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


Published in:
Intensive Care Medicine

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
© Springer-Verlag Berlin Heidelberg and ESICM 2016
The final publication is available at Springer via http://link.springer.com/article/10.1007/s00134-016-4573-3

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen’s institutional repository that provides access to Queen’s research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person’s rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
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

Jonathan A Silversides1,2*, Emmet Major2, Andrew J Ferguson3, Emma E Mann2, Daniel F McAuley1,4, John C Marshall5,6, Bronagh Blackwood1#, Eddy Fan5#

1. Centre for Experimental Medicine
   Wellcome-Wolfson Institute
   Queen’s University of Belfast
   97 Lisburn Road
   Belfast BT9 7BL
   United Kingdom

2. Department of Critical Care Services
   Belfast Health and Social Care Trust
   Belfast City Hospital
   Lisburn Road
   Belfast BT9 7AB
   United Kingdom

3. Department of Intensive Care
   Southern Health and Social Care Trust
   Craigavon Area Hospital
   68 Lurgan Road
   Portadown BT63 5QQ
   United Kingdom

4. Regional Intensive Care Unit
   Department of Critical Care Services
   Belfast Health and Social Care Trust
   Royal Victoria Hospital
   Grosvenor Road
   Belfast BT12 6BA
   United Kingdom

5. Interdepartmental Division of Critical Care
   University of Toronto
   585 University Avenue
   PMB 11-123
   Toronto, Ontario, M5G 2N2
   Canada

6. Department of Critical Care Medicine
   St Michael’s Hospital
   30 Bond Street,
   Bond 4-014
   Toronto, Ontario, M5B 1W8
   Canada

*Corresponding author
Email: jsilversides01@qub.ac.uk
Telephone: +44 2895 041101
Facsimile: +44 2890 263892

# These authors contributed equally to the work

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

**Background:** It is unknown whether a conservative approach to fluid administration or deresuscitation (active removal of fluid using diuretics or renal replacement therapy (RRT)) 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:** 49 studies met 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 to a liberal strategy or usual care (pooled risk ratio [RR] 0.92, 95% confidence interval [CI] 0.82-1.02, I²=0%). A conservative or deresuscitative strategy resulted in increased ventilator-free days (mean difference 1.82 days, 95% CI 0.53 to 3.10 days, I²=9%) and reduced length of ICU stay (mean difference -1.88 days, 95% CI -0.12 to -3.64 days, I²=75%) compared to a liberal strategy or standard care.

**Conclusions:** In adults and children with ARDS, sepsis or SIRS, a conservative or deresuscitative fluid strategy results in increased number of ventilator-free days and 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.

**Keywords:** Fluid therapy; Diuretics; Water-electrolyte balance; Critical Illness; Sepsis; Respiratory Distress Syndrome, Adult; Systemic Inflammatory Response Syndrome.
Background

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 24th 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 6 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 also 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 per 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, 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. Of these, 11 randomised controlled trials, recruiting a total of 2051 patients, provided data for meta-analysis. 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 United States, 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 (Figure 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 a number of studies. While blinding was used in only 2 studies [17, 18], likely due to 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, I²=0%) (Figure 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) (Figure 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 (Figure 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 to 3.10 days], I²=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 (Figure 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 (I²=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 versus 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).

**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 day) mortality as an outcome.

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, I²=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 seventy-five 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 twelve 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 one and four days post-randomisation, however clinically-significant separation of fluid balance between groups was not achieved over five 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 five 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 five 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 was 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 pre-specified subgroups: adults [3, 4, 28, 30-33, 36-38, 40-46, 48, 50-53], 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, 50-53]. This association was absent or present only in subgroups in seven studies in which mortality was reported as an outcome [54-60]. One study reported a lower mortality with greater fluid administration and more positive fluid balance over 3 days [61]. A more positive fluid balance was associated with increased [32, 55] or similar [29, 42] duration of mechanical ventilation, fewer ventilator-free days [35, 54, 56, 60] and increased [32, 52, 60] or similar [42, 55] length of ICU stay. Rates of AKI or RRT use were similar [29, 33, 56, 59, 61, 62] or higher [36, 60] with a more positive fluid balance.

Discussion

Although reference is made in current guidelines to the use of intravenous fluid for resuscitation in sepsis [63], 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 provide 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 [64], a clinical outcome
known to be associated with longer term cognitive dysfunction [65]. 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. Due to 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 (Figure 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 [66]. 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 [67].

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 [68] and polytrauma [69]) 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. Based on 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 inter-group 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.

Acknowledgements

The authors wish to acknowledge the invaluable assistance of information specialists Ms Viola Machel, Ms Melanie Anderson, and Ms Marina Englesakis (University Health Network) and Richard Fallis (Queen's University of Belfast) in the development and implementation of the search strategies; Ms Adrienne Ruddock for assistance with image preparation, and Dr Hong Guo Parke, Dr Edmund Skibowski and Ms Chuer Zhang for translation of non-English manuscripts.

This work was supported by a doctoral fellowship award to JS by the Northern Ireland Health and Social Care research and development division.

Supplementary Material

Appendix 1 – Characteristics and key findings of included observational studies

Appendix 2 - Assessment of study quality (modified Newcastle Ottawa scale) for observational studies

Appendix 3 - Additional analyses: (3.1) Pre-planned sensitivity analysis excluding studies at high or moderate risk of bias with mortality as outcome. (3.2) Pre-planned subgroup analysis including only adult studies with mortality as outcome. (3.3) Post-hoc sensitivity analysis excluding studies lacking a clinically-important separation in fluid balance between groups (3.4) Univariate meta-regression analysis with RR for mortality as dependent variable and between-group difference in mean daily fluid balance as exposure. \(R^2=0.11, P=0.30\). (3.5) Forest plot for renal replacement therapy use, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy.

Appendix 4 – List of excluded studies

References


Figure 1. Study flow diagram. *Some studies had multiple reasons for exclusion.
Figure 2. Risk of bias assessment for randomised trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjortrup et al. 2016</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Martin et al. 2002</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Martin et al. 2005</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Richard et al. 2015</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wiedemann et al. 2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zhang et al. 2015</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Figure 3. Forest plot for mortality at most protracted time point available, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th>Liberal fluid</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total Events Total Weight</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al. 2014</td>
<td>4 15 3 14 0.7%</td>
<td>1.24 [0.34, 4.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2002</td>
<td>7 20 9 20 2.0%</td>
<td>0.78 [0.36, 1.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2005</td>
<td>3 19 3 18 0.6%</td>
<td>0.95 [0.22, 4.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>28 50 30 50 10.8%</td>
<td>0.93 [0.67, 1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiedemann et al. 2006</td>
<td>128 503 141 497 28.8%</td>
<td>0.90 [0.73, 1.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>607 599 43.0%</td>
<td>0.91 [0.77, 1.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>170</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.42, df = 4 (P = 0.98); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P = 0.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Sepsis or SIRS   |                    |               |            |            |
| Benakatti et al. 2014 | 10 54 11 47 2.1% | 0.79 [0.37, 1.70] |            |
| Chen and Kollef. 2015 | 23 41 20 41 7.0% | 1.15 [0.76, 1.74] |            |
| Hjortrup et al. 2016 | 25 75 31 76 6.9% | 0.82 [0.54, 1.24] |            |
| Richard et al. 2015 | 7 30 14 30 2.1% | 0.50 [0.24, 1.06] |            |
| Subtotal (95% CI) | 200 194 18.1%    | 0.86 [0.62, 1.17] |            |
| Total events      | 65                 | 76            |            |            |
| Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.06, df = 3 (P = 0.26); I^2 = 26% |
| Test for overall effect: Z = 0.98 (P = 0.33) |

| Mixed ARDS and sepsis |                    |               |            |            |
| Mitchell et al. 1992 | 29 52 32 49 12.1% | 0.85 [0.62, 1.17] |            |
| Zhang et al. 2015    | 83 168 90 182 26.9% | 1.00 [0.81, 1.24] |            |
| Subtotal (95% CI)    | 220 231 38.9%     | 0.95 [0.80, 1.14] |            |
| Total events         | 112                | 122           |            |            |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.66, df = 1 (P = 0.42); I^2 = 0% |
| Test for overall effect: Z = 0.55 (P = 0.58) |

| Total (95% CI)       | 1027 1024 100.0% | 0.92 [0.82, 1.02] |            |
| Total events         | 347 384           |            |            |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.37, df = 10 (P = 0.87); I^2 = 0% |
| Test for overall effect: Z = 1.53 (P = 0.13) |
| Test for subgroup differences: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 = 0% |

Favours conservative Favours liberal fluid
### Figure 4. Forest plot for outcome of ventilator-free days.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th></th>
<th>Liberal fluid</th>
<th></th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [Days] SD [Days]</td>
<td>Total</td>
<td>Mean [Days] SD [Days]</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Chen and Kelief. 2015</td>
<td>5.5 9.4</td>
<td>41</td>
<td>7.4 12.9</td>
<td>41</td>
<td>6.5%</td>
</tr>
<tr>
<td>Zhang et al. 2015</td>
<td>9 17.9</td>
<td>168</td>
<td>10.3 18.7</td>
<td>182</td>
<td>10.3%</td>
</tr>
<tr>
<td>Hjertrup et al. 2016</td>
<td>21.4 9.7</td>
<td>75</td>
<td>19.8 11.1</td>
<td>76</td>
<td>13.3%</td>
</tr>
<tr>
<td>Martin et al. 2005</td>
<td>10.3 8</td>
<td>20</td>
<td>8 8</td>
<td>20</td>
<td>6.4%</td>
</tr>
<tr>
<td>Wiedemann et al. 2006</td>
<td>14.6 11.2</td>
<td>503</td>
<td>12.1 11.1</td>
<td>497</td>
<td>51.6%</td>
</tr>
<tr>
<td>Richard et al. 2015</td>
<td>12.7 18.7</td>
<td>30</td>
<td>9.7 16.3</td>
<td>30</td>
<td>2.1%</td>
</tr>
<tr>
<td>Benakati et al. 2014</td>
<td>15.8 10.8</td>
<td>54</td>
<td>12.1 9.4</td>
<td>47</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>891</td>
<td></td>
<td>893</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total (95% CI): 891 893

Heterogeneity: \( \tau^2 = 0.33; \ Chi^2 = 6.63, df = 6 (P = 0.36); I^2 = 9\%

Test for overall effect: \( Z = 2.78 (P = 0.005) \)

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th>Liberal fluid</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [Days]</td>
<td>SD [Days]</td>
<td>Total Mean [Days]</td>
</tr>
<tr>
<td>Benakatti et al. 2014</td>
<td>7.1</td>
<td>5.5</td>
<td>54</td>
</tr>
<tr>
<td>Hjortrup et al. 2016</td>
<td>6.7</td>
<td>6.1</td>
<td>75</td>
</tr>
<tr>
<td>Hu et al. 2014</td>
<td>12.5</td>
<td>3.5</td>
<td>15</td>
</tr>
<tr>
<td>Mitchell et al. 1992</td>
<td>13.5</td>
<td>10.7</td>
<td>52</td>
</tr>
<tr>
<td>Richard et al. 2015</td>
<td>18.7</td>
<td>17.1</td>
<td>30</td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>12.1</td>
<td>3.2</td>
<td>50</td>
</tr>
<tr>
<td>Zhang et al. 2015</td>
<td>9</td>
<td>6</td>
<td>168</td>
</tr>
</tbody>
</table>

Total (95% CI) 444 448 100.0% -1.88 [-3.64, -0.12]

Heterogeneity: Tau² = 3.74; Chi² = 24.47, df = 6 (P = 0.0004); I² = 75%
Test for overall effect: Z = 2.09 (P = 0.04)
<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>Methods and Setting</th>
<th>Participants</th>
<th>Summary of conservative or deresuscitative fluid strategy</th>
<th>Summary of liberal fluid strategy or usual care</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell et al, 1992</td>
<td>RCT</td>
<td>n=101</td>
<td>-Extra-Vascular Lung Water (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 hours* -Mean daily fluid balance over study period: 0.8 ml/kg/day</td>
<td>-Pulmonary capillary wedge pressure (PCWP) – guided strategy with target range of 10-17 mmHg. -Mean fluid balance was 2239 +/-3695 ml at 47 hours* -Mean daily fluid balance over study period: 16.3 ml/kg/day</td>
<td>-ICU mortality -Hospital mortality -Duration of mechanical ventilation -Length of ICU stay</td>
</tr>
<tr>
<td>Martin et al, 2002</td>
<td>RCT</td>
<td>n=37</td>
<td>-Furosemide infusion titrated to weight loss of ≥ 1 kg/day, and 25g IV albumin 8 hourly for 5 days -Mean weight loss of 10.0 kg after 5 days* -Mean daily fluid balance over study period: -47.6 ml/kg/day</td>
<td>-Dual placebo -Mean weight loss of 4.7 kg after 5 days* -Mean daily fluid balance over study period: -22.4 ml/kg/day</td>
<td>-30 day mortality -ICU-free days -Ventilator-free days -Length of hospital stay</td>
</tr>
<tr>
<td>Martin et al, 2002</td>
<td>RCT</td>
<td>n=40</td>
<td>-Furosemide 20mg IV bolus</td>
<td>-Furosemide 20mg IV bolus</td>
<td>-30 day mortality</td>
</tr>
<tr>
<td>Year</td>
<td>Study Type</td>
<td>Study Details</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Outcomes</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2005</td>
<td>RCT</td>
<td>Two academic centres in United States</td>
<td>- Inclusion criteria: ARDS, Serum total protein &lt; 6 g/dL</td>
<td>- Exclusion criteria: Haemodynamic instability, Renal disease or cirrhosis, Age &lt; 18 years, Pregnancy, Serum sodium &gt; 155 mmol/L or potassium &lt; 2.5 mmol/L</td>
<td>- Mean net fluid balance after 3 days was -5480 ml*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Followed by infusion, and 25g IV albumin 8 hourly for 3 days</td>
<td></td>
<td>- Mean daily fluid balance over study period: -15.7 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Mean net fluid balance at 3 days was -1490 ml*</td>
<td></td>
<td>- Mean daily fluid balance over study period: -4.3 ml/kg/day</td>
</tr>
<tr>
<td>Wiedemann et al, 2006</td>
<td>RCT</td>
<td>Multiple community and academic ICUs in United States and Canada</td>
<td>- Inclusion criteria: ARDS, Intubated and mechanically ventilated, Presence or intention to insert a central venous catheter</td>
<td>- Exclusion criteria: Presence of ALI/ARDS for &gt; 48 hours, Severe chronic illness likely to independently influence survival, Irreversible terminal illness</td>
<td>- Mean net fluid balance after 3 days was -136 ml +/- 11012 ml*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Complex algorithm with fluid boluses or diuretics administered as directed by filling pressures (CVP or PCWP).</td>
<td></td>
<td>- Mean daily fluid balance over study period: -0.3 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 41% of protocol instructions involved administration of furosemide, 6% involved fluid boluses</td>
<td></td>
<td>- Mean daily fluid balance over study period: 14.3 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- At 7 days, net fluid balance was 6992 ml +/- 1191 ml*</td>
<td></td>
<td>- 60-day mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pulmonary artery occlusion pressure target of 8-12 mmHg, using diuretics or CRRT</td>
<td></td>
<td>- Ventilator-free days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fluid administration not</td>
<td></td>
<td>- ICU-free days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Extravascular lung water target value set at 3-7 ml/kg, using diuretics or CRRT</td>
<td></td>
<td>- Renal failure-free days</td>
</tr>
<tr>
<td>Hu et al, 2014</td>
<td>RCT</td>
<td>Single centre in China</td>
<td>- Inclusion criteria: ALI/ARDS (AECC criteria), Admitted to ICU</td>
<td></td>
<td>- RRT use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fluid administration not</td>
<td></td>
<td>- CNS failure-free days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pulmonary artery occlusion pressure target of 8-12 mmHg, using diuretics or CRRT</td>
<td></td>
<td>- 60 day mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Fluid administration not protocolised</td>
<td></td>
<td>- Duration of mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Length of ICU stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Benakatti et al, 2014</td>
<td>RCT</td>
<td>Single centre in India</td>
<td>n=101</td>
<td>Children aged 3-144 months, Septic shock following fluid resuscitation</td>
<td>None reported</td>
</tr>
<tr>
<td>Wang et al, 2014</td>
<td>RCT</td>
<td>Single centre in China</td>
<td>n=100</td>
<td>ARDS (AECC definition)</td>
<td>Age &lt; 13 years, Contraindication to central venous catheter, ARDS criteria met for &gt; 48 hours pre-enrollment, Myocardial infarction in last 30 days, History of COPD or neuromuscular disorder affecting respiration</td>
</tr>
<tr>
<td>Chen and Kollef, 2015</td>
<td>RCT</td>
<td>n=82</td>
<td>-Targeted fluid minimisation comprising: fluid-responsiveness</td>
<td>-Usual care</td>
<td>Hospital mortality, Ventilator-free days</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Single academic centre in United States | RCT      | n=350        | - Hypotension due to septic shock  
- Requirement for ≥ 12 hours of vasoactive drugs to treat hypotension after fluid resuscitation ≥ 30 ml/kg IV fluid  
- 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 - 1837-5075)  
- Estimated mean daily fluid balance over study period: 7.5 ml/kg/day | - Age <18 years  
- Pre-existing end stage renal disease  
- Pregnancy  
- Comfort-only goals of care  
- At 5 days, median net fluid balance was 3616 ml (IQR - 1513-9746 ml)  
- Estimated mean daily fluid balance over study period: 10.3 ml/kg/day | - RRT use |
| Zhang et al, 2015            | RCT      | n=350        | - Septic shock or ARDS (Berlin definition)  
- <24 hours since ICU admission  
- Fluid boluses targeted to intrathoracic blood volume index (ITBVI) 850-1000 ml/m²  
- Identical algorithm for noradrenaline, dobutamine and nitrate use in both groups  
- At 7 days, mean net fluid balance was 3821.6 ml  
- Estimated mean daily fluid balance over study period: 7.8 ml/kg/day | - Age <18 years  
- Haemorrhagic shock  
- Moribund state  
- Absence of informed consent  
- Contra-indication to catheter insertion  
- Conditions likely to render PiCCO inaccurate  
- Fluid boluses targeted to CVP ≥ 8-12 mmHg.  
- Identical algorithm for noradrenaline, dobutamine and nitrate use in both groups  
- At 7 days, mean net fluid balance was 3974.5 ml  
- Estimated mean daily fluid balance over study period: 8.1 ml/kg/day | - 28 day mortality  
- Ventilator-free days  
- ICU length of stay  
- Maximum SOFA score  
- RRT-free days |
| Richard et al, 2015           | RCT      | N=60         | - Fluid boluses targeted to pulse pressure variation < 13% (if CVP ≥ 8 mmHg for duration of shock) | - Fluid boluses targeted to CVP ≥ 8 mmHg for duration of shock | - 28 day mortality  
- Ventilator-free days |
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Single centre in France | - Age ≥ 18 years  
- Septic shock  
- Pre-enrollment fluid loading ≥ 25 ml/kg body weight  
- Onset of hypotension <12 hours pre-enrollment | - 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 | - Noradrenaline used to maintain mean arterial pressure ≥ 65 mmHg or appropriate target  
- Crystalloid boluses could be administered only if evidence of hypoperfusion (lactate ≥ 4 mmol/L, mean arterial pressure <50mmHg, skin mottling beyond criteria for PPV use met) and Δ stroke volume <10% in response to passive leg raise manoeuver for duration of shock  
- Identical protocol for use of noradrenaline, dobutamine, and red blood cells  
- Identical protocol for use of noradrenaline, dobutamine, and red blood cells  
- Median daily fluid balance for duration of shock was 888 ml (IQR 153 to 2816 ml)*  
- Estimated mean daily fluid balance over study period: 2.6 ml/kg/day  
- Medial 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  
- Length of ICU stay (survivors)  
- Number of days with SOFA ≥ 6 | - Length of ICU stay (survivors)  
- Number of days with SOFA ≥ 6 |
| Hjortrup et al, 2016 | Nine centres in Denmark and Finland | N=151 | - Age ≥ 18 years  
- Treated in ICU  
- Sepsis with circulatory impairment  
- Fluid bolus administration ≥ 30 ml/kg ideal body weight | - Noradrenaline used to maintain mean arterial pressure ≥ 65 mmHg or appropriate target  
- 250 to 500 ml crystalloid boluses could be administered provided evidence of fluid responsiveness present according to static or dynamic variables of clinician’s choice | - 90 day mortality  
- Ventilator-free days  
- Length of ICU stay  
- RRT use  
- Worsening AKI |
| - Noradrenaline infusion used to maintain blood pressure | edge of kneecap, urine output ≤ 0.1 ml/kg ideal body weight within 2 hours of randomisation | - At 5 days, median fluid balance was 2680 ml (IQR -1153 to 3758 ml) |
| - Receiving RRT (or deemed imminent) | - At 5 days, median fluid balance was 1752 ml (IQR 407 to 5114 ml) | - Estimated mean daily fluid balance over study period: 9.1 ml/kg/day |
| - Plasma potassium > 6 mmol/L within last 6 hours | - Estimated mean daily fluid balance over study period: 5.4 ml/kg/day | -estimated mean daily fluid balance over study period: 5.4 ml/kg/day |
| - Creatinine level > 350 μmol/L | -FiO2 > 0.8 and positive end expiratory pressure > 10 cmH₂O | -Life-threatening bleeding |
| - Life-threatening bleeding | -Burns > 10% BSA | -Lack of commitment to full life support |
| - Consent unobtainable | -Kidney or liver transplant during same admission | -Previous enrollment in this trial |

Table 1. Characteristics of included randomised trials. Unless otherwise specified, standard definitions are used for ALI, ARDS, SIRS, sepsis and septic shock. [70-72]. *Denotes studies in which between-group differences in fluid balance was considered to be clinically-significant. Unless otherwise specified, data are presented as mean +/- standard deviation. RCT: Randomised controlled trial; EVLW: Extravascular lung water; PCWP: Pulmonary capillary wedge pressure; MI: 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; FiO₂: Fraction of Inspired Oxygen.
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Mortality</td>
<td>11</td>
<td>randomised trials</td>
<td>serious ¹</td>
<td>not serious</td>
</tr>
<tr>
<td>Ventilator free days</td>
<td>7</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Intensive Care Unit (ICU) length of stay</td>
<td>7</td>
<td>randomised trials</td>
<td>serious ³</td>
<td>serious ⁴</td>
</tr>
<tr>
<td>Renal Replacement Therapy (RRT) use</td>
<td>3</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Post-ICU Cognitive function (assessed with: QLQ-C30 cognitive function domain; Scale from: 0 to 100, with higher scores denoting better cognitive function)</td>
<td>1</td>
<td>randomised trials</td>
<td>very serious ⁶</td>
<td>not serious</td>
</tr>
</tbody>
</table>
Table 2. GRADE Summary of findings table for key outcomes. **CI:** Confidence interval; **RR:** Risk ratio; **MD** Mean difference. Explanatory notes: 1. Only five studies were at low risk of bias, the remainder were at moderate or high risk of bias. 2. Significant variability in populations, interventions and comparators studied. 3. Only two studies were at low risk of bias, the remainder were at moderate or high risk of bias. 4. Considerable heterogeneity present across studies ($I^2=75\%$). 5. Insufficient number of participants to exclude clinically important benefit or harm. 6. Single study, uncertain risk of bias across all domains. 7. Limited available information on intervention strategy.
Appendix 1. Summary of included observational studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Inclusion and exclusion criteria</th>
<th>Patient characteristics</th>
<th>Key outcomes</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abulebda et al, 2014.</td>
<td>- Secondary analysis of multicentre prospective observational study of genomics in sepsis - USA</td>
<td>Inclusion: - Age ≤10 years - Septic shock - Enrolement in an ongoing genomic study Exclusion: - None reported</td>
<td>N=317</td>
<td>-28 day mortality</td>
<td>- Non-survivors had a higher cumulative fluid balance 7 at day 7 (median 19.5% of body weight, IQR 10.4 to 40.1) compared to survivors (median 6.5% body weight, IQR -1.3 to 14.6), p= &lt;0.001</td>
</tr>
<tr>
<td>Acheampong &amp; Vincent, 2015.</td>
<td>- Single centre prospective cohort study - Belgium</td>
<td>Inclusion: -&gt;15yrs of age - Admitted during 2012 - Suspected or proven infection treated with antibiotics - Sepsis-associated organ failure by SOFA subscore 3 or 4 - ICU stay &gt;48h Exclusion: - None reported</td>
<td>N=173</td>
<td>- ICU mortality</td>
<td>- Daily fluid balance was greater in non-survivors than survivors (29 ± 22 vs. 13 ± 19 ml/kg, p &lt; 0.001). - Positive fluid balance was independently associated with higher mortality (adjusted hazard ratio 1.014 per ml/kg, P&lt;0.001) - Diuretics were used in 41% of non-survivors, 29% of survivors</td>
</tr>
<tr>
<td>Bhaskar et al,</td>
<td>- Retrospective</td>
<td>Inclusion:</td>
<td>N=114</td>
<td>- ICU mortality</td>
<td>- Independent risk factors for</td>
</tr>
</tbody>
</table>
| Year     | Study Type            | Country          | Inclusion                                      | Exclusion                                                                 | Median Age | Median Paediatric Index of Mortality Score | Sepsis or Septic Shock | Duration of Mechanical Ventilation (Survivors) | Renal Replacement Therapy Use | Length of ICU Stay | Mortality Included | Mortality included  
|----------|-----------------------|------------------|-----------------------------------------------|---------------------------------------------------------------------------|------------|------------------------------------------|------------------------|-------------------------------------------------|---------------------------|------------------|-------------------|----------------------|
| 2015     | Cohort study          | USA              | Shock states (majority sepsis or SIRS)        | - Age ≤ 18 years                                                          | 1.1 yrs    | 5.1                                      | 83%                    | 1.61 per day (95% CI 1.21-2.28)                  | N/A                       | 9 days           | Presence of fluid overload (≥10% body weight at 3 days) | 37% versus 3%, P=0.002; peak fluid overload within 7 days (adjusted OR 1.13 per % body weight, 95% CI 1.07-1.23); and duration of fluid overload (adjusted OR 1.61 per day, 95% CI 1.21-2.28)
| Bihari et al, 2013 | Single centre prospective observational study investigating the prevalence and efficacy of fluid boluses after initial resuscitation in septic patients. | Australia | Inclusion: - Age > 18 years  
- Severe sepsis or septic shock  
- Within 2 hours of completing initial 6 hours of resuscitation | - Expectation of death within 24 hours  
- Patients not undergoing active treatment  
- Patients with clinically obvious ongoing | 72.5 yrs | 80 (IQR 68-93) | 26% mechanically ventilated | N=50 | Median age 72.5 yrs. (61.0-82.8) | 66% male (33) | 9 (IQR 6-11) | Cumulative fluid balance was weakly correlated with Δ SOFA score at 48 and 72 hours (r=0.32, P=0.001) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>N</th>
<th>Median Age</th>
<th>Male</th>
<th>Median APACHE 4 Score</th>
<th>48-hour Net Fluid Balance</th>
<th>28-day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botdorf et al, 2015.</td>
<td>Single centre retrospective cohort study</td>
<td>- Suspected sepsis - ICU stay &gt; 24 hrs</td>
<td>None reported</td>
<td>162</td>
<td>68 yrs (IQR 58-79)</td>
<td>55%</td>
<td>83 (IQR 67-104)</td>
<td>8790 ml (IQR 4530 to 11400) vs 5380 ml (IQR 2900 to 7820, p=0.023)</td>
<td></td>
</tr>
<tr>
<td>Boyd et al, 2011.</td>
<td>Secondary analysis of a multicentre randomised controlled trial of vasopressin versus norepinephrine in 27 centres in Canada, Australia and USA</td>
<td>- Septic shock - Minimum of 5 mcg/min noradrenaline infusion</td>
<td>None reported, unstable coronary syndrome, suspected or proven mesenteric ischaemia, underlying chronic heart disease, anticipation of imminent death or lack of commitment to aggressive care</td>
<td>778</td>
<td>6 months &gt; 50%</td>
<td>50%</td>
<td>Not reported for overall cohort</td>
<td>Higher net fluid balance at 4 days (and at 12 hours) was an independent risk factor for mortality: adjusted hazard ratios by quartiles with decreasing fluid balances 0.739 (95% CI 0.503-1.087), 0.512 (0.339-0.775), 0.466 (0.299 – 0.724).</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>N</td>
<td>Outcomes</td>
<td>Note</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al, 2011.</td>
<td>Single centre retrospective cohort study - China</td>
<td>Inclusion: Septic shock (ACP/SCCM criteria)</td>
<td>Exclusion: Fluid bolus or vasopressor administration in another hospital</td>
<td>107</td>
<td>-28 day mortality</td>
<td>Absence of conservative late fluid management, negative fluid balance in first week &lt; 2 litres, and total intake in first week &gt; 20 litres were independent risk factors for mortality.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Survivors (n=68): Age 66.7 +/- 14.5, 78% male, APACHE score 14.7 +/-3.1, SOFA score 6.5 +/- 1.5</td>
<td>Non-survivors (n=39): Age 68.88 +/- 13.1 years, 69% male, APACHE score 16.3 +/- 3.6, SOFA score 7.2 +/- 1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cordemans et al, 2012.</td>
<td>Retrospective observational cohort study comparing an intervention group who received PAL treatment (PEEP, hyperoncotic albumin boluses, and furosemide or CRRT to target neutral to negative fluid balance with a control group. -2 academic ICUs (1 centre) -Belgium</td>
<td>Inclusion: Intubated and mechanically ventilated ALI Transpulmonary thermodilution catheter monitored</td>
<td>Exclusion: None reported</td>
<td>114</td>
<td>28-day mortality, ICU length of stay, Hospital length of stay, Duration of mechanical ventilation</td>
<td>Cumulative fluid balance in PAL treatment group -1451 +/- 1761ml at 1 week versus 8027 +/- 1451ml in control group. 28 day mortality was lower in the PAL-treated group (28.1% vs 49.1%, P=0.034) ICU length of stay was shorter in the PAL-treated group (23.6+/= 15 days vs 38.1 +/- 19.9 days, p = 0.006) No difference in Hospital length of stay (69.8 +/- 66.9 days in PAL-treated vs 82.5 +/- 57.6) Duration of mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Table Information</td>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cronhjort et al, 2016.</td>
<td>Secondary analysis of a multicentre RCT of transfusion strategies in septic shock in Denmark, Norway, Sweden and Finland</td>
<td>Inclusion: - Adults with septic shock - Haemoglobin level &lt; 90g/dL - ICU stay ≥ 3 days Exclusion: - Receipt of blood transfusion pre-enrollment - Life-threatening bleeding - Active myocardial ischaemia</td>
<td>N=841 - Quartile 1 (Lowest fluid balance): - Age 63 +/- 14 - 56.8% male - SOFA score 10.2 +/- 3.1 - Quartile 2: - Age 66 +/- 12 - 59% male - SOFA score 9.7 +/- 3.1 - Quartile 3: - Age 65 +/- 13 - 50.6% male - SOFA score 10.1 +/- 3.5 - Quartile 4 (Highest fluid balance): - Age 65 +/- 12 - 51.6% male - SOFA score 10.2 +/- 3.4 - 90 day mortality - RRT-free days (% of 90 days) - VFDs (% of 90 days) - Days alive and out of hospital (% of 90 days)</td>
<td>Fluid balance (by quartiles) was not associated with 90-day mortality in multivariate analysis (Q2 HR 1.11 (95% CI 0.83-1.50, Q3 HR 1.19, 95% CI 0.90-1.56, Q4 HR 1.30, 95% CI 0.97-1.75) - A more positive fluid balance was associated with similar number of days on RRT (Q1 82%, Q2 85% Q3 87% Q4 81%, P=0.27) - A more positive fluid balance was associated with fewer VFDs (Q1 – 72%, Q2 68%, Q3 67%, Q4 58%, P=0.01) - A more positive fluid balance was associated with fewer days alive and out of hospital (Q1 36%, Q2 30%, Q3 30%, Q4 23%, P&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Oliveira et al, 2015.</td>
<td>Retrospective analysis of a single centre prospective cohort study in an tertiary centre in Brazil</td>
<td>Inclusion: - Age &gt; 18 years - Severe sepsis or septic shock Exclusion: - Pregnancy</td>
<td>N=116 - Median age 60 yrs. (IQR 44-74) - 63.5% male - Median APACHE 2 score 17 (IQR was significantly shorter in the PAL treated group (14.6 +/- 10.7 days vs 25.5 +/- 20.2, p = 0.02)</td>
<td>Hospital mortality - Acute kidney injury (RIFLE-F) - No difference in fluid balance at 6 hours, 12 hours or 24 hours between survivors and non-survivors - Fluid balance at 24-48 hours &gt; 3000ml was an independent risk factor for mortality (adjusted OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>N</td>
<td>Outcomes</td>
<td>Details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----------</td>
<td>-----------</td>
<td>---</td>
<td>----------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiorenza &amp; Pass, 2013.</td>
<td>Single centre retrospective cohort study -USA</td>
<td>-Severe sepsis or septic shock in critical care unit - CVC in situ and CVP measured</td>
<td>-None reported</td>
<td>N=78</td>
<td>28-day mortality</td>
<td>-Non-survivors had a more positive fluid balance than survivors on days 1-3 (Day 1: 4071 mL vs. 1640 mL, respectively; p = 0.002; Day 2: 3473 mL vs. 1082 mL, p = 0.029; Day 3: 1090 mL vs. 59 mL, p = 0.004).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flori et al, 2011.</td>
<td>Post-hoc analysis of a prospective observational study in 2 centres -USA</td>
<td>-Children admitted to participating PICU during study period (1996-2000) -ALI</td>
<td>-&lt;36 weeks corrected gestational age or &gt;18 years -Evidence of left atrial hypertension clinically or by echo - Echocardiographic evidence of intra-cardiac shunt -Exchange transfusions -ECMO -CRRT</td>
<td>N=320</td>
<td>PICU mortality -Ventilator-free days</td>
<td>-Positive fluid balance was an independent risk factor for mortality (adjusted OR of 1.08 per 10ml/kg/day, 95% CI 1.01-1.15, p=0.02) -More positive fluid balance (in 10ml/kg/day increments) was negatively correlated with number of VFDs (coefficient -0.21, 95% CI -0.39 to -0.04, p=0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>N</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-----------</td>
<td>-----------</td>
<td>---</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grissom et al, 2015.</td>
<td>Retrospective analysis of data from 4 large RCTs</td>
<td>- Enrolment in one of 4 randomised trials in ARDS – FACTT, EDEN, OMEGA and ALTA. - Presence of CVC</td>
<td>- Chronic dialysis dependence</td>
<td>2124</td>
<td>FACTT Lite group: - Age 51.5 yrs. +/- 0.5 - Male 52% - APACHE 3 score 91.0 +/- 0.8 FACTT conservative: - Age 50.1 yrs. +/- 0.7 - Male 52% - APACHE 3 score 93.1 +/- 1.4 FACTT liberal: - Age 49.5 yrs. +/- 0.7 - 55% male - APACHE 3 score 95.2 +/- 1.4</td>
<td>60 day mortality - Ventilator free days - ICU-free days - Acute kidney injury (increase in serum creatinine by ≥ 0.3 mg/dl or by ≥ 50%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrera Gutierrez et al, 2013.</td>
<td>Single centre prospective cohort study</td>
<td>- Sepsis (undefined)</td>
<td>- Unclear</td>
<td>129</td>
<td>- Age 56.8 yrs +/- 16.7 - 58.8% male - APACHE 2 score</td>
<td>- 28 day mortality - Acute kidney injury (KDIGO) during ICU stay</td>
<td>- Fluid balance at 7 days in the FACTT Lite group was intermediate between the two arms of the FACTT trial [15] (1918 +/- 323 ml versus -136 +/- 491 ml and 6992 +/- 502 ml). - 60-day mortality was similar in all 3 cohorts (FACTT Lite vs FACTT Liberal p=0.56, FACTT Lite vs FACTT Conservative p=0.91) after adjustment for age and severity of illness. - The number of ventilator free days was similar between FACTT Lite and FACTT conservative groups, but there were more in FACTT Lite compared to FACTT Liberal (14.9 +/- 0.3 vs 12.1 +/- 0.5 days, P&lt;0.001). - The number of ICU free days was similar between FACTT Lite and FACTT Conservative, but there were more in FACTT Lite compared to FACTT Liberal (14.4 +/- 0.3 vs 11.2 +/- 0.4, P&lt;0.001) - Acute kidney injury rates (adjusted for fluid balance) were similar between FACTT Lite and FACTT Conservative groups, but were lower in FACTT Lite compared to FACTT Liberal (56% vs 66%, p=&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>N</td>
<td>Outcomes</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>-----------</td>
<td>-----------</td>
<td>---</td>
<td>----------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kongsayreepong &amp; Nitikaroon, 2013.</td>
<td>Prospective single centre cohort study</td>
<td>Thailand</td>
<td>Post noncardiac surgery, Age ≥ 18 years, Severe sepsis or septic shock</td>
<td>None reported</td>
<td>196</td>
<td>Acute kidney injury (Acute Kidney Injury Network score ≥ stage 1)</td>
<td>Fluid overload was not an independent risk factor for AKI.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koonrangsesomboon &amp; Khwannimit, 2015.</td>
<td>Single centre retrospective cohort study</td>
<td>Thailand</td>
<td>Septic shock requiring ICU</td>
<td>ICU length of stay &lt; 24 hours</td>
<td>1048</td>
<td>ICU mortality, Hospital mortality</td>
<td>After grouping based on 72-hour fluid balance quartiles, the 3rd and 4th quartiles were independently associated with ICU mortality (adjusted OR 3.04 [95% CI 1.90-4.84] and 4.16 [95% CI 2.49-6.95] per litre respectively. After grouping based on 72-hour fluid balance, the 3rd and 4th quartiles were independently associated with hospital mortality (adjusted OR 2.75 [95% CI 1.74-4.36] and 3.16 [95% CI 1.87-5.35] per litre respectively.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micek et al, 2013.</td>
<td>Single centre</td>
<td></td>
<td></td>
<td></td>
<td>325</td>
<td>Hospital mortality</td>
<td>Non-survivors had a more positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23.9 +/- 7.7 at admission - SOFA score 12.2 +/- 5.1 at admission

1.67 (KDIGO Stage 2, P=0.08), 7.87% +/- 6.29 (KDIGO Stage 3, P<0.001)

Day 3 net fluid balance was significantly lower in survivors than non-survivors (0.7% +/- 6.4 vs 6.7% +/-6.6, P<0.0001).

Day 3 net fluid balance was an independent risk factor for mortality (adjusted OR 1.13, 95% CI 1.06-1.22).
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Survivors:</th>
<th>Non-survivors:</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort study - USA</td>
<td>Septic shock</td>
<td>Exclusion: Pre-existing non-sepsis related cardiovascular compromise - ECMO or VAD use - Shock onset at outside hospital prior to transfer</td>
<td>Survivors: Age 58.5 yrs. +/- 14.6 - Male 46.3% - APACHE 2 score 21.7 +/- 6.3</td>
<td>Non-survivors: Age 63.0 yrs. +/- 14.0 - Male 44.8% - APACHE 2 score 25.1 +/- 6.7</td>
<td>Fluid balance in the 8 days following shock onset (median 7742 ml [2914-15992] versus 3286.5 ml [1508.5 – 7467], P&lt;0.001) - The quartile with the highest fluid balance had significantly higher mortality risk (P&lt;0.001 compared to the lowest fluid balance quartile) - Being in the highest fluid balance quartile was an independent risk factor for death (adjusted OR 1.66 [1.39-1.98], P=0.004)</td>
</tr>
<tr>
<td>Multicentre retrospective cohort study - Japan</td>
<td>ARDS - Mechanical ventilation - Transpulmonary thermodilution monitoring used</td>
<td>None reported</td>
<td>N=207</td>
<td>Patient characteristics not reported</td>
<td>28 day mortality - Fluid balance after 3 days was higher in non-survivors than survivors, both before (5.1 +/- 4.3 L vs 3.5 +/- 0.4 L, P=0.03) and after exclusion of patients with SOFA-CV or SOFA-renal score &gt;2 (3.8 +/- 1.6 L vs 2.2 +/- 4.0 L, P=0.03). - Fluid balance after 3 days was an independent predictor of 28 day mortality (adjusted OR 1.0001, 95% CI 1.000017 – 1.00022, P=0.03)</td>
</tr>
<tr>
<td>Retrospective cohort study - 2 academic centres in USA</td>
<td>Septic shock - ALI (AECC definition) - Mechanical ventilation &gt; 24 hrs.</td>
<td>Hospitalisation for - Hospitalisation for</td>
<td>N=212</td>
<td>Survivors: Age 58.5yrs +/- 15.8 - 62% male - APACHE 2 score 23.9 +/- 6.0 - SOFA score 9.5 +/- 2.5</td>
<td>Hospital mortality - Net fluid balance after 7 days was higher in non-survivors than survivors (median 13,694 ml; IQR 7113-20249 vs 8062 ml; IQR 2412-13833, p &lt; 0.001). - Absence of ‘conservative late fluid management’ (defined as even to negative fluid balance on ≥ 2 consecutive days) was an</td>
</tr>
</tbody>
</table>
| Author et al, 2011. | > 7 days following septic shock onset  
- Reason for cardiovascular compromise other than septic shock  
- ECMO or VAD use  
- Onset of septic shock while at non-participating hospital | Non-survivors:  
- Age 60.7yrs +/- 14.9  
- 47% male  
- APACHE 2 score 26.7 +/- 7.3  
- SOFA score 11.0 +/- 3.3 | Independent risk factor for hospital mortality (adjusted OR 6.13, 95% CI 2.77-13.57, P<0.001)  
- Absence of ‘adequate initial fluid resuscitation’ (defined as ≥ 20 ml/kg fluid bolus before administration of vasopressors and CVP ≥ 8 mmHg within 6 hours of shock onset) was also an independent risk factor for mortality (adjusted OR 4.94, 95% CI 2.07-11.79, P<0.001) |
|---|---|---|---|
| Perez-Fernandez et al, 2011. | - Prospective single centre cohort study  
- Spain | Inclusion:  
- Septic shock  
- Acute renal failure on CRRT for >24 hours | N=262  
- Age 62yrs +/- 13  
- 69.8% male  
- APACHE 2 score 26 +/- 8  
- SOFA score 12 +/- 3.8  
- 57% medical, 43% surgical  
- 87.9% mechanically ventilated | - 90-day mortality  
- Mortality higher in positive balance group (> +ve 1000ml/initial 24hr on initial 24 hours of CRRT) compared with “isovolaemic” group (< +ve 1000ml/initial 24hr on CRRT) (70.8% vs 55%).  
- Positive fluid balance over 24hrs on CRRT was an independent risk factor for 90 day mortality (p < 0.0001) |
| Raimundo et al, 2012. | - Single centre retrospective cohort study  
- Portugal | Inclusion:  
- All patients admitted to ICU over 1 year due to sepsis  
- ICU stay <24 hours | N=68  
- Age 63.4 yrs. +/- 16.2  
- 73.5% male  
- APACHE 2 score 20.1 +/- 10.3  
- SOFA score 7.1 +/- 3.4 | - ICU mortality  
- Incidence of ARDS  
- ICU Length of stay  
- Duration of mechanical ventilation  
- Comparison between liberal (positive fluid balance at ICU discharge, n=47) and conservative fluid management (neutral or negative fluid balance at ICU discharge, n=21)  
- ICU mortality 39.7% with higher mortality in liberal vs conservative fluid balance group (55.3% vs 4.8%, P not reported)  
- ARDS more common in the liberal
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>N</th>
<th>Mortality (time point undefined)</th>
<th>Duration of mechanical ventilation</th>
<th>ICU Length of stay</th>
<th>vs conservative fluid balance group (25.5% vs 14.3%, P not reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez et al, 2013.</td>
<td>Retrospective single centre cohort study</td>
<td>Severe sepsis or septic shock</td>
<td>None reported</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No significant difference in mortality between group with positive fluid balance group after 2 days and negative fluid balance after 2 days group (35.3 vs 18.6 %, p = 0.072)</td>
</tr>
</tbody>
</table>
| Rosenberg et al, 2008. | Secondary analysis of a clinical trial comparing lung protective ventilation to traditional ventilation in patients with ARDS in 24 US academic hospitals [59] | ARDS or ALI (AECC definition) | Fluid balance data available | 794 | - | - | - | Cumulative fluid balance at day 4 was an independent risk factor for hospital mortality (adjusted OR 1.034 per litre, 95% CI 1.187-1.432, P=0.001).
<p>| | | Intubated and receiving mechanical ventilation in a participating centre | | | Survivors: | - | - | Hospital mortality | A negative fluid balance at day 4 was associated with a lower risk of hospital mortality (adjusted OR 0.502 per litre, 95% CI 0.284-0.887, P&lt;0.001) |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al, 2012</td>
<td>Retrospective cohort study</td>
<td>Japan</td>
<td>Severe sepsis or septic shock requiring mechanical ventilation</td>
<td>Pregnancy, &lt;18 years, Participation in another clinical trial in &lt;30 days, Physician refusal</td>
<td>Incidence of ARDS, Incidence of AKI (RIFLE-F), 28 day mortality, OFM group (n=47) achieved a negative fluid balance earlier than the 'before' group (n=49), Mortality was similar between groups (14.3% vs 17.0%), Incidence of ARDS was lower in the ‘OFM’ group (20.4% vs 57.4%, P=0.02), Incidence of AKI similar between groups, OFM was an independent protective factor for ARDS (adjusted OR 0.17, CI 0.06-0.51, P=0.001)</td>
</tr>
<tr>
<td>Simmons et al, 1987</td>
<td>Prospective cohort study</td>
<td>USA</td>
<td>ARDS defined as: Acute respiratory failure with bilateral infiltrates requiring intubation and mechanical ventilation, PaO2/FiO2 ratio &lt; 150mmHg within 72 hours</td>
<td>- None reported - Median age 69.5 (IQR 55.5 – 78.5) - Median APACHE 2 score 23.0 (IQR 19-27) - Median SOFA score 10.0 (7.0-12.0) - 75% septic shock</td>
<td>Hospital mortality, Overall mortality 77.9%, Survivors had a significantly less positive fluid balance and significantly greater weight gain over 14 days in univariate analysis, By day 14, survivors were on average 9.72 litres less positive than non-survivors</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>---------</td>
<td></td>
</tr>
</tbody>
</table>
| Smith & Perner, 2012. | Prospective cohort study in 6 Danish ICUs (3 academic, 3 community) | - Admission to participating ICU during study period  
- Septic shock | - Pulmonary arterial wedge pressure >18mmHg or not recorded within 24 hours | N=164  
- Median age 66yrs (IQR 59-74)  
- 57% male  
- Median SAPS II score 54 (IQR 46-67)  
- 90-day mortality  
- RRT use | - Cohort dichotomised into ‘high fluid intake’ (median 9.2 L, IQR 5.3-13.6 at 72 hrs.) and ‘low fluid intake’ (2.9 L, IQR 0.9-5.4 L at 72 hours) groups  
- Similar SAPS II scores, SOFA scores, and maximum vasopressor dose over 3 days between groups  
- 90 day mortality was higher in the low fluid intake group (62% vs 40%, P=0.03, unadjusted comparison)  
- Similar rates of RRT use between groups (38% vs 33%, p=0.61) |
| Spicer et al, 2014. | Multi-centre cohort study in USA | - Children  
- ARDS | None reported | N=209  
AKI cohort:  
- Age 86 months +/- 73  
- 56% male  
- PRISM 3 score 13 +/- 8  
Non-AKI cohort:  
- Age 86 months +/- 74  
- 55% male  
- PRISM 3 score 21 +/- 11 | Mortality (time point undefined) | Net fluid balance at day 3 was an independent risk factor for mortality in a cohort with AKI (adjusted OR 1.89 per 100ml/kg [1.08-3.31], P=0.027) but not in a cohort without AKI |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Country</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Study Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al, 2015.</td>
<td>Single centre retrospective cohort study - China</td>
<td>- Age &gt;18 years - Sepsis - AKI requiring RRT</td>
<td>- Cause of AKI other than sepsis - Duration of RRT &lt;72 hours - Incomplete medical records - Unexpected death within follow-up period</td>
<td>N=117</td>
<td>Positive fluid balance group: - Age 68.3 +/- 14.4 - 75.5% male - APACHE II score 29.6 +/- 6.2 - SOFA score 11.1 +/- 2.4 Negative fluid balance group: - Age 67.2 +/- 16.8 - 75.4% male - APACHE II score 30.0 +/- 7.2 - SOFA score 11.0 +/- 2.7</td>
</tr>
<tr>
<td>Udeozo et al, 2009.</td>
<td>Retrospective cohort study of prospectively-collected database - USA</td>
<td>- Septic shock</td>
<td>- Refusal of consent - Readmissions to ICU</td>
<td>N=390</td>
<td>Median age 68 yrs. (IQR 56 – 79) -54% male -Median APACHE 3 score 87 (IQR 67-105)</td>
</tr>
<tr>
<td>Valentine et al, 2012.</td>
<td>Multi-centre (5 PICUs) retrospective cohort study - USA</td>
<td>- Age ≥ 1 month and &lt; 18 years -IPPV via ETT -ALI (AECC definition)</td>
<td>-Chronic conditions that could</td>
<td>N=168</td>
<td>Median age 3 years (IQR 0.8 – 11) -54% male -Median PRISM 3 score 9 (IQR 3-13)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Vincent et al, 2006. (sepsis)</td>
<td>Prospective multicentre cohort study</td>
<td>All patients &gt;15 years admitted to participating ICU; Sepsis cohort: presence of infection + SIRS criteria (ACP/SCCM); ALI/ARDS cohort: AECC criteria</td>
<td>Re-admission to ICU; Routine post-operative admission &lt;24 hours</td>
<td>ICU mortality: Net fluid balance at 72 hours was an independent risk factor for ICU mortality (adjusted OR 1.1 per litre, 95% CI 1.0-1.1, $P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td>Sakr et al, 2005 (ARDS)</td>
<td>-198 European ICUs</td>
<td>Sepsis cohort (N=1177): Median age 65yrs (IQR 51-74); 63% male; SAPS 2 score 42.3 +/- 16.6; SOFA score 6.5 +/- 4.0</td>
<td></td>
<td>ALI/ARDS cohort (N=393): Age 59 +/- 17; 60.5% male; SAPS 2 score 46.6 +/- 17.6; Sepsis 47.5%</td>
<td>Fluid balance at 72 hours was higher for non-survivors than survivors (3.6 +/- 6.4 litres vs 1.8 +/- 5.4 litres, $P=0.002$)</td>
</tr>
<tr>
<td>Wang et al, 2016.</td>
<td>-Single centre retrospective cohort study</td>
<td>Severe sepsis; Age ≥ 18 years; Use of PICCO monitoring; CVP target of 8-10 mmHg</td>
<td></td>
<td>28 day mortality: Fluid balance in the 24 hour and 24-48 hour periods post-initial resuscitation both independently predicted 28-day mortality (adjusted OR 1.001 per ml, 95% CI 1.000-1.001, $P=0.016$ for 24 hours;</td>
<td></td>
</tr>
<tr>
<td>12mmHg reached within 6 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Requirement for Norepinephrine ≥ 0.1 mcg/kg/min or Dopamine ≥ 5 mcg/kg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Survival time ≥ 72 hours following shock onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Pregnancy or breast-feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Shock in the absence of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PiCCO used for &lt;48 hours or absent data at ≥ 2 timepoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute blood loss, acute myocardial infarction, pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Treatment withheld or withdrawn during hospital stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-survivors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age 65 +/- 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 63.3% male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- APACHE II score 25.5 +/- 6.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.8 +/-7.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted OR 1.001 per ml, 95% CI 1.000-1.002, P=0.08 for 24-48 hours).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Single centre retrospective cohort study
- Germany

Inclusion:
- ICU patients with ARDS, defined as acute respiratory failure after a typical insult, PaO2 < 50mmHg with FiO2 ≥ 0.6 and radiological

N=124
- Age 45.4 yrs. (range 16-78)
- 61.3% male

-ICU mortality

- No significant difference in mortality between 3 treatment groups: (1) patients treated with diuretics (2) patients treated with haemofiltration as diuretic-unresponsive, and (3) patients who died or had spontaneous diuresis before any diuretics given.
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al, 2015</td>
<td>Age &lt;18 years, ALI of direct aetiology, Enrolment in CARDS trial (surfactant vs placebo) within 48 hours of intubation</td>
<td>Indirect lung injury, Pre-existing lung disease, Limitations on level of support, Significant non-pulmonary organ dysfunction</td>
<td>ICU mortality was higher in patients with a positive net fluid balance over the ICU stay (85.2% vs 66.7%, P&lt;0.05)</td>
</tr>
<tr>
<td>Yao et al, 2014</td>
<td>Septic shock (ACCP/SCCM definition)</td>
<td>Net fluid balance at day 7 which was positive or less negative than -1330ml was an independent risk factor for mortality (adjusted OR 2.98, P=0.037)</td>
<td>Cumulative fluid balance at 7 days was greater in non-survivors than survivors (11745 ml/m² [10817] versus 1234 ml/m² [2393], P&lt;0.001)</td>
</tr>
</tbody>
</table>

- Prospective single-centre cohort study investigating the prognostic utility of BNP on clinically important outcomes and assessing correlation between fluid balance and changes in BNP

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>N=67</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis - Age 18-80 years - PiCCO system in use for haemodynamic monitoring</td>
<td></td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
</tr>
<tr>
<td>- Acute kidney injury (AKIN Stage 2 or above) - Patients considered moribund or with DNAR order - Pre-existing renal dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

- Hospital mortality

- Net fluid balance at day 2 was an independent risk factor for hospital mortality (OR 1.50 per 100ml, 95% CI 1.10 – 2.04, p = 0.01).

- Change in BNP was correlated with change in fluid balance (Spearman’s rho =0.63, p < 0.01)

Zhang et al, 2013.

- Single centre retrospective cohort study

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>N=160</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis induced AKI admitted to ICU</td>
<td></td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
</tr>
<tr>
<td>- Immune</td>
<td></td>
</tr>
</tbody>
</table>

- 28 day mortality - Length of ICU stay

- Positive fluid balance (defined as no days of negative balance >500ml in first 3 days of ICU stay) was associated with higher mortality (68.4% vs 37%, p<0.01), and a longer ICU stay (10.1 +/- 4.9 days vs 12.4 +/- 8.0 days, p<0.05)
<table>
<thead>
<tr>
<th>Compromise</th>
<th>APACHE 2 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage chronic illness</td>
<td>17.9 +/- 6.1</td>
</tr>
<tr>
<td>Age &lt; 12 or &gt; 80</td>
<td></td>
</tr>
<tr>
<td>Pregnancy or lactation</td>
<td></td>
</tr>
<tr>
<td>Learning disability or severe psychiatric illness</td>
<td></td>
</tr>
<tr>
<td>Terminal illness</td>
<td></td>
</tr>
</tbody>
</table>

Positive fluid balance group:
- Age 56 yrs. +/- 18.2
- 77.2% male
- APACHE 2 score 18.8 +/- 5.1
Appendix 2. Modified Newcastle-Ottawa scale for included cohort studies.

Selection:
1) **Representativeness of the exposed cohort**
   a) truly representative of the average ARDS / SIRS / sepsis population in the community
   b) somewhat representative of the average ARDS / SIRS / sepsis population in the community
   c) selected group of patients
   d) no description of the derivation of the cohort

2) **Selection of the non exposed cohort**
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) **Ascertainment of exposure**
   a) secure record (eg surgical records)
   b) structured interview
   c) written self report
   d) no description

4) **Demonstration that outcome of interest was not present at start of study**
   a) yes
   b) no

Comparability:
1) **Comparability of cohorts on the basis of the design or analysis**
   a) study controls for severity of illness
   b) study controls for haemodynamic status

Outcome:
1) **Assessment of outcome**
   a) independent blind assessment
   b) record linkage
   c) self report
   d) no description

2) **Was follow-up long enough for outcomes to occur**
   a) yes
   b) no

3) **Adequacy of follow up of cohorts**
   a) complete follow up - all subjects accounted for
   b) subjects lost to follow up unlikely to introduce bias > 98 % follow-up or description provided of those lost
   c) follow up rate < 99%and no description of those lost
   d) no statement
Newcastle-Ottawa scores for included observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abulebda et al, 2014.</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Acheampong &amp; Vincent, 2015.</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Boldt &amp; al., 2015.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Boyd et al, 2011.</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Chen et al, 2011.</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cronhjort et al, 2016.</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>De Oliveira et al, 2015.</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fiorenza &amp; Pass, 2013.</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Flori et al, 2011.</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Herrera Gutierrez et al, 2013.</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Koonrangsesomboon &amp; Khwannimit, 2015</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Murai et al, 2014.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Murphy et al, 2009.</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Perez-Fernandez et al, 2011.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Raimundo et al, 2012.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Rodriguez et al, 2013.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Simmons et al, 1987.</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Smith &amp; Perner, 2012.</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Sun et al, 2015.</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Udeoza et al, 2009.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Vincent et al, 2006. (sepsis)</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sakr et al., 2005. (ARDS)</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Wang et al, 2016.</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Wilkowski et al, 1988.</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Willson et al, 2015.</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Zhang et al, 2013.</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Appendix 3. Additional analyses.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th>Liberal fluid</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Hjortrup et al. 2016</td>
<td>25 75</td>
<td>31 76</td>
<td>0.82 [0.54, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2002</td>
<td>7 20</td>
<td>9 20</td>
<td>0.78 [0.36, 1.68]</td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2005</td>
<td>3 19</td>
<td>3 18</td>
<td>0.95 [0.22, 4.10]</td>
<td></td>
</tr>
<tr>
<td>Richard et al. 2015</td>
<td>7 30</td>
<td>14 30</td>
<td>0.50 [0.24, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Wedemann et al. 2006</td>
<td>128 503</td>
<td>141 497</td>
<td>0.90 [0.73, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 2015</td>
<td>83 168</td>
<td>90 182</td>
<td>1.00 [0.81, 1.24]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>795 803</td>
<td>100.0%</td>
<td>0.91 [0.80, 1.04]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 246 279

Heterogeneity: *I²* = 0.00, *Chi²* = 3.48, df = 4 (P = 0.48), *I²* = 0%

Test for overall effect: *Z* = 1.34 (P = 0.18)

3.1 Pre-planned sensitivity analysis excluding studies at high or moderate risk of bias with mortality as outcome.
3.2 Pre-planned subgroup analysis including only adult studies with mortality as outcome.
In a post-hoc sensitivity analysis in which we excluded studies lacking a clinically-important separation in fluid balance between groups, we found a non-significant reduction in mortality with a conservative or deresuscitative strategy compared to a liberal strategy or standard care. We used these findings to calculate the required sample size to test the hypothesis that conservative fluid management or deresuscitation strategy reduces mortality compared to a liberal strategy or standard care. Based on a 13% relative risk reduction (assuming a comparable difference in mortality to those studies in which a clinically-significant difference in fluid balance was achieved), a baseline mortality risk of 34%, two-tailed alpha of 0.05 and power of 90%, we calculated this to be 4704 patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th>Liberal fluid</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total Events</td>
<td>Total Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benakatti et al. 2014</td>
<td>10 54 11 47 3.6%</td>
<td>0.79 [0.37, 1.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2002</td>
<td>7 20 9 20 3.5%</td>
<td>0.78 [0.36, 1.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2005</td>
<td>3 19 3 18 1.0%</td>
<td>0.95 [0.22, 4.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. 1992</td>
<td>29 52 32 49 20.6%</td>
<td>0.85 [0.62, 1.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richard et al. 2015</td>
<td>7 30 14 30 3.6%</td>
<td>0.50 [0.24, 1.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>28 50 30 50 18.5%</td>
<td>0.93 [0.67, 1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiedemann et al. 2006</td>
<td>128 503 141 497 49.3%</td>
<td>0.90 [0.73, 1.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>728 711 100.0%</td>
<td>0.87 [0.75, 1.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>212 240</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.50$, df = 6 ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 1.93$ ($P = 0.05$)
3.4 Univariate meta-regression analysis with RR for mortality as dependent variable and between-group difference in mean daily fluid balance as exposure. \( R^2=0.11, P=0.30 \)
3.5 Forest plot for renal replacement therapy use, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Conservative fluid</th>
<th>Liberal fluid</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Chen and Kollef. 2015</td>
<td>17</td>
<td>41</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>Hjortrup et al. 2016</td>
<td>16</td>
<td>75</td>
<td>14</td>
<td>76</td>
</tr>
<tr>
<td>Wiedemann et al. 2006</td>
<td>50</td>
<td>503</td>
<td>70</td>
<td>497</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>619</strong></td>
<td><strong>614</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.88</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>83</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 2.76, df = 2 (P = 0.25); I² = 27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.78 (P = 0.44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5. List of excluded studies


- Observational study with n<50


- Duplicate / overlap


- Duplicate / overlap


- Duplicate / overlap


- Fluid type study


- Duplicate / overlap


- Observational study with n<50

Andrews et al. Simplified Severe Sepsis Protocol: A Randomized Controlled Trial of Modified Early Goal-Directed Therapy In Zambia. Critical Care Medicine 2014;42:2315-2324

- Complex haemodynamic intervention
- Resuscitation phase study

Angelo et al. Fluid Status and Clinical Outcomes In Critically Ill Children With Sepsis: A Retrospective Analysis. Critical Care Medicine 2010;38(12 S1):386

- Duplicate / overlap

Angelo et al. Fluid Status and Clinical Outcomes In Critically Ill Children With Sepsis: A Retrospective Analysis. Critical Care Medicine 2010;38(12 S1):386

- Duplicate / overlap


- Resuscitation phase study
- Complex haemodynamic intervention


- Observational study with n<50
- Resuscitation phase study

Azevedo et al. Should We Need Fluid Overload In the Critically Ill Patients? Nephrology Dialysis Transplantation 2013;28:I331

- Study population did not match criteria

Azevedo et al. Association Between Early Fluid Balance, Organ Failures and Outcomes In Ventilated Patients. Critical Care Medicine 2015;43(12 S1):170

- Study population did not match criteria

Balakumar et al. Fluid Balance Has Variable Association With Long-Term Survival In the Critically Ill. Critical Care Medicine 2015;43(12 S1):244


Bhaskar et al. Impact of Early Fluid Overload On Mortality In Critically Ill Children - A Nested Case-Control Study. Critical Care Medicine 2013;41(12 S1):1000


- Not original study
- Study population did not match criteria
- Observational study with n<50
- Observational study with n<50
- Fluid type study
- Fluid type study
- Duplicate / overlap
- Duplicate / overlap
- Duplicate / overlap
- Duplicate / overlap
- Pre-1980
- Resuscitation phase study
- Duplicate / overlap
- Duplicate / overlap
- Duplicate / overlap


Cordemans et al. Effect of Negative Fluid Balance With PAL Therapy (Peep + Albumin + Lasix) On Capillary Leak Index, Intra-Abdominal and Abdominal Perfusion Pressure, Extravascular Lung Water and Organ Function In Acute Lung Injury. Critical Care 2010:36(S2);97


Cuartero et al. Negative Fluid Balance 48 Hours After Admission Improves Survival At 28 Days In Critically Ill Patients. Critical Care 2012;16(S1):P241

Cuartero et al. Negative Fluid Balance 48 H After Admission Improves Survival At 28 Days In Critically Ill Patients. Critical Care 2012;16(S1):P241
Cuartero et al. Negative Fluid Balance 48 H After Admission Improves Survival At 28 Days In Critically Ill Patients. Intensive Care Medicine 2012;38(S1):0167

Cuartero et al. Negative Fluid Balance 48 H After Admission Improves Survival At 28 Days In Critically Ill Patients. Intensive Care Medicine 2012;38(S1):0167


Diaz-Rubia et al. Effect of Maintained Negative Fluid Balance In Hypoxemic and High Extravascular Lung Water Patients. Intensive Care Medicine 2011;37(S1):0370

Diaz-Rubia et al. Effect of Maintained Negative Fluid Balance In Hypoxemic and High Extravascular Lung Water Patients. Intensive Care Medicine 2011;37(S1):0370

Dulhunty et al. Increased Fluid Resuscitation Can Lead To Adverse Outcomes In Major-Burn Injured Patients, But Low Mortality Is Achievable. Burns 2008;34:1090-1097


El-Akabawy et al. The Concept of Early Goal-Directed Therapy In Sepsis Syndrome. Intensive Care Medicine 2011;37(S1):0439


Guidet et al. Assessment of Hemodynamic Efficacy and Safety of 6% Hydroxyethylstarch 130/0.4 Vs. 0.9% NaCl Fluid Replacement In Patients With Severe Sepsis: The CRYSTMAS Study. Critical Care 2012;16:R94


Hjortrup et al. Patient and Site Characteristics and Volumes of Resuscitation Fluids In Severe Sepsis-A Post Hoc Analysis Of A Randomised Clinical Trial. Intensive Care Medicine 2014;40(S1):0779


Jog et al. Stroke Volume Variation Guided Fluid Therapy In Septic Shock With ARDS. Critical Care 2012;16(S1):P233


Jones et al. Lactate Clearance Versus Central Venous Oxygen Saturation As Endpoints Of Early Sepsis Therapy: A Randomized Clinical Trial. Critical Care Medicine 2009; 37(12 Supp.):49


Kalra et al. Fluid Balance At 72 Hours In Severe Sepsis And Septic Shock Patients Treated With Early Goal-Directed Therapy (EGDT) Is Associated With Increased Length Of Mechanical Ventilation. Chest 2010;138 (4):A388


• Study population did not match criteria
• Clinical outcomes of interest not reported
• Resuscitation phase study
• Pre-1980
• Fluid type study
• Pre-1980
• Fluid type study
• Pre-1980
• Fluid type study
• Observational study with n<50
• Observational study with n<50
• Observational study with n<50
• Resuscitation phase study
• Complex haemodynamic intervention
• Resuscitation phase study
• Fluid balance not reported
• Fluid balance not reported
• Complex haemodynamic intervention
Katsaragakis et al. Rapid Fluid Removal Via Continuous Venovenous Hemodiafiltration and Oxygen Delivery, Oxygen Consumption, and Outcome In Septic Patients With Renal Dysfunction. Dialysis and Transplantation 2005;34:608-615

• Observational study with n<50


• Not original study


• Duplicate / overlap

Kelm et al. Fluid Overload In Patients With Severe Sepsis and Septic Shock Treated With Early Goal-Directed Therapy Is Associated With Increased Acute Need For Fluid-Related Medical Interventions and Hospital Death. Shock 2015;43(1):68-73

• Fluid balance not reported

Kelm et al. Fluid Overload In Patients With Severe Sepsis and Septic Shock Treated With Early Goal-Directed Therapy Is Associated With Increased Acute Need For Fluid-Related Medical Interventions and Hospital Death. Shock 2015;43:68-73

• Fluid balance not reported


• Resuscitation phase study


• Duplicate / overlap


• Study population did not match criteria


• Fluid balance not reported


• Resuscitation phase study

• Observational study with n<50

• Pre-1980

• Clinical outcomes of interest not reported


Lee et al. Is Fluid Administration Within Six Hours Early Enough For Better Patient Outcomes In Sepsis and Septic Shock? Critical Care Medicine 2012;40(12):26

Lee et al. Increased Fluid Administration In The First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality: A Retrospective Cohort Study. Chest 2014;146:908-915


Lee et al. Is Fluid Administration Within Six Hours Early Enough For Better Patient Outcomes In Sepsis and Septic Shock? Critical Care Medicine 2012;40(12):26

Lee et al. Increased Fluid Administration In The First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality: A Retrospective Cohort Study. Chest 2014;146:908-915


Lin et al. A Modified Goal-Directed Protocol Improves Clinical Outcomes In Intensive Care Unit Patients With Septic Shock: A Randomized Controlled Trial. Shock 2006;26:551-557


Mahrous et al. Renal Effect of Colloid Versus Crystalloid In Septic Neutropenic Patients. Critical Care Medicine 2013;41(12 S1):996

- Resuscitation phase study

- Not relevant

- Resuscitation phase study

- Not original study

- Resuscitation phase study

- Clinical outcomes of interest not reported

- Duplicate / overlap

- Duplicate / overlap

Morisawa et al. Combined Use of Transpulmonary Thermodilution Technique In Fluid Management For Sepsis Patients. Intensive Care Medicine 2014;40(S1):0147
- Observational study with n<50

- Complex haemodynamic intervention

Muller et al. Fluid Management and Risk Factors For Renal Dysfunction In Patients With Severe Sepsis and/or Septic Shock. Critical Care 2012;16:R34
- Fluid type study

- Resuscitation phase study

- Study population did not match criteria

Oliveira et al. Early and Late Positive Fluid Balance In Sepsis: Are They Both Related To Mortality and Acute Kidney Injury? Critical Care Medicine 2011;12(S1):56
- Duplicate / overlap

Oliveira et al. Early and Late Positive Fluid Balance In Sepsis: Are They Both Related To Mortality and Acute Kidney Injury? Critical Care Medicine 2011;12(S1):56
- Duplicate / overlap
Olupot-Olupot. Fluid Expansion As Supportive Therapy (Feast) Trial: Mortality After Fluid Bolus In African Children. Tropical Medicine and International Health 2012;17:43


Ozuzun et al. Early Fluid Resuscitation of End Stage Renal Disease Patients With Severe Sepsis and Septic Shock. Critical Care Medicine 2014;42(12):923


Patolia et al. Predicting Clinical Deterioration In Severe Sepsis Patients With Cryptic Shock. Intensive Care Medicine 2014;40(S1):1025


Perner et al. Long-Term Outcomes In Patients With Severe Sepsis Randomised To Resuscitation With Hydroxyethyl Starch 130/0.42 Or Ringer's Acetate. Intensive Care Medicine 2014;40:927-934


Puskarich et al. One Year Mortality of Patients Treated With An Emergency Department Based Early Goal Directed Therapy Protocol For Severe Sepsis and Septic Shock: A Before and After Study. Critical Care 2009;13:R167

Raimundo et al. Impact of Fluid Balance In The Outcome of Septic Critically Ill Patients. Intensive Care Medicine 2012;38(S1):0696


• Not original study

• Fluid type study

• Resuscitation phase study

• Study population did not match criteria

• Resuscitation phase study

• Study population did not match criteria

• Study population did not match criteria

• Duplicate / overlap

• Resuscitation phase study

• Fluid type study

• Fluid type study

• Resuscitation phase study

• Resuscitation phase study

• Complex haemodynamic intervention

• Duplicate / overlap

• Pre-1980
Reddy et al. Furosemide Infusion In Children With Dengue Fever and Hypoxemia. Indian Pediatrics 2014;51:303-305

Richard et al. Preload-Dependence Indices To Titrate Volume Expansion During Septic Shock: A Randomized Controlled Trial. Intensive Care Medicine 2014;40(S1):0881

Richard et al. Preload-Dependence Indices To Titrate Volume Expansion During Septic Shock: A Randomized Controlled Trial. Intensive Care Medicine 2014;40(S1):0881


Rinka et al. Fluid Therapy In Patients With Severe Sepsis After The Earliest Phases of Treatment. Critical Care Medicine 2009: 37(12):913

Rinka et al. Fluid Therapy In Patients With Severe Sepsis After The Earliest Phases of Treatment. Critical Care Medicine 2009;37(12 S1): 913


Sabater et al. Diuretics In Septic Acute Renal Failure Needing Continuous Renal Replacement Therapies. Intensive Care Medicine 2011;37(S1):0977


Sammani et al. Positive Fluid Balance Is A Risk Factor For Acute Kidney Injury In Critically Ill Patients. Critical Care Medicine 2014;42(12 S1):928

• Fluid type study

• Fluid balance not reported

• Duplicate / overlap

• Duplicate / overlap

• Resuscitation phase study

• Observational study with n<50

• Fluid balance not reported

• Duplicate / overlap

• Resuscitation phase study

• Complex haemodynamic intervention

• Fluid balance not reported

• Resuscitation phase study

• Resuscitation phase study

• Resuscitation phase study

• Duplicate / overlap

• Resuscitation phase study

• Duplicate / overlap

• Duplicate / overlap

• Study population did not match criteria

Santhanam et al. A Prospective Randomized Controlled Study of Two Fluid Regimens In The Initial Management of Septic Shock In The Emergency Department. Pediatric Emergency Care 2008;24:647-655

Schwab et al. Standard Operating Procedure In Patients With Severe Sepsis and Septic Shock. Critical Care 2009;13(S1):P343


Silversides et al. Fluid Balance and Renal Outcomes In Patients Requiring Renal Replacement Therapy In The ICU. Critical Care 2013;17(S2):P434


Smith and Perner. Lower Mortality With Higher Fluid Volume In Patients With Persisting Septic Shock. Critical Care 2011;37(S1):905

Smith et al. Higher Vs. Lower Fluid Volume For Septic Shock: Clinical Characteristics and Outcome In Unselected Patients In A Prospective, Multicenter Cohort. Critical Care 2012;16:R76


Sun et al. The Clinical Application of Pulse Indicator Continuous Cardiac Output Monitoring In Early Fluid Resuscitation For Patients With Severe Acute Pancreatitis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014;26:571-575


Uchino et al. Pulmonary Artery Catheter Versus Pulse Contour Analysis: A Prospective Epidemiological Study. Critical Care 2006;10:R174

Vaara et al. 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. Critical Care 2012;16:R197


Yu et al. Comparison of The Effect of Fluid Resuscitation As Guided Either By Lactate Clearance Rate Or By Central Venous Oxygen Saturation In Patients With Sepsis. Chinese Critical Care Medicine 2013;25(10):578-583

Yu et al. Comparison of The Effect of Fluid Resuscitation As Guided Either By Lactate Clearance Rate Or By Central Venous Oxygen Saturation In Patients With Sepsis. Chinese Critical Care Medicine 2013;25(10):578-583


Zhang et al. Effectiveness of Treatment Based On PICCO Parameters In Critically Ill Patients With Septic Shock and/Or Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. Intensive Care Medicine 2015;41:444-451


- Fluid type study
- Observational study with n<50
- Fluid type study