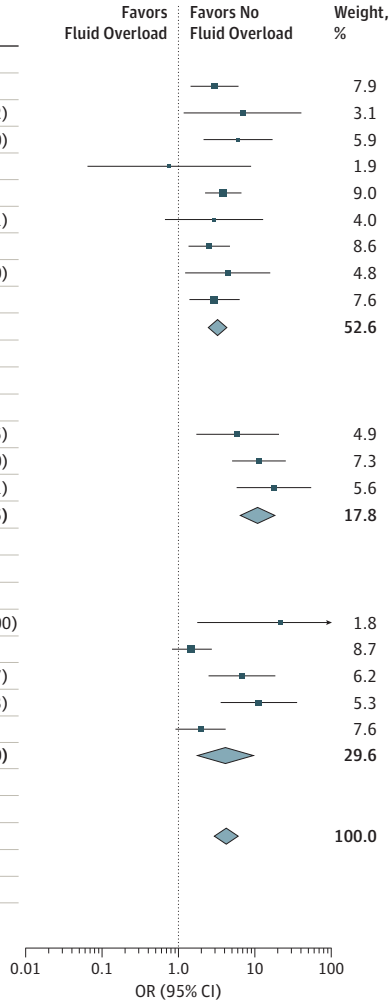
Additional outcomes in association with fluid overload are summarized in eTable 7 in the Supplement. These data include the use of RRT, ECMO, and composite outcomes.

Discussion

In this rigorous and comprehensive systematic review and meta-analysis, we synthesized the evidence from 44 studies, including 7507 children, to describe the methods used to assess fluid balance, define fluid overload, and describe the association between fluid balance and outcomes in critically ill children. We found the current evidence to be largely

Figure 1. Random-Effects Meta-analysis of Fluid Overload (Categorical Exposure) and Mortality Stratified by Case Mix

Source	Log (OR)	SE	OR (95% CI)	Weight, %
CRRT				
Gillespie et al,[31] 2004	1.1053	0.3570	3.02 (1.50-6.08)	7.9
Michael et al,[42] 2004	1.9459	0.8997	7.00 (1.20-40.82)	3.1
Hayes et al,[35] 2009	1.8036	0.5252	6.07 (2.17-17.00)	5.9
Elbahlawan et al,[28] 2010	-0.2719	1.2440	0.76 (0.07-8.73)	1.9
Sutherland et al,[51] 2010	1.3604	0.2643	3.90 (2.32-6.54)	9.0
Selewski et al,[49] 2012	1.0922	0.7478	2.98 (0.69-12.91)	4.0
Modem et al,[43] 2014	0.9442	0.3021	2.57 (1.42-4.65)	8.6
Jhang et al,[38] 2014	1.4956	0.6452	4.46 (1.26-15.80)	4.8
de Galasso et al,[27] 2016	1.0963	0.3765	2.99 (1.43-6.26)	7.6
Subtotal (95% CI)			**3.37 (2.55-4.44)**	**52.6**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 4.86$, ($P = .77$); $I^2 = 0\%$				
Test for overall effect: $z = 8.57$, ($P < .001$)				
Sepsis/shock				
Bhaskar et al,[5] 2015	1.7971	0.6228	6.03 (1.78-20.45)	4.9
Chen et al,[24] 2016	2.4368	0.4052	11.44 (5.17-25.30)	7.3
Naveda et al,[44] 2016	2.8856	0.5574	17.91 (6.01-53.41)	5.6
Subtotal (95% CI)			**11.24 (6.37-19.85)**	**17.8**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 1.70$, ($P = .43$); $I^2 = 0\%$				
Test for overall effect: $z = 8.34$, ($P < .001$)				
General				
Ketharanathan et al,[40] 2014	3.1023	1.2792	22.25 (1.81-273.00)	1.8
Sinitsky et al,[50] 2015	0.4152	0.2926	1.51 (0.85-2.69)	8.7
Li et al,[6] 2016	1.9313	0.4969	6.90 (2.60-18.27)	6.2
Sutawan et al,[52] 2016	2.4384	0.5790	11.45 (3.68-35.63)	5.3
Diaz et al,[26] 2017	0.6799	0.3777	1.97 (0.94-4.14)	7.6
Subtotal (95% CI)			**4.22 (1.73-10.30)**	**29.6**
Heterogeneity: $\tau^2 = 0.72$; $\chi^2_8 = 17.10$, ($P = .002$); $I^2 = 77\%$				
Test for overall effect: $z = 3.17$, ($P = .002$)				
Total (95% CI)			**4.34 (3.01-6.26)**	**100.0**
Heterogeneity: $\tau^2 = 0.31$; $\chi^2_8 = 41.11$, ($P < .001$); $I^2 = 61\%$				
Test for overall effect: $z = 7.88$, ($P < .001$)				
Test for subgroup differences: $\chi^2_8 = 13.95$, ($P < .001$); $I^2 = 85.7\%$				



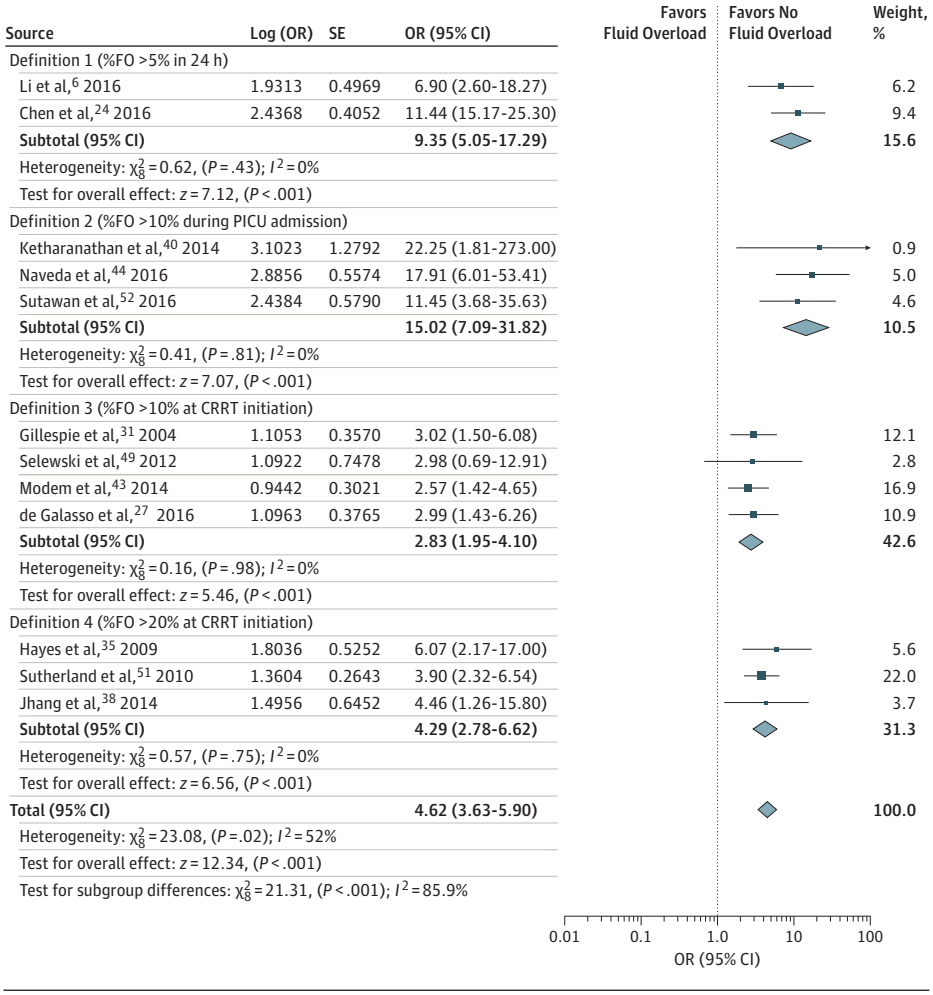
Included were 17 studies.[5,6,24,26-28,31,35,38,40,42-44,49-52] CRRT indicates continuous renal replacement therapy; and OR, odds ratio.

composed of small observational studies applying heterogeneous metrics to assess fluid balance and define fluid overload. This variation was particularly evident in the following 3 areas: (1) the methods used to measure fluid balance, (2) the methods used to quantify fluid overload, and (3) the thresholds and duration of fluid overload assessment in relation to outcome assessment. Nevertheless, our findings were robust and consistent in suggesting that fluid overload was common and portended greater risk for death, worsened respiratory physiology that included prolonged mechanical ventilation, and additional outcomes implying greater intensification of support. These findings align with growing evidence describing the negative association between fluid accumulation and outcomes in adult critically ill populations, including acute respiratory distress syndrome,[56-58] sepsis,[59-61] and AKI,[62-65] and in perioperative settings.[66-69]

Despite accumulating observational data showing the harmful effect of fluid overload on outcomes, there is currently no consensus on how best to define it. The current definitions of fluid overload include 3 components. First are the methods of fluid balance assessment: accurate monitoring of fluid balance is an imperative first step to recognize fluid overload. We identified 2 main methods of assessing fluid balance based on either recorded daily intake-output or serial weight measurements. Recording daily intake and output can be time-consuming to track and prone to error. Serial weight measurements offer some theoretical advantages, including presumed integration of insensible fluid losses. However, frequent weight measurements might not be feasible in the PICU environment due to the unstable condition of many PICU patients. More objective tools, such as electrical bioimpedence and point-of-care ultrasound, have shown promise in providing more objective assessment of fluid status. However, none of the studies identified in this systematic review and meta-analysis evaluated their clinical utility.

Second are the methods used to quantify fluid overload. The calculation of percentage fluid overload proposed by Goldstein and colleagues[7] was the most frequently used method to quantify fluid overload. Some studies used percentage weight change as an alternative. Two studies[8,10] of the 3 that compared both

Figure 2. Random-Effects Meta-analysis of Fluid Overload (Categorical Exposure) and Mortality Stratified by Fluid Overload Definition



Included were 12 studies.[6,24,27,31,35,38,40,43,44,49,51,52] CRRT indicates continuous renal replacement therapy; %FO, percentage fluid overload; OR, odds ratio; and PICU, pediatric intensive care unit.

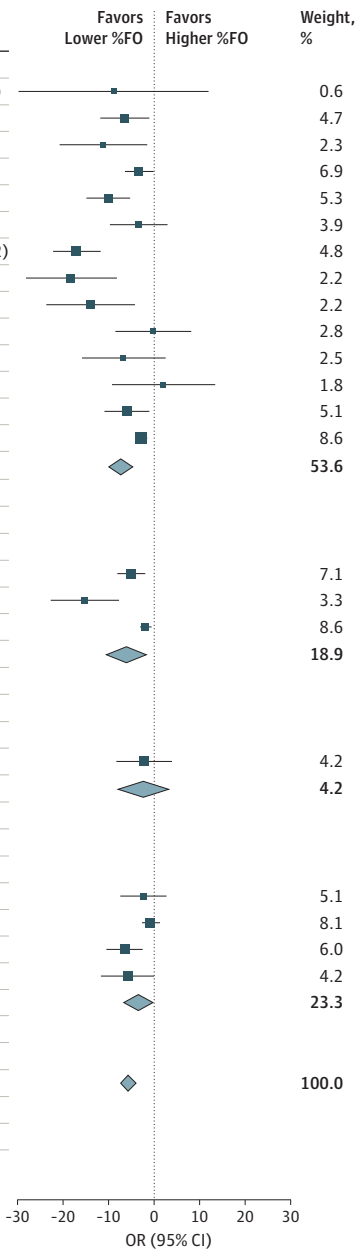
methods showed that they were highly correlated. Based on that observation and until further evidence suggests otherwise, it seems reasonable to consider both methods to be clinically useful.

Third are threshold and duration of fluid overload assessment. While various combinations of thresholds and durations were used, we identified the following 4 common definitions that showed significant association with outcomes: (1) early fluid overload, with cumulative percentage fluid overload exceeding 5% in the first 24 hours; (2) peak percentage fluid overload exceeding 10% during PICU admission; (3) cumulative percentage fluid overload exceeding 10% at CRRT initiation; and (4) cumulative percentage fluid overload exceeding 20% at CRRT initiation. These definitions align with a similar threshold of 10% that has been used in some adult studies[63,65] and showed association with worse outcomes.

Available evidence describing the negative effect of fluid overload highlights the potential for evaluation of strategies to prevent, mitigate, and manage fluid accumulation in critically ill children. Clinical trials have suggested that conservative fluid management strategies are feasible and may be associated with improved outcomes. The Fluid and Catheter Treatment Trial (FACTT) reported that a conservative fluid management strategy during the first 7 days of intensive care unit admission among adults with acute lung injury portended shorter duration of mechanical ventilation and intensive care unit stay compared with a liberal fluid management strategy.[57] However, in a planned secondary analysis, those allocated to the conservative strategy showed greater risk of cognitive impairment compared with those in the liberal management group, a finding that demands consideration in the context of critically ill children.[70] The Fluid Expansion as Supportive Therapy (FEAST) study[71] was a randomized controlled trial of 3141 African children with severe febrile illness and clinical evidence of organ hypoperfusion. Children were randomized to receive fluid boluses with 20 to 40 mL/kg (0.9% saline or 5% albumin) or no fluid bolus therapy. Children receiving fluid boluses had significantly greater mortality within 48 hours largely due to cardiovascular collapse.[72] While FEAST has limited generalizability to modern PICU care, it raises concerns about our primitive understanding of the context and volume of fluid administered to critically ill children both acutely and during their PICU course and its association with

Figure 3. Percentage Fluid Overload (Continuous Variable)

Source	Survivors Mean	SD	Total	Nonsurvivors Mean	SD	Total	Mean Difference (95% CI)	Weight, %
CRRT								
Goldstein et al,[7] 2001	16.40	13.80	9	25.40	32.90	12	-9.00 (-29.68 to 11.68)	0.6
Foland et al,[30] 2004	8.80	10.80	69	15.30	15.50	44	-6.50 (-11.74 to -1.26)	4.7
Goldstein et al,[32] 2005	14.20	15.90	60	25.40	32.90	56	-11.20 (-20.71 to -1.69)	2.3
Flores et al,[29] 2008	10.60	5.55	23	13.90	5.03	28	-3.30 (-6.24 to -0.36)	6.9
Hayes et al,[35] 2009	18.75	10.10	42	28.80	10.30	34	-10.05 (-14.67 to -5.43)	5.3
Elbahlawan et al,[28] 2010	1.45	6.90	5	4.90	3.65	25	-3.45 (-9.66 to 2.76)	3.9
Selewski et al,[8] 2011	8.00	8.80	50	25.00	18.50	63	-17.00 (-22.18 to -11.82)	4.8
Selewski et al,[49] 2012	20.10	16.30	18	38.30	18.50	35	-18.20 (-27.91 to -8.49)	2.2
Askenazi et al,[21] 2013	9.45	14.50	36	23.40	29.60	48	-13.95 (-23.57 to -4.33)	2.2
Boschee et al,[23] 2014	17.60	23.10	66	17.80	15.10	24	-0.20 (-8.42 to 8.02)	2.8
Jhang et al,[38] 2014	13.10	16.97	43	19.84	24.61	44	-6.74 (-15.61 to 2.13)	2.5
Gulla et al,[33] 2015	11.10	14.30	14	9.10	15.30	13	2.00 (-9.19 to -13.19)	1.8
Kaempfen et al,[39] 2017	6.15	7.56	41	12.20	11.76	30	-6.05 (-10.85 to -1.25)	5.1
Choi et al,[25] 2017	0.76	1.33	73	3.50	3.63	50	-2.74 (-3.79 to -1.69)	8.6
Subtotal (95% CI)			**549**			**506**	**-7.21 (-10.08 to -4.33)**	**53.6**
Heterogeneity: $\tau^2 = 17.57$; $\chi^2_8 = 55.19$, ($P < .001$); $I^2 = 76\%$								
Test for overall effect: $z = 4.91$, ($P < .001$)								
Shock/sepsis								
Abulebda et al,[4] 2014	5.20	6.30	277	10.30	8.80	40	-5.10 (-7.93 to -2.27)	7.1
Bhaskar et al,[5] 2015	16.00	12.00	99	31.25	13.50	15	-15.25 (-22.48 to -8.02)	3.3
Chen et al,[24] 2016	0.78	1.97	141	2.68	4.08	61	-1.90 (-2.97 to -0.83)	8.6
Subtotal (95% CI)			**517**			**116**	**-6.01 (-10.91 to -1.11)**	**18.9**
Heterogeneity: $\tau^2 = 14.85$; $\chi^2_8 = 16.39$, ($P < .001$); $I^2 = 88\%$								
Test for overall effect: $z = 2.40$, ($P = .02$)								
ALI								
Arikan et al,[20] 2012	13.70	10.00	66	15.90	10.30	14	-2.20 (-8.11 to 3.71)	4.2
Subtotal (95% CI)			**66**			**14**	**-2.20 (-8.11 to 3.71)**	**4.2**
Heterogeneity: Not applicable								
Test for overall effect: $z = 0.73$, ($P = .47$)								
General								
Ketharanathan et al,[40] 2014	3.40	2.10	90	5.70	7.74	10	-2.30 (-7.12 to 2.52)	5.1
Sinitsky et al,[50] 2015	7.80	5.70	583	8.50	6.30	53	-0.70 (-2.46 to 1.06)	8.1
Sutawan et al,[52] 2016	1.40	8.20	60	7.90	12.90	60	-6.50 (-10.37 to -2.63)	6.0
Diaz et al,[26] 2017	12.70	13.80	189	18.40	16.60	35	-5.70 (-11.54 to 0.14)	4.2
Subtotal (95% CI)			**922**			**158**	**-3.39 (-6.64 to -0.14)**	**23.3**
Heterogeneity: $\tau^2 = 6.90$; $\chi^2_8 = 8.86$, ($P = .03$); $I^2 = 66\%$								
Test for overall effect: $z = 2.04$, ($P = .04$)								
Total (95% CI)							**-5.62 (-7.28 to -3.97)**	**100.0**
Heterogeneity: $\tau^2 = 8.03$; $\chi^2_8 = 87.77$, ($P < .001$); $I^2 = 76\%$								
Test for overall effect: $z = 6.66$, ($P < .001$)								
Test for subgroup differences: $\chi^2_8 = 4.14$, ($P = .25$); $I^2 = 27.6\%$								



Shown is the association with mortality, stratified by case mix. Included were 22 studies.[4,5,7,8,20,21,23-26,28-30,32,33,35,38-40,49,50,52] ALI indicates acute lung injury; CRRT, continuous renal replacement therapy; %FO, percentage fluid overload; and OR, odds ratio.

outcomes. Two pilot studies[73,74] have shown that a restrictive fluid management strategy after initial resuscitation is safe in septic adults. Currently under way is a similar study in children known as SQUEEZE[75] to determine whether septic shock reversal is quicker in pediatric patients randomized to an early goal-directed fluid-sparing strategy vs usual care.

Our findings also suggest that fluid balance may represent an identifiable and modifiable target for intervention. The concept of "active deresuscitation" after initial stabilization using pharmacological or extracorporeal interventions has been introduced in the literature.[76] A post hoc analysis of the FACTT showed that diuretic-induced negative fluid balance was associated with improved survival in adults with AKI.[64] In a recent randomized clinical trial involving 73 infants after cardiac surgery, prophylactic peritoneal dialysis was more effective than furosemide in mitigating the development of fluid overload (>10%) and was associated with shorter duration of mechanical ventilation and inotrope use.[77] However, it currently remains uncertain whether the earlier initiation of RRT in critical illness, particularly when confronted with AKI and fluid accumulation, can improve outcomes.[78,79] The data summarized in our systematic review and meta-analysis would

appear to support the evaluation of active strategies to prevent and mitigate fluid overload in critically ill children and should be tested in rigorous clinical trials.

Strengths and Limitations

Our systematic review and meta-analysis is strengthened by the use of a comprehensive search strategy, by rigorous screening and eligibility criteria, and by transparent reporting of our findings.[13,14] We also found that our primary and secondary outcome findings were robust in sensitivity analyses considering prespecified case-mix subgroups, variable fluid overload definitions, and after including only studies in which illness severity adjustment was possible. However, the studies included in our systematic review and meta-analysis have important limitations. First, almost all studies were observational and mostly retrospective, with many having limited capacity for adjustment, and thus are at risk of selection bias and residual confounding. Second, as such, we cannot definitively confirm the causal link between fluid overload and adverse outcomes given the paucity of rigorous experimental trials evaluating fluid management strategies in critically ill children. Third, studies included had wide variation in case mix and in operational definitions for fluid balance and fluid overload, as well as significant heterogeneity in outcomes, which limited our capacity for pooled analyses in selected circumstances. Moreover, some selected studies reported fluid overload as a continuous exposure using the median and range, necessitating transformation of the data to the mean (SD) using previously described formulas. This process may have contributed to imprecise effect estimates.[17] Some PICU subpopulations, such as trauma and burn patients, were underrepresented in the included studies, which could limit the generalizability of the findings. Few studies evaluated the temporal changes in fluid balance during the PICU course. Fourth, few studies considered the potential fluid deficit state of children or accounted for fluid administration and accumulation before PICU admission. This factor may have contributed to misclassification of fluid overload considering that many PICU patients receive fluid resuscitation in the emergency department, operating theater, or on general wards before transfer to the PICU.

Conclusions

Fluid overload is common among critically ill children and exerts a strong negative association with outcomes. The findings of our systematic review and meta-analysis support the hypothesis that a threshold may exist beyond which fluid accumulation becomes unhelpful or frankly harmful. Clinicians should monitor fluid balance and consider the hazard associated with avoidable fluid accumulation and overload. We believe that our work further provides a foundation for the development of optimal strategies for fluid management among critically ill children, specifically in the form of rigorous clinical trials aimed at avoiding and mitigating iatrogenic or avoidable fluid overload.

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