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

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Abstract

Background: It is unknown whether a conservative approach to fluid administration or deresuscitation (active removal of fluid using diuretics or renal replacement therapy (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, I^2=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, I^2=9%) and reduced length of ICU stay (mean difference -1.88 days, 95% CI -0.12 to -3.64 days, I^2=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, I^2=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], I^2=9%). In addition, studies by Hu et al [21] and Wang et al [22] reported shorter duration of mechanical ventilation in a more conservative fluid strategy group compared with the liberal fluid strategy group (10.13 +/- 3.02 days vs. 12.64 +/- 2.89, P<0.05 and 9.62 +/- 2.55 days vs 12.51 +/-2.92 days, P<0.05 respectively).

Length of ICU stay
Nine studies reported the duration of ICU admission of which seven were suitable for meta-analysis (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 (I^2=75%). Two studies in ARDS patients reported a composite outcome of ICU-free days: Martin et al [18] reported a numerically greater number of ICU-free days in the fluid conservative group (median 1.5 days greater, 95% CI -3.4 to +6.4 days), while in the Fluids and Catheter Treatment Trial (FACTT) [16], a conservative strategy resulted in a significantly greater number of ICU-free days compared to a liberal strategy (13.4 +/- 8.97 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, I^2=27%) (Appendix 3.5). Zhang et al [23] reported fewer days free of continuous RRT in the conservative fluid strategy group (median 15.5 days [IQR 3-28] versus 21 [4-28], P<0.05).

Cognitive function
In a cohort of 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.

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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

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

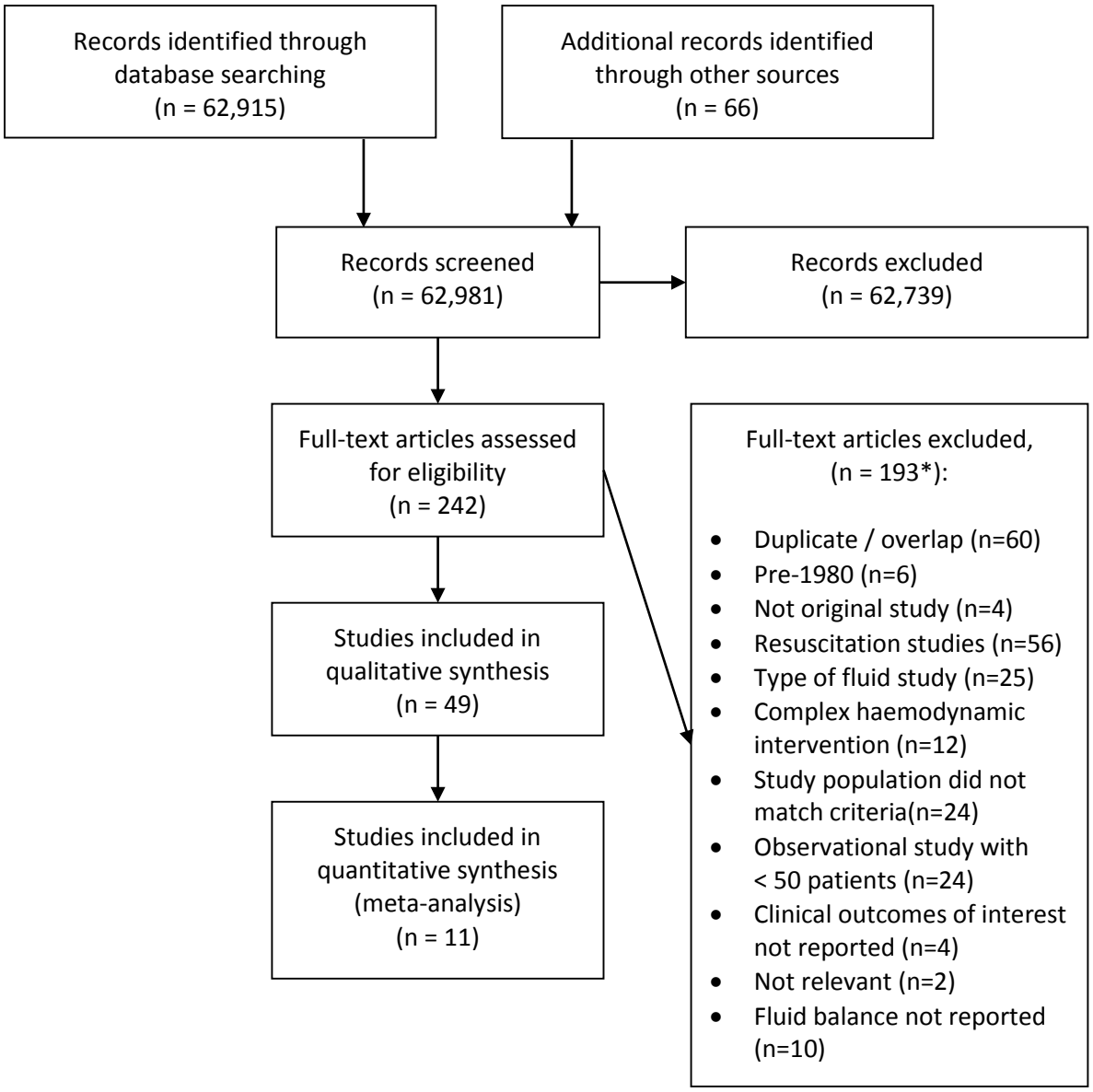


Figure 2. Risk of bias assessment for randomised trials.

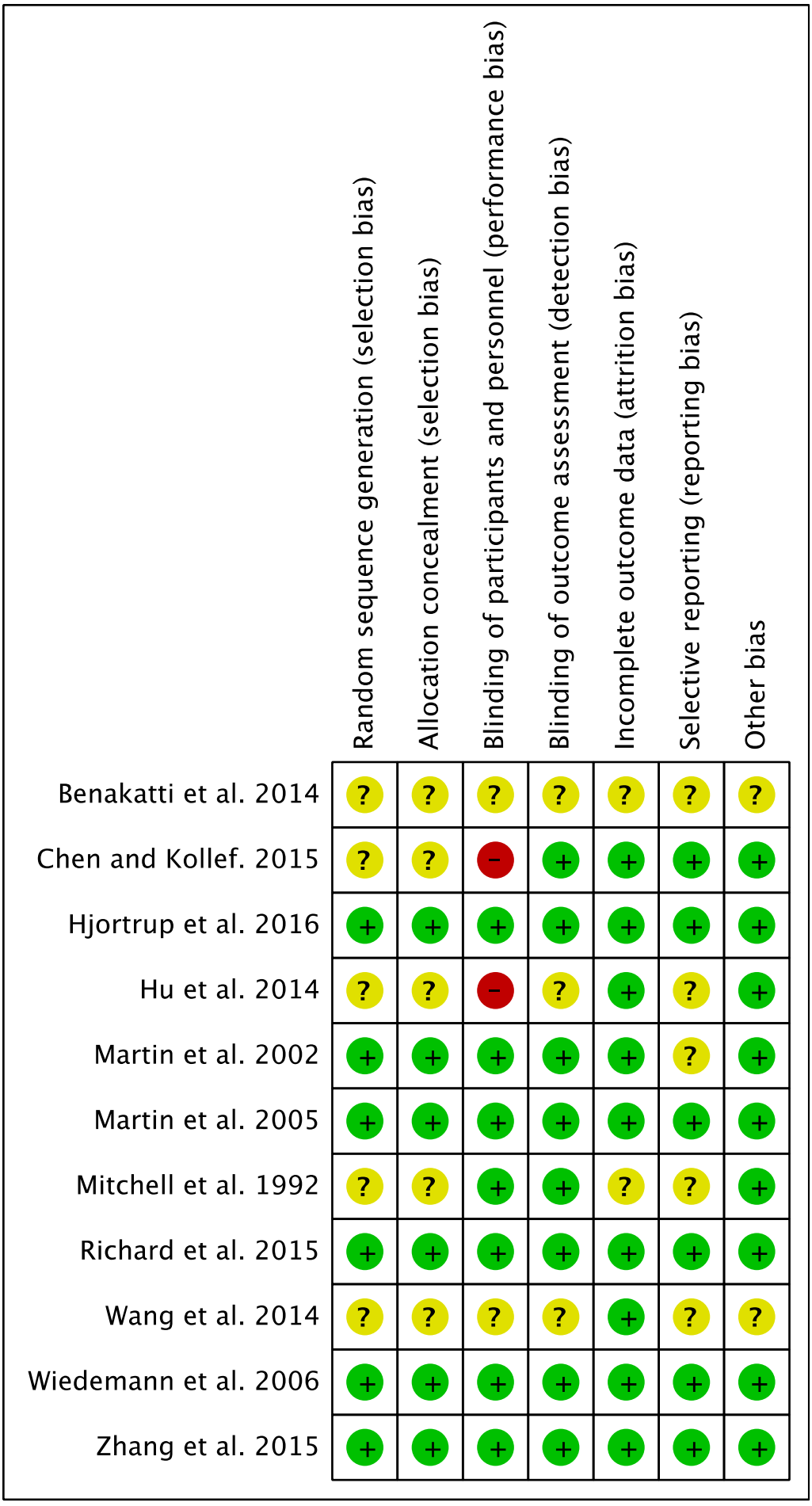


Figure 3. Forest plot for mortality at most protracted time point available, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy.

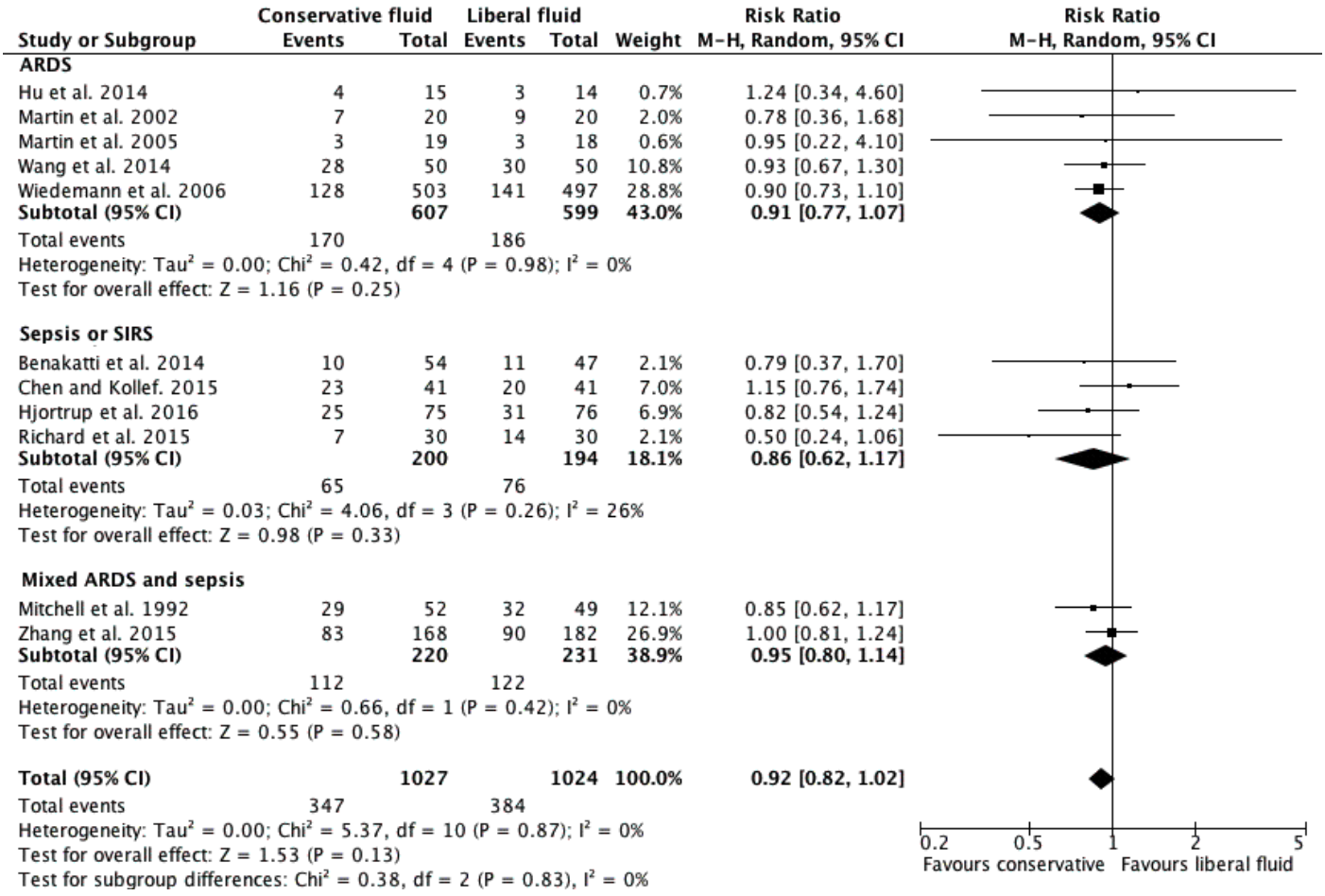


Figure 4. Forest plot for outcome of ventilator-free days.

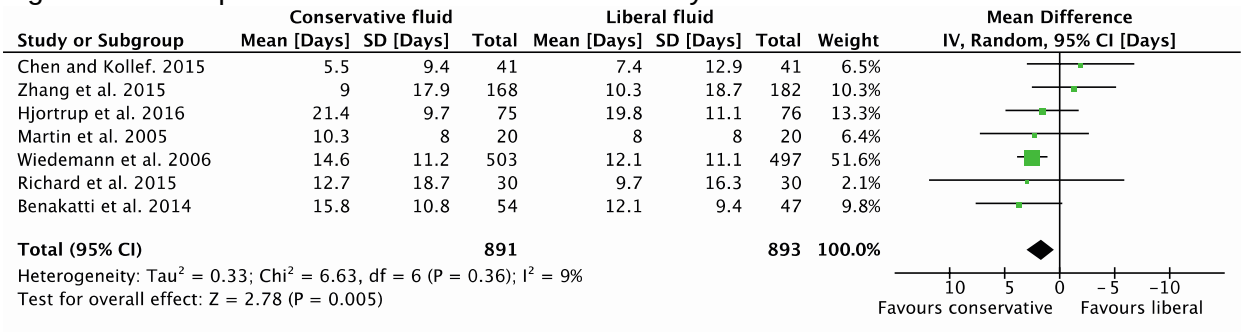
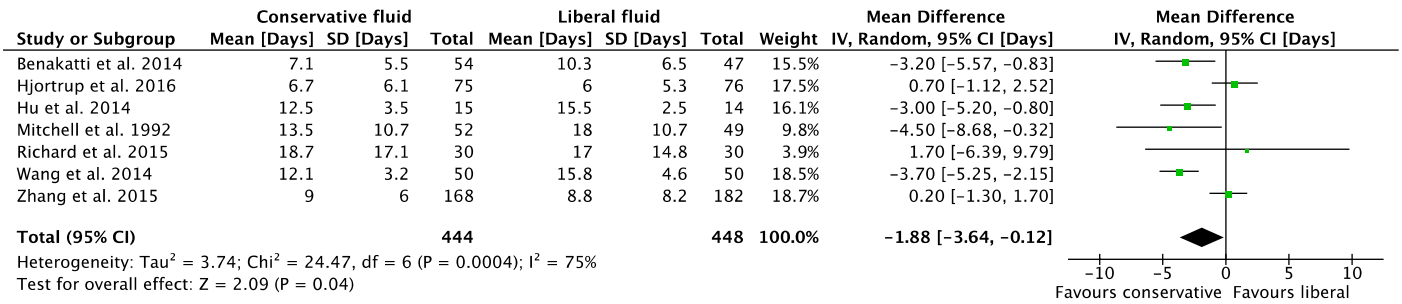


Figure 5. Forest plot for ICU length of stay, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strategy.



Author and publication year	Methods and Setting	Participants	Summary of conservative or deresuscitative fluid strategy	Summary of liberal fluid strategy or usual care	Key Outcomes
Mitchell et al, 1992	RCT Single academic centre in United States	n=101 Inclusion criteria: -Admitted to medical ICU -Pulmonary artery catheter inserted Exclusion criteria: -Technical reasons -Logistical reasons -Allergy to iodine dye -Pregnancy or lactation	-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	-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	-ICU mortality -Hospital mortality -Duration of mechanical ventilation -Length of ICU stay
Martin et al, 2002	RCT Two academic centres in United States	n=37 Inclusion criteria: -ARDS -Serum total protein ≤ 5g/dL -Ongoing nutritional support -Mechanical ventilation ≥ 48 hours Exclusion criteria: -Haemodynamic instability -Renal disease -Hepatic failure or cirrhosis -Age <8 or >80 years -Pregnancy -Serum sodium >150 mmol/L or potassium <2.5 mmol/L	-Furosemide infusion titrated to weight loss of ≥ 1 kg/day, and 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	-Dual placebo -Mean weight loss of 4.7 kg after 5 days* -Mean daily fluid balance over study period: -22.4 ml/kg/day	-30 day mortality -ICU-free days -Ventilator-free days -Length of hospital stay
Martin et al,	RCT	n=40	-Furosemide 20mg IV bolus	-Furosemide 20mg IV bolus	-30 day mortality

2005	Two academic centres in United States	Inclusion criteria: -ARDS -Serum total protein < 6 g/dL Exclusion criteria: -Haemodynamic instability -Renal disease or cirrhosis -Age < 18 years -Pregnancy -Serum sodium > 155 mmol/L or potassium < 2.5 mmol/L	followed by infusion, and 25g IV albumin 8 hourly for 3 days -Mean net fluid balance after 3 days was -5480 ml* -Mean daily fluid balance over study period: -15.7 ml/kg/day	followed by infusion, with 0.9% saline placebo for 3 days. -Mean net fluid balance at 3 days was -1490 ml* -Mean daily fluid balance over study period: -4.3 ml/kg/day	-Ventilator-free days -Change in SOFA scores
Wiedemann et al, 2006	RCT Multiple community and academic ICUs in United States and Canada	n=1000 Inclusion criteria: -ARDS -Intubated and mechanically ventilated -Presence or intention to insert a central venous catheter Exclusion criteria: -Presence of ALI/ARDS for > 48 hours -Severe chronic illness likely to independently influence survival -Irreversible terminal illness	-Complex algorithm with fluid boluses or diuretics administered as directed by filling pressures (CVP or PCWP). -41% of protocol instructions involved administration of furosemide, 6% involved fluid boluses -At 7 days, net fluid balance was -136 ml +/- 11012 ml* -Mean daily fluid balance over study period: -0.3 ml/kg/day	-Complex algorithm with fluid boluses or diuretics administered as directed to target higher filling pressures (CVP or PCWP) than in conservative group. -10% of protocol instructions involved administration of furosemide, 15% involved fluid boluses -At 7 days, net fluid balance was 6992 ml +/- 11191 ml* -Mean daily fluid balance over study period: 14.3 ml/kg/day	-60-day mortality -Ventilator-free days -ICU-free days -Renal failure-free days -RRT use -CNS failure-free days
Hu et al, 2014	RCT Single centre in China	n=29 Inclusion criteria: -ALI/ARDS (AECC criteria) -Admitted to ICU	-Extravascular lung water target value set at 3-7 ml/kg, using diuretics or CRRT -Fluid administration not	-Pulmonary artery occlusion pressure target of 8-12 mmHg, using diuretics or CRRT -Fluid administration not protocolised	-60 day mortality -Duration of mechanical ventilation -Length of ICU stay

		Exclusion criteria: -Pre-existing comorbidities including pulmonary hypertension, pneumonectomy, and interstitial lung disease	protocolised -Mean fluid balance at 7 days was -783 ml +/- 391ml -Estiamted mean daily fluid balance over study period: -1.6 ml/kg/day	-Mean fluid balance at 7 days was -256 ml +/- 514 ml -Estimated mean daily fluid balance over study period: -0.5 ml/kg/day	
Benakatti et al, 2014	RCT Single centre in India	n=101 Inclusion criteria: -Children aged 3-144 months -Septic shock following fluid resuscitation Exclusion criteria: -None reported	-Maintenance fluid administered at 80% of calculated required rate -At 10 days, mean net fluid balance was -42.6 ml/kg +/- 82.6 ml/kg* -Mean daily fluid balance over study period: -33.9 ml/kg/day	-Regimen not clearly reported -At 10 days, net fluid balance was 339 ml/kg +/- 117 ml/kg* -Mean daily fluid balance over study period: -4.26 ml/kg/day	-28 day mortality -Ventilator-free days -Length of ICU stay
Wang et al, 2014	RCT Single centre in China	n=100 Inclusion criteria: -ARDS (AECC definition) Exclusion criteria: -Age < 13 years -Contraindication to central venous catheter -ARDS criteria met for > 48 hours pre-enrollment -Myocardial infarction in last 30 days -History of COPD or neuromuscular disorder affecting respiration	-Extravascular lung water index target of 3-7ml/kg. Regimen used not clearly reported -At 7 days, mean net fluid balance was -9.6 ml* -Estiamted mean daily fluid balance over study period: -0.02 ml/kg/day	-Regimen used not clearly reported -At 7 days, mean net fluid balance was 7083.6 ml* -Estiamted mean daily fluid balance over study period: 14.5 ml/kg/day	-60 day mortality -Duration of mechanical ventilation -Length of ICU stay -Cognitive function domain of QLQ-C30 quality of life score
Chen and Kollef, 2015	RCT	n=82	-Targeted fluid minimisation comprising: fluid-responsiveness	-Usual care	-Hospital mortality -Ventilator-free days

	Single academic centre in United States	Inclusion criteria: -Hypotension due to septic shock -Requirement for ≥ 12 hours of vasoactive drugs to treat hypotension after fluid resuscitation ≥ 30 ml/kg IV fluid Exclusion criteria: -Age <18 years -Pre-existing end stage renal disease -Pregnancy -Comfort-only goals of care	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	-At 5 days, median net fluid balance was 3616 ml (IQR -1513-9746 ml) -Estiamted mean daily fluid balance over study period: 10.3 ml/kg/day	-RRT use
Zhang et al, 2015	RCT Two tertiary centres in China	n=350 Inclusion criteria: -Septic shock or ARDS (Berlin definition) -<24hours since ICU admission Exclusion criteria: -Age <18 years - Haemorrhagic shock - Moribund state - Absence of informed consent - Contra-indication to catheter insertion - Conditions likely to render PiCCO innaccurate	-Fluid boluses targeted to intrathoracic blood volume index (ITBVI) 850-1000 ml/m^2 -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	-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	-Fluid boluses targeted to CVP ≥8 mmHg for duration of shock	-28 day mortality -Ventilator-free days

	Single centre in France	Inclusion criteria: -Age ≥ 18 years -Septic shock -Pre-enrollment fluid loading ≥ 25 ml/kg body weight -Onset of hypotension <12 hours pre-enrollment Exclusion criteria: -Pregnancy -Acute coronary syndrome or cardiogenic pulmonary oedema -Acute cerebral event <30 days -Cannulation contraindicated -Uncontrolled haemorrhage, need for immediate surgery -Trauma or burns > 20% BSA -Previous inclusion in RCT -Limitation of treatment -Absence of consent, legal protection order or lack of social security	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 -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	- Identical protocol for use of noradrenaline, dobutamine, and red blood cells -Median daily fluid balance for duration of shock was 1749 ml (IQR 146 to 2788 ml)* -Estimated mean daily fluid balance over study period: 3.2 ml/kg/day	-Length of ICU stay (survivors) -Number of days with SOFA ≥ 6
Hjortrup et al, 2016	RCT Nine centres in Denmark and Finland	N=151 Inclusion criteria: -Age ≥ 18 years -Treated in ICU -Sepsis with circulatory impairment -Fluid bolus administration ≥ 30 ml/kg ideal body weight	-Noradrenaline used to maintain mean arterial pressure ≥ 65 mmHg or appropriate target -250 to 500 ml crystalloid boluses could be administered only if evidence of hypoperfusion (lactate ≥ 4 mmol/L, mean arterial pressure <50mmHg, skin mottling beyond	-Noradrenaline used to maintain mean arterial pressure ≥ 65 mmHg or appropriate target -Crystalloid boluses could be administered provided evidence of fluid responsiveness present according to static or dynamic variables of clinician's choice	-90 day mortality -Ventilator-free days -Length of ICU stay -RRT use -Worsening AKI

		-Noradrenaline infusion used to mainatin blood pressure Exclusion criteria: -Receiving RRT (or deemed imminent) -Plasma potassium > 6 mmol/L within last 6 hours -Creatinine level > 350 µmol/L -FiO2 > 0.8 and positive end expiratory pressure > 10 cmH_2O -Life-threatening bleeding -Burns > 10% BSA -Lack of commitment to full life support -Consent unobtainable -Kidney or liver transplant during same admission -Previous enrollment in this trial	edge of kneecap, urine output ≤ 0.1 ml/kg ideal body weight within 2 hours of randomisation) -At 5 days, median fluid balance was 1752 ml (IQR 407 to 5114 ml) -Estimated mean daily fluid balance over study period: 5.4 ml/kg/day	-At 5 days, median fluid balance was 2680 ml (IQR -1153 to 3758 ml) -Estimated mean daily fluid balance over study period: 9.1 ml/kg/day	

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; **Ml:** Millilitres; **IV:** intravenous; **SOFA:** Sequential organ failure assessment; **CVP:** Central venous pressure; **ALI:** Acute lung injury; **AECC:** American-European Consensus Conference; **CRRT:** continuous renal replacement therapy; **PiCCO:** Pulse Index Continuous Cardiac Output; **QLQ-C30:** Quality of life questionnaire core-30; **COPD:** Chronic obstructive pulmonary disease; **ITBVI:** Intrathoracic blood volume index; **IQR:** Interquartile range; **PPV:** Pulse pressure variation; **BSA:** Body surface area; **FiO_2:** Fraction of Inspired Oxygen.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conservative or deresuscitative fluid strategy	Liberal fluid strategy or usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
11	randomised trials	serious [1]	not serious	very serious [2]	serious	none	337/973 (34.6%)	373/977 (38.2%)	RR 0.92 (0.82 to 1.03)	31 fewer per 1,000 (from 11 more to 69 fewer)	◯◯◯ VERY LOW	CRITICAL
Ventilator free days												
7	randomised trials	not serious	not serious	very serious [2]	not serious	none	891	893	-	MD 1.82 days more (0.53 more to 3.1 more)	◯◯ LOW	IMPORTANT
Intensive Care Unit (ICU) length of stay												
7	randomised trials	serious [3]	serious [4]	very serious [2]	not serious	none	444	448	-	MD 1.88 days fewer (0.12 fewer to 3.64 fewer)	◯◯◯ VERY LOW	IMPORTANT
Renal Replacement Therapy (RRT) use												
3	randomised trials	not serious	not serious	very serious [2]	serious [5]	none	83/619 (13.4%)	100/614 (16.3%)	RR 0.88 (0.64 to 1.22)	20 fewer per 1,000 (from 36 more to 59 fewer)	◯◯◯ VERY LOW	CRITICAL
Post-ICU Cognitive function (assessed with: QLQ-C30 congitive function domain; Scale from: 0 to 100, with higher scores denoting better cognitive function)												
1	randomised trials	very serious [6]	not serious	serious [7]	serious [5]	none	50	50	-	MD 10.71 Points higher (5.22 higher to 16.2 higher)	◯◯◯ VERY LOW	CRITICAL

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.

Author	Methods	Inclusion and exclusion criteria	Patient characteristics	Key outcomes	Key findings
Abulebda et al, 2014.	- Secondary analysis of multicentre prospective observational study of genomics in sepsis - USA	Inclusion: - Age ≤10 years -Septic shock - Enrolment in an ongoing genomic study Exclusion: -None reported	N=317 <u>Non-survivors:</u> -Median age 1.3 yrs. (IQR 0.2-4.5) -65% male -Median PRISM score 28 (IQR 17-37) <u>Survivors:</u> -Median age 2.9 (IQR 1.1-6.7) -59% male -Median PRISM score 12 (IQR 7-18)	-28 day mortality	- 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= <0.001
Acheampong & Vincent, 2015.	-Single centre prospective cohort study -Belgium	Inclusion: ->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 >48h Exclusion: -None reported	N=173 -Age 61yrs +/- 16 -68% male -SOFA score 8.2 +/- 3.4 -78% septic shock -60% medical, 17% elective surgery, 23% emergency surgery	-ICU mortality	-Daily fluid balance was greater in non-survivors than survivors (29 ± 22 vs. 13 ± 19 ml/kg, p <0.001). -Positive fluid balance was independently associated with higher mortality (adjusted hazard ratio 1.014 per ml/kg, P<0.001) -Diuretics were used in 41% of non-survivors, 29% of survivors
Bhaskar et al,	-Retrospective	Inclusion:	N=114	-ICU mortality	-Independent risk factors for

2015.	cohort study - USA	- Shock states (majority sepsis or SIRS) - Age ≤ 18 years Exclusion: - PICU length of stay < 48 hours -Premature neonates -Post-operative congenital heart disease	-Median age 1.1 yrs. (Range 0-17.4) -59% male -Median Paediatric Index of Mortality 2 score 5.1 (Range 0.2-99.3) -Sepsis or septic shock 83%	-Duration of mechanical ventilation (survivors) -Renal replacement therapy use -Length of ICU stay	mortality included presence of fluid overload (≥10% body weight at 3 days) (adjusted OR 9.17, 95% CI 2.22-55.57); 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) - Compared with matched controls, cases with fluid overload ≥10% body weight at 3 days, had higher mortality (37% versus 3%, P=0.002); similar duration of mechanical ventilation (median 6 days versus 5 days, P=0.36), similar rates of RRT use (37% vs 13%, P=0.07) and similar length of ICU stay (median 9 days versus 8 days, P=0.73).
Bihari et al, 2013.	-Single centre prospective observational study investigating the prevalence and efficacy of fluid boluses after initial resuscitation in septic patients. -Tertiary centre in Australia	Inclusion: -Age > 18 years - Severe sepsis or septic shock -Within 2 hours of completing initial 6 hours of resuscitation Exclusion: -Expectation of death within 24 hours - Patients not undergoing active treatment -Patients with clinically obvious ongoing	N=50 -Median age 72.5 yrs. (61.0-82.8) -66% male (33) -Median APACHE 3 score 80 (IQR 68-93) -Median SOFA score 9 (IQR 6-11) -26% mechanically ventilated	- Change (Δ) in SOFA score	-Cumulative fluid balance was weakly correlated with Δ SOFA score at 48 and 72 hours (r=0.32, P=0.001)

		haemorrhage, GI or other fluid loss - Pregnancy			
Botdorf et al, 2015.	- Single centre retrospective cohort study - USA	Inclusion: -Suspected sepsis -ICU stay > 24hrs Exclusion: - None reported	N=162 -Median age 68 yrs. (IQR 58-79) -55% male -Median APACHE 4 score 83 (IQR 67-104)	-ICU mortality	- Net fluid balance at 48 hours was higher in non-survivors compared to survivors (median 8790 ml, IQR 4530 to 11400 vs median 5380 ml, IQR 2900 to 7820, p=0.023)
Boyd et al, 2011.	-Secondary analysis of a multicentre randomised controlled trial of vasopressin versus norepinephrine in 27 centres in Canada, Australia and USA	Inclusion: -Septic shock -Minimum of 5mcg/min noradrenaline infusion Exclusion: - Unstable coronary syndrome ->24 hours since enrolment criteria met -Estimated 6 month mortality >50% -Suspected or proven mesenteric ischaemia -Underlying chronic heart disease -Anticipation of imminent death or lack of commitment to aggressive care	N=778 Not reported for overall cohort	- 28-day mortality	- 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).

Chen et al, 2011.	-Single centre retrospective cohort study -China	Inclusion: -Septic shock (ACP/SCCM criteria) Exclusion: -Fluid bolus or vasopressor administration in another hospital	N=107 <u>Survivors (n=68):</u> -Age 66.7 years +/- 14.5 -78% male -APACHE score 14.7 +/-3.1 -SOFA score 6.5 +/- 1.5 <u>Non-survivors (n=39)</u> -Age 68.88 +/- 13.1 years -69% male -APACHE score 16.3 +/- 3.6 -SOFA score 7.2 +/- 1.5	-28 day mortality	-Absence of conservative late fluid management, negative fluid balance in first week < 2 litres, and total intake in first week > 20 litres were independent risk factors for mortality.
Cordemans et al, 2012.	-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	Inclusion: -Intubated and mechanically ventilated -ALI -Transpulmonary thermodilution catheter monitored Exclusion: - None reported	N=114 <u>Control Group (n=57):</u> -Age 61.4 +/- 16.8 -73.7% male -Medical ICU 87.7% -SAPS II 52.3 +/- 17.3 -APACHE II 22.7 +/- 11.1 <u>Treatment Group (n=57):</u> -Age 63.0 +/- 14.3 -66.7% male -Medical ICU 91.2%	-28-day mortality -ICU length of stay -Hospital length of stay -Duration of mechanical ventilation	- 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

			-SAPS II 47.9 +/- 18.4 -APACHE II 22.9 +/- 11.4		was significantly shorter in the PAL treated group (14.6 +/- 10.7 days vs 25.5 +/- 20.2, p = 0.02)
Cronhjort et al, 2016.	- Secondary analysis of a multicentre RCT of transfusion strategies in septic shock - Denmark, Norway, Sweden and Finland	Inclusion: - Adults with septic shock - Haemoglobin level < 90g/dL - ICU stay ≥ 3 days Exclusion: -Receipt of blood transfusion pre-enrollment -Life-threatening bleeding - Active myocardial ischaemia	N=841 <u>Quartile 1 (Lowest fluid balance):</u> - Age 63 +/-14 - 56.8% male - SOFA score 10.2 +/- 3.1 <u>Quartile 2:</u> - Age 66 +/- 12 - 59% male - SOFA score 9.7 +/- 3.1 <u>Quartile 3:</u> - Age 65 +/- 13 - 50.6% male - SOFA score 10.1 +/- 3.5 <u>Quartile 4 (Highest fluid balance):</u> - 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)	- 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<0.001)
De Oliveira et al, 2015.	-Retrospective analysis of a single centre prospective cohort study in an tertiary centre in Brazil	Inclusion: -Age > 18 years -Severe sepsis or septic shock Exclusion: -Pregnancy	N=116 - Median age 60 yrs. (IQR 44-74) - 63.5% male - Median APACHE 2 score 17 (IQR	- 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 > 3000ml was an independent risk factor for mortality (adjusted OR

		-Expectation of death within 24 hours	23-26)		3.19, 95% CI 1.19-8.54, p=0.021) - -Fluid balance was not associated with AKI
Fiorenza & Pass, 2013.	-Single centre retrospective cohort study -USA	Inclusion: -severe sepsis or septic shock in critical care unit - CVC in situ and CVP measured Exclusion: -None reported	N=78 Patient characteristics not reported	28-day mortality	- 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).
Flori et al, 2011.	-Post-hoc analysis of a prospective observational study in 2 centres -USA	Inclusion: -Children admitted to participating PICU during study period (1996-2000) -ALI Exclusion: -<36 weeks corrected gestational age or >18 years -Evidence of left atrial hypertension clinically or by echo - Echocardiographic evidence of intra-cardiac shunt -Exchange transfusions -ECMO -CRRT	N=320 -Median age 3.4 years (IQR 1d – 18yrs) -Male 56% -PRISM III score 10.3 +/- 8.7	-PICU mortality -Ventilator-free days	-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)

Grissom et al, 2015.	-Retrospective analysis of data from 4 large RCTs -Multicentre data, mainly from USA - 3-way comparison of outcomes using comparing a simplified conservative fluid management protocol (FACTT Lite) with conservative and liberal fluid regimens from FACTT trial [15]	Inclusion: -Enrolment in one of 4 randomised trials in ARDS – FACTT, EDEN, OMEGA and ALTA. - presence of CVC Exclusion: -Chronic dialysis dependence	N=2124 <u>FACTT Lite group:</u> -Age 51.5 yrs. +/- 0.5 -Male 52% -APACHE 3 score 91.0 +/-0.8 <u>FACTT conservative:</u> -Age 50.1 yrs. +/- 0.7 -Male 52% -APACHE 3 score 93.1 +/- 1.4 <u>FACTT liberal:</u> -Age 49.5 yrs. +/- 0.7 -55% male -APACHE 3 score 95.2 +/- 1.4	- 60 day mortality - Ventilator free days -ICU-free days -Acute kidney injury (increase in serum creatinine by ≥ 0.3 mg/dl or by ≥ 50%)	-Fluid balance at 7 days in the FACCT lite group was intermediate between the two arms of the FACCT trial [15] (1918 +/-323 ml versus -136 +/- 491 ml and 6992 +/-502ml). - 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 FACCT 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<0.001). -The number of ICU free days was similar between FACCT 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<0.001) - Acute kidney injury rates (adjusted for fluid balance) were similar between FACCT Lite and FACTT Conservative groups, but were lower in FACTT Lite compared to FACTT Liberal (56% vs 66%, p=<0.001)
Herrera Gutierrez et al, 2013.	-Single centre prospective cohort study -Spain	Inclusion: -Sepsis (undefined) Exclusion: -Unclear	N=129 -Age 56.8yrs +/- 16.7 -58.8% male -APACHE 2 score	-28 day mortality -Acute kidney injury (KDIGO) during ICU stay	-Increasing severity of AKI was associated with more positive fluid balance (as percentage of body weight) at day 3: 0.23% +/- 6.3 (KDIGO Stage 0), 6.65% +/- 2.15 (KDIGO Stage 1, P=0.08), 6.95% +/-

			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 (as % of total body weight) 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)
Kongsayreepong & Nitikaroon, 2013.	-Prospective single centre cohort study -Thailand	Inclusion: - Post noncardiac surgery - Age ≥ 18 years -Severe sepsis or septic shock Exclusion: -None reported	N=196 Patient characteristics not reported	-Acute kidney injury (Acute Kidney Injury Network score ≥ stage 1)	-Fluid overload was not an independent risk factor for AKI.
Koonrangsesomboon & Khwannimit, 2015.	-Single centre retrospective cohort study -Thailand	Inclusion: - Septic shock requring ICU Exclusion: - ICU length of stay < 24 hours	N=1048 - Median age 59 (IQR 44.75 – 73) - 58.3% Male - Median APACHE II score 27 (21-34.5) -Median SOFA score 10 (IQR 8-13)	- ICU mortality - Hospital mortality	- 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.
Micek et al, 2013.	- Single centre	Inclusion:	N=325	- Hospital mortality	- Non-survivors had a more positive

	retrospective cohort study - USA	-Septic shock -Transthoracic echocardiogram performed within 24 hours of onset of shock Exclusion: -Pre-existing non-sepsis related cardiovascular compromise -ECMO or VAD use - Shock onset at outside hospital prior to transfer	<u>Survivors:</u> -Age 58.5 yrs. +/- 14.6 - Male 46.3% -APACHE 2 score 21.7 +/- 6.3 <u>Non-survivors:</u> -Age 63.0 yrs. +/- 14.0 -male 44.8% -APACHE 2 score 25.1 +/- 6.7		fluid balance in the 8 days following shock onset (median 7742 ml [2914-15992] versus 3286.5 ml [1508.5 – 7467], P<0.001) - The quartile with the highest fluid balance had significantly higher mortality risk (P<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)
Murai et al, 2014.	- Multicentre retrospective cohort study - Japan	Inclusion: - ARDS - Mechanical ventilation - Transpulmonary thermodilution monitoring used Exclusion: - None reported	N=207 Patient characteristics not reported	- 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 >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)
Murphy et al, 2009.	-Retrospective cohort study - 2 academic centres in USA	Inclusion: -Septic shock - ALI (AECC definition) -Mechanical ventilation > 24 hrs. Exclusion: -Hospitalisation for	N=212 Survivors: - Age 58.5yrs +/- 15.8 - 62% male - APACHE 2 score 23.9 +/- 6.0 - SOFA score 9.5 +/- 2.5	- 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 < 0.001). -Absence of ‘conservative late fluid management’ (defined as even to negative fluid balance on ≥ 2 consecutive days) was an

		> 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 Exclusion: - None reported	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 Exclusion: - 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

					vs conservative fluid balance group (25.5% vs 14.3%, P not reported) -No significant difference in ICU length of stay between groups (10.7 +/- 8.8 vs 16.5 +/- 4.9 days, P not reported) -No significant difference in duration of mechanical ventilation between groups (9.2 +/- 8.1 vs 10.2 +/- 8.2 days, P not reported)
Rodriguez et al, 2013.	-Retrospective single centre cohort study -Spain	Inclusion: -Severe sepsis or septic shock Exclusion: -None reported	N=99 -Age 66.68 yrs. +/- 14 -APACHE 2 score 18.52 +/- 7 -58.6% male	-Mortality (time point undefined) -Duration of mechanical ventilation -ICU Length of stay	-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) -Longer duration of mechanical ventilation in positive fluid balance group (9.63 ± 3.10 vs 5.59 ± 9.56, p < 0.05) -No significant difference in length of ICU stay between groups (16.96 ± 15.38 vs 11.88 ± 12.72, p = 0.085).
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]	Inclusion: -ARDS or ALI (AECC definition) -Intubated and receiving mechanical ventilation in a participating centre -Fluid balance data available	N=794 <u>Survivors:</u> - Age 48yrs +/- 17 - 59% male -Acute physiology score (APS) 70 +/- 26 <u>Non-survivors:</u> - Age 59yrs +/- 16 - 61% male	- Hospital mortality	- 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). - 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<0.001)

		Exclusion: - >36 hours since inclusion criteria met - Pregnancy - <18 years - Participation in another clinical trial in <30 days - Physician refusal	- APS 82 +/- 26		
Saito et al, 2012.	-Retrospective cohort study evaluating outcomes before and after implementation of an 'optimal fluid management' strategy utilising PiCCO to guide fluid and diuretic use -Single centre -Japan	Inclusion: -Severe sepsis or septic shock requiring mechanical ventilation Exclusion: - None reported	N=96 - 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	- 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)
Simmons et al, 1987.	- Prospective cohort study - Single centre - USA	Inclusion: -ARDS defined as: -Acute respiratory failure with bilateral infiltrates requiring intubation and mechanical ventilation -PaO2/FiO2 ratio < 150mmHg within 72 hours	N=113 -Age 54.9yrs +/- 16.7 -67.3% male -54.9% medical ICU	- 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

		Exclusion: -Pulmonary arterial wedge pressure >18mmHg or not recorded within 24hours			
Smith & Perner, 2012.	- Prospective cohort study in 6 Danish ICUs (3 academic, 3 community)	Inclusion: - Admission to participating ICU during study period - Septic shock Exclusion: - None reported	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 - USA	Inclusion: -Children -ARDS Exclusion: -None reported	N=209 <u>AKI cohort:</u> - Age 86 months +/-73 - 56% male - PRISM 3 score 13 +/- 8 <u>Non-AKI cohort:</u> -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

Sun et al, 2015.	-Single centre retrospective cohort study -China	Inclusion: - Age >18 years - Sepsis - AKI requiring RRT Exclusion: - Cause of AKI other than sepsis - Duration of RRT <72 hours - Incomplete medical records - Unexpected death within follow-up period	N=117 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	- 60 day mortality	- Fluid overload (defined as positive fluid balance >10% body weight in 3 days prior to RRT initiation) was not independent risk factor for 60 day mortality (HR 1.47, 95% CI 0.78-2.76) - Negative fluid balance during RRT use (up to 7 days) was independently associated with lower risk of 60 day mortality (HR 0.44, 95% CI 0.24-0.82)
Udeozo et al, 2009.	-Retrospective cohort study of prospectively-collected database -Single centre in USA	Inclusion: -Septic shock Exclusion: -Refusal of consent -Readmissions to ICU	N=390 -Median age 68 yrs. (IQR 56 – 79) -54% male -Median APACHE 3 score 87 (IQR 67-105)	- Hospital mortality	- Non-survivors had a lower fluid balance at 12 hours, but a more positive fluid balance in the 24-72 hour period (median 7057 ml, 3249-31377 vs 4196 ml, IQR 348 – 24235, P=0.024, unadjusted analysis)
Valentine et al, 2012.	-Multi-centre (5 PICUs) retrospective cohort study -USA	Inclusion: -Age ≥ 1 month and < 18years -IPPV via ETT -ALI (AECC definition) Exclusion: -Chronic conditions that could	N=168 -Median age 3 years (IQR 0.8 – 11) -54% male -Median PRISM 3 score 9 (IQR 3-13)	-Mortality – time point not specified - Ventilator free days	-Comparison of study cohort with conservative and liberal fluid groups from FACTT trial[15]. -Secondary analysis comparing survivors and non-survivors in study cohort. - No significant differences in fluid balance between survivors and non-survivors

		independently impair weaning, especially lung or neuromuscular conditions -Cyanotic heart disease -Post-lung, renal or bone marrow transplant -Chronic renal failure -Burns > 40% BSA -Continuous RRT or ECMO			- A more positive fluid balance at day 3 was correlated with fewer VFDs (coefficient -0.02, p = 0.01 per ml/kg) - Total furosemide dose by day 3 was not associated with number of VFDs
Vincent et al, 2006. (sepsis) Sakr et al, 2005 (ARDS).	-Prospective multicentre cohort study -198 European ICUs	Inclusion: -All patients >15 years admitted to participating ICU -Sepsis cohort: presence of infection + SIRS criteria (ACP/SCCM) -ALI/ARDS cohort: AECC criteria Exclusion: -Re-admission to ICU -Routine post-operative admission <24 hours	<u>Sepsis cohort (N=1177):</u> -Median age 65yrs (IQR 51-74) -63% male -SAPS 2 score 42.3 +/- 16.6 -SOFA score 6.5 +/- 4.0 <u>ALI/ARDS cohort (N=393):</u> -Age 59 +/- 17 -60.5% male -SAPS 2 score 46.6 +/- 17.6 -Sepsis 47.5%	-ICU mortality	<u>Sepsis cohort:</u> -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<0.001) <u>ALI/ARDS cohort:</u> -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) -Mean daily fluid balance was an independent risk factor for ICU mortality (adjusted OR 1.5 per litre, 95% CI 1.1-1.9, p = 0.003)
Wang et al, 2016.	-Single centre retrospective cohort study -China	Inclusion: - Septic shock - Age ≥ 18 years - Use of PiCCO monitoring - CVP target of 8-	N=105 <u>Survivors:</u> - Age 66 +/- 17 - 64.6% male - APACHE II score	- 28 day mortality	- Fluid balance in the 24 hour and 24-48 hour periods post-initial resuscitiation both independently predicted 28-day mortality (adjusted OR 1.001 per ml, 95% CI 1.000-1.001, P=0.016 for 24 hours;

		12mmHg reached within 6 hours - Requirement for Norepinephrine ≥ 0.1 mcg/kg/min or Dopamine ≥ 5 mcg/kg/min - Survival time ≥ 72 hours following shock onset Exclusion: -Pregnancy or breast-feeding - Shock in the absence of infection - PiCCO used for <48 hours or absent data at ≥ 2 timepoints - Acute blood loss, acute myocardial infarction, pulmonary embolism - Treatment witheld or withdrawn during hopsital stay	21.8 +/-7.8 <u>Non-survivors:</u> - Age 65 +/- 18 - 63.3% male - APACHE II score 25.5 +/- 6.9		adjusted OR 1.001 per ml, 95% CI 1.000-1.002, P=0.08 for 24-48 hours).
Wilkowski et al, 1988.	-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

		evidence of pulmonary oedema Exclusion: -Cardiogenic pulmonary oedema -COPD -PE -Pneumonia without pulmonary oedema			-ICU mortality was higher in patients with a positive net fluid balance over the ICU stay (85.2% vs 66.7%, P<0.05)
Willson et al, 2015.	-Secondary analysis of a large multi-centre randomised controlled trial investigating surfactant vs placebo in paediatric ARDS -27 sites in 6 countries	Inclusion: -Age <18 years -ALI of direct aetiology -Enrolment in CARDS trial (surfactant vs placebo) within 48 hours of intubation Exclusion: -Indirect lung injury -Pre-existing lung disease -Limitations on level of support -Significant non-pulmonary organ dysfunction	N=109 -Age 6.1 years +/- 5.8 -51% male -PRISM 3 score 11.4 (+/- 6.8)	-Hospital mortality	-Cumulative fluid balance at 7 days was greater in non-survivors than survivors (11745 ml/m^2 [10817] versus 1234 ml/m^2 [2393], P<0.001)
Yao et al, 2014.	-Single centre retrospective cohort study -China	Inclusion: -Septic shock (ACCP/SCCM definition)	N=105 <u>Survivors (n=77):</u> -Median age 64 yrs. (46-74)	-Mortality (time point undefined)	-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)

		Exclusion: - Age<18 years - Pregnancy or lactation	-59.7% male -Median APACHE 2 score 15 (14-18) -Median SOFA score 7 (6-8) <u>Non-survivors (n=28):</u> -Median age 62 yrs. (47-74) -53.6% male -Median APACHE 2 score 19 (14-21) -Median SOFA score 9 (7-11)		
Zhang et al, 2012.	-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 -China	Inclusion: -Sepsis -Age 18-80 years - PiCCO system in use for haemodynamic monitoring Exclusion: -Acute kidney injury (AKIN Stage 2 or above) -Patients considered moribund or with DNAR order -Pre-existing renal dysfunction	N=67 -Age 59yrs +/- 16 -64.2% male -Median APACHE 2 score 23 (IQR 19-31) -46.3% mechanically ventilated	-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 -China	Inclusion: -Sepsis induced AKI admitted to ICU Exclusion: -Immune	N=160 <u>Negative fluid balance group</u>: -Age 51.1 yrs. +/- 18.4 -75.3% male	-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)

		compromise -End-stage chronic illness -Age < 12 or > 80 -Pregnancy or lactation -Learning disability or severe psychiatric illness -Terminal illness	-APACHE 2 score 17.9 +/- 6.1 <u>Positive fluid balance group</u>: -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

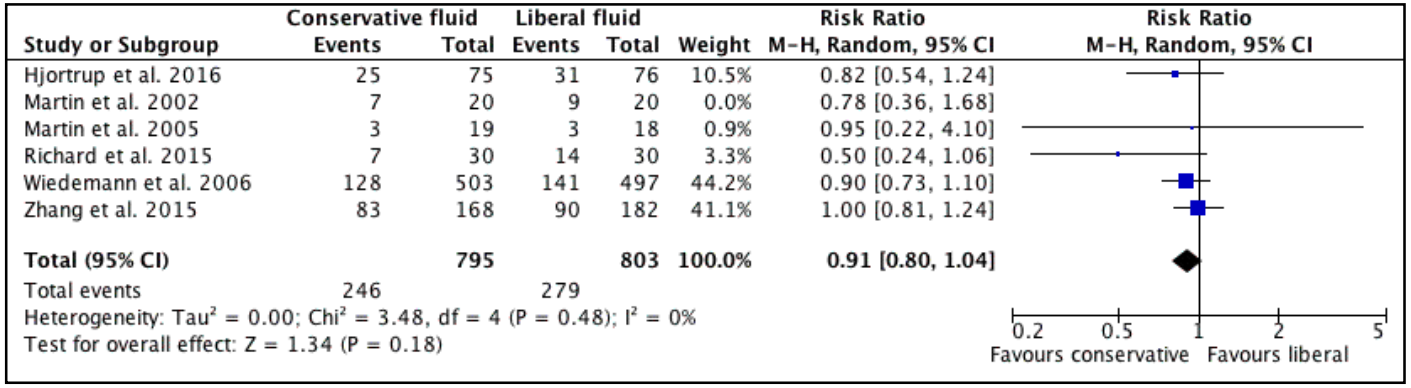
2) Was follow-up long enough for outcomes to occur
   a) yes
   b) no

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

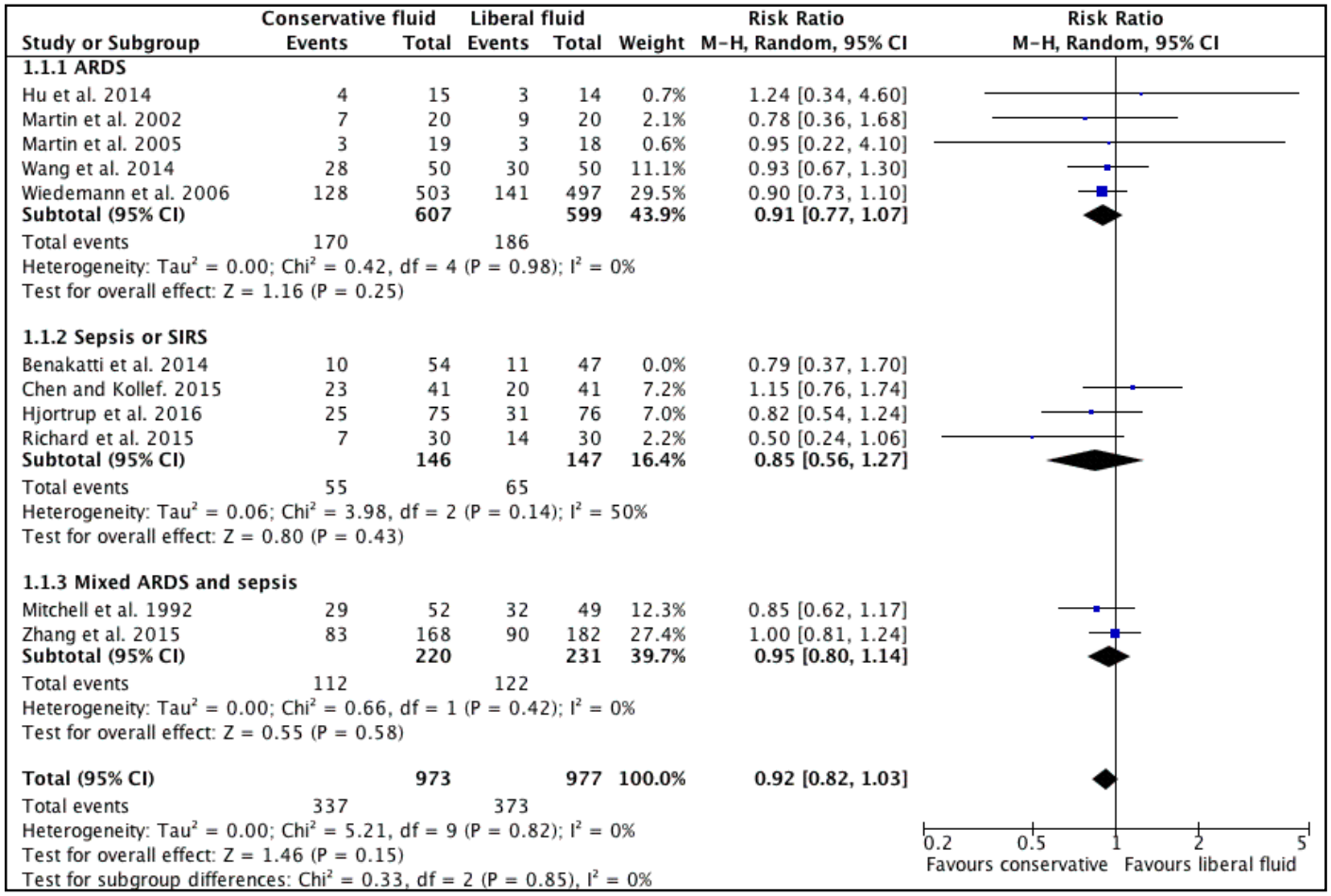
Newcastle-Ottawa scores for included observational studies

	Selection	Comparability	Outcome
Abulebda et al, 2014.	++++	-	+++
Acheampong & Vincent, 2015.	++++	+	+++
Bhaskar et al, 2015.	++++	++	+++
Bihari et al, 2013.	++++	++	++
Botdorf et al, 2015.	+++	-	+
Boyd et al, 2011.	++++	++	++
Chen et al, 2011.	+++	+	+
Cordemans et al, 2012.	++	++	+
Cronhjort et al, 2016.	++++	++	+++
De Oliveira et al, 2015.	++++	+	++
Fiorenza & Pass, 2013.	+++	-	+
Flori et al, 2011.	++++	+	+
Grissom et al, 2015.	+++	+	+++
Herrera Gutierrez et al, 2013.	++	++	++
Kongsayreepong & Nitikaroon, 2013.	+	++	+
Koonrangsesomboon & Khwannimit, 2015	++++	+	+++
Micek et al, 2013.	++++	+	++
Murai et al, 2014.	+++	-	+
Murphy et al, 2009.	++++	++	++
Perez-Fernandez et al, 2011.	+++	-	+
Raimundo et al, 2012.	+++	-	+
Rodriguez et al, 2013.	+++	-	+
Rosenberg et al, 2008.	++++	++	+++
Saito et al, 2012.	+	+	+
Simmons et al, 1987.	+++	-	++
Smith & Perner, 2012.	+++	-	+++
Spicer et al, 2014.	+	+	+
Sun et al, 2015.	+++	+	+++
Udeozo et al, 2009.	+++	-	+
Valentine et al, 2012.	++++	++	+
Vincent et al, 2006. (sepsis) Sakr et al , 2005. (ARDS)	++++ ++++	++ +	++ ++
Wang et al, 2016.	+++	+	++
Wilkowski et al, 1988.	++	-	+
Willson et al, 2015.	+++	-	+++
Yao et al, 2014.	+++	+	+
Zhang et al, 2012.	+++	++	++
Zhang et al, 2013.	+++	-	+

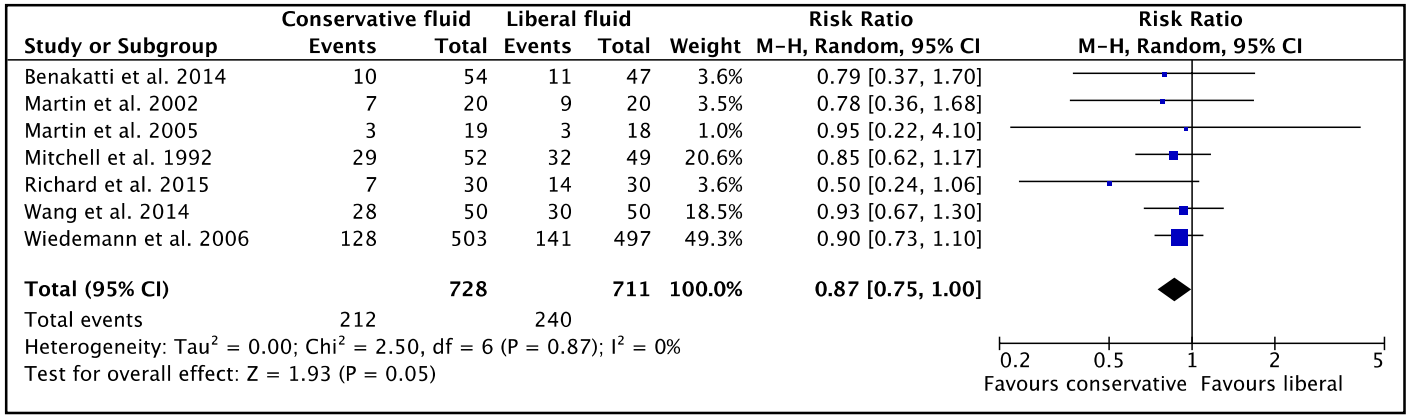
Appendix 3. Additional analyses.



3.1 Pre-planned sensitivity analysis excluding studies at high or moderate risk of bias with mortality as outcome.

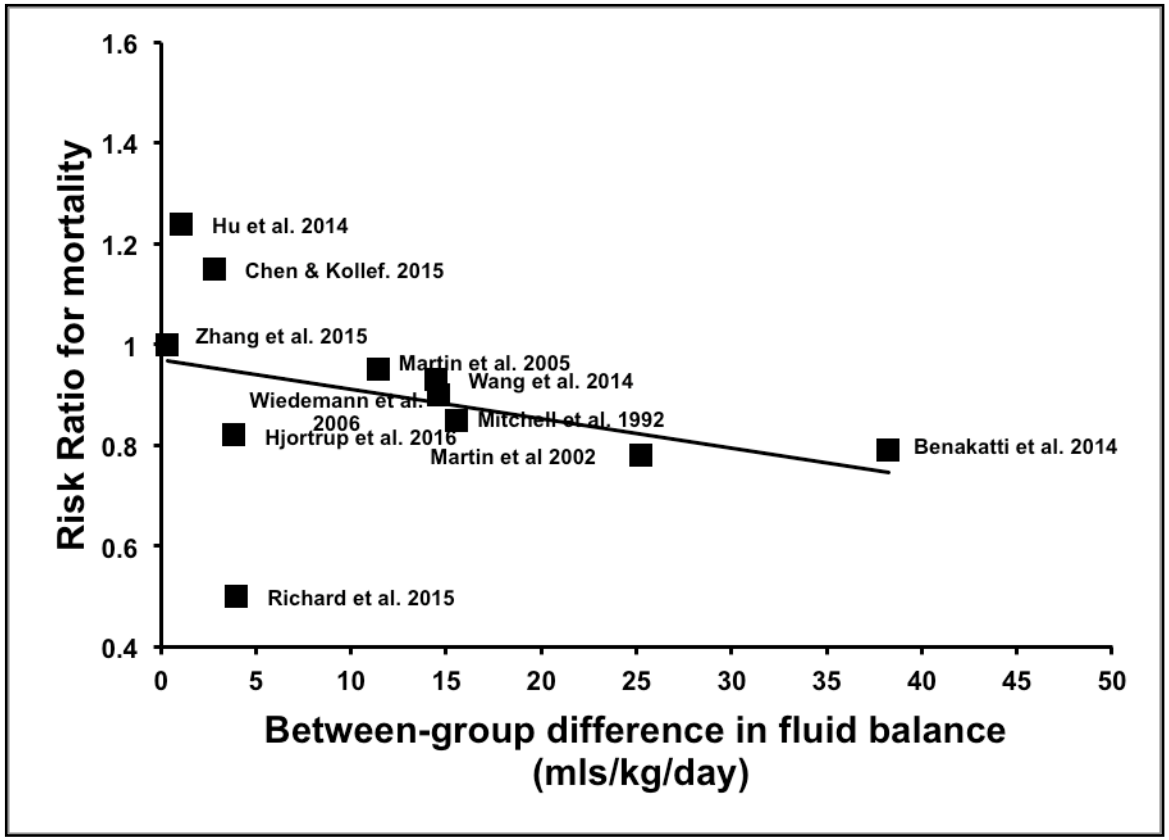


3.2 Pre-planned subgroup analysis including only adult studies with mortality as outcome.

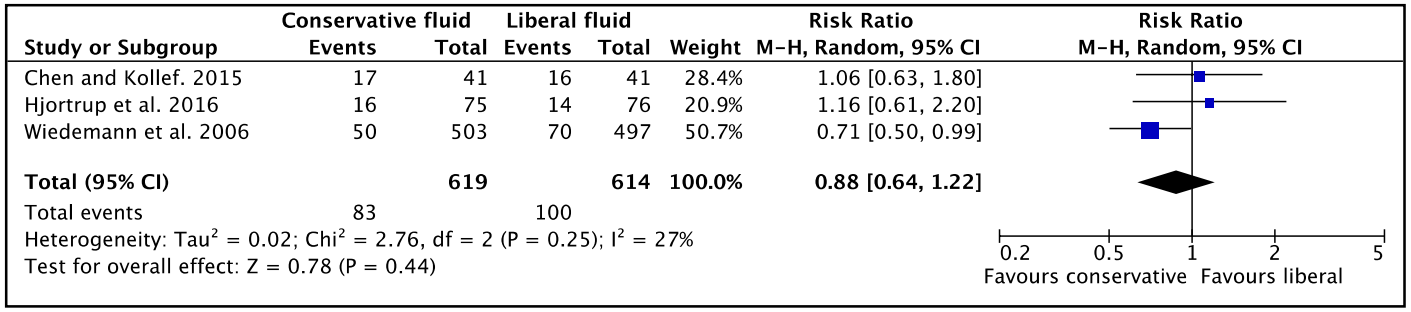


3.3 In a *post-hoc* sensitivity analysis in which we excluded studies lacking a clinically-important separation in fluid balance between groups, we found a non-significant reduction in mortality with a conservative or deresuscitative strategy compared to a liberal strategy or standard care.

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.



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 5. List of excluded studies

Aboelatta and Abdelsalam. Volume Overload of Fluid Resuscitation In Acutely Burned Patients Using Transpulmonary Thermodilution Technique. Journal of Burn Care and Research 2013;34:349-354	• Observational study with n<50
Acheampong and Vincent. Early Negative Fluid Balance Is Independently Associated With Improved Survival In Septic Patients. American Journal of Respiratory and Critical Care Medicine 2014;189;A5496	• Duplicate / overlap
Acheampong and Vincent. Early Negative Fluid Balance Is Independently Associated With Improved Survival In Septic Patients. American Journal of Respiratory and Critical Care Medicine 2014;189;A5496	• Duplicate / overlap
Acheampong and Vincent. A Positive Fluid Balance Is An Independent Prognostic Factor In Patients With Sepsis. Critical Care 2015;19:251	• Duplicate / overlap
Aharoni et al. Burn Resuscitation With A Low-Volume Plasma Regimen--Analysis of Mortality. Burns 1989;15:230-232	• Fluid type study
Almeida et al. Impact of Positive Fluid Balance On Survival In Critically Ill Cancer Patients. Critical Care 2010;14(S1): S524	• Duplicate / overlap
Alsous et al. Negative Fluid Balance Predicts Survival In Patients With Septic Shock: A Retrospective Pilot Study. Chest 2000;117:1749-1754	• 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
ARISE Investigators. Goal-Directed Resuscitation For Patients With Early Septic Shock. The New England Journal of Medicine 2014;371:1496-1506	• Resuscitation phase study • Complex haemodynamic intervention
Arlati et al. Decreased Fluid Volume To Reduce Organ Damage: A New Approach To Burn Shock Resuscitation? A Preliminary Study. Resuscitation 2007;72:371-378	• 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

Bachmann et al. Fluid Loading During Septic Shock. Remplissage Vasculaire Dans Les Etats De Chocs Septiques. Reanimation Soins Intensifs Medecine D'urgence 1989;5:334-336	• Not original study
Balakumar et al. Fluid Balance Has Variable Association With Long-Term Survival In the Critically Ill. Critical Care Medicine 2015;43(12 S1):244	• Study population did not match criteria
Bataller et al. Goal Directed Fluid Management In Resuscitated Sepsis: Evaluation of An Algorithm Based On Volumetric Parameters. European Journal of Anaesthesiology 2011;28:181	• Observational study with n<50
Bayer et al. Fluid Balance In Septic Patients Receiving Only Crystalloid Or Synthetic Fluids Plus Crystalloids. Intensive Care Medicine 2010;36:0926	• Observational study with n<50 • Fluid type study
Bayer et al. Effects of Fluid Resuscitation With Synthetic Colloids Or Crystalloids Alone On Shock Reversal, Fluid Balance, and Patient Outcomes In Patients With Severe Sepsis: A Prospective Sequential Analysis. Critical Care Medicine 2012; 40:2543-2551	• Fluid type study
Benakatti et al. Conventional Vs. Restrictive Maintenance Fluid Regime In Children With Septic Shock After Initial Resuscitation: A Randomized Open Label Controlled Trial. Archives of Disease In Childhood 2012;97:A5	• Duplicate / overlap
Bhaskar et al. Early Fluid Accumulation In Children With Shock and ICU Mortality: A Matched Case-Control Study. Intensive Care Medicine 2015;41:8	• Duplicate / overlap
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	• Duplicate / overlap
Bihari et al. Post Resuscitation Fluid Boluses In Severe Sepsis Or Septic Shock: Prevalence and Efficacy (PRICE Study). American Journal of Respiratory and Critical Care Medicine 2013;187:A3952	• Duplicate / overlap
Bocanegra et al. A Long-Term Study of Early Fluid Therapy In Severely Burned Adults. 3. Simultaneous Comparison of Saline Solution Alone Or Combined With Plasma. Jama : The Journal of The American Medical Association 1966;195:268-274	• Pre-1980 • Resuscitation phase study
Botdorf et al. Retrospective Analysis of Fluid Balance In The First 48 Hours of Sepsis and Outcome. American Journal of Respiratory and Critical Care Medicine 2015;191:A4497	• Duplicate / overlap
Boyd et al. Over-Resuscitation With Fluid In Septic Shock Decreases Survival and Increases Time On The Ventilator. American Journal of Respiratory and Critical Care Medicine 2010;181:A1137	• Duplicate / overlap
Boyd et al. Over-Resuscitation With Fluid In Septic Shock Decreases Survival and Increases Time On The Ventilator. American Journal of Respiratory and Critical Care Medicine 2010;181:A1137	• Duplicate / overlap

Carcillo et al. Role of Early Fluid Resuscitation In Pediatric Septic Shock. JAMA 1991;266:1242-1245	• Resuscitation phase study
Carlsen and Perner. Initial Fluid Resuscitation of Patients With Septic Shock In The ICU. Acta Anaesthesiologica Scandinavica, Suppement 2009; 53 (119):72	• Duplicate / overlap
Carlsen et al. Initial Fluid Resuscitation of Patients With Septic Shock In The Intensive Care Unit. Acta Anaesthesiologica Scandinavica 2011;55:394-400	• Resuscitation phase study
Chang et al. Volume of Fluids Administered During Resuscitation For Severe Sepsis and Septic Shock and The Development of The Acute Respiratory Distress Syndrome. Journal of Critical Care 2014;29:1011-1015	• Resuscitation phase study
Chen and Kollef. Fluid Balance In The ICU-Interventions To Minimize Fluids In Patients With Septic Shock. American Journal of Respiratory and Critical Care Medicine 2015;191:A5218	• Duplicate / overlap
Chen and Kollef. Targeted Fluid Minimization Following Initial Resuscitation In Septic Shock: A Pilot Study. Chest 2015; 148(6):1462-9	• Duplicate / overlap
Chen et al. The Impact of Different Fluid Management On Mortality In Patients With Septic Shock. Chinese Critical Care Medicine 2011;23:142-145	• 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	• Duplicate / overlap • Fluid type study
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. Intensive Care Medicine 2010;36(S2):97	• Duplicate / overlap • Fluid type study
Cordemans et al. Aiming For A Negative Fluid Balance In Patients With Acute Lung Injury and Increased Intra-Abdominal Pressure: A Pilot Study Looking At The Effects of PAL-Treatment. Annals of Intensive Care 2012;2 (S1):S15	• Duplicate / overlap • Fluid type study
Cordemans et al. Aiming For A Negative Fluid Balance In Patients With Acute Lung Injury and Increased Intraabdominal Pressure: A Pilot Study Looking At The Effects of PAL-Treatment. Annals of Intensive Care 2012;2(S1):S15	• Duplicate / overlap • Fluid type study
Crowe et al. Evaluation of A Modified Early Goal-Directed Therapy Protocol. American Journal of Emergency Medicine 2010;28:689-693	• Resuscitation phase study
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	• Study population did not match criteria
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	• Duplicate / overlap

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	• Duplicate / overlap
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	• Duplicate / overlap
De Almeida et al. Positive Fluid Balance Is Associated With Reduced Survival In Critically Ill Patients With Cancer. Acta Anaesthesiologica Scandinavica 2012;56:712-717	• Study population did not match criteria
De Oliveira et al. Positive Fluid Balance As A Prognostic Factor For Mortality and Acute Kidney Injury In Severe Sepsis and Septic Shock. Journal of Critical Care 2015;30(1):97-101	• Duplicate / overlap
Depaye et al. Impact of Fluid Resuscitation Volume On The Severity of Organ Failures In Severely Burned Patients. Critical Care 2012;16(S1):P461	• Resuscitation phase study
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	• Observational study with n<50
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	• Duplicate / overlap
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	• Resuscitation phase study
Early Goal-Directed Therapy Collaborative Group of Zhejiang. The Effect of Early Goal-Directed Therapy On Treatment of Critical Patients With Severe Sepsis/Septic Shock: A Multi-Center, Prospective, Randomized, Controlled Study. Chinese Critical Care Medicine 2010;22:331-334	• Resuscitation phase study
Eisenberg et al. A Prospective Study of Lung Water Measurements During Patient Management In An Intensive Care Unit. Am Rev Respir Dis 1987;136:662-668	• Fluid balance not reported • Study population did not match criteria
El-Akabawy et al. The Concept of Early Goal-Directed Therapy In Sepsis Syndrome. Intensive Care Medicine 2011;37(S1):0439	• Complex haemodynamic intervention • Resuscitation phase study
Finfer et al. A Comparison of Albumin and Saline For Fluid Resuscitation In The Intensive Care Unit. The New England Journal of Medicine 2004;350:2247-2256	• Fluid type study
Finfer et al. Impact of Albumin Compared To Saline On Organ Function and Mortality of Patients With Severe Sepsis. Intensive Care Medicine 2011;37:86-96	• Fluid type study • Duplicate / overlap
Flori et al. Positive Fluid Balance Is Associated With Higher Mortality and Prolonged Mechanical Ventilation In Pediatric Patients With Acute Lung Injury. Critical Care Research and Practice 2011:854142	• Duplicate / overlap

Garcia Olivares et al. Clinical Implication of Resuscitation With Fluids Guided By Central Venous Pressure In Septic Shock. Intensive Care Medicine 2010;36(S1):1349	• Resuscitation phase study
Gardner et al. Faster Rate of Initial Fluid Resuscitation In Severe Acute Pancreatitis Diminishes In-Hospital Mortality. Pancreatology 2009;9:770-779.	• Observational study with n<50
Gomez et al. Late Fluid Management and Risk of Respiratory Failure In Septic Patients. American Journal of Respiratory and Critical Care Medicine 2009:179:A4730	• Resuscitation phase study
Grams et al. Fluid Balance, Diuretic Use, and Mortality In Acute Kidney Injury. Clinical Journal of The American Society of Nephrology: CJASN 2011;6:966-973	• Duplicate / overlap
Grams et al. Fluid Balance, Diuretic Use, and Mortality In Acute Kidney Injury. Clinical Journal of The American Society of Nephrology: CJASN 2011;6:966-973	• Duplicate / overlap
Grissom et al. Retrospective Comparison of A Simpler Modified Fluid Conservative Protocol With The Original Factt Fluid Conservative Protocol In The ARDS Network. American Journal of Respiratory and Critical Care Medicine 2013;187:A4482	• Duplicate / overlap
Grissom et al. Retrospective Comparison of A Simpler Modified Fluid Conservative Protocol With The Original Factt Fluid Conservative Protocol In The ARDS Network. American Journal of Respiratory and Critical Care Medicine 2013;187:A4482	• Duplicate / overlap
Gu et al. Effect of Fluid Resuscitation On Extravascular Lung Water In Early Stage of Septic Shock. Chinese Critical Care Medicine 2007;19:283-286	• Resuscitation phase study • Observational study with n<50
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	• Fluid type study
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	• Fluid type study • Duplicate / overlap
Heung et al. Fluid Overload At Initiation of Renal Replacement Therapy Is Associated With Lack of Renal Recovery In Patients With Acute Kidney Injury. Nephrology Dialysis Transplantation 2012:27:956-961	• Study population did not match criteria
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	• Clinical outcomes of interest not reported
Hou et al. Positive Fluid Balance Worsens Clinical Outcomes For Hospitalized Pneumonia Patients. American Journal of Respiratory and Critical Care Medicine 2013;187:A5985	• Study population did not match criteria • Resuscitation phase study

Hu et al. Extravascular Lung Water and Pulmonary Arterial Wedge Pressure For Fluid Management In Patients With Acute Respiratory Distress Syndrome. Multidisciplinary Respiratory Medicine 2014;9(1):3	• Study population did not match criteria
Hunter et al. Fluid Creep In Colloid Resuscitated Burns Patients: Is Less More? Burns 2009;35:S14	• Clinical outcomes of interest not reported
Jacob et al. Severe Sepsis In Two Ugandan Hospitals: A Prospective Observational Study of Management and Outcomes In A Predominantly HIV-1 Infected Population. PLoS One 2009;4:E7782	• Resuscitation phase study
Jelenko et al. Shock and Resuscitation. Ii: Volume Repletion With Minimal Edema Using The HALFD(Hypertonic Albuminated Fluid Demand) Regimen. Jacep 1978;7:326-333.	• Pre-1980 • Fluid type study
Jelenko et al. Studies In Shock and Resuscitation, I: Use of A Hypertonic, Albumin-Containing, Fluid Demand Regimen (HALFD) In Resuscitation. Critical Care Medicine 1979;7:157-167	• Pre-1980 • Fluid type study
Jelenko et al. Shock and Resuscitation Ii: Volume Repletion With Minimal Edema Using The 'Halfd' Method. Journal of The American College of Emergency Physicians 1978;7:326-333	• Pre-1980 • Fluid type study
Jog et al. Stroke Volume Variation-Guide To Fluid Therapy In Septic Shock With ARDS. Intensive Care Medicine 2009; 35(S1):0098	• Observational study with n<50
Jog et al. Stroke Volume Variation Guided Fluid Therapy In Septic Shock With ARDS. Critical Care 2012;16(S1):P233	• Observational study with n<50
Jog et al. Stroke Volume Variation Guided Fluid Therapy In Severe Septic Shock: When To Stop Chasing High SVV? Intensive Care Medicine 2013;39(S2):0084	• Observational study with n<50
Jones et al. Prospective External Validation of The Clinical Effectiveness of An Emergency Department-Based Early Goal-Directed Therapy Protocol For Severe Sepsis and Septic Shock. Chest 2007;132:425-432	• Resuscitation phase study • Complex haemodynamic intervention
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	• Resuscitation phase study
Juneja et al. Use of Stroke Volume Variation To Guide Fluid Therapy In Septic Shock For Prevention of Acute Kidney Injury. Intensive Care Medicine 2009;35(S1):0104	• Fluid balance not reported
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	• Fluid balance not reported
Kanji et al. Limited Echocardiography-Guided Therapy In Subacute Shock Is Associated With Change In Management and Improved Outcomes. Journal of Critical Care 2014;29:700-705	• 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
Kaufman et al. Fluid Resuscitation In Circulatory Shock. Colloids Versus Crystalloids. Current Studies In Hematology & Blood Transfusion 1986:186-198	• Not original study
Kelm et al. The Potential Burdens of Fluid Overload In Patients With Septic Shock. American Journal of Respiratory and Critical Care Medicine 2013;187:A3063	• 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 Aute Need For Fluid-Related Medical Interventions and Hospital Death. Shock 2015;43(1):68-73	• 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;43:68-73	• Fluid balance not reported
Kiers et al. Early Goal-Directed Therapy of Septic Patients Coming From The Ward Does Not Protect The Kidneys. Critical Care 2009;13(S1):P259	• Resuscitation phase study
Kiers et al. Effect of Early Achievement of Physiologic Resuscitation Goals In Septic Patients Admitted From The Ward On The Kidneys. Journal of Critical Care 2010;25:563-569	• Duplicate / overlap • Resuscitation phase study
Kim et al. A Positive Fluid Balance and Used Loop Diuretics Amount Are Associated Increased Mortality In Intensive Care Unit. Intensive Care Medicine 2012;38(S1):0911	• Study population did not match criteria
Klein et al. The Association Between Fluid Administration and Outcome Following Major Burn: A Multicenter Study. Annals of Surgery 2007;245:622-628	• Resuscitation phase study
Koonrangsesomboon and Khwannimit. Positive Fluid Balance and Prognostic Factors of ICU Mortality In Patients Admitted With Septic Shock. Critical Care 2014;18(S2):P70	• Study population did not match criteria
Kraft et al. Outcomes of Optimized Fluid Resuscitation After Severe Burn Injury Utilizing Hemodynamic Measurements By Transpulmonary Thermodilution. Surgical Infections 2011;12:S16-S17	• Fluid balance not reported
Krausz et al. Cardiopulmonary Effects of Volume Loading In Patients In Septic Shock. Annals of Surgery 1977;185:429-434	• Resuscitation phase study • Observational study with n<50 • Pre-1980 • Clinical outcomes of interest not reported

Lau et al. Fluid Management For Shock In The First 24 Hours of Intensive Care Unit Stay: Impact of A Simple Clinical Protocol. Annals of The Academy of Medicine Singapore 2014;1:S319	• Resuscitation phase study
Lechliter and Shibli. Impact of Fluid Management Strategies In Patients With Acute Respiratory Distress Syndrome (ARDS). Chest 2009;136(S4):S77	• Observational study with n<50
Lee et al. Association Between Fluid Balance and Survival In Critically Ill Patients. Journal of Internal Medicine 2015;277(4):468-77	• Study population did not match criteria
Lee et al. Association Between Fluid Balance and Survival In Critically Ill Patients. Journal of Internal Medicine 2015;277(4):468-77	• Study population did not match criteria
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	• Resuscitation phase study
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	• Resuscitation phase study
Legrand et al. A Role of Renal Venous Congestion In Septic Acute Kidney Injury? Intensive Care Medicine 2011;37(S1):0968	• Fluid balance not reported
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	• Resuscitation phase study • Complex haemodynamic intervention
Liu et al. Acute Kidney Injury In Patients With Acute Lung Injury: Impact of Fluid Accumulation On Classification of Acute Kidney Injury and Associated Outcomes. Critical Care Medicine 2011; 39:2665-2671	• Duplicate / overlap
Lobo and Cunha. Time To Recover From Shock Is Determinant of A Positive Fluid Balance In Septic Shock. Critical Care 2013:17(S2):P238	• Observational study with n<50 patients.
Lobo and Cunha. Time To Recover From Shock Is Determinant of A Positive Fluid Balance In Septic Shock. Critical Care 2013; 17(S2):P238	• Duplicate / overlap
Lyu et al. Efficacies of Fluid Resuscitation As Guided By Lactate Clearance Rate and Central Venous Oxygen Saturation In Patients With Septic Shock. National Medical Journal of China 2015;95: 496-500	• Resuscitation phase study
Mahrous et al. Renal Effect of Colloid Versus Crystalloid In Septic Neutropenic Patients. Critical Care Medicine 2013;41(12 S1):996	• Fluid type study
Maitland et al. Mortality After Fluid Bolus In African Children With Severe Infection. The New England Journal of Medicine 2011;364:2483-2495	• Resuscitation phase study

Maitland et al. Exploring Mechanisms of Excess Mortality With Early Fluid Resuscitation: Insights From The FEAST Trial. BMC Medicine 2013;11:Pp	• Resuscitation phase study
Mao et al. Therapeutic Experience of Fulminant Acute Pancreatitis In Acute Response Stage. Chinese Journal of Surgery 2006;44:1185-1188	• Not relevant
Mao et al. Fluid Therapy For Severe Acute Pancreatitis In Acute Response Stage. Chinese Medical Journal 2009;122:169-173	• Resuscitation phase study
Martin. Fluid Balance and Colloid Osmotic Pressure In Acute Respiratory Failure: Emerging Clinical Evidence. Critical Care 2000;4:S21-S25	• Not original study
Mcintyre et al. Resuscitating Patients With Early Severe Sepsis: A Canadian Multicentre Observational Study. Canadian Journal of Anaesthesia 2007;54:790-798	• Resuscitation phase study
Mitchell et al. Volume Overload: Prevalence, Risk Factors, and Functional Outcome In Survivors of Septic Shock. Annals of The American Thoracic Society 2015;12(12):1837-44	• Clinical outcomes of interest not reported
Mitchell et al. Fluid Management of Sepsis After Shock Resolution: An Analysis of Intensive Care Unit Volume Status In Relation To Mobility On Hospital Discharge. American Journal of Respiratory and Critical Care Medicine 2013;187:A3951	• Duplicate / overlap
Mitchell et al. Fluid Management of Sepsis After Shock Resolution: An Analysis of Practice Variation and Risk Factors. American Journal of Respiratory and Critical Care Medicine 2012;185:A1124	• 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
Mouncey et al. Trial of Early, Goal-Directed Resuscitation For Septic Shock. New England Journal of Medicine 2015;372:1301-1311	• Complex haemodynamic intervention • Resuscitation phase study
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
Ngo et al. Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens In The First Hour. Clinical Infectious Diseases 2001; 32:204-213	• Resuscitation phase study
Nogueira et al. Positive Daily Fluid Balance As An Independent Predictor of Mortality In Critically Ill Patients. Intensive Care Medicine 2013;39(S2):0250	• 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	• Not original study
Orbegozo et al. Colloids For Fluid Resuscitation: What Is Their Role In Patients With Shock? Minerva Anestesiologica 2014;80:963-969	• Fluid type study
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	• Resuscitation phase study
Park et al. Early Cumulative Fluid Balance and Development of Acute Lung Injury. American Journal of Respiratory and Critical Care Medicine 2011;183:A5592	• Study population did not match criteria
Patolia et al. Predicting Clinical Deterioration In Severe Sepsis Patients With Cryptic Shock. Intensive Care Medicine 2014;40(S1):1025	• Resuscitation phase study
Payen et al. A Positive Fluid Balance Is Associated With A Worse Outcome In Patients With Acute Renal Failure. Critical Care 2008;12:R74	• Study population did not match criteria
Pereira et al. Impact of Fluid Balance To Organ Dysfunction In Critically Ill Patients. Critical Care 2016;20:P171	• Study population did not match criteria
Perez-Fernandez et al. Fluid Balance On Early Stages of Septic Shock Patients With Continuous Renal Replacement Techniques. Intensive Care Medicine 2011;37(S1):0970	• Duplicate / overlap
Permpikul et al. Impact of Septic Shock Hemodynamic Resuscitation Guidelines On Rapid Early Volume Replacement and Reduced Mortality. Journal of The Medical Association of Thailand 2010; 93 (S1):S102-S109	• Resuscitation phase study
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	• Fluid type study
Phillips et al. Crystalloids Vs. Colloids: Ko At The Twelfth Round? Critical Care 2013;17:319	• Fluid type study
Puffinbarger et al. Rapid Isotonic Fluid Resuscitation In Pediatric Thermal Injury. Journal of Pediatric Surgery 1994;29:339-342	• Resuscitation phase study
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	• Resuscitation phase study • Complex haemodynamic intervention
Raimundo et al. Impact of Fluid Balance In The Outcome of Septic Critically Ill Patients. Intensive Care Medicine 2012;38(S1):0696	• Duplicate / overlap
Recinos et al. Fluid Resuscitation of Burn Patients Comparing A Crystalloid With A Colloid Containing Solution: A Prospective Study. Journal of The Iowa Medical Society 1975;65:426-432	• Pre-1980

	• Fluid type study
Reddy et al. Furosemide Infusion In Children With Dengue Fever and Hypoxemia. Indian Pediatrics 2014;51:303-305	• Fluid balance not reported
Richard et al. Preload-Dependence Indices To Titrate Volume Expansion During Septic Shock: A Randomized Controlled Trial. Intensive Care Medicine 2014;40(S1):0881	• Duplicate / overlap
Richard et al. Preload-Dependence Indices To Titrate Volume Expansion During Septic Shock: A Randomized Controlled Trial. Intensive Care Medicine 2014;40(S1):0881	• Duplicate / overlap
Rinaldi et al. Effectiveness of Sepsis Bundle Application In Cirrhotic Patients With Septic Shock: A Single-Center Experience. Journal of Critical Care 2013;28:152-157	• Resuscitation phase study • Observational study with n<50
Rinka et al. Fluid Therapy In Patients With Severe Sepsis After The Earliest Phases of Treatment. Critical Care Medicine 2009: 37(12):913	• Fluid balance not reported
Rinka et al. Fluid Therapy In Patients With Severe Sepsis After The Earliest Phases of Treatment. Critical Care Medicine 2009;37(12 S1): 913	• Duplicate / overlap
Rivers et al. Early Goal-Directed Therapy In The Treatment of Severe Sepsis and Septic Shock. The New England Journal of Medicine 2001;345:1368-1377	• Resuscitation phase study • Complex haemodynamic intervention
Sabater et al. Diuretics In Septic Acute Renal Failure Needing Continuous Renal Replacement Therapies. Intensive Care Medicine 2011;37(S1):0977	• Fluid balance not reported
Sadaka et al. Fluid Resuscitation In Septic Shock: The Effect of Increasing Fluid Balance On Mortality. Critical Care Medicine 2012;40(12 S1):533	• Resuscitation phase study
Sadaka et al. Fluid Resuscitation In Septic Shock: The Effect of Increasing Fluid Balance On Mortality. Critical Care Medicine 2012;40(12 S1):533	• Resuscitation phase study
Sadaka et al. Fluid Resuscitation In Septic Shock: The Effect of Increasing Fluid Balance On Mortality. Journal of Intensive Care Medicine 2014;29:213-217.	• Duplicate / overlap • Resuscitation phase study
Saito et al. Implementation of An Optimal Fluid Management Protocol Using The PICCO System Delays Development of ARDS Secondary To Severe Sepsis. Critical Care 2012;16(S1):P243	• Duplicate / overlap
Sakr et al. High Tidal Volume and Positive Fluid Balance Are Associated With Worse Outcome In Acute Lung Injury. Chest 2005;128:3098-3108.	• Duplicate / overlap
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	• Study population did not match criteria

Samransamruajkit et al. A Comparison of NSS vs Balanced Salt Solution As A Fluid Resuscitation and Impact of Fluid Balance On Clinical Outcomes In Pediatric Septic Shock. American Journal of Respiratory and Critical Care Medicine 2015;191:A4072	• Observational study with n<50
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	• Fluid type study
Schwab et al. Standard Operating Procedure In Patients With Severe Sepsis and Septic Shock. Critical Care 2009;13(S1):P343	• Resuscitation phase study
Seymour et al. Prehospital Intravenous Access and Fluid Resuscitation In Severe Sepsis: An Observational Cohort Study. Critical Care 2014;18:533	• Resuscitation phase study
Shimazaki et al. Fluid Distribution and Pulmonary Dysfunction Following Burn Shock. Journal of Trauma-Injury Infection & Critical Care 1991;31:623-626	• Duplicate / overlap
Silversides et al. Fluid Balance and Renal Outcomes In Patients Requiring Renal Replacement Therapy In The ICU. Critical Care 2013;17(S2):P434	• Study population did not match criteria
Sirvent et al. Fluid Balance In Sepsis and Septic Shock As A Determining Factor of Mortality. American Journal of Emergency Medicine 2015;33:186-189	• Observational study with n<50
Sirvent et al. Fluid Balance In Sepsis and Septic Shock As A Determining Factor of Mortality. The American Journal of Emergency Medicine. 2015;33(2):186-9	• Observational study with n<50 • Duplicate / overlap
Sivayoham et al. Outcomes From Implementing Early Goal-Directed Therapy For Severe Sepsis and Septic Shock : A 4-Year Observational Cohort Study. European Journal of Emergency Medicine 2012;19:235-240	• Resuscitation phase study
Smith and Perner. Lower Mortality With Higher Fluid Volume In Patients With Persisting Septic Shock. Critical Care 2011:37(S1):905	• Duplicate / overlap
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	• Duplicate / overlap
Somasetia et al. Early Resuscitation of Dengue Shock Syndrome In Children With Hyperosmolar Sodium-Lactate: A Randomized Single-Blind Clinical Trial of Efficacy and Safety. Critical Care 2014;18:466	• Resuscitation phase study • Fluid type study
Sterling et al. The Effect of Early Quantitative Resuscitation On Organ Function In Survivors of Septic Shock. Journal of Critical Care 2015;30:261-263	• Resuscitation phase study

Stewart et al. Less Is More: Improved Outcomes In Surgical Patients With Conservative Fluid Administration and Central Venous Catheter Monitoring. Journal of The American College of Surgeons 2009; 208:725-735	• Duplicate / overlap
Stewart et al. Less Is More: Improved Outcomes In Surgical Patients With Conservative Fluid Administration and Central Venous Catheter Monitoring. Journal of The American College of Surgeons 2009;208:725-735	• Duplicate / overlap
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	• Observational study with n<50
Toy et al. Transfusion-Related Acute Lung Injury: Incidence and Risk Factors. Blood 2012;119:1757-1767	• Not relevant
Trof et al. Volume-Versus Pressure-Guided Hemodynamic Management In The Critically Ill Septic and Non-Septic Patient: Transpulmonary Thermodilution With PICCO Technology Versus Pulmonary Artery Catheter. Intensive Care Medicine 2010; 36(S1):1052	• Resuscitation phase study
Trof et al. Volume-Limited Versus Pressure-Limited Hemodynamic Management In Septic and Nonseptic Shock. Critical Care Medicine 2012;40:1177-1185	• Resuscitation phase study
Uchino et al. Pulmonary Artery Catheter Versus Pulse Contour Analysis: A Prospective Epidemiological Study. Critical Care 2006;10:R174	• Study population did not match criteria
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	• Study population did not match criteria
Valentine et al. Fluid Balance In Critically Ill Children With Acute Lung Injury Approximates The ARDSnet Fluid and Catheter Treatment Trial (Factt) Liberal Fluid Protocol and Is Associated With A Longer Duration of Mechanical Ventilation. American Journal of Respiratory and Critical Care Medicine 2011;183:A6280	• Duplicate / overlap
Van Biesen et al. Relationship Between Fluid Status and Its Management On Acute Renal Failure (Arf) In Intensive Care Unit (ICU) Patients With Sepsis: A Prospective Analysis. Journal of Nephrology 2005;18:54-60	• Fluid balance not reported
Van Genderen et al. Early Peripheral Perfusion Targeted Fluid Therapy Leads To Less Fluid Administration In Patients With Septic Shock: A Prospective Randomized Controlled Trial. Intensive Care Medicine 2014:40(S1):0452	• Resuscitation phase study
Van Der Voort et al. Testing A Conceptual Model On Early Opening of The Microcirculation In Severe Sepsis and Septic Shock: A Randomised Controlled Pilot Study. European Journal of Anaesthesiology 2015;32:189-198	• Complex haemodynamic intervention

Vladimir and Niksa . Delivery Dependent Oxygen Consumption In Patients With ARDS: Relationship Between Volume Loading and Outcome. Clinical Intensive Care 1992;3:42	• Observational study with n<50
Waechter et al. Early Administration of Crystalloid Fluids Reduces Mortality In Septic Shock. American Journal of Respiratory and Critical Care Medicine 2010;181:A4097	• Resuscitation phase study
Waechter et al. Interaction Between Fluids and Vasoactive Agents On Mortality In Septic Shock: A Multicenter, Observational Study. Critical Care Medicine 2014;42:2158-2168	• Resuscitation phase study
Warndorf et al. The Effect of Early Aggressive Fluid Resuscitation On Morbidity and Mortality In Acute Pancreatitis. Gastroenterology 2011;140(5):S13	• Study population did not match criteria
Wiedemann et al. Comparison of Two Fluid-Management Strategies In Acute Lung Injury. The New England Journal of Medicine 2006;354:2564-2575	• Duplicate / overlap
Williams et al. Implementation of Early Goal-Directed Therapy For Children With Suspected Sepsis: Minimizing Unnecessary Variation and Maximizing Benefit. Critical Care Medicine 2010;38(12 S1):62	• Resuscitation phase study
Yan. The Effect of Early Goal-Directed Therapy On Treatment of Critical Patients With Severe Sepsis/Septic Shock: A Multi-Center, Prospective, Randomized, Controlled Study. Chinese Critical Care Medicine 2010;22:331-334	• Complex haemodynamic intervention • Complex haemodynamic intervention • Resuscitation phase study
Yang et al. Effects of Early Goal-Directed Fluid Therapy on Intra-abdominal Hypertension and Multiple Organ Dysfunction in Patients with Severe Acute Pancreatitis. Chinese Journal of Surgery 2009;47:1450-1454	• Fluid type study
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	• Study population did not match criteria
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	• Study population did not match criteria
Zhang et al. Comparative Study On The Effect of Restrictive Fluid Management Strategy On The Early Pulmonary Function of Patients With Severe Burn. Chinese Journal of Burns 2012;28:165-169	• Observational study with n<50
Zhang et al. The Influence of Volume Load On Prognosis of Patients With Sepsis Induced Acute Kidney Injury. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2013;25:411-414	• Duplicate / overlap
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	• Duplicate / overlap

Zhao et al. Effects of Different Resuscitation Fluid On Severe Acute Pancreatitis. World Journal of Gastroenterology 2013;19:2044-2052	• Fluid type study
Zhi et al. Influence of Fluid Loading In Patients At Different Stages of Septic Shock: A Prospective Study. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2015;27:13-16	• Observational study with n<50
Zhu et al. The Study of Hypertonic Saline and Hydroxyethyl Starch Treating Severe Sepsis. Chinese Critical Care Medicine 2011;23:150-153	• Fluid type study