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Original article

Active fluid de-resuscitation in critically ill patients with septic shock: A systematic review and meta-analysis

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ABSTRACT

Purpose: To evaluate the impact of active fluid de-resuscitation on mortality in critically ill patients with septic shock.

Methods: A systematic search was performed on PubMed, EmBase, and the Cochrane Library databases. Trials investigating active fluid de-resuscitation and reporting data on mortality in patients with septic shock were eligible. The primary objective was the impact of active de-resuscitation in patients with septic shock on short-term mortality. Secondary outcomes were whether de-resuscitation lead to a fluid separation, and the impact of de-resuscitation on patient-centred outcomes.

Results: Thirteen trials (8,030 patients) were included in the systematic review, whereof 5 randomised-controlled trials (RCTs) were included in the meta-analysis. None of the RCTs showed a reduction in mortality with active de-resuscitation measures (relative risk (RR) 1.12 [95%-CI 0.84 – 1.48]). Fluid separation was achieved by two RCTs. Evidence from non-randomised trials suggests a mortality benefit with de-resuscitation strategies and indicates a trend towards a more negative fluid balance. Patient-centred outcomes were not influenced in the RCTs, and only one non-randomised trial revealed an impact on the duration of mechanical ventilation and renal replacement requirement (RRT).

Conclusion: We found no evidence for superiority of active fluid de-resuscitation compared to usual care regarding mortality, fluid balance or patient-centred outcomes in patients with septic shock. Current evidence is limited by the lack of high-quality RCTs in patients with septic shock, the small sample sizes and the heterogeneity of the applied de-resuscitation techniques. In addition, validity of the majority of RCTs is compromised by their inability to achieve fluid separation.

1. Background

Intravenous fluids therapy is one of the most commonly applied therapies in intensive care [1]. The amount of fluid administrated to critically ill patients may add up to several litres a day, thus making the critically ill patient especially prone to suffer from the effects of fluid overload (FO) [2,3]. While some of the fluid is administrated as resuscitation fluids with the aim of improving tissue perfusion, a considerable amount comes in the form of drug infusion, nutrition or as maintenance fluids [4,5]. However, the accumulation of fluids in the tissues is not only a result of vast amounts of fluid administration, but also of capillary leakage, renal failure, sodium and/or water retention [6].

In patients with sepsis and septic shock, volume loss into the third space often occurs due to venous pooling and alterations in the endothelial barrier secondary to inflammation leading to a relative intravascular volume deficit [7,8]. Additionally, there is an ongoing recommendation for liberal fluid resuscitation for patients with septic shock [9]. Thus, this patient population is especially prone to develop FO [[10]].

Over the past decades, the awareness for the detrimental effects of FO and its association with increased mortality and morbidity in the critically ill has risen considerably [2,11–14]. Therefore, strategies such as restrictive fluid administration or active removal of accumulated fluid have evolved to prevent or minimise FO in the critically ill. The idea of fluid restriction is to minimise fluid administration through a combination of predefined clinical or invasive parameters to assess tissue perfusion in addition to the assessment of fluid responsiveness to guide

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List of abbreviations

AIFR	Adequate initial fluid resuscitation
AKI	Acute kidney injury
APACHE II	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BIVA	Bioelectrical impedance vector analysis
CCUS	Critical care ultrasound
CI	Confidence interval
CLFM	Conservative late fluid management
CRRT	Continuous Renal Replacement Therapy
EGDT	Early goal-directed therapy
FACTT	ARDS Network Fluid and Catheter Treatment Trial
FFAKI	Forced fluid removal in intensive care patients with acute kidney injury
FO	Fluid overload
HR	Hazard Ratio
ICU	Intensive care unit
IV	Intravenous fluids
MOOSE	Meta-analysis of Observational Trials in Epidemiology
MV	Mechanical ventilation
N/A	Not applicable
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews
RADAR-2	Active Deresuscitation after Resuscitation-2
RCT	Randomised controlled trials
RRT	Renal replacement therapy
SAPS II	Simplified Acute Physiology Score II

fluid therapy [15–17]. Active de-resuscitation aims at off-loading excess fluid after the patient's condition could be stabilised, and is usually initiated during the first four days of intensive care unit (ICU) stay [4,18,19].

Several small trials and one meta-analysis have shown a potential benefit of a restrictive fluid administration regimen with regard to patient-centred outcomes (mechanical ventilation requirement, ICU length of stay). They have also shown that fluid restriction is feasible and leads to less resuscitation fluid administration [16,17,20,21]. A large trial investigating fluid restriction in patients with septic shock revealed that fluid restriction did not decrease mortality at 90 days compared to standard fluid therapy [22,23].

While fluid restriction has gained more recognition over the past years, de-resuscitation strategies were much less studied. Currently, there is little data on active protocolised de-resuscitation and critical care outcome measures in patients with septic shock. Therefore, the aim of this systematic review and meta-analysis is to evaluate the impact of active fluid de-resuscitation on mortality in critically ill patients with septic shock.

2. Methods

This systematic review and meta-analysis was conducted and reported in adherence with the guidelines for Preferred Reporting Items for Systematic Reviews (PRISMA) [24] and the Meta-analysis of Observational Trials in Epidemiology (MOOSE) guidelines for data extraction and risk assessment [25]. The protocol was registered on PROSPERO (No. CRD42021252769. Registered 11 August 2021).

2.1. In- and Exclusion criteria

Studies investigating active fluid de-resuscitation treatment reporting data on short-term mortality and/or FO in general population of patients with septic shock, or published data on subpopulation of septic patients, were included. Studies on patients with acute respiratory distress syndrome (ARDS) were included, if ARDS was secondary to septic shock. Studies investigating different fluid strategies (i.e. liberal vs. restrictive) were excluded if they lacked an active de-resuscitation strategy. Further, exclusion criteria were: Non-English studies, studies in the paediatric patients (<16 years), and studies exclusively evaluating de-resuscitation strategies in the emergency department (ED). In addition, we excluded studies targeting only selected patient populations (e.g. patients with CKD, transplant or cancer patients), as their underlying disease could represent a potential confounder due to differences in pathophysiology (transplant, significant impact on due to differences in pathophysiology (transplant), significant impact on mortality (cancer) or the ability for fluid separation (CKD). Furthermore, all review articles (narrative, systematic, meta-analysis), and case reports were excluded. The PRISMA flowchart is shown in Fig. 1.

2.2. Information sources and search strategy

A systematic search on PubMed, EmBase, and the Cochrane Library databases for articles published from 01.01.2001 until 31.12.2021 was performed. We chose 2001 as the start of our search, since this was the year of Rivers' publication on early goal-directed therapy (EGDT) [26], changing the gold standard of fluid administration in intensive care (liberal fluid administration) [27]. Thereafter, awareness about the detrimental side effects of fluid accumulation increased and thus triggered studies investigating interventions to reduce fluid accumulation [11,21,23]. Furthermore, we systematically searched the bibliographies of eligible publications and references of reviews, editorials and case reports for further investigations. Database search entry terms used are described in Figure S1. Study full texts and data were accessible in all trials extracted for full text analysis. Details are described in the online supplement.

2.3. Study selection

All titles and abstracts identified in the databases as well as through screening of bibliographic references (reviews and all eligible articles) were screened applying the pre-defined exclusion and inclusion criteria. In case of an unequivocal violation of a criterion, the study was excluded. If the violation of a criterion could not be evaluated because of insufficient information in the abstract, the article was considered for full text screening. Decisions were made by the two independent investigators (CAP, ASM) and discrepancies resolved by consensus.

2.4. Definitions

Mortality was defined as short-term mortality including ICU-, in-hospital, and 30-day mortality. Active de-resuscitation was defined as measures taken to actively offload accumulated fluid, e.g. administration of diuretics, renal replacement therapy, application of compression stockings, or any other method aiming to achieve active fluid removal. Fluid separation was defined as a significantly different fluid balance between the de-resuscitation and control group.

2.5. Risk of bias assessment

Risk of bias of included trials were assessed by two investigators independently using the Cochrane risk of bias tool for randomised controlled trials (RCTs) [28], and the Newcastle-Ottawa Scale for non-randomised trials [29].

RCTs were classified to have a high, unknown or low risk of bias. The following types of bias were considered: A) selection bias (population,

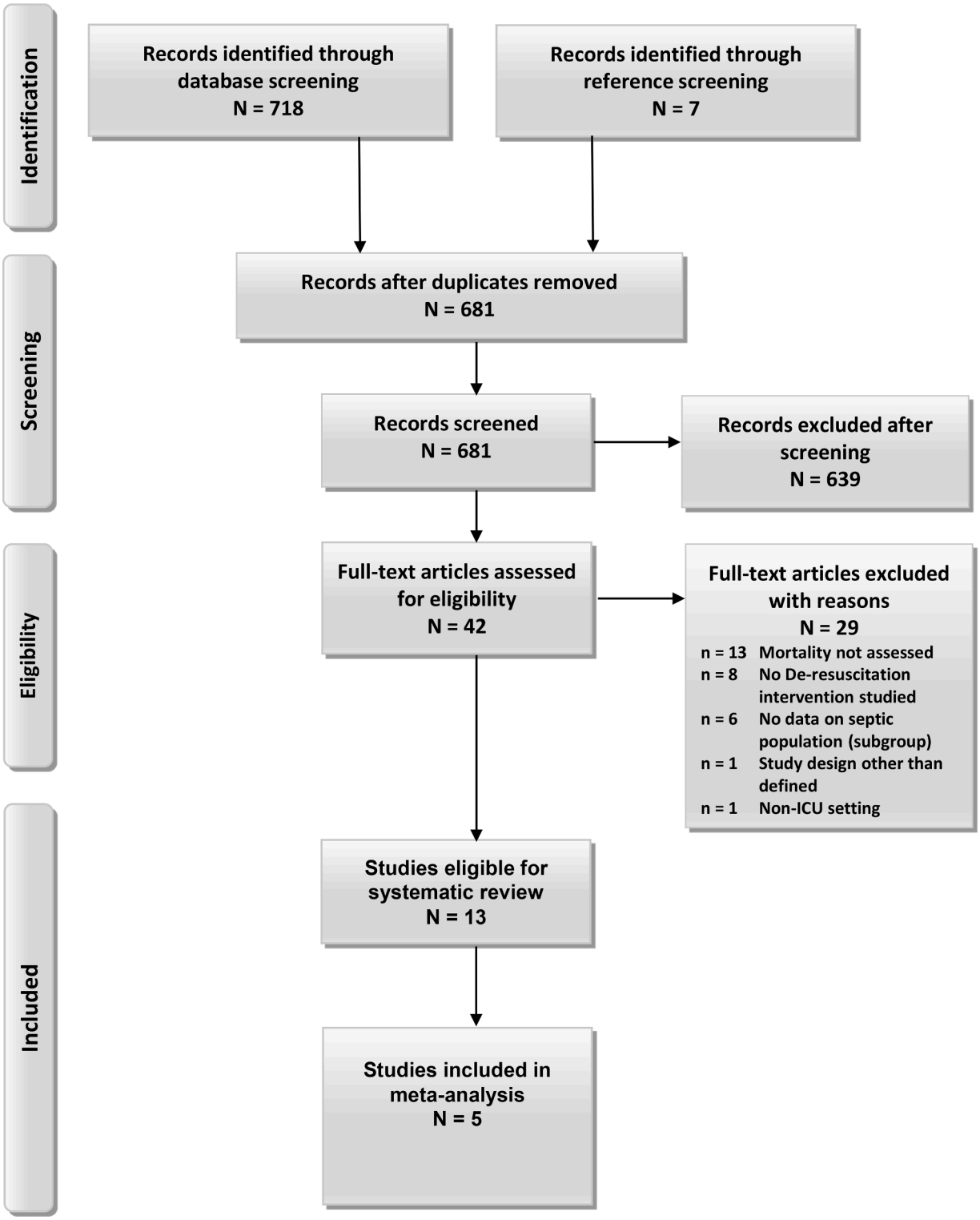

Fig. 1. PRISMA flowchart.

allocation), B) information bias (comparability of design and analysis, case definition, consistency, control for important confounders), C) attrition bias (incomplete data, outcome assessment) and D) reporting bias (selective outcome reporting).

Non-randomised trials were classified as good, fair or poor quality. The following criteria were assessed: A) Selection: 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort 3) Ascertainment of exposure, 4) Demonstration that outcome of interest was not present at start of study, B) Comparability: 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders, C) Outcome: 1) Assessment of outcome, 2) Was follow-up long enough for outcomes to occur, 3) Adequacy of follow-up of cohorts.

2.6. Objectives

The primary objective was to evaluate the impact of active fluid de-

resuscitation on short-term mortality in patients with septic shock. Secondary objectives were whether active de-resuscitation resulted in a more negative cumulative fluid balance and/or less FO during ICU stay (i.e. if fluid separation was achieved), and to evaluate the impact of de-resuscitation on patient centred outcomes (mechanical ventilation, vasopressors, RRT, and secondary infections).Data synthesis and statistical analysis

Data was extracted by two investigators separately using a predefined spreadsheet, following the recommendations by the Cochrane Collaboration handbook [28]. Data from non-randomised studies was summarised in tables and descriptive texts regarding study characteristics and results. Meta-analysis was performed only for RCTs. For meta-analyses, the extracted risk ratios, as well as risk differences with 95% confidence intervals (CI) were pooled using a random-effect model as proposed by DerSimonian and Laird method [30] to compute summary estimates of the association of active de-resuscitation and mortality. If the effect sizes were not given, data to calculate respective effect sizes was extracted. Heterogeneity amongst trials was assessed using I2-statistics. Funnel plots and Egger's regression asymmetry test were used to assess publication bias and small study effects. Stata, version 16.1 (StataCorp LLC) was used to perform the statistical analysis.

3. Results

A total of 718 articles were retrieved and screened for eligibility. In 42 trials, a full text analysis was performed, and 13 trials on 8030 patients were included (see Fig. 1). Five RCTs (38.5%) [31–35], five prospective cohort studies (38.5%) [36–40], and three retrospective cohort studies (23%) [41–43] met the eligibility criteria (Table 1).

Risk of Bias in the RCTs was low, however the overall quality of the included non-randomised studies was low (see Tables S1 and S2). Included trials were published between 2009 and 2021. Excluded studies with reason are shown in Table S3.

3.1. Method of de-resuscitation

The majority of studies (10 out of 13, 76%) used either renal replacement therapy (RRT) or diuretics or both as intervention for active de-resuscitation [31,35,37–39,41,42]. One study used bioelectrical impedance vector analysis as guidance for de-resuscitation in septic patients requiring RRT for fluid removal [33], and one trial investigated the application of corporeal compression [36]. Regarding the criteria for applying the de-resuscitation intervention, two RCTs used a predefined fluid protocol assessing fluid responsiveness or clinical signs of impaired peripheral perfusion [31,35], one RCT applied the de-resuscitation measure based on the fluid balance and concurrent peripheral oedema [32], and two trials used ultrasound or BIVA for assessment of fluid overload to commence de-resuscitation measures [33,34]

3.2. Primary endpoint – mortality

None of the five RCTs showed a reduction in mortality with active de-resuscitation measures [31–35]. The pooled risk ratio (RR) for mortality was 1.12 [95% CI 0.84 – 1.48], heterogeneity was low $I^2 = 4.9\%$, see Fig. 2. Absolute risk difference was 0.07 [95% CI −0.04 – 0.18], see Fig. S2. The funnel plot was visually symmetric and Egger's test showed no evidence of small study effect ($p = .860$), see Fig. S3. Thus, there was no evidence for a publication bias. In contrast, several observational studies (7/8) show a reduction in mortality when an active de-resuscitation strategy was applied [36–41,43]. A detailed description of study characteristics and mortality can be found in the online supplement. See also Table 1 for a summary of all findings.

3.3. Secondary endpoints

Table 2 shows secondary endpoints.

Table 1
Primary outcome of included studies.

Author	N	Active De-resuscitation Measure	Criteria for De-Resuscitation	Reduction in Short-term Mortality
		Randomised Controlled Trials		
Chen, 2014 [31]	82	Diuretics or RRT	Absence of fluid responsiveness (assessed by passive leg raise or fluid bolus administration)	No
Nuchpramool, 2019 [33]	36	RRT	BIVA (target% total body water)	No
Semler, 2020 [35]	30	Diuretics	Absence of shock defined as MAP < 60 mmHg or vasopressor receipt in the last 12 h)	No
Silversides, 2021 [32]	72†	Diuretics or RRT	Cumulative FB > 2 L or oedema in at least 2 areas (lung, flanks, upper or lower limbs), assessment only between day 2 to 5 after randomisation	No
Yu, 2021 [34]	86	Diuretics		No
		Prospective Cohort Studies		
Dargent, 2019 [36]	96	Corporeal Compression (bandages)	Applied immediately after randomisation (< 24 h of admission, fulfilling sepsis-2 criteria) and stopped once FB was negative for 2 consecutive days or at day 7	**Yes**
Jiang, 2021 [37]	138	Diuretics or RRT	After stabilisation of shock (no further defined)	**Yes**
Ganter, 2012 [38]	10	RRT	Persistent volume overload, need for RRT and deemed hemodynamically stable (no further definition)	**Yes**
Kron, 2015 [39]	21	RRT	Depending on the relative blood volume during RRT (marker for vascular refilling), UF was adapted (no pre-specified protocol for volume management given)	**Yes**
Zhang, 2021 [40]	206†	Diuretics	Depending on signs of effective circulation (cardiac index ≥ 2.5 L/min/m^2; no mottling, warm skin and capillary refill time < 2 s) and on protocol assignment (conservative versus liberal fluid administration)	**Yes**
		Retrospective Cohort Studies		
Chotalia, 2020 [41]	240	Diuretics	**None**††	**Yes**
Libório, 2020 [42]	6801†	Diuretics	None††	No
Murphy, 2009 [43]	212	Diuretics or RRT	**None**††	**Yes**

RRT = Renal Replacement Therapy, BIVA = Body impedance vector analysis, MAP = Mean arterial pressure, FB = Fluid balance, UF = Ultrafiltration,.
† Sepsis subgroup,.
†† Patients were retrospectively divided into groups.

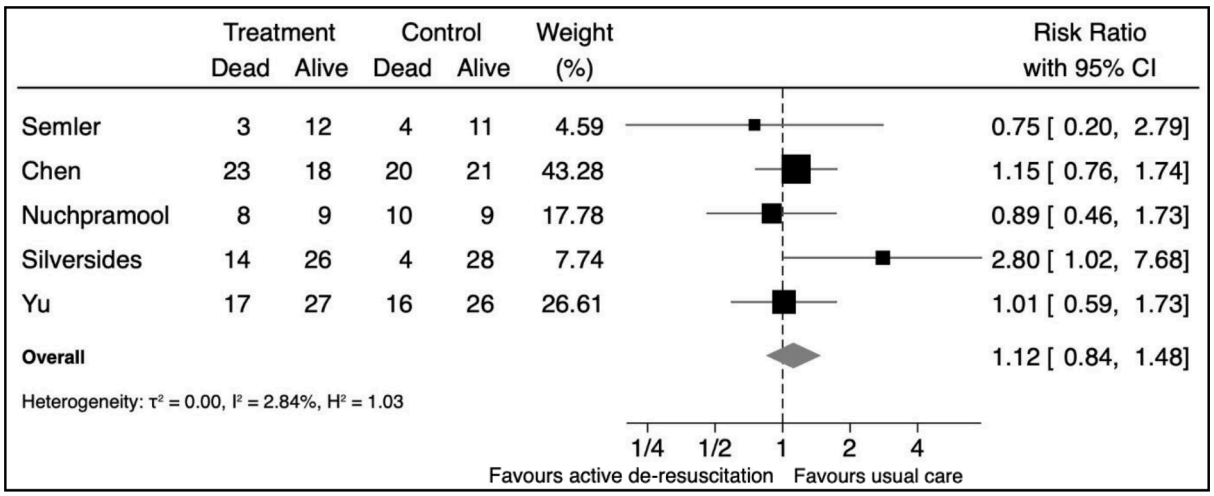

Fig. 2. Active de-resuscitation and short-term mortality.

Table 2
Secondary outcomes of included studies.

Author	Intervention	Control	Secondary Outcomes			
			Fluid Separation	Reduction of Time on MV	Reduction of Time on RRT	Reduction of time on/ requirement of Vasopressors
Randomised Controlled Trials						
Chen, 2014 [31]	Fluid protocol using diuretics +/- RRT	Usual Care	No	No	No	No
Nuchpramool, 2019 [33]	Bioelectrical impedance vector analysis (BIVA) guided fluid removal via RRT	RRT without guidance	No	No	N/A	No
Semler, 2020 [35]	Loop diuretics	Usual Care	No	No	No	No
Silversides, 2021 [32]	Diuretics +/- RRT	Usual Care	**Yes**	No	N/A	N/A
Yu, 2021 [34]	Ultrasound-guided goal directed resuscitation with deresuscitation part (diuretics)	EGDT	**Yes**	No	No	No
Prospective Cohort Studies						
Dargent, 2019 [36]	Corporeal Compression with bandages	Historical control	**Yes**	N/A	N/A	N/A
Jiang, 2021 [37]	Diuretics or RRT plus fluid restriction after stabilisation	Usual care	**Yes**	**Yes**	**Yes**	N/A
Ganter, 2012 [38]	Protocol-driven Fluid removal with RRT	Pre Study period	**Yes**	N/A	N/A	N/A
Kron, 2015 [39]	Fluid removal via RRT with relative blood volume (RBV) monitoring	None	N/A	N/A	N/A	N/A
Zhang, 2021 [40]	Diuretics	No diuretics	N/A	N/A	N/A	N/A
Retrospective Cohort Studies						
Chotalia, 2020 [41]	Furosemide use	–	N/A	N/A	N/A	N/A
Libório, 2020 [42]	Loop diuretics (>50% of ICU stay)	No diuretics or < 50% of ICU stay	**Yes**	No	N/A	N/A
Murphy, 2009 [43]	CLFM or AIFR (= > 20 ml/kg initial fluid bolus) plus CLFM	only AIRF/none	N/A	N/A	N/A	N/A

Legend: AIFR = Adequate Initial Fluid Resuscitation; APACHE II = Acute Physiology and Chronic Health Evaluation Score II; CFB = Cumulative Fluid Balance; CFLM = Conservative Late Fluid Management; CRRT = Continuous Renal Replacement Therapy; EGDT = Early Goal-directed Therapy; ICU = Intensive Care Unit; MV = Mechanical Ventilation; N/A = Not applicable; RRT = Renal Replacement Therapy; SAPS II = Simplified Acute Physiology Score II.

3.4. Cumulative fluid balance

Nine studies (69%) assessed the impact of de-resuscitation on cumulative fluid balance [31–34,36–39,42]. Only two of the five RCTs achieved a significant fluid separation (reduction in cumulative fluid balance) with the de-resuscitation intervention [32,34]. In the RADAR-2 trial, significant fluid separation was achieved in the subgroup of patients with sepsis up to day 2 and on day 5 after ICU admission (Intervention vs usual care: - 1088 mL (+/- 1858) vs 218 mL (+/- 1448), $p <$ .01; and 739 mL (+/- 4873) vs 3444 mL (+/- 4717), $p =$ .02) [32]. However fluid separation did not reach significance on day 3 after ICU admission (Intervention vs usual care: 2162 mL (+/- 3826) vs3413 mL (+/- 3800), $p =$ .06) [32]. And Yu et al. revealed a lower fluid balance at the 24th hour after enrolment using ultrasound – guided goal-directed fluid therapy vs. early goal-directed therapy (1184.5 mL [−27 – 2304] vs. 2031 mL [780 – 3583], $p =$ .031) [34]. All of observational trials analysing fluid separation revealed a lower fluid balance in the group with active de-resuscitation measures [36–38,42].

3.5. Mechanical ventilation

Seven studies (54%) analysed the impact of active de-resuscitation on mechanical ventilation [31–35,37]. None of the RCTs showed a difference in ventilator free days: Silversides et al. (4.5 days (+/−8) vs 3 days (+/- 7.3), $p = .53$) [32], Yu et al. (9 days [0 – 23.5] vs. 13 days [0 – 25], $p = .293$) [34], Chen et al. (5.5 days [0 - 12.25] vs. 5.5 days [0 –

16.75], $p = .05$) [31], Nuchpramool et al. (no data published) [33], Semler et al. (12 days [0 – 14] vs. 13 days [0 – 14], $p = .60$) [35]. One observational trial showed a reduction in duration of mechanical ventilation (MV) (26.2 +/- 22.5 days vs. 35.6 +/- 27.0, $p = .027$) [37]. One study revealed a an association between loop diuretics and prolonged mechanical ventilation (no data published) [42].

3.6. Renal replacement therapy

The impact of de-resuscitation strategies on duration or requirement of renal replacement therapy was assessed in four studies (31%) [31,34,35,37]. None of the three RCTs investigating this outcome revealed any difference in patients requiring RRT (41.5% vs. 39%, $p = .82$) [31], or RRT free days (14 days [14 – 14] vs. 14 days [0 – 14], $p = .36$ [41], and 18.5 days [0 – 28] vs 21.5 days [0 – 28], $p = .529$) [34]. A shorter duration of RRT was only observed in one observational investigation (3.5 +/- 4.9 days vs. 8.3 +/- days, $p > 0.001$) [37]. The same study also revealed fewer cases of new-onset acute kidney injury in the de-resuscitation strategy group (5.6% vs. 19.7%, $p = .012$) [37].

3.7. Vasopressor requirement

Only four studies (all of them RCTs) assessed the association of active de-resuscitation and vasopressor requirement, and none of them showed a significant difference in days free of vasopressors (5.5 days [0 – 10] vs. 5 days [0 – 16], $p = .84$ [31]; 12 days [0 – 14] vs. 13 days [0 - 14], $p = .60$ [35], and 13 days [0 - 23.5] vs. 20 days

[0 – 26], $p = .29$ [34]), or vasopressor requirement (no data published) [33].

3.8. Secondary infections

The occurrence or frequency of secondary infections was not investigated in any of the studies included.

4. Discussion

This systematic review and meta-analysis evaluated the de-resuscitation strategies in patients with septic shock and their impact on mortality. We identified thirteen studies, that underwent systematic evaluation, whereof five RCTs which were included in the meta-analysis. While none of the RCTs showed any evidence that active fluid de-resuscitation reduced mortality, the observational trials included in this review hint towards an improved survival with active de-resuscitation. In general, the availability of high-quality evidence on de-resuscitation strategies and their influence on short-term mortality and other important patient-centred outcomes in patients with septic shock is limited.

Our systematic review and meta-analysis shows no evidence of fluid de-resuscitation being superior to usual care in terms of mortality, fluid balance or important patient centred outcomes. This review reveals a substantial knowledge and research gap regarding the benefits and potential harm of active de-resuscitation strategies in critically ill patients with sepsis. While none of the included RCTs showed any benefit with active de-resuscitation, they only included a total of 306 patients, of which 155 were randomised into the de-resuscitation intervention arm [31–35]. Thus, the five RCTs resemble pilot trials with limited sample sizes and therefore caution must be applied before drawing any conclusions. Most importantly, only two of the current RCTs achieved significant fluid separation. This indicates that in the remaining RCTs the applied de-resuscitation interventions were not sufficient to achieve a significantly higher negative fluid balance compared to usual care. Thus, not surprisingly mortality and other important outcomes were not different between the two arms. In addition, in four of five trials mortality was not the primary endpoint and the studies were not powered for this endpoint.

Furthermore, the RCTs were heterogeneous in their de-resuscitation strategies and applied criteria. Some studies commenced de-resuscitation measures based on fluid protocols assessing fluid responsiveness or clinical signs of shock [31,35], while others [32] applied de-resuscitation measures (diuretics or RRT) based on fluid balance or fluid assessment (ultrasound or BIVA) [33,34]. Since each of these strategies may have different advantages and disadvantages it is difficult to draw any conclusion whether active de-resuscitation strategies in general are beneficial for critically ill patients with sepsis.

In contrast to the RCTs, non-randomised evidence shows a tendency towards improved mortality with active de-resuscitation [36,40,43], however apart from the obvious limitation of these studies in being of observational nature, a significant percentage of these investigations is of poor scientific quality as this systematic review and meta-analysis shows. Further high-quality data, preferably from RCTs, is warranted to shed more light on the effect of active fluid de-resuscitation strategies on outcomes in patients with sepsis. However, the initial step should be to develop a de-resuscitation protocol that actually achieves significant fluid separation before proceeding to investigate mortality.

While the survival benefit of active de-resuscitation remains unclear in patients with sepsis, there is evidence from other critical care patient populations stating that de-resuscitation in the form of early and targeted fluid removal might improve critical care outcomes [14,19,44–47], including reduced mortality [48–53]. In the general ICU population, one pilot trial with a diuretic-based de-resuscitation protocol in mechanically ventilated critically ill patients with volume overload (clinically or positive cumulative fluid balance) revealed a significant decrease in 72-h post-shock fluid balance, a lower in-hospital mortality compared to a historic control (5.5% vs 16.1%, $p = .008$), as well as higher ICU-free days (19 days [13 – 22] vs 17 days [7 – 21], $p = .03$) [48]. Similar results were shown by a RCT in mechanically ventilated patients, where a protocolised diuretic therapy significantly reduced fluid balance, was well tolerated, and led to less worsening of AKI. However, there was no difference in mortality in this study [44]. In patients with AKI, a large meta-analysis including 28 RCTs showed that the use of loop diuretics (i.e. furosemide) in patients with or at risk of AKI was not associated with increased mortality [46], however superiority of de-resuscitation with loop diuretics was could not be shown either. In contrast, an analysis using propensity score-matching in critically ill patients on vasopressor support revealed a significantly lower mortality in patients receiving early diuretic treatment [49]. Furthermore, study on 820 patients receiving continuous RRT revealed that a decrease in fluid balance during RRT was independently associated with a lower ICU- and a lower hospital mortality [50]. These results are supported by another investigation demonstrating a correlation between higher amount of fluid removal in critically ill patients with AKI undergoing continuous RRT and reduced mortality [51].

In ARDS, two trials revealed an improvement in fluid balance and oxygenation in ARDS patients with hypoproteinaemia when placebo was compared to furosemide in combination with albumin [19], or furosemide alone [45]. However, both studies did not demonstrate a reduction in mortality with these strategies. Additionally, the recently published RADAR-2 trial included in this review revealed no difference in 28-day mortality in the general critical care population between intervention and usual care group (21.4% vs. 15.6%, $p = .32$) [32].

A crucial question is what type of de-resuscitation strategy one should apply, if at all. In our review, the majority of trials used diuretics and/or RRT with net ultrafiltration in patients with septic shock as active de-resuscitation method. Both interventions are routinely used in ICU to treat FO in the general critical care population [54,55]. As to the effectiveness of forced fluid removal by RRT, data remains controversial. The FFAKI pilot feasibility trial investigating forced fluid removal versus standard care in patients with moderate to high risk of AKI and 10% fluid accumulation revealed that fluid removal aiming for 1 ml/kg/hour may be an effective treatment for fluid accumulation [53]. Nonetheless, the trial had to be prematurely stopped due to recruitment issues leaving

only 20 patients included in the final analysis and therefore no reliable conclusion on mortality and other secondary outcomes can be drawn [53]. On the contrary, a retrospective data analysis of the RENAL trial (normal vs augmented level of RRT) indicates that every 1 ml/kg/h increase of UF rate is associated with a lower probability of kidney recovery and a longer time to independence of RRT [52]. However, in this trial the investigators did not distinguish between different aetiologies of AKI, and approximately a third of the patients in the high UF group had severe acidaemia suggesting that patients were included who were not ready for de-resuscitation measures yet [52]. Interestingly, one investigation demonstrated that the use of loop diuretics in patients with FO, may even facilitate AKI resolution [47].

Overall, based on the available data one cannot draw any conclusion to change current practice of fluid management in septic shock in the critically ill. In the majority of included RCTs fluid separation could not be achieved fluid separation or patients with sepsis represented only a subgroup of the studied population and therefore lacked adequate sample size to answer our research question. It seems that the first step should be to develop an active fluid de-resuscitation protocol that actually achieves fluid de-resuscitation. Moreover, it might well be that the combination of restrictive fluid administration followed by active de-resuscitation is key to reach the goal of minimizing FO in patients with septic shock and should be further investigated in high quality clinical trials.

4.1. Limitations

There are several limitations warranting discussion. The majority of trials are of observational nature with only five RCTs eligible for this systematic review/meta-analysis. In addition, all investigations included are limited by their small sample size. Moreover, a significant percentage of observational investigations is of low scientific quality, which might hamper any conclusions drawn based on their findings. Furthermore, we only included studies evaluating de-resuscitation in patients with septic shock and we excluded studies involving only highly-selected subgroups and patients with ARDS (unless specified as sepsis-related ARDS). One might discuss whether all patients with ARDS belong in this group. However, ARDS is a heterogenic disease with distinct pathophysiological patterns and with many different aetiologies of which sepsis/septic shock is only one out of many causes. In addition, we excluded studies on selected subgroups of patients with septic shock, such as transplant recipients, oncological patients or patients with chronic kidney injury, as their underlying disease might influence patient outcome. However, these patients might be part of the study population within the included trials, and thus could potentially be confounders of the respective trials. Another limitation arises from the collinearity of sepsis/septic shock with other diseases such as AKI. However, critical illness per se is most commonly a multi-organ disease and thus a degree of collinearity reflects clinical practise [56]. Further limitations are caused by using different measures for short-term mortality. As our analysis consists mainly of observational investigations, in these types of investigations reverse causality (e.g. disease severity) cannot be excluded. Furthermore, defining RRT as de-resuscitation method as well as an outcome parameter might lead to an impression of a self-fulfilling prophecy. RRT is a means for de-resuscitation, however, de-resuscitation itself may lead to acute kidney injury, and therefore we added this important outcome to our systematic review. Lastly, we have chosen the year 2001 as start of our literature search as this was the year the publication by Rivers et al. on EGDT for severe sepsis and septic shock, and landmark research on general management including fluid guidance in septic shock followed thereafter [26,56–58,23]. However, this could have led to potential selection bias.

5. Conclusion

Our systematic review and meta-analysis revealed no evidence for superiority of active fluid de-resuscitation compared to usual care regarding mortality, fluid balance or patient-centred outcomes in patients with septic shock. Current evidence is largely limited by the lack of sufficient high-quality RCTs, small sample sizes and the heterogeneity of the applied de-resuscitation techniques. In addition, validity of most current RCTs is significantly compromised by their inability to achieve fluid separation. Nonetheless, investigations in other fields of critical care show beneficial results of active fluid de-resuscitation, which might be applied to patients with septic shock. Furthermore, high quality investigations are highly warranted to close the existing knowledge and research gap regarding fluid minimisation and de-resuscitation in patients with septic shock.

Trial Registration: PROSPERO (No. CRD42021252769. Registered 11 August 2021).

Declarations

Ethical approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Source of funding

None

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ASM and CAP performed the literature search and selected eligible trials. ASM and MM did the data extraction on all trials selected for the quantitative analysis. ASM, CAP and TD performed the risk of bias assessment. ASM and CAP drafted the manuscript, with all other authors co-drafting and revising the manuscript for important intellectual content. MM performed all statistical analyses. All authors approved the final version of the manuscript and agreed to submission.

Declaration of Competing Interest

ASM, TD and CAP report grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, and Nycomed outside the submitted work. The money was paid into departmental funds; no personal financial gain applied. MM has nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.01.009.

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