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Resuscitation Guided by Volume Responsiveness Does Not Reduce Mortality in Sepsis: A Meta-Analysis

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Objectives: Resuscitation with IV fluids is a critical component in the management of sepsis. Although the optimal volume of IV fluid is unknown, there is evidence that excessive administration can be deleterious. Static measures of volume status have not proven to be meaningful resuscitative endpoints. Determination of volume responsiveness has putative benefits over static measures, but its effect on outcomes is unknown. The goal of this systematic review and meta-analysis was to determine if resuscitation with a volume responsiveness-guided approach leads to improved outcomes in septic patients.

Data Sources: We searched PubMed, EMBASE, CINAHL, Web of Science, Cochrane Library, and Google Scholar from inception until April 2018.

Study Selection: Prospective studies of patients with sepsis, severe sepsis, or septic shock that compared volume responsiveness-guided fluid resuscitation to standard techniques and reported mortality data.

Data Extraction: We extracted study details, patient characteristics, volume responsiveness assessment method, and mortality data.

Data Synthesis: Of the 1,224 abstracts and 31 full-texts evaluated, four studies (total 365 patients) met inclusion criteria. Using random effects modeling, the pooled odds ratio for mortality at time of longest follow-up with a volume responsiveness-guided strategy was 0.87 (95% CI, 0.49–1.54). Pooling of clinical data was not possibly owing to heterogeneity of reporting in individual studies.

Conclusions: We found no significant difference in mortality between septic patients resuscitated with a volume responsiveness-guided approach compared with standard resuscitative strategies. It remains unclear whether the findings are due to the small sample size or a true lack of efficacy of a volume responsiveness-guided approach.

Key Words: cardiac output; echocardiography; fluid responsiveness; mortality; sepsis; volume responsiveness

Resuscitation with IV fluids (IVFs) is a cornerstone in the management of sepsis. Patients may have absolute or relative volume depletion leading to hemodynamic

perturbations, and thus the putative benefit of volume expansion has face validity. Early fluid resuscitation is recommended by the 2016 Surviving Sepsis Campaign Guidelines (30 cc/kg in the first 3 hr), but the quality of evidence supporting this intervention is low (1). Further, the optimal volume of IVF is unknown, and there is some evidence that excessive administration can be deleterious, especially in patients with acute kidney or acute lung injury (ALI) (2).

The goal of IVF administration is reduction in tissue hypoperfusion by increasing circulating blood volume. A variety of static variables have been targeted as resuscitative endpoints, such as central venous pressure and pulmonary artery occlusion pressure (3). The physiologic rationale for this approach is that increased preload results in increased cardiac output (CO), thereby increasing oxygen delivery to the peripheral tissues and reducing metabolic derangements. The critical flaw in this approach is the predication on optimal Frank-Starling mechanics, which are not present in all patients. Multiple studies demonstrate that use of static markers does not accurately identify which patients will increase their CO in response to preload augmentation (4).

An alternative to static methods, volume responsiveness (VR), provides a theoretical advantage over assessment of preload to guide therapy. VR—a dynamic measure—is defined as an increase in stroke volume, or CO, by 10–15% after a 200–500 cc IVF bolus (4–7). Alternatively, a passive leg raise (PLR), which increases preload by rapid return of blood from the lower extremities to the central circulation, is considered equivalent to an IVF challenge (8). There are numerous dynamic methods for identifying VR; some are invasive, requiring placement of a right-heart catheter for thermodilution measurement, whereas newer devices use proprietary algorithms to calculate hemodynamic variables via intra-arterial pressure monitoring. Noninvasive methods use transcutaneous measurements to derive hemodynamic data. Echocardiography can also be used to determine CO, with similar accuracy to invasive methods (9). As obtaining the necessary views to calculate CO using echocardiography can be technically challenging, other sonographic techniques have been described that use arterial waveform analysis at the carotid, brachial, or femoral artery (10).

A 2017 meta-analysis investigated whether a VR-guided strategy improves clinical outcomes as compared with standard resuscitation in adults admitted to the ICU requiring volume resuscitation (11). The authors reported an absolute risk reduction in death of –2.9% (95% CI, –5.6% to –0.2%) and modest reductions in ICU length of stay and duration of mechanical ventilation. Only one of the studies included solely septic patients, whereas the remaining 12 were postsurgical patients. However, the resuscitative needs and pathophysiology of postsurgical patients may not mirror those of patients with sepsis. Therefore, the aim of this systematic review and meta-analysis was to determine whether a VR-guided strategy (as measured by dynamic variables), as compared with usual care, improves clinical outcomes in patients with sepsis.

DATA SOURCES, DATA EXTRACTION, AND DATA SYNTHESIS

Data Sources

This review was conducted in accordance with the preferred reporting items for systematic review and meta-analyses statement (12). We registered our review with the international prospective register of systematic reviews, registry number CRD42018092727.

Literature searches were conducted in PubMed, EMBASE, CINAHL, and Web of Science from database inception to March 2018. The full search strategy is available as **supplementary material** (Supplemental Digital Content 1, http://links.lww.com/CCX/A38).

Studies were included if they used a prospective design, evaluated adults with sepsis by any definition, compared VR-guided fluid resuscitation (by any method) to standard techniques, and reported mortality data for each group. "VR-guided fluid resuscitation" was defined as a resuscitative strategy guided by any measure that dynamically quantified the effect of either IVF loading or a PLR, such as CO, stroke volume variation, pulse pressure variation, or stroke volume index. To avoid confounding from baseline differences in physiology and varied physiologic response to infectious insult, trials of immune-compromised patients, those on immune-suppressive therapy, or in which a mechanical circulatory device was used were excluded; case reports, case series, cross-sectional, and case-control studies were excluded. The primary outcome was the difference in mortality between groups (VR-guided vs standard care) at the longest reported time point; secondary outcomes were ICU and hospital length-of-stay, duration of mechanical ventilation, and occurrence of ALI or acute respiratory distress syndrome (ARDS).

A flowchart of study screening is shown in **Supplemental Figure 1** (Supplemental Digital Content 2, http://links.lww.com/CCX/A39). After deduplication, 1,224 studies were screened by two independent reviewers (abstracts: R.R.E., R.K.S.; full-text: R.R.E., R.L.S.), and consensus was reached through discussion with input from a third author (J.Z.G.) in cases of disagreement. A total of 31 full-text studies were assessed for eligibility, and four were included in the final analysis (13–16). Both phases of screening were conducted using Covidence systematic review software (Veritas Health Innovation, Melbourne, VIC, Australia).

Data Extraction and Quality Assessment

Data were independently extracted from the four included studies into a standardized data collection formed by two investigators (R.R.E., J.Z.G.) and compared; disagreements were discussed and adjudicated by a third investigator (R.L.S.). We extracted the following data (when available): study design, study size, mortality (30 d or nearest equivalent), age, sex, source of sepsis, method of VR determination, vasopressor use (medication and duration), use and duration of mechanical ventilation, admission location, occurrence of ALI and ARDS, and ICU and hospital length-of-stay (**Table 1**). The Cochrane Risk of Bias Tool was used to assess the quality of included studies (17) (**Supplemental Fig. 2**, Supplemental Digital Content 3, http://links.lww.com/CCX/A40).

TABLE 1. Characteristics of Included Studies

Study	Kuan et al (15)	Chen et al (13)	Richard et al (16)	Juneja et al (14)
Study design and location	Open-label RCT, single-center, emergency department	Open-label RCT, single-center, ICU	Open-label RCT, single-center, ICU	Open-label RCT, single-center, ICU
Study country	Singapore	United States	France	India
n intervention	61	41	30	53
n control	61	41	30	48
n total	122	82	60	101
Mean age	67 vs 64	58 vs 60	65 vs 64	53 vs 51
Cardiac output monitoring tool	Bioreactance (Cheetah NICOM)	Transesophageal Doppler monitoring (CardioQ; Deltex Medical, West Sussex, UK) or Transthoracic Echocardiography (USCOM Ltd, Sydney, Australia)	Combined Thermodilution and Pulse Contour Measurement (PiCCO; Maquet Getinge Group, Rastatt, Germany)	Arterial waveform (FloTrac Vigeleo; Edwards Lifesciences, Irvine, CA)
Volume responsiveness determinant	SVI after PLR	PPV, IVC, and SVI after PLR/ IVF bolus	PPV and SVI after PLR	SVV
Definition of fluid responsiveness	SVI increase > 10% after PLR	PPV ↓ < 13%, ↓ IVC size < 18%, and SVI ↑ > 10%	SVI ↑ > 10%, or PPV > 13%	SVV > 13%
Guided volume administration	1 L IVF if SVI > 20%; 500 mL IVF if SVI > 10%	500 mL aliquots of crystalloid until not fluid responsive	500 mL aliquots of IVF until not fluid responsive	Maintenance of SVV at < 13%
Inclusion	> 21 yr old, sepsis, lactate ≥3 mmol/L	> 18 yr old, septic shock requiring vasopressors 12 hr after initial 30 mL/cc IVF bolus	> 18 yr old, septic shock, given ≥ 25 mL/kg IVF, mean arterial pressure < 65 for > 12 hr	MV, septic shock, on vasopressors
Study primary outcome	Lactate clearance of > 20% after 3 hr	Volume of IVF at days 3 and 5 and fluid balance	Time to pressor wean	Acute kidney injury development
Study secondary outcomes	28-d mortality, ICU LOS, hospital LOS, cost, pressor requirement	Vasopressor days, RRT, MV days, in-hospital mortality, and maximum pressor dose	28-d mortality, ICU LOS, MV-free days, and organ failure	RRT, ICU LOS, ICU mortality
Primary outcome	70.5% vs 73.8%	6,244 vs 8,690 (day 5)	2.3 vs 2.0 d	21 (40%) vs 29 (60%)
Mortality, *n* (%)	6 (9.8) vs 6 (9.8)	23 (56.1) vs 20 (48.8)	7 (23) vs 14 (47)	18 (34) vs 19 (39.6)
Mortality report	28-d	In-hospital	28-d	ICU
IVF (L)	2.1 vs 1.6 (at 3 hr)	6.2 vs 8.6 (at 5 d)	0.4 vs 0.9 (mL/d)	NA
MV, *n* (%)	18	28 (68%) vs 31 (76%)	20 (67%) vs 26 (87%)	NA

IVC = inferior vena cava diameter, IVF = IV fluid, LOS = length of stay, MV = mechanical ventilation, NA = not applicable, PLR = passive leg raise, PPV = pulse pressure variation, RCT = randomized controlled trial, RRT = renal replacement therapy, SVI = stroke volume index, SVV = stroke volume variation.
Comparisons are intervention vs control.

Odds ratios (ORs) and associated 95% CIs for mortality at the longest reported interval were calculated for each study. The pooled OR (95% CI) was determined using random effects modeling (inverse variance method); VR status was the dependent variable, with standard care as the referent group. Heterogeneity was evaluated using chi-square test and I^2 test.

Data Synthesis

The four included studies had a total of 365 patients who were analyzed with respect to the primary endpoint (mortality). There was no difference in mortality with respect to a VR-guided resuscitation strategy (OR, 0.87; 95% CI, 0.49–1.54), no significant heterogeneity among studies was detected ($p = 0.23$), and I^2 was 30% (**Fig. 1**). Protocol compliance in the intervention was high in two studies: Richard et al (16) reported 100% compliance with IVF administration recommendations, and Kuan et al (15) reported 95.1% compliance (three patients switched from intervention to control arm). Chen et al (13) had a fluid administration portion and a fluid minimization portion of their intervention arm, each assessed on ICU days 1–5; they reported 100% compliance with the

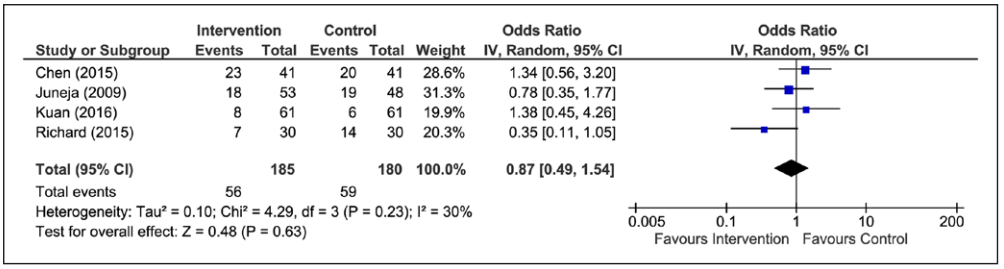

Figure 1. Forest plot of mortality for volume responsiveness-guided fluid resuscitation versus usual care. *df* = degrees of freedom.

IVF administration recommendations, but varying compliance in minimization aspects with 100% compliance with concentration of all IVFs, 22–35% compliance diuresis recommendations, and 36–43% compliance with renal replacement therapy recommendations. Juneja et al (14) did not report protocol compliance.

The Cochrane Risk of Bias Tool revealed low-to-moderate risk of bias in all domains except for blinding of participants and personnel, which is expected based on the nature of patient care intervention (Supplemental Fig. 2, Supplemental Digital Content 3, http://links.lww.com/CCX/A40). No secondary outcomes could be subject to meta-analysis due to variability in data presentation.

DISCUSSION

The results of this systematic review and meta-analysis indicate that a VR-guided resuscitation strategy in sepsis patients confers no mortality benefit compared with usual care. Whether our finding is due to a true absence of benefit versus inability to detect such a benefit due to the small number of patients in eligible trials ($n = 365$) is unknown. Owing to variability in the reporting of secondary outcomes, no analyses were possible for these measures.

There was substantial clinical heterogeneity between studies, which likely confounds the relationship between VR and mortality (Table 1), although the direction and magnitude of these effect(s) are unknown. For example, one study was performed in the emergency department (15), and three in the ICU (13, 14, 16), which makes comparison of illness severity (even with severity scores) and effects of treatments difficult. Even among the ICU trials, one only enrolled patients after at least 12 hours of hypotension, one with less than 12 hours of hypotension, and one did not specify. Similarly, treatment protocols varied across studies, and only one study (16) found a significant difference between IVF administered per VR status (917 in controls vs 383 cc in the intervention group; $p = 0.01$). Although overall fluid administration was not statistically different between groups within studies, there were between-study differences with those in the study by Richard et al (16) receiving less (2.8 L intervention and 2.9 L control) than in either Kuan et al (15) (5.1 L vs 5.4 L) or Chen et al (13) (4.4 vs 4.1), respectively. Clinical interventions outside the treatment protocols, such as mechanical ventilation, differed across these studies as well, ranging from 20% to 100%. These variations may affect clinical outcomes, including morality, so our finding of no mortality difference should be interpreted with caution.

Early resuscitation with IVF has been a mainstay of sepsis treatment for 2 decades. Although this is beneficial overall (18), development of volume overload is a clinical problem with deleterious consequences (2, 19). Guidelines call for delivery of a universal standard of 30 cc/kg within the first 3 hours of presentation for all septic patients with hypoperfusion, but this "one-size-fits-all" approach, which ignores individual patient physiology at the time of presentation, is a recognized limitation. The optimal resuscitative fluid volume—one that maintains perfusion without inducing unfavorable Frank-Starling mechanics—remains unknown.

The utility of determining a patient's VR status is physiologically plausible and provides theoretical advantage over static measures of preload. Patients who are non-VR but still have signs of shock or hypoperfusion may benefit from vasopressor or inotropic support rather than additional volume expansion, but this approach has not been rigorously studied. However, our search of the literature reveals that while many studies evaluating and comparing the accuracy of individual methods have been performed, few report clinically meaningful outcomes. This represents a serious limitation, and it remains unclear whether patients receive any benefit from VR assessment despite substantial costs. We believe, therefore, that further study in this field is warranted with large-scale randomized controlled trials that focus on patient-oriented outcomes. Provision of high-quality data therefrom is needed to ascertain whether VR determination is a salubrious or specious endeavor.

LIMITATIONS

Our meta-analysis has several important limitations. The methods of VR determination, and definitions thereof, differed among studies. While each approach is generally accurate when used appropriately, subtle differences between methods may affect pooled results. The direction of the effect is unknown but is likely smaller than the effect of patient-level differences owing to varied inclusion criteria. Data presentation from included studies was variable, precluding quantitative analysis of all secondary outcomes. For instance, while fluid administration was an endpoint in all studies, it was presented at varied time points (over 3 hr, 5-d total, and daily average). The primary outcome of our study, mortality, was also presented at variable times, including 28-day, in-hospital, and ICU mortality. Although we did not detect significant statistical heterogeneity among studies (possibly due to relatively small numbers), there is good reason to suspect it exists, and random effects modeling was considered more appropriate. We felt that, because sepsis is an acute disease process, the longest time point provided would be a reasonable approximation of the absolute mortality related to an episode of sepsis; this variability, however, adds further uncertainty to the final analysis. Therefore, to maximize patient-oriented benefit, we propose that future studies should adopt uniform definitions of sepsis (e.g., Sepsis-3) for inclusion criteria and that standard in data reporting be adopted to allow robust meta-analyses.

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