

# Fluid Administration in Emergency Department Patients With Uncontrolled Hemorrhage: How Much and When?

## EBEM Commentator Contact

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician(s) knowledgeable in the subject area.

The source for this systematic review abstract is: Kwan I, Bunn F, Roberts I. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev*. 2003; (3)CD002245. PMID: 12917926. The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

The objectives of this review were to examine the efficacy of early versus delayed fluid resuscitation and large- versus small-volume fluid administration in patients with hemorrhagic hypovolemia, with regard to mortality and coagulation times.

## DATA SOURCES

The authors searched the Cochrane Injuries Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2003), MEDLINE (1966 to November 2002), EMBASE (1966 to 2003, week 5), the National Research Register, Science Citation Index and Web-based trials registers such as Current Controlled Trials. Their search was updated to February 2003. The reviewers also checked the reference list of all articles included and also contacted the authors, as well as other experts in the field.

## STUDY SELECTION

Randomized trials looking at the timing and volume of intravenous fluid administration in trauma patients with bleeding were included. The reviewers also included studies examining fluid resuscitation in nontrauma patients with hemorrhagic hypovolemia because the response to bleeding and to fluid resuscitation is likely to be similar among patients with internal hemorrhage (eg, gastrointestinal bleeding) and those with external hemorrhage (eg, penetrating trauma). Trials in which different types of intravenous fluid were compared were excluded.

The measured outcomes included mortality from all causes and changes in prothrombin time and partial thromboplastin times after fluid administration.

## DATA EXTRACTION AND ANALYSIS

A single reviewer selected trials from electronic search results and contacted experts in the field for information about ongoing or unpublished trials. A second reviewer checked a sample of the electronic results for eligibility; disagreements were adjudicated by a third reviewer. Two reviewers then extracted information and sought outcome data on mortality, prothrombin time, and partial thromboplastin time.

The data were analyzed by comparing early versus delayed intravenous fluid administration and larger versus smaller intravenous fluid administration. Mortality data were presented as the relative risk of death and 95% confidence interval (CI). Because coagulation times are continuous variables, the results were calculated and reported as weighted mean differences. Because of the differences in the patient populations and the nature of the interventions, the authors did not pool the data in their analysis.

## MAIN RESULTS

Based on the authors' search strategy, 4,487 potential eligible reports were found, of which 6 trials met the inclusion criteria. Three trials analyzed early versus delayed resuscitation and 3 trials examined large versus small volume of fluid administration. A summary of the reported outcomes of such resuscitation strategies extracted from the reviewed trials is presented in [Table 1](#).

## CONCLUSIONS

According to the evidence available, the authors conclude that there are insufficient data for or against the use of early or larger-volume intravenous fluid resuscitation in uncontrolled hemorrhage. Further controlled trials are necessary to establish an ideal fluid resuscitation strategy.

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**Table 1.** Summary of reported outcomes for early vs. late resuscitation and large versus small fluid volume in the reviewed trials.

Study, by First Author	Study Population	Outcome	
		Mortality, RR (95% CI)	Coagulation, WMD (95% CI)
<b>Early vs late resuscitation</b>			
Bickell, 1994	598 hypotensive trauma patients (early vs late administration of crystalloids)	1.26 (1–1.58)	PTT: 2.7 (0.90–4.5) PT: 4.3 (1.7–6.9)
Blair, 1986	50 hypotensive patients with GI bleeding (early vs late blood transfusion)	5.4 (0.3–107.1)	PTT: 7 (6–8)
Turner, 2000	1,309 trauma patients (early vs no or delayed fluid resuscitation)	1.06 (0.77–1.47)	—
<b>Large vs small fluid volume</b>			
Dunham, 1991	36 hypotensive trauma patients (large vs small fluid volume)	0.80 (0.28–22.29)	—
Dutton, 2002	110 hypotensive trauma patients (large vs small fluid volume)	1.0 (0.26–3.81)	—
Fortune, 1987	25 hypotensive trauma patients	No mortalities reported	—

*RR*, Relative risk; *WMD*, weighted mean difference; *PTT*, partial thromboplastin time (seconds); *PT*, prothrombin time (seconds); *GI*, gastrointestinal; —, data not included in particular study.

## COMMENTARY: CLINICAL IMPLICATION

Hemorrhagic shock is frequently associated with poor outcome. In fact, the mortality of this entity exceeds 50%.<sup>1</sup> Traditional teaching in management of hemorrhagic shock consists of establishing 2 large-bore intravenous lines, volume replacement (intravenous fluids or blood), and definitive surgical control of the hemorrhage. Logically, blood transfusion appears to be the most appropriate volume replacement strategy because, in addition to restoring perfusion, it improves tissue oxygenation. However, even when benefits of blood transfusion outweigh its potential harms (eg, possible transmission of infections, transfusion reactions), limited availability of blood products and related resources remains an obstacle to its use. For this reason, blood volume replacement is still considered the mainstay of treatment until the hemorrhage is controlled definitively.

More recently, decisions about the volume and type of fluid resuscitation during hemorrhage have become a topic of intense debate.<sup>2–4</sup> Experimental evidence suggests that administration of resuscitation fluids is not entirely innocuous and that conventional management of hemorrhage with bolus volumes of crystalloid solutions, followed by rapid blood transfusion to restore the blood pressure, may be deleterious to the outcome.<sup>5–7</sup> It has been proposed that a more judicious approach to fluid resuscitation is required in the face of continuing hemorrhage. However, there continues to be discussion about the timing, volume, and type of fluid to be administered to hypovolemic injured patients.

It has been suggested that in uncontrolled hemorrhage, before hemostasis is achieved, hypotensive fluid resuscitation may be beneficial.<sup>2</sup> The studies reviewed in this Cochrane Review fail to demonstrate that the choice of large- versus small-volume administration influences mortality. Titrating the fluid

resuscitation to low blood pressure (systolic blood pressure 70 mm Hg) or conventional normal blood pressure (systolic blood pressure >100 mm Hg) has failed to show any impact on mortality.<sup>3</sup> These results were based on a small number of trials and a small total sample size, so the results do not imply equivalence in the approaches. More recent studies have suggested a potential benefit for using hypertonic saline solution in hypovolemic trauma patients in that this particular fluid may require less volume to maintain controlled hypotension compared to isotonic or near-isotonic crystalloid solutions.<sup>4,8</sup>

Studies have also questioned the timing of fluid administration in hypotensive hypovolemic trauma patients. In animal models of uncontrolled hemorrhage, delaying fluid resuscitation may decrease the rate, volume, and duration of blood loss.<sup>7,9</sup> Most important, human studies have demonstrated a possible decrease in mortality in patients with penetrating thoracic trauma when a delayed fluid resuscitation protocol is used.<sup>1</sup> The increased hemorrhage volume after early resuscitation is attributed to a combination of increased systemic pressure, disruption of clot formation, dilution of coagulation factors, and lowering blood viscosity.<sup>1</sup> The studies reviewed in this Cochrane Review fail to conclusively demonstrate that the timing of fluid administration in hypotensive hypovolemic trauma patients influences mortality.

## TAKE-HOME MESSAGE

Despite the presence of a great deal of literature about resuscitation schemes for the hypovolemic bleeding patient, this review reveals the current debate about essentially every aspect of fluid management in such cases, including timing, volume, and type of fluid administration. These issues are currently the subject of further randomized clinical trials, and new evidence will emerge to guide emergency physicians in the upcoming years. In the

meantime, emergency physicians should use clinical judgment and make their choices according to individual cases.

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### EBEM TEACHING POINT

Systematic reviews characterize a rigorous method of assembling scientific evidence to answer questions about issues of treatment, diagnosis, or prognosis. Although systematic

reviews are ranked as the highest level of evidence, the strength of the evidence offered by a systematic review depends on how well the review is performed. In fact, 2 or more systematic reviews on the same topic may provide quite different results, raising questions on the validity of the conclusions. Regardless of their source, all systematic reviews require critical appraisal to establish their validity (similar to all other types of research evidence). Therefore, the readers must be able to identify a high-quality systematic review and understand the elements that contribute to a well-designed and well-performed one. This is particularly so in emergency medicine, in which research has indicated that the quality of systematic reviews is low and the presence of methodological flaws warrants caution when these results are used.<sup>10</sup> Several instruments have been proposed for

**Table 2.** A sample of quality assessment tool for systematic reviews.<sup>12</sup>

1. Was an a priori design provided? The research question and inclusion criteria should be established before the conduct of the review.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
2. Was there duplicate study selection and data extraction? There should be at least 2 independent data extractors, and a consensus procedure for disagreements should be in place.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
3. Was a comprehensive literature search performed? At least 2 electronic sources should be searched. The report must include years and databases used (eg, Central, EMBASE, MEDLINE). Key words or MeSH terms must be stated, and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study and by reviewing the references in the studies found.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
4. Was the status of publication (ie, grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review) according to their publication status, language, etc.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, eg, age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases, should be reported.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
7. Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided (eg, for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review and explicitly stated in formulating recommendations.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (ie, $\chi^2$ test for homogeneity, I <sup>2</sup> ). If heterogeneity exists, a random effects model should be used or the clinical appropriateness of combining should be taken into consideration (ie, is it sensible to combine?).	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (eg, funnel plot, other available tests) or statistical tests (eg, Egger regression test).	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in the systematic review and the included studies.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable

assessing the quality of a systematic review. The first and most widely used tool was the Overview Quality Assessment Questionnaire (OQAQ).<sup>11</sup> The most recent one is Assessment of Multiple Systematic Reviews, referred to as the AMSTAR, which is summarized in Table 2.<sup>12</sup> The continuous emergence of new research on quality of systematic reviews and identification of new sources of bias in conducting such reviews warrant constant updating of these quality assessment instruments.

Some of the major components of a systematic review that must be critically appraised include development of the focused question, avoidance of publication and selection bias, quality assessment of primary studies, assessment of heterogeneity of the individual study results, and appropriateness of the pooling and interpretation of summary results. Emergency physicians should familiarize themselves with one of these tools when reading systematic reviews.

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