The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis

Jones AE, Brown MD, Trzeciak S, Shapiro NI, Garrett JS, Heffner AC, Kline JA

CRD summary
The review concluded that applying an early quantitative resuscitation strategy to patients with sepsis imparted a significant reduction in mortality (which was lost if the intervention was initiated late). The authors' conclusions appeared appropriate and are likely to be reliable.

Authors' objectives
To assess the effectiveness of quantitative resuscitation interventions on mortality in patients with sepsis.

Searching
MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched to April 2008 with no restrictions on language or publication type; search terms were reported. Two experts in sepsis resuscitation were contacted. Abstracts from Society of Critical Care Medicine, American College of Chest Physicians, American College of Emergency Physicians and Society for Academic Emergency Medicine annual meetings from 1997 to 2007 were handsearched. Published practice guidelines for sepsis care from 2000 to 2007, clinical trial registration websites and reference lists of included studies and reviews were searched.

Study selection
Randomised controlled trials (RCTs) of adults (aged >17 years) with a presumptive or confirmed diagnosis of sepsis comparing a clearly defined intervention (structured cardiovascular resuscitation protocol administered to achieve predefined haemodynamic end points) with standard care were eligible. In-hospital mortality was the main outcome of interest.

In all studies except one the setting was an intensive care unit. Two-thirds of the trials were of early resuscitation (within 24 hours of recognition of sepsis). Oxygen delivery, oxygen delivery index, central venous pressure and cardiac index were the most common targeted quantitative resuscitation group endpoints. Overall mortality rates ranged from 19% to 67%.

Two reviewers independently assessed titles and abstracts. Disagreements were resolved via consensus with a third reviewer. Methods for selecting full papers were unclear.

Assessment of study quality
Study quality was evaluated by graded assessment of how patients were selected (standard, non-standard or unclear diagnostic criteria) and description of randomisation and allocation concealment. Jadad scores were reported.

Three reviewers independently performed the quality assessment; disagreements were resolved by consensus.

Data extraction
Data were extracted in order to calculate odds ratios (OR) with 95% confidence intervals (CI). Study investigators were contacted for data clarification where necessary.

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Methods of synthesis
Meta-analyses to calculate pooled odds ratios were performed using a random-effects and a fixed-effect model. Heterogeneity was assessed with $\chi^2$ and I$^2$ statistics. A funnel plot and Egger regression were used to detect publication bias.

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bias. Subgroups analyses were planned to examine the effect of timing of resuscitation; also, the effect of excluding individual studies from the early resuscitation subgroup was examined. A sensitivity analysis investigated the effect of study quality.

**Results of the review**

Nine RCTs were included (n=1,001, range 33 to 263 participants). Jadad scores ranged from zero to 4 (most studies scored 2 or less). Four studies had adequately reported methods of allocation concealment and two studies described inadequate methods; no allocation concealment details were described in the other three studies. All studies assessed patients using standard diagnostic criteria.

Quantitative resuscitation resulted in a significant reduction in mortality compared to standard care (OR 0.64, 95% CI 0.43 to 0.96, $I^2=45%$; nine studies). There was no indication of publication bias. Similar results were seen for the six studies of early resuscitation, but with less heterogeneity (OR 0.50, 95% CI 0.37 to 0.69, $I^2=2%$); this result remained similar when only high-quality studies were analysed and when each individual study was excluded. Late resuscitation had no significant effect on mortality (three studies). Results when a fixed-effect model was used were not significantly different from those with the random-effects model.

**Authors' conclusions**

Application of an early quantitative resuscitation strategy to patients with sepsis imparted a significant reduction in mortality (which was lost if the intervention was initiated late).

**CRD commentary**

The review addressed a clear question supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken via a variety of methods, which included searches for unpublished studies. Suitable methods were employed to reduce risks of reviewer error and bias throughout the review. A fairly basic study quality assessment was performed and the results used in interpreting the results of the review. Few study details were provided, particularly in relation to the participants and interventions. Appropriate methods were used to synthesise the data and assess heterogeneity.

The authors' conclusions appear appropriate and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the review results provided the strongest support to date for the Surviving Sepsis Campaign recommendation of providing quantitative resuscitation at the time of severe sepsis recognition.

**Research:** The authors stated that future investigations should compare the relative efficacy of various quantitative resuscitation endpoints in an RCT.

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