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SYSTEMATIC REVIEW

Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis

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Abstract

Background: It is unknown whether a conservative approach to fluid administration or deresuscitation (active removal of fluid using diuretics or renal replacement therapy) is beneficial following haemodynamic stabilisation of critically ill patients.

Purpose: To evaluate the efficacy and safety of conservative or deresuscitative fluid strategies in adults and children with acute respiratory distress syndrome (ARDS), sepsis or systemic inflammatory response syndrome (SIRS) in the post-resuscitation phase of critical illness.

Methods: We searched Medline, EMBASE and the Cochrane central register of controlled trials from 1980 to June 2016, and manually reviewed relevant conference proceedings from 2009 to the present. Two reviewers independently assessed search results for inclusion and undertook data extraction and quality appraisal. We included randomised trials comparing fluid regimens with differing fluid balances between groups, and observational studies investigating the relationship between fluid balance and clinical outcomes.

Results: Forty-nine studies met the inclusion criteria. Marked clinical heterogeneity was evident. In a meta-analysis of 11 randomised trials (2051 patients) using a random-effects model, we found no significant difference in mortality with conservative or deresuscitative strategies compared with a liberal strategy or usual care [pooled risk ratio (RR) 0.92, 95 % confidence interval (CI) 0.82–1.02, $I^2 = 0$ %]. A conservative or deresuscitative strategy resulted in increased ventilator-free days (mean difference 1.82 days, 95 % CI 0.53–3.10, $I^2 = 9$ %) and reduced length of ICU stay (mean difference −1.88 days, 95 % CI −0.12 to −3.64, $I^2 = 75$ %) compared with a liberal strategy or standard care.

Conclusions: In adults and children with ARDS, sepsis or SIRS, a conservative or deresuscitative fluid strategy results in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care. The effect on mortality remains uncertain. Large randomised trials are needed to determine optimal fluid strategies in critical illness.

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Introduction

Optimising fluid status is a fundamental concern of critical care practice. Ample data suggest that the optimisation of intravascular volume status can increase cardiac output and global oxygen delivery, and large volumes of intravenous fluids are often administered for this purpose. In addition, critically ill patients frequently receive large volumes of fluid as drug diluents, as artificial nutrition, and as maintenance fluid.

In the face of increased capillary permeability, sodium and water retention, and acute kidney injury (AKI), all of which are common in critical illness, the accumulation of large volumes of fluid in the interstitium is a frequent occurrence and may impair oxygen delivery at the cellular level. Clinically this fluid overload is apparent as peripheral and pulmonary oedema, although other organs may be affected [1]. A number of cohort studies have demonstrated an association between fluid overload and mortality [2–4], and it has been suggested that strategies aimed at prevention or treatment of fluid overload may be beneficial following haemodynamic stabilisation [5].

A previous systematic review and meta-analysis on the topic of fluid overload and the relationship between fluid balance and mortality [6] in critically ill patients reported studies with considerable heterogeneity in design, presence of comparator groups, populations, as well as the timing and nature of interventions. By narrowing our focus to specific populations, and by including but not attempting to meta-analyse observational studies, we aimed to maximise both the external and internal validity of our review.

The aim of this review is to evaluate the impact of a conservative fluid or active deresuscitation strategy compared with standard care or a liberal fluid strategy in critically ill adult or paediatric patients with sepsis, systemic inflammatory response syndrome (SIRS), or acute respiratory distress syndrome (ARDS) on mortality and other clinical outcomes. Secondary aims were to identify criteria used to judge suitability for conservative fluid management or deresuscitation; to describe the interventions used to minimise fluid intake or deresuscitate patients, and to identify contraindications to deresuscitation or conservative fluid management in published studies.

Methods

The protocol for this review was prospectively registered with PROSPERO (International prospective register of systematic reviews; CRD42013005608) and published previously [7]. We used Cochrane review methodology [8] in protocol development and review conduct, and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9] in reporting the review.

Search strategy

MEDLINE, EMBASE and the Cochrane central register of controlled trials (CENTRAL) were searched (up to 24 June 2016) for potentially relevant studies without language constraints. In addition, we manually searched indexed abstracts from the American Thoracic Society, Society of Critical Care Medicine, and European Society of Intensive Care Medicine annual congresses and the International Symposium on Intensive Care and Emergency Medicine from 2009 to the present. A full list of MEDLINE search terms is available as an appendix to the published protocol [7].

Inclusion and exclusion criteria

We included randomised and quasi-randomised clinical trials of adult or paediatric patients with ARDS, SIRS or sepsis in which two or more fluid strategies were compared and in which fluid balance differed between groups; and observational studies in which the relationship between fluid balance and clinical outcomes in ARDS, SIRS or sepsis was the major focus of the study.

We excluded studies that focused only on the resuscitation phase of critical illness, and studies in which fluids were only one element of a complex haemodynamic strategy. We also excluded case series, case reports, observational studies with fewer than 50 participants, studies published prior to 1980, studies involving predominantly neonates, post-cardiac surgery patients, or patients with heart failure, and studies subject to post-publication retraction or investigation.

Selection of studies and data extraction

Titles and abstracts of all reports identified in the literature searches were screened by two of three authors (JS, EEM and AF) for further review with discrepancies resolved by consensus. Full text review of eligibility was conducted by two authors independently (JS and EM) and relevant data extracted in duplicate from included studies to a standard piloted form [7]. Discrepancies were resolved by discussion and adjudication by a third author (EF). Where relevant, attempts were made to contact authors of randomised studies for missing data.

The reference lists of included randomised trials were reviewed for additional trials meeting eligibility criteria.

Outcome measures

The primary outcome was all-cause mortality at the latest time point available up to 90 days. Key secondary outcomes included ventilator-free days (VFDs), length of intensive care unit (ICU) stay, incidence of AKI, renal replacement therapy (RRT) use, and cognitive impairment.

Risk of bias assessment

Two authors (JS and EM) independently assessed risk of bias and quality. Randomised controlled trials were assessed as being at low, uncertain or high risk of bias for each of six domains using the Cochrane risk of bias tool [8]. Cohort and case–control studies were assessed for quality using the Newcastle–Ottawa scale [10] (Appendix 2).

Analysis

RevMan software [8] was used to carry out meta-analysis using a random effects model for outcomes for which two or more randomised studies were available. Results for outcomes for which meta-analysis was deemed inappropriate because of an insufficient number of studies or clinical or statistical heterogeneity were reported in narrative form, and observational studies were reported in tabular form (Appendix 1). Where necessary to standardise reporting of central tendency between studies, we converted standard error to standard deviation, and estimated mean and standard deviation from reported median and interquartile ranges using a standard approach [11]. For key outcomes, we assessed the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [12].

We undertook a pre-planned sensitivity analysis excluding studies at high risk of bias, and subgroup analyses for ARDS, sepsis or SIRS, and adults. We undertook a post hoc analysis in which we excluded studies lacking a clinically significant difference in fluid balance between groups, which we defined as a minimum difference in mean or median fluid balance of 750 mL/day for adults or 10 mL/kg/day for children. We also carried out a meta-regression analysis with difference in mean daily fluid balance as the independent variable and risk ratio (RR) for mortality as the dependent variable.

Results

The search was conducted up to 24 June 2016 and during the editorial process we obtained one further study in press from the editor. Forty-nine studies met criteria for inclusion (Fig. 1). Of these, 11 randomised controlled trials, recruiting a total of 2051 patients, provided data for meta-analysis (Table 1). The remaining 38 studies were observational in design and are summarised in Appendix 1. The Newcastle–Ottawa score for observational studies is reported in Appendix 2. Secondary publications from included studies are reported along with the original study [13–15]. A summary of evidence is found in Table 2.

Description of included randomised trials

Considerable clinical heterogeneity was present. Five studies [16–20] took place in the USA, three in China [21–23], one in France [24], one in India [25], and one in Denmark and Finland [26]. Sample sizes ranged from 29 [21] to 1000 [16]. One was conducted in children [25] and the remainder in adults. Five studies included only patients with ARDS [16–18, 21, 22], four included only patients with septic shock [19, 24–26]; one included patients with ARDS, septic shock, or both [23] and one included a mixed critically ill population, the majority of whom had sepsis, ARDS, or both [20]. Further characteristics of included randomised trials are presented in Table 1.

Methodological quality and risk of bias

The overall quality of included randomised trials was moderate (Fig. 2). The use of random sequence generation and allocation concealment [19–22, 25] and the risk of reporting bias [18, 20–22, 25] were unclear in

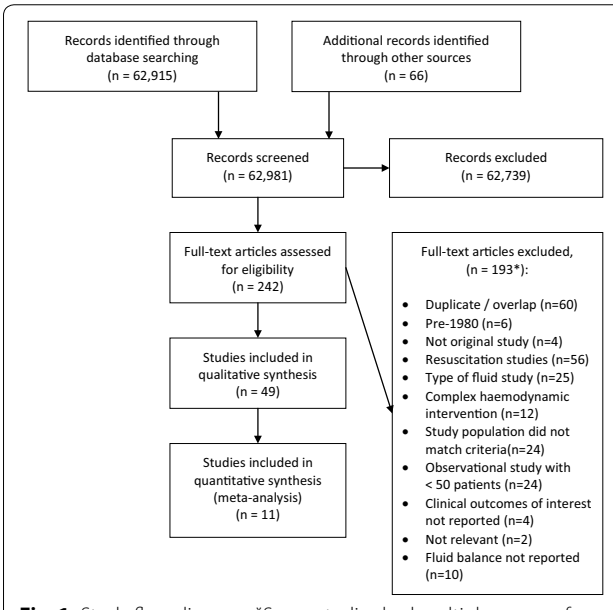

Fig. 1 Study flow diagram. *Some studies had multiple reasons for exclusion

Table 1 Characteristics of included randomised trials

References	Methods and setting	Participants	Summary of conservative or dere-suscitative fluid strategy	Summary of liberal fluid strat-egy or usual care	Key outcomes
Mitchell et al. [20]	RCT Single academic centre in USA	$n = 101$ Inclusion criteria: Admitted to medical ICU Pulmonary artery catheter inserted Exclusion criteria: Technical reasons Logistical reasons Allergy to iodine dye Pregnancy or lactation	EVLW-guided strategy. Restriction of fluid intake when ELVW ≥ 7 mL/kg and diuresis if stable Mean fluid balance was 142 ± 3632 mL at 60 h[a] Mean daily fluid balance over study period: 0.8 mL/kg/day	PCWP-guided strategy with target range of 10–17 mmHg Mean fluid balance was 2239 ± 3695 mL at 47 h[a] Mean daily fluid balance over study period: 16.3 mL/kg/day	ICU mortality Hospital mortality Duration of mechanical ventilation Length of ICU stay
Martin et al. [18]	RCT Two academic centres in USA	$n = 37$ Inclusion criteria: ARDS Serum total protein ≤5 g/dL Ongoing nutritional support Mechanical ventilation ≥48 h Exclusion criteria: Haemodynamic instability Renal disease Hepatic failure or cirrhosis Age <8 or >80 years Pregnancy Serum sodium >150 mmol/L or potassium <2.5 mmol/L	Furosemide infusion titrated to weight loss of ≥1 kg/day, and 25 g IV albumin 8 hourly for 5 days Mean weight loss of 10.0 kg after 5 days[a] Mean daily fluid balance over study period: −47.6 mL/kg/day	Dual placebo Mean weight loss of 4.7 kg after 5 days[a] Mean daily fluid balance over study period: −22.4 mL/kg/day	30-day mortality ICU-free days Ventilator-free days Length of hospital stay
Martin et al. [17]	RCT Two academic centres in USA	$n = 40$ Inclusion criteria: ARDS Serum total protein <6 g/dL Exclusion criteria: Haemodynamic instability Renal disease or cirrhosis Age <18 years Pregnancy Serum sodium >155 mmol/L or potassium <2.5 mmol/L	Furosemide 20 mg IV bolus followed by infusion, and 25 g IV albumin 8 hourly for 3 days Mean net fluid balance after 3 days was −5480 mL[a] Mean daily fluid balance over study period: −15.7 mL/kg/day	Furosemide 20 mg IV bolus followed by infusion, with 0.9 % saline placebo for 3 days Mean net fluid balance at 3 days was −1490 mL[a] Mean daily fluid balance over study period: −4.3 mL/kg/day	30-day mortality Ventilator-free days Change in SOFA scores

Table 1 continued

References	Methods and setting	Participants	Summary of conservative or deresuscitative fluid strategy	Summary of liberal fluid strategy or usual care	Key outcomes
Wiedemann et al. [16]	RCT Multiple community and academic ICUs in USA and Canada	$n = 1000$ Inclusion criteria: ARDS Intubated and mechanically ventilated Presence or intention to insert a central venous catheter	Complex algorithm with fluid boluses or diuretics administered as directed by filling pressures (CVP or PCWP)	Complex algorithm with fluid boluses or diuretics administered as directed to target higher filling pressures (CVP or PCWP) than in conservative group	60-day mortality Ventilator-free days ICU-free days Renal failure-free days RRT use CNS failure-free days
			41 % of protocol instructions involved administration of furosemide, 6 % involved fluid boluses	10 % of protocol instructions involved administration of furosemide, 15 % involved fluid boluses	
		Exclusion criteria: Presence of ALI/ARDS for >48 h Severe chronic illness likely to independently influence survival Irreversible terminal illness	At 7 days, net fluid balance was −136 ± 11,012 mL[a] Mean daily fluid balance over study period: −0.3 mL/kg/day	At 7 days, net fluid balance was 6992 ± 11,191 mL[a] Mean daily fluid balance over study period: 14.3 mL/kg/day	
Hu et al. [21]	RCT Single centre in China	$n = 29$ Inclusion criteria: ALI/ARDS (AECC criteria) Admitted to ICU Exclusion criteria: Pre-existing comorbidities including pulmonary hypertension, pneumonectomy, and interstitial lung disease	EVLW target value set at 3–7 mL/kg, using diuretics or CRRT Fluid administration not protocolised Mean fluid balance at 7 days was −783 ± 391 mL Estimated mean daily fluid balance over study period: −1.6 mL/kg/day	Pulmonary artery occlusion pressure target of 8–12 mmHg, using diuretics or CRRT Fluid administration not protocolised Mean fluid balance at 7 days was −256 ± 514 mL Estimated mean daily fluid balance over study period: −0.5 mL/kg/day	60-day mortality Duration of mechanical ventilation Length of ICU stay
Benakatti et al. [25]	RCT Single centre in India	$n = 101$ Inclusion criteria: Children aged 3–144 months Septic shock following fluid resuscitation Exclusion criteria: None reported	Maintenance fluid administered at 80 % of calculated required rate At 10 days, mean net fluid balance was −42.6 ± 82.6 mL/kg[a] Mean daily fluid balance over study period: −33.9 mL/kg/day	Regimen not clearly reported At 10 days, net fluid balance was 339 ± 117 mL/kg[a] Mean daily fluid balance over study period: −4.26 mL/kg/day	28-day mortality Ventilator-free days Length of ICU stay

Table 1 continued

References	Methods and setting	Participants	Summary of conservative or deresuscitative fluid strategy	Summary of liberal fluid strategy or usual care	Key outcomes
Wang et al. [22]	RCT Single centre in China	$n = 100$ Inclusion criteria: ARDS (AECC definition) Exclusion criteria: Age <13 years Contraindication to central venous catheter ARDS criteria met for >48 h pre-enrolment Myocardial infarction in last 30 days History of COPD or neuromuscular disorder affecting respiration	Extravascular lung water index target of 3–7 mL/kg. Regimen used not clearly reported At 7 days, mean net fluid balance was −9.6 mL[a] Estiamted mean daily fluid balance over study period: −0.02 mL/kg/day	Regimen used not clearly reported At 7 days, mean net fluid balance was 7083.6 mL[a] Estimated mean daily fluid balance over study period: 14.5 mL/kg/day	60-day mortality Duration of mechanical ventilation Length of ICU stay Cognitive function domain of QLQ-C30 quality of life score
Chen and Kollef [19]	RCT Single academic centre in USA	$n = 82$ Inclusion criteria: Hypotension due to septic shock Requirement for ≥12 h of vasoactive drugs to treat hypotension after fluid resuscitation ≥30 mL/kg IV fluid Exclusion criteria: Age <18 years Pre-existing end-stage renal disease Pregnancy Comfort-only goals of care	Targeted fluid minimisation comprising fluid-responsiveness testing before fluid administration, concentration of drug infusions, discontinuation of maintenance fluids Diuretics and ultrafiltration not protocolised At 5 days, median net fluid balance was 2641 mL (IQR −1837 to 5075) Estimated mean daily fluid balance over study period: 7.5 mL/kg/day	Usual care At 5 days, median net fluid balance was 3616 mL (IQR −1513 to 9746 mL) Estiamted mean daily fluid balance over study period: 10.3 mL/kg/day	Hospital mortality Ventilator-free days RRT use

Table 1 continued

References	Methods and setting	Participants	Summary of conservative or deresuscitative fluid strategy	Summary of liberal fluid strategy or usual care	Key outcomes
Zhang et al. [23]	RCT Two tertiary centres in China	$n = 350$	Fluid boluses targeted to ITBVI 850–1000 mL/m^2	Fluid boluses targeted to CVP 8–12 mmHg	28-day mortality Ventilator-free days ICU length of stay Maximum SOFA score RRT-free days
		Inclusion criteria: Septic shock or ARDS (Berlin definition) <24 h since ICU admission	Identical algorithm for noradrenaline, dobutamine and nitrate use in both groups	Identical algorithm for noradrenaline, dobutamine and nitrate use in both groups	
		Exclusion criteria: Age <18 years Haemorrhagic shock Moribund state Absence of informed consent Contraindication to catheter insertion Conditions likely to render PiCCO inaccurate	At 7 days, mean net fluid balance was 3821.6 mL Estimated mean daily fluid balance over study period: 7.8 mL/kg/day	At 7 days, mean net fluid balance was 3974.5 mL Estimated mean daily fluid balance over study period: 8.1 mL/kg/day	
Richard et al. [24]	RCT Single centre in France	$N = 60$ Inclusion criteria: Age ≥18 years Septic shock Pre-enrolment fluid loading ≥25 mL/kg body weight Onset of hypotension <12 h pre-enrolment	Fluid boluses targeted to pulse pressure variation <13 % (if criteria for PPV use met) and Δ stroke volume <10 % in response to passive leg raise manoeuvre for duration of shock	Fluid boluses targeted to CVP ≥ 8 mmHg for duration of shock	28-day mortality Ventilator-free days Length of ICU stay (survivors)
		Exclusion criteria: Pregnancy Acute coronary syndrome or cardiogenic pulmonary oedema Acute cerebral event <30 days Cannulation contraindicated Uncontrolled haemorrhage, need for immediate surgery Trauma or burns >20 % BSA Previous inclusion in RCT Limitation of treatment Absence of consent, legal protection order or lack of social security	Identical protocol for use of noradrenaline, dobutamine, and red blood cells Median daily fluid balance for duration of shock was 888 mL (IQR 153–2816 mL)[a] Estimated mean daily fluid balance over study period: 2.6 mL/kg/day	Identical protocol for use of noradrenaline, dobutamine, and red blood cells Median daily fluid balance for duration of shock was 1749 mL (IQR 146 to 2788 mL)* Estimated mean daily fluid balance over study period: 3.2 mL/kg/day	Number of days with SOFA ≥6

Table 1 continued

References	Methods and setting	Participants	Summary of conservative or dere-suscitative fluid strategy	Summary of liberal fluid strat-egy or usual care	Key outcomes
Hjortrup et al. [26]	RCT Nine centres in Denmark and Finland	$N = 151$ Inclusion criteria: Age ≥18 years Treated in ICU Sepsis with circulatory impairment Fluid bolus administration ≥30 mL/kg ideal body weight Noradrenaline infusion used to maintain blood pressure Exclusion criteria: Receiving RRT (or deemed imminent) Plasma potassium >6 mmol/L within last 6 h Creatinine level >350 µmol/L FiO_2 > 0.8 and positive-end expiratory pressure >10 cmH_2O Life-threatening bleeding Burns >10 % BSA Lack of commitment to full life support Consent unobtainable Kidney or liver transplant during same admission Previous enrolment in this trial	Noradrenaline used to maintain mean arterial pressure ≥65 mmHg or appropriate target 250–500 mL crystalloid boluses could be administered only if evidence of hypoperfusion (lactate ≥4 mmol/L, mean arterial pressure <50 mmHg, skin mottling beyond edge of kneecap, urine output ≤0.1 mL/kg ideal body weight within 2 h of randomisation) At 5 days, median fluid balance was 1752 mL (IQR 407–5114 mL) Estimated mean daily fluid balance over study period: 5.4 mL/kg/day	Noradrenaline used to maintain mean arterial pressure ≥65 mmHg or appropriate target Crystalloid boluses could be administered provided evidence of fluid responsiveness present according to static or dynamic variables of clinician's choice At 5 days, median fluid balance was 2680 mL (IQR −1153 to 3758 mL) Estimated mean daily fluid balance over study period: 9.1 mL/kg/day	90-day mortality Ventilator-free days Length of ICU stay RRT use Worsening AKI

Unless otherwise specified, standard definitions are used for ALI, ARDS, SIRS, sepsis and septic shock [69–71]. Unless otherwise specified, data are presented as mean ± standard deviation
RCT randomised controlled trial, *EVLW* extravascular lung water, *PCWP* pulmonary capillary wedge pressure, *Ml* millilitres, *IV* intravenous, *SOFA* sequential organ failure assessment, *CVP* central venous pressure, *ALI* acute lung injury, *AECC* American–European Consensus Conference, CRRT continuous renal replacement therapy, *PiCCO* pulse index continuous cardiac output, *QLQ-C30* quality of life questionnaire core-30, *COPD* chronic obstructive pulmonary disease, *ITBVI* intrathoracic blood volume index, *IQR* interquartile range, *PPV* pulse pressure variation, *BSA* body surface area, FiO_2 fraction of inspired oxygen

[a] Denotes studies in which between-group differences in fluid balance was considered to be clinically significant

Table 2 GRADE summary of evidence table for key outcomes

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conservative or deresuscitative fluid strategy	Liberal fluid strategy or usual care	Relative (95 % CI)	Absolute (95 % CI)		
Mortality												
11	Randomised trials	Serious[a]	Not serious	Very serious[b]	Serious	None	337/973 (34.6 %)	373/977 (38.2 %)	RR 0.92 (0.82–1.03)	31 fewer per 1000 (from 11 more to 69 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Ventilator-free days												
7	Randomised trials	Not serious	Not serious	Very serious[b]	Not serious	None	891	893	–	MD 1.82 days more (0.53 more to 3.1 more)	⨁⨁◯◯ LOW	IMPORTANT
ICU length of stay												
7	Randomised trials	Serious[c]	Serious[d]	Very serious[b]	Not serious	None	444	448	–	MD 1.88 days fewer (0.12 fewer to 3.64 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
RRT use												
3	Randomised trials	Not serious	Not serious	Very serious[b]	Serious[e]	None	83/619 (13.4 %)	100/614 (16.3 %)	RR 0.88 (0.64–1.22)	20 fewer per 1000 (from 36 more to 59 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Post-ICU cognitive function (assessed with QLQ-C30 cognitive function domain; scale from 0 to 100, with higher scores denoting better cognitive function)												
1	Randomised trials	Very serious[f]	Not serious	Serious[g]	Serious[e]	None	50	50	–	MD 10.71 points higher (5.22 higher to 16.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI confidence interval, *RR* risk ratio, *MD* mean difference

[a] Only five studies were at low risk of bias, the remainder were at moderate or high risk of bias

[b] Significant variability in populations, interventions and comparators studied

[c] Only two studies were at low risk of bias, the remainder were at moderate or high risk of bias

[d] Considerable heterogeneity present across studies ($I^2 = 75$ %)

[e] Insufficient number of participants to exclude clinically important benefit or harm

[f] Single study, uncertain risk of bias across all domains

[g] Limited available information on intervention strategy

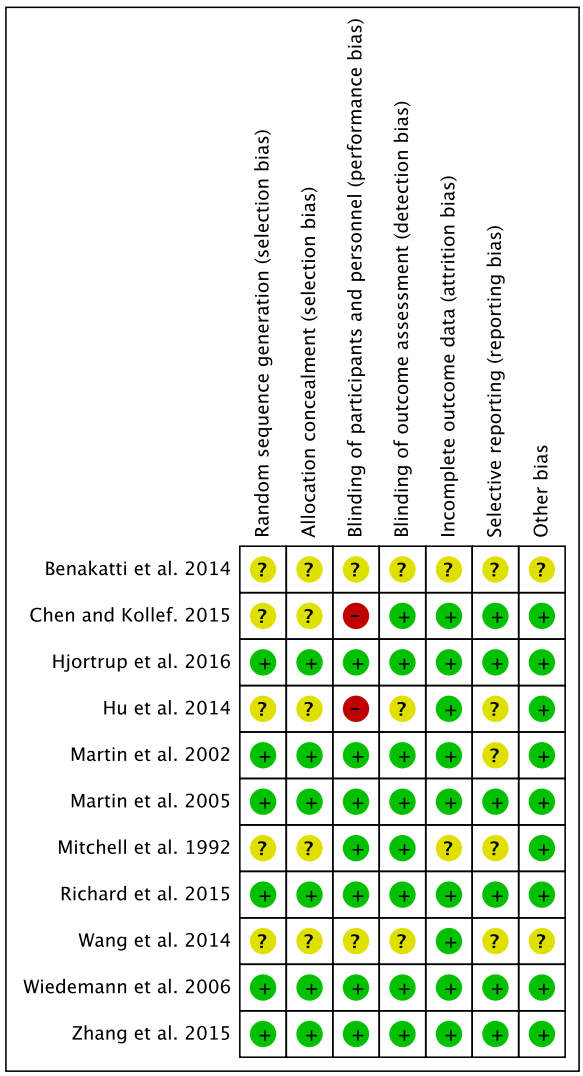

Fig. 2 Risk of bias assessment for randomised trials

a number of studies. While blinding was used in only two studies [17, 18], likely because of difficulties in concealment of the different fluid regimens and/or haemodynamic monitoring technologies employed, strict protocolisation of fluid and diuretic use was felt to ameliorate the effects of this potential bias in all but two studies [19, 21].

Mortality (primary outcome)

Eleven studies (2051 patients) reported mortality as an outcome with variable duration of follow-up, including 90-day [26], 60-day [16, 21, 22], in-hospital [19, 20] and 28- or 30-day mortality [17, 18, 23–25]. We found no significant difference in mortality between patients receiving a conservative or deresuscitative fluid strategy compared with those receiving a liberal strategy or standard care (pooled RR 0.92; 95 % confidence interval [CI] 0.82–1.02, $I^2 = 0$ %) (Fig. 3).

One trial [16] accounted for the majority of patients in the ARDS subgroup, and the results for this subgroup (5 studies, $n = 1206$, pooled RR 0.91; 95 % CI 0.77–1.07) were similar to those in the overall analysis. In the sepsis/SIRS subgroup, three trials were conducted in adults [19, 24, 26] and one in children [25]. Results from this subgroup analysis were also similar to those in the overall analysis (394 patients, pooled RR 0.86; 95 % CI 0.62–1.17) (Fig. 3).

Secondary outcomes

Ventilator-free days

Data on the number of VFDs within a 28- or 30-day period were available for seven studies, including 1784 participants (Fig. 4). We found increased VFDs with a conservative or deresuscitative fluid strategy in comparison with a liberal strategy or standard care (mean difference 1.82 days [95 % CI interval 0.53–3.10 days], $I^2 = 9$ %). In addition, studies by Hu et al. [21] and Wang et al. [22] reported shorter duration of mechanical ventilation in a more conservative fluid strategy group compared with the liberal fluid strategy group (10.13 ± 3.02 days vs. 12.64 ± 2.89, $P < 0.05$ and 9.62 ± 2.55 days vs 12.51 ± 2.92 days, $P < 0.05$ respectively).

Length of ICU stay

Nine studies reported the duration of ICU admission of which seven were suitable for meta-analysis (Fig. 5). We found a shorter length of ICU stay in patients receiving a conservative or deresuscitative fluid strategy compared with those receiving a liberal strategy or standard care (mean difference 1.88 days fewer (95 % CI −0.12 to −3.64 days). Considerable heterogeneity was present ($I^2 = 75$ %). Two studies in ARDS patients reported a composite outcome of ICU-free days: Martin et al. [18] reported a numerically greater number of ICU-free days in the fluid conservative group (median 1.5 days greater, 95 % CI −3.4 to +6.4 days), while in the fluids and catheter treatment trial (FACTT) [16], a conservative strategy resulted in a significantly greater number of ICU-free days compared to a liberal strategy (13.4 ± 8.97 vs 11.2 ± 8.92, $P < 0.001$).

Length of hospital stay

One study [18] reported no significant reduction in the length of hospital stay for survivors of ARDS with a deresuscitative strategy (median 4.5 fewer days in hospital, 95 % CI −5.8 to 14.8 days).

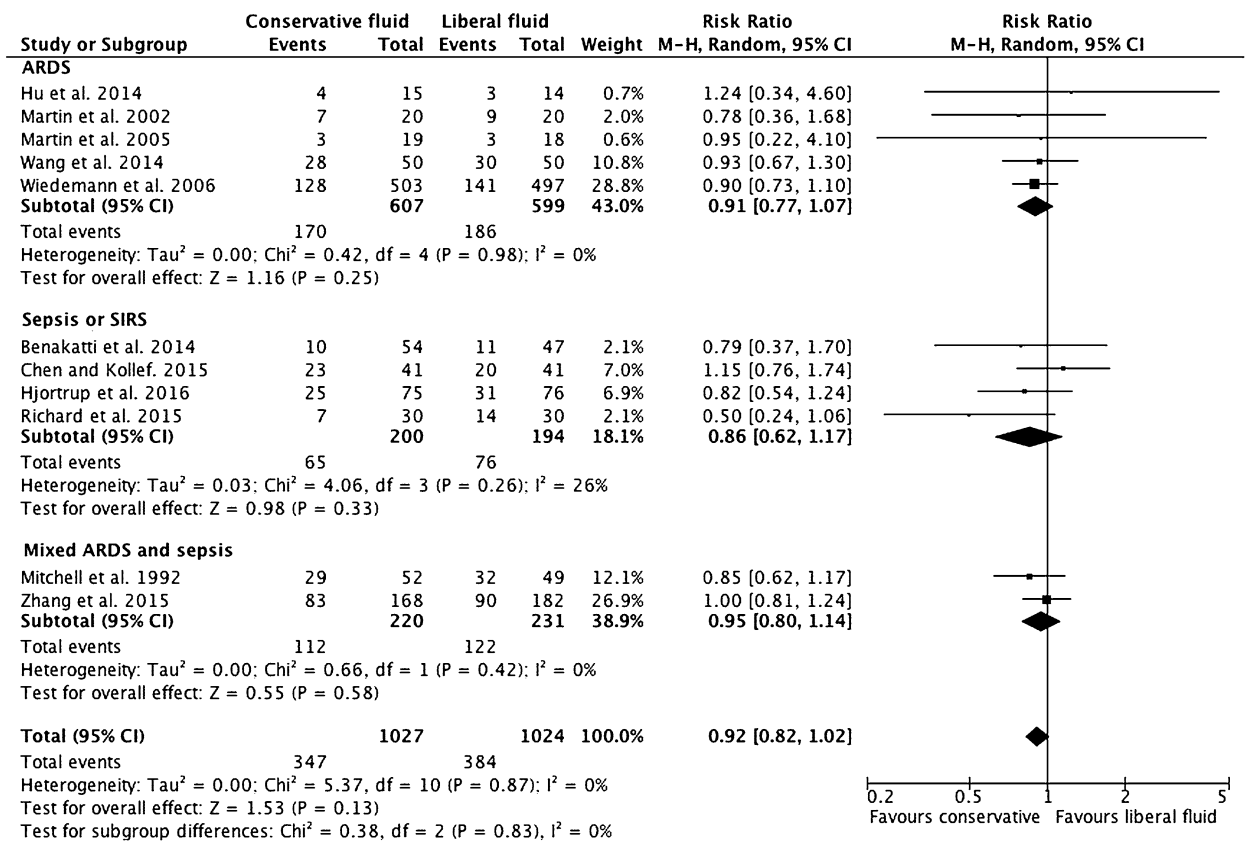

Fig. 3 Forest plot for mortality at most protracted time point available, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy

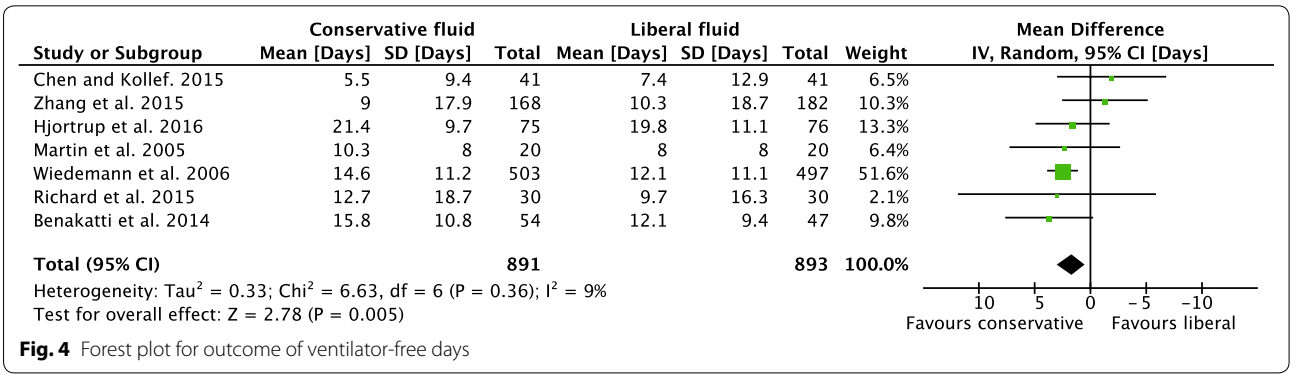

Fig. 4 Forest plot for outcome of ventilator-free days

Organ dysfunction scores

Martin et al. [17] reported a fall in mean sequential organ failure assessment (SOFA) score of 0.6 with a deresuscitation strategy compared with an increase of 1.1 in the control group over the 5-day study period ($P = 0.01$). Zhang et al. [23] reported higher maximum SOFA scores in the more conservatively managed group, although this difference was also present at baseline; and Richard et al. [24] reported similar duration of SOFA score ≥6.

Long-term mortality

No studies reported long-term (>90 days) mortality as an outcome.

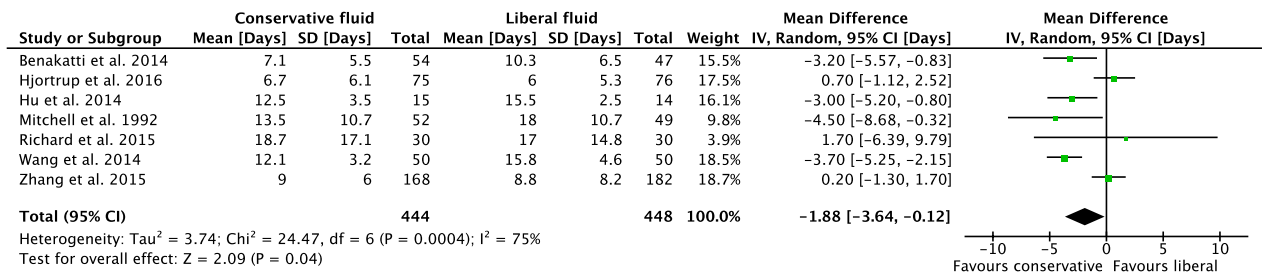

Fig. 5 Forest plot for ICU length of stay, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy

Incidence of ARDS

No studies reported incidence of ARDS as an outcome.

Incidence of acute kidney injury

Martin et al. [18] reported no difference in change in serum creatinine between patients in a deresuscitation group compared with placebo, while in the FACTT study [16] the incidence of AKI was similar between conservative and liberal fluid management groups (21.5 ± 11.21 renal failure-free days versus 21.2 ± 11.15, $P = 0.59$). Hjortrup et al. [26] reported a lower incidence of worsening of AKI in a conservative fluid group than with standard care (37 % versus 54 %, $P = 0.03$). In separate post hoc analyses of the FACTT study, Liu and colleagues showed that after correcting serum creatinine levels for fluid balance, AKI incidence was lower with a conservative than with a liberal fluid strategy [14]; and Grams et al. reported that in patients with AKI, cumulative diuretic dose was independently associated with lower mortality [15].

Renal replacement therapy use

In three studies [16, 19, 26] (1233 patients), the rate of RRT use was similar between patients receiving a conservative fluid or deresuscitative strategy compared with a liberal fluid strategy or standard care (RR 0.88; 95 % CI 0.64–1.22, $I^2 = 27$ %) (Appendix 3.5). Zhang et al. [23] reported fewer days free of continuous RRT in the conservative fluid strategy group (median 15.5 days [IQR 3–28] versus 21 [4–28], $P < 0.05$).

Cognitive function

In a cohort of 75 survivors from FACTT [16] who underwent follow-up assessment of cognitive function, Mikkelsen et al. [13] identified enrolment in the conservative fluid management arm as an independent risk factor for cognitive impairment at 12 months post hospital discharge. In contrast, Wang and colleagues [22] assessed post-ICU cognitive function as one component of the QLQ-C30 quality of life score, and found better cognitive function scores in patients treated with a conservative fluid strategy than a liberal fluid strategy (85.02 ± 15.06 vs. 74.31 ± 12.88, $P < 0.05$).

Additional analyses

Additional sensitivity and subgroup analyses are found in Appendix 3.

Readiness for conservative fluid management or deresuscitation

The majority of studies did not attempt to use specific physiological or time criteria to determine readiness for conservative fluid management or deresuscitation. One study [19] postponed initiation of a conservative fluid management strategy until patients were demonstrated to be volume unresponsive. Fluid minimisation occurred between 1 and 4 days post-randomisation; however, clinically significant separation of fluid balance between groups was not achieved over 5 days.

Interventions

There was considerable variation in fluid strategies applied and fluid balances achieved in both conservative/deresuscitative and liberal/standard care groups. In three studies [16–18], protocolised diuretic use was used in the conservative/deresuscitative arm, in four the intervention strategy involved protocolised fluid restriction or minimisation [16, 19, 25, 26]; and in five the main intervention was the use of alternative haemodynamic targets for fluid management, based on extravascular lung water (EVLW) [20–22], pulse pressure variation (PPV) [24], or intrathoracic blood volume index (ITBVI) [23]. In two trials hyperoncotic albumin infusions were used to potentiate diuresis in a deresuscitative group [17, 18]. Fluid strategies in study control arms included protocolised liberal fluid administration [16], protocolised diuretic use without hyperoncotic albumin [17], and central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP)-guided fluid administration [20, 21, 23, 24].

As a result of variability in fluid strategies used, there was wide variation in fluid balances and considerable overlap between conservative and liberal groups. For example, in the study by Martin et al. [17] the 'liberal' group received diuretics and achieved a weight loss of 4700 mL over 5 days, equating to an estimated mean fluid balance of −22.4 mL/kg/day; while in the study by Chen and Kollef [19], a targeted fluid minimisation strategy in the conservative arm yielded a median positive fluid balance of 2641 mL over 5 days, equating to a positive mean fluid balance of 7.5 mL/kg/day.

Contraindications to deresuscitative fluid management

Two studies of deresuscitation [17, 18] excluded patients with AKI, those with more than a minimal requirement for vasopressors, and those with uncorrected hypernatraemia or hypokalaemia. Deresuscitation was suspended if hypotension, hypernatraemia or hypokalaemia developed during the intervention period, and fluid boluses were given at the discretion of the clinical team. In FACTT [16], fluid administration and diuretic use were protocolised, so that haemodynamic insufficiency triggered fluid bolus administration or vasoactive medication use, and diuretics were withheld in the presence of AKI.

Observational studies

We included a total of 38 observational studies in this review; characteristics are reported in Appendix 1. The majority were cohort studies in which fluid balance was compared between survivors and non-survivors of critical illness, with or without adjustment for severity of illness and other potential confounders. The majority of observational studies were assessed as moderate or low quality using the Newcastle–Ottawa scale (Appendix 2).

The main finding was a consistent positive association between more positive fluid balance and higher mortality [3, 4, 27–52] which was present within all prespecified subgroups: adults [3, 4, 28, 30–33, 36–38, 40–48, 50–52], children [27, 29, 35, 49], ARDS [3, 32, 35, 39, 40, 43, 46, 48, 49] and sepsis [4, 27–31, 33–38, 40–42, 44, 45, 47, 50–52]. This association was absent or present only in subgroups in seven studies in which mortality was reported as an outcome [53–59]. One study reported a lower mortality with greater fluid administration and more positive fluid balance over 3 days [60]. A more positive fluid balance was associated with increased [32, 54] or similar [29, 42] duration of mechanical ventilation, fewer ventilator-free days [35, 53, 55, 59] and increased [32, 52, 59] or similar [42, 54] length of ICU stay. Rates of AKI or RRT use were similar [29, 33, 55, 58, 60, 61] or higher [36, 59] with a more positive fluid balance.

Discussion

Although reference is made in current guidelines to the use of intravenous fluid for resuscitation in sepsis [62], fluid management goals following the resuscitation phase of critical illness remain the subject of considerable uncertainty. Our review evaluated the efficacy and safety of a conservative or deresuscitative fluid strategy compared with standard care or a liberal fluid strategy in critically ill patients with sepsis, SIRS, or ARDS.

We found no clear evidence for the superiority of one fluid strategy over another for our primary outcome of mortality. This is in contrast to a previous meta-analysis [6], and likely reflects our exclusion of observational data from our meta-analysis. We found that a conservative or deresuscitative fluid strategy resulted in a greater number of VFDs and decreased length of ICU stay than a liberal fluid strategy or standard care, with no increase in acute kidney injury, use of RRT, or cognitive dysfunction. When we excluded those studies in which we considered inter-group differences in fluid balance to be clinically unimportant, we found a non-significant reduction in mortality with conservative or deresuscitative fluid management (Appendix 3.3). The quality of evidence was low or very low across all outcomes.

We found no difference in rates of renal replacement therapy use between fluid strategies. Along with post hoc analyses of the FACTT study showing a reduced incidence of AKI with a conservative fluid strategy [14] and a protective effect of diuretic use [15], this provides reassurance as to the safety of a conservative or deresuscitative approach to fluid management in terms of renal outcomes.

The effect of a conservative fluid strategy or deresuscitation in terms of cognitive outcomes is unclear, with a secondary analysis of a small cohort of patients from the FACTT study showing evidence of harm from a conservative approach [13]. This contrasts with the findings of Wang and colleagues in which post-ICU discharge cognitive function was improved in a conservative fluid management group [22], and those of a small randomised trial in patients undergoing major vascular surgery where a conservative fluid strategy was associated with a reduction in post-operative complications including delirium [63], a clinical outcome known to be associated with longer-term cognitive dysfunction [64]. This merits further investigation in future trials investigating fluid strategy.

Our review has a number of strengths. It was conducted using high-quality systematic review methodology. A highly sensitive search strategy was developed which was independently reviewed by a second information specialist. In order to minimise bias, no language restrictions were employed, and broad date criteria were

applied. At least two reviewers were involved independently at each stage of the review process, and all studies were evaluated for quality and risk of bias.

There are a number of important limitations in this review, however. Even in the small number of studies included, considerable heterogeneity was evident with respect to study populations, interventions, and outcomes. As a result of lack of standardised definitions, the timing and duration of the 'post-resuscitation' intervention period varied between studies, although the available data did not allow in-depth exploration of this issue. This highlights the need to standardise these definitions for future clinical trials. Because of insufficient data, we were unable to separate the differential impact of restrictive fluid administration and active deresuscitation. Some of the interventions employed resulted in minimal separation between groups in fluid balance. As we did not define what constituted a clinically significant difference in fluid balance between groups a priori, we included all in our main analysis (Fig. 3) but undertook a sensitivity analysis in which studies were excluded on the basis of clinically insignificant differences in fluid balance between groups (Appendix 3.3).

There was considerable inconsistency in reporting which precluded some studies for inclusion in meta-analyses, exemplified by some studies reporting duration of mechanical ventilation with others reporting a composite outcome of ventilator-free days. This is a recognised problem in studies of patients receiving mechanical ventilation [65]. Even for the uniformly reported outcome of mortality, there was variability in the duration of follow-up from 28 to 90 days, although this is unlikely to have had a major impact on summary estimates of effect [66].

We limited our review to patients with sepsis, SIRS, and ARDS. The inevitable consequence is a loss of generalizability to other types of critically ill patients, although since these are common syndromes rather than specific diagnoses, and since patients admitted to ICU with a range of pathologies (e.g. traumatic brain injury [67] and polytrauma [68]) frequently develop SIRS, ARDS, and sepsis, the generalizability of these findings is likely go beyond simply those patients who meet rigidly applied consensus criteria.

We identified a large number of observational studies in which fluid accumulation or overload was associated with worse outcomes, particularly mortality. The potential for residual confounding is present to some extent in all of these, in that greater cumulative fluid balances may reflect greater severity of illness and greater perceived or actual need for fluid resuscitation or clinician reluctance to either withhold fluid or to administer diuretics to more severely ill patients.

Robust multicentre trials are needed to evaluate the effectiveness of restrictive fluid administration, deresuscitation, or a combined fluid strategy to improve patient outcomes. On the basis of our data, a sample size of over 4700 patients would be required to detect or exclude a significant mortality benefit for a conservative and/or deresuscitative fluid strategy (Appendix 3.3). However, the heterogeneity illustrated in this review highlights the need for considerable further pilot work to define the optimal intervention strategy or strategies to be subsequently tested in high-quality, adequately powered multicentre randomised trials. Pilot studies should, for example, address the questions of physiological or other criteria to define the appropriate timing for conservative fluid management, the utility of deresuscitation in addition to fluid restriction alone, the comparative benefits and harms of ultrafiltration and diuretics, and the use of adjunctive hypertonic albumin among others.

Conclusions

Despite a considerable body of observational evidence showing a positive association between fluid balance and mortality, our review found no significant difference in mortality from included randomised trials addressing the question of optimal fluid strategy for critically ill patients. We found that a conservative or deresuscitative approach resulted in increased ventilator-free days and decreased length of ICU stay compared to a liberal strategy or standard care.

Large robust trials are needed in which clear intergroup differences in fluid balance are present to evaluate the efficacy and safety of a conservative or deresuscitative fluid strategy in terms of both short- and long-term outcomes. The optimum strategy to be tested in such trials remains to be defined. Meanwhile, clinicians caring for critically ill patients may consider the use of a conservative fluid management strategy in patients with sepsis, ARDS, and SIRS following initial resuscitation and stabilisation.

Electronic supplementary material
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Compliance with the ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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