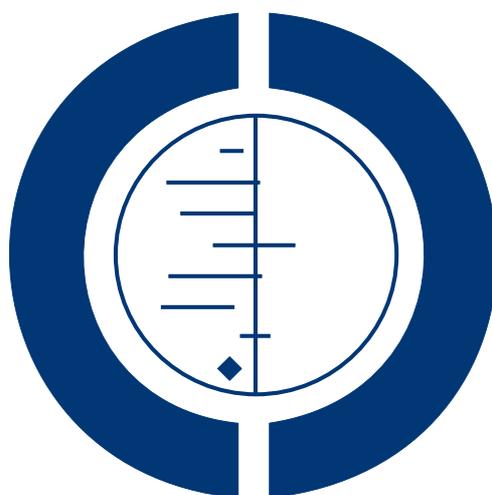


# Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review)

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[Intervention Review]

# Colloids versus crystalloids for fluid resuscitation in critically ill patients

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## ABSTRACT

### Background

Colloid solutions are widely used in fluid resuscitation of critically ill patients. There are several choices of colloid and there is ongoing debate about the relative effectiveness of colloids compared to crystalloid fluids.

### Objectives

To assess the effects of colloids compared to crystalloids for fluid resuscitation in critically ill patients.

### Search strategy

We searched the Cochrane Injuries Group Specialised Register, CENTRAL (*The Cochrane Library* 2008, Issue 3), MEDLINE, EMBASE, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED), ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S), and The Controlled Trials metaRegister ([www.controlled-trials.com](http://www.controlled-trials.com)). Reference lists of relevant studies and review articles were searched for further trials. The searches were last updated in September 2008.

### Selection criteria

Randomised controlled trials (RCTs) of colloids compared to crystalloids, in patients requiring volume replacement. We excluded cross-over trials and trials in pregnant women and neonates.

### Data collection and analysis

Two authors independently extracted data and rated quality of allocation concealment. We analysed trials with a 'double-intervention', such as those comparing colloid in hypertonic crystalloid to isotonic crystalloid, separately. We stratified the analysis according to colloid type and quality of allocation concealment.

### Main results

We identified 65 eligible trials; 56 of these presented mortality data.

### Colloids compared to crystalloids

**Albumin or plasma protein fraction** - 23 trials reported data on mortality, including a total of 7754 patients. The pooled relative risk (RR) from these trials was 1.01 (95% confidence interval (95% CI) 0.92 to 1.10). When we excluded the trial with poor quality

allocation concealment, pooled RR was 1.00 (95% CI 0.91 to 1.09). **Hydroxyethyl starch** - 17 trials compared hydroxyethyl starch with crystalloids, n = 1172 patients. The pooled RR was 1.18 (95% CI 0.96 to 1.44). **Modified gelatin** - 11 trials compared modified gelatin with crystalloid, n = 506 patients. The pooled RR was 0.91 (95% CI 0.49 to 1.72). (When the trials by Boldt et al were removed from the three preceding analyses, the results were unchanged.)

**Dextran** - nine trials compared dextran with a crystalloid, n = 834 patients. The pooled RR was 1.24 (95% CI 0.94 to 1.65).

### **Colloids in hypertonic crystalloid compared to isotonic crystalloid**

Eight trials compared dextran in hypertonic crystalloid with isotonic crystalloid, including 1283 randomised participants. Pooled RR was 0.88 (95% CI 0.74 to 1.05).

### **Authors' conclusions**

There is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs.

## **PLAIN LANGUAGE SUMMARY**

### **Are colloids more effective than crystalloids in reducing mortality in people who are critically ill or injured**

Trauma, burns or surgery can cause people to lose large amounts of blood. Fluid replacement, giving fluids intravenously (into a vein) to replace lost blood, is used to try to maintain blood pressure and reduce the risk of dying. Blood products, non-blood products or combinations are used, including colloid or crystalloid solutions. Colloids are increasingly used but they are more expensive than crystalloids. The review of trials found no evidence that colloids reduce the risk of dying compared with crystalloids.

## **BACKGROUND**

Fluid resuscitation for hypovolaemia is a mainstay of the medical management of critically ill patients, whether as a result of trauma, burns, major surgery or sepsis. Although recent studies (Bickell 1994) have suggested that the timing of volume replacement deserves careful consideration, when it comes to selecting the resuscitation fluid, clinicians are faced with a range of options. At one level the choice is between a colloid or crystalloid solution. Colloids are widely used, having been recommended in a number of resuscitation guidelines and intensive care management algorithms (Armstrong 1994; Vermeulen 1995).

The US Hospital Consortium Guidelines recommend that colloids are used in haemorrhagic shock prior to the availability of blood products, and in non-haemorrhagic shock following an initial crystalloid infusion. A 1995 survey of US academic health centres, however, found that the use of colloids far exceeded even the Hospital Consortium recommendations (Yim 1995). Surveys of burn care in the US (Fakhry 1995) and in Australia (Victorian DUAC 1991) found that the use of colloids for resuscitation varied without a set pattern.

The choice of fluid has considerable cost implications. Volume replacement with colloids is considerably more expensive than with crystalloids. Clinical studies have shown that colloids and crystalloids have different effects on a range of important physiological parameters. Because of these differences, all-cause mortality is arguably the most clinically relevant outcome measure in randomised trials comparing the two fluid types.

### **Why it is important to do this review**

Although there have been previous meta-analyses of mortality in randomised trials comparing colloids and crystalloids (Bisonni 1991; Velanovich 1989), neither of these satisfy the criteria that have been proposed for scientific overviews (Oxman 1994), and they predate most of the trials that have been conducted using synthetic colloids, and hypertonic crystalloid solutions. The purpose of this systematic review is to identify and synthesise all available unconfounded evidence of the effect on mortality in critically ill patients of colloids compared to crystalloids for volume replacement.

## OBJECTIVES

To assess the effects on mortality of using colloids compared to crystalloids, during fluid resuscitation in critically ill patients.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Controlled trials in which participants were randomised to treatment groups (colloid or control) on the basis of random allocation. As the comparison between fluid type was in terms of effects on mortality, we excluded randomised cross-over trials.

#### Types of participants

Critically ill patients (excluding neonates) who required volume replacement. We included patients who were critically ill as a result of trauma, burns, were undergoing surgery, or had other critical conditions such as complications of sepsis.

We excluded pre-operative elective surgical patients.

#### Types of interventions

We considered the following colloids: Dextran 70, hydroxyethyl starches, modified gelatins, albumin or plasma protein fraction. There is overlap between albumin given for volume replacement and albumin given as a nutritional supplement, and many patients with a critical illness have low serum albumin. Where the trial was of total parenteral nutrition with or without albumin, we excluded it. We included trials where the albumin was given as part of volume replacement guided by colloid osmotic pressure or albumin levels.

The control group received crystalloid (isotonic or hypertonic) for fluid replacement. We included trials in which both groups received blood.

We excluded trials of fluids used for other purposes. For example, we excluded trials of pre-loading in preparation for elective surgery, and trials in patients undergoing fluid loading before cardiopulmonary bypass.

#### Types of outcome measures

The principal outcome measure was mortality from all causes, assessed at the end of the follow-up period scheduled for each trial.

## Search methods for identification of studies

The searches were not restricted by date, language or publication status.

### Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched 30 Sept 2008)
- CENTRAL (*The Cochrane Library* 2008, Issue 3)
- MEDLINE (1966 to September 2008)
- PubMed (searched 30 September, last three months)
- EMBASE (1980 to September 2008)
- ISI Web of Knowledge (1970 to September 2008)
- National Research Register (2006, Issue 4)
- Controlled Trials metaRegister ([www.controlled-trials.com](http://www.controlled-trials.com)) (searched 30 Sept 2008)

The search strategy can be found in [Appendix 1](#).

### Searching other resources

We checked the reference lists of all identified trials and review articles, and contacted the trialists to identify any studies that may have been missed.

## Data collection and analysis

### Selection of studies

We independently examined titles, abstracts, and keywords of citations from electronic databases for eligibility. We obtained the full text of all relevant records and independently assessed whether each met the pre-defined inclusion criteria. We resolved disagreement by discussion.

### Assessment of risk of bias in included studies

We scored allocation concealment as described by [Higgins 2008](#), assigning 'No' to poorest quality and 'Yes' to best quality (the presence of solutions in identical containers was only taken to mean adequate concealment if the fluid containers were used sequentially).

- Yes = trials deemed to have taken adequate measures to conceal allocation (that is, central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).
- Unclear = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories.

- No = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

We collected but did not score information on blinding and loss to follow up.

### Data synthesis

As a result of comments on the previous version of this review, we have stratified trials by type of fluid rather than type of original injury.

We calculated relative risks (RRs) and 95% confidence intervals (95% CI) for each study using a fixed-effect model. We then inspected each comparison visually for evidence of heterogeneity and performed a  $\text{Chi}^2$  test. If there was no evidence of heterogeneity (visually or with a P value  $< 0.1$ ) the trials were pooled within each type of fluid, but not combined between type of fluid.

### Sensitivity analysis

We then excluded trials with allocation concealment judged as inadequate and repeated the calculations.

The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author on the conclusions of the review.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We identified 65 trials meeting the inclusion criteria for study design, participants and interventions. We were able to obtain mortality data for 56 of these. We have reported details of the included trials in the 'Characteristics of included studies' table.

Reasons for exclusion of trials were: the use of a cross-over design, testing a resuscitation algorithm, giving the control group oral fluids, the intervention being directed to the maintenance of serum albumin levels, for haemodilution, for fluid loading and for the reduction of intracranial pressure (see 'Characteristics of excluded studies' table).

Of the 56 trials with data on deaths, the quality of allocation concealment was adequate in seven trials and unclear in most of the others.

There were 60 comparisons of colloids and crystalloids (add-on colloid), nine comparisons of colloid in hypertonic crystalloid with isotonic crystalloid, and three comparisons of colloid with hypertonic crystalloid.

### Risk of bias in included studies

In general, the design of studies was not well reported. This is reflected in the number of unclear scores given for allocation concealment. We also collected information on blinding and loss to follow up. Blinding was not well reported and loss to follow up was generally small. The characteristics for each trial are listed in the 'Characteristics of included studies' table.

### Effects of interventions

#### Colloids compared to crystalloids

##### Albumin or plasma protein fraction

Twenty-three trials reported data on mortality, including a total of 7754 patients. The pooled relative risk (RR) was 1.01 (95% confidence interval (95% CI) 0.92 to 1.10). When trials by Boldt were removed, the results were unchanged (RR 1.01 (95% CI 0.92 to 1.10)). When we excluded the trial with poor quality allocation concealment (Lucas 1978), pooled RR was 1.00 (95% CI 0.91 to 1.09).

##### Hydroxyethyl starch

Seventeen trials compared hydroxyethyl starch with crystalloids, including a total of 1172 randomised patients. The pooled RR was 1.18 (95% CI 0.96 to 1.44). When trials by Boldt were removed, the results were unchanged.

##### Modified gelatin

Eleven trials compared modified gelatin with crystalloid, including a total of 506 randomised patients. The pooled RR was 0.91 (95% CI 0.49 to 1.72). When trials by Boldt were removed, the results were unchanged.

##### Dextran

Nine trials compared dextran with a crystalloid, including a total of 834 randomised patients. The pooled RR was 1.24 (95% CI 0.94 to 1.65).

### Colloids in hypertonic crystalloid compared to isotonic crystalloid

One trial compared albumin and hypertonic saline with isotonic crystalloid. The RR of death was 0.50 (95% CI 0.06 to 4.33). Eight trials compared dextran in hypertonic crystalloid with isotonic crystalloid, including 1283 randomised patients. The pooled RR was 0.88 (95% CI 0.74 to 1.05).

### Colloids in isotonic crystalloid compared to hypertonic crystalloid

Three trials compared colloids in isotonic crystalloid with hypertonic crystalloid. In two of these, where the colloid was either gelatin or starch, there were no deaths in either group. In the remaining trial, with 38 patients, there was a RR of death of 7.00 (0.39 to 126.93) for use of colloid, based on three deaths in the treatment group and none in the control group.

#### Sensitivity analysis

All three trials by Prof. Boldt (Boldt 1986; Boldt 1993; Boldt 2001) were of low methodological quality and were excluded as part of the sensitivity analysis in the original review.

## DISCUSSION

This systematic review synthesises the evidence from RCTs comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions. The review has been updated and extensively revised to take into account the comments made since it was first published. In particular, several commentators pointed out that it is inappropriate to combine effect estimates from studies of different colloids. For example, it was argued that large molecular weight colloids such as hydroxyethyl starch may be better retained in the vascular compartment than albumin and gelatins, and would therefore be more likely to show a favourable effect on mortality (Gosling 1998). In response to these concerns, the review has been stratified by type of colloid. However, the pooled relative risks fail to show a mortality benefit for resuscitation with any type of colloid.

There was a trend towards a favourable effect on mortality for colloids in hypertonic crystalloid, compared to isotonic crystalloids. Nevertheless, the results are compatible with the play of chance.

Common to all meta-analyses, this systematic review may have included studies whose interventions and patient characteristics are sufficiently incomparable that the calculation of a summary effect measure may be questioned. The resuscitation regimen differed between trials. Some trials randomised participants to an initial quantity of colloid or crystalloid, and then proceeded with some

form of standard resuscitation for all participants. Other trials resuscitated with the allocated fluid to pre-determined end-points, either resuscitation end-points, or in the case of trauma, until corrective surgery. In addition, the type of colloid or crystalloid, the concentration, and the protocol to determine the quantity of fluid varied. Despite these differences, all participants were in need of volume replacement, and we believe that this variation in the intervention would have an impact on the size of the effect, rather than on its direction.

As regards the effects of albumin versus crystalloid, most of the information (as indicated by the weighting in the meta-analysis) was provided by the SAFE trial (SAFE 2004). The SAFE trial used central randomisation with a minimisation algorithm to ensure balance on known potential confounders. Blinding was assured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The trial authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated. In brief, this was a well-conducted, high-quality trial. There were 726 deaths (20.9%) in the albumin-treated group and 729 deaths (21.1%) in the saline-treated group (RR of death 0.99; 95% CI 0.91 to 1.09). Although even this large trial was unable to confirm or refute the possibility of a modest benefit or harm from albumin, it has provided some reassurance that any hazard from albumin, if indeed there is any, is unlikely to be as extreme as was suggested by the results from the previously published (now here updated) meta-analysis of much smaller trials. The pooled RR for death with albumin in this updated meta-analysis is now 1.02 (95% CI 0.93 to 1.11). It is important to note that the effect estimate from the SAFE trial is entirely consistent with the results of previous trials of albumin in hypovolaemia and there is no significant heterogeneity ( $I^2 = 0\%$ ,  $P = 0.46$ ).

The results of this updated meta-analysis have important policy implications. There is still no evidence that colloids are superior to crystalloids as a treatment for intravascular volume resuscitation in critically ill patients. Importantly, the SAFE trial also provided no evidence of any other clinical advantages from using albumin. It also debunked the belief, from pathophysiological inference, that very large volumes of crystalloid must be administered to reach the same resuscitation end-points as can be achieved using much smaller volumes of colloid. In the SAFE trial, the ratio of albumin administered to saline administered was approximately 1:1.4. Colloids, in particular albumin, are considerably more expensive than crystalloids, and albumin is a blood product and so carries at least a theoretical infectious disease risk. The economic opportunity cost of ongoing colloid use, particularly albumin use, is likely to be considerable and for this reason its ongoing use in this context is unjustified.

## AUTHORS' CONCLUSIONS

## Implications for practice

There is no evidence from RCTs that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and further, colloids are considerably more expensive than crystalloids, it is hard to see how their continued use outside the context of RCTs in subsets of patients of particular concern, can be justified.

## Implications for research

Future trials may need to concentrate on specific subgroups of patients to identify people who may benefit from colloids rather than crystalloids.

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We thank Dr. Frank M. Brunkhorst for providing the Supplementary Appendix to the paper Brunkhorst 2008.

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### Schierhout 1998

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\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Boldt 1986

Methods	Randomised controlled trial, using sealed opaque envelopes. Information on allocation concealment was obtained on contact with the authors. Blinding and loss to follow up not mentioned.	
Participants	55 patients undergoing elective aorta-coronary bypass surgery. Exclusion criteria were ejection fraction < 50% and LVEDP > 15 mmHg.	
Interventions	<ol style="list-style-type: none"> <li>1. 300ml 20% human albumin solution (n = 15).</li> <li>2. 500ml 3% hydroxyethyl starch (n = 13).</li> <li>3. 500ml 3.5% gelatin (n = 14).</li> <li>4. No colloid (n = 13).</li> </ol>	
Outcomes	Haemodynamic variables were measured. Deaths not reported.	
Notes	Follow up until discharge from intensive care.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

#### Boldt 1993

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes (information from author). Blinding and loss to follow up not mentioned.	
Participants	75 males undergoing elective aortocoronary bypass grafting, who had a pulmonary capillary wedge pressure of less than 5 mmHg after induction of anaesthesia.	
Interventions	<ol style="list-style-type: none"> <li>1. 5% albumin (n = 15).</li> <li>2. 6% HES, mean molecular weight 450,000 (n = 15).</li> <li>3. 6% HES, mean molecular weight 200,000 (n = 15).</li> <li>4. 3.5% gelatin (n = 15).</li> <li>5. No colloid (n = 15).</li> </ol> Fluid used through operation and on intensive care post-op.	
Outcomes	Deaths not reported, author confirmed there were no deaths.	
Notes	Follow up to 1 day.	

**Boldt 1993** (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Boldt 2001**

Methods	Randomised controlled trial, using a closed-envelope system.
Participants	100 patients undergoing major abdominal surgery.
Interventions	<ol style="list-style-type: none"> <li>1. Ringer's lactate (n = 25).</li> <li>2. 6% HES, mean molecular weight 200kDa, degree of substitution 0.5 (n = 25).</li> <li>3. 6% HES, mean molecular weight 130kDa, degree of substitution 0.4 (n = 25).</li> <li>4. 4% modified fluid gelatin, molecular weight 35kDa (n = 25).</li> </ol>
Outcomes	Deaths. Orthostatic problems. Haemodynamics and laboratory data. Fluid input and output. Costs.
Notes	Follow-up period unclear.

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Boutros 1979**

Methods	Randomised controlled trial ("randomly divided"). Method of allocation concealment not described. Blinding not mentioned. No loss to follow up.
Participants	24 people undergoing major operative procedures on the abdominal aorta.
Interventions	<ol style="list-style-type: none"> <li>1. Albumin in 5% dextrose (n = 7).</li> <li>2. 5% dextrose and Ringer's lactate (n = 8).</li> <li>3. 5% dextrose in 0.45% saline (n = 9).</li> </ol> Allocated fluids were used on admission to ICU, following surgery, guided by PAWP. Whole blood also given if clinically needed.
Outcomes	Deaths reported.

**Boutros 1979** (Continued)

Notes	Follow up to discharge from hospital.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Bowser-Wallace 1986**

Methods	Quasi-randomised controlled trial (allocation by alternation). Blinding not mentioned. No loss to follow up.	
Participants	Admitted for burns of 30% or more. Age range 5 months to 21 years. Excluded if already given more than half calculated daily requirement before reaching hospital.	
Interventions	<ol style="list-style-type: none"> <li>2ml/kg/%burn Ringer's lactate over 24 hrs, then 0.5ml plasmanate/kg/%burn over 24 hrs plus 5% dextrose (n = 19).</li> <li>2ml/kg/%burn hypertonic lactated saline over 24 hrs, then 0.6ml/kg/%burn hypertonic lactated saline over 24 hrs plus oral Haldane's solution (n = 19).</li> </ol> IV fluids stopped at 48 hrs (n = 19).	
Outcomes	Deaths reported. Fluid and electrolytes given, weight, haematocrit.	
Notes	Follow up to 5 days.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	No	Inadequate.

**Brunkhorst 2008**

Methods	Multicenter, randomised control study. Blinding not mentioned. Use of a two-by-two factorial, open label study design.	
Participants	Critically ill patients with severe sepsis or septic shock of at least 18 years of age. Excluded if onset of symptoms commenced more than 24 hours before admission to the ICU, if the symptoms commenced more than 12 hours after onset in the ICU or if patient had received more than 1000 ml of HES in the 24 hours before randomisation.	

**Brunkhorst 2008** (Continued)

Interventions	1. 10% Pentastarch/HES (200/0.5) (n = 262) 2. Modified Ringer's Lactate (n = 275)	
Outcomes	Deaths reported at 28 and 90 days. 90 day mortality rate was cited as it marked the end of the follow-up period.	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Chavez-Negrete 1991**

Methods	Randomised controlled trial (allocation by "random numbers"). Blinding not mentioned. No loss to follow up.	
Participants	Adults admitted to an emergency room with acute gastrointestinal haemorrhage, systolic blood pressure 90 mmHg or less for up to 1 hr and normal electrocardiograph. Excluded if pregnant or had renal, cardiac or neurological disease.	
Interventions	1. Initial infusion of 250ml 7.5% saline/6% Dextran 60 given IV (16 patients) or intraosseous (n = 10). 2. Initial IV infusion of 250ml Ringer's lactate (n = 23). Resuscitation continued with red cells, 0.9% saline and Dextran 40 according to clinical judgement.	
Outcomes	Death. Haemodynamic variables.	
Notes	Follow up to 24 hours.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear.

**Cifra 2003**

Methods	Quasi-randomised controlled trial (allocation by alternation). Allocation concealment not reported. Blinding not reported. No loss to follow up.
Participants	27 children with dengue shock syndrome. Exclusion criteria included: Other severe infection, protein-deficient abnormalities, bleeding diathesis, patients who have been given multiple plasma substitutes.
Interventions	1. 6% Haes-Steril (n = 11). 2. Ringer's Lactate (n = 16). One patient from group 1 and three from group 2 were excluded because they needed inotropic support and multiple plasma substitute.
Outcomes	Duration of control of shock. Recurrence of shock. Length of ICU stay. Death not reported as an outcome but they reported that 4 patients died.
Notes	Length of follow up not reported but all outcomes were in-hospital.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not used

**Dawidson 1991**

Methods	Randomised controlled trial (allocation by drawing a card from a deck). Blinding not mentioned. No loss to follow up.
Participants	Adults undergoing elective abdominal aortic surgery. No exclusions mentioned.
Interventions	1. 3% Dextran 70 in Ringer's lactate (n = 10). 2. IV Ringer's lactate (n = 10). Fluid used during and for 24 hrs after operation, guided by haemodynamic variables.
Outcomes	Death. Volume transfused, weight change, haemodynamic variables.
Notes	Follow up to discharge from hospital.

***Risk of bias***

Item	Authors' judgement	Description
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**Dawidson 1991** (Continued)

Allocation concealment?	No	Inadequate
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**Dehne 2001**

Methods	Randomised controlled trial; allocation by sealed envelope assignment.
Participants	60 male patients (of American Society of Anesthesiologists physical status 1 or 2) scheduled for middle ear surgery.
Interventions	<ol style="list-style-type: none"> <li>1. Lactated Ringer's solution (n = 15).</li> <li>2. 6% HES: molecular weight 200kD, degree of substitution 0.5 (n = 15).</li> <li>3. 6% HES: molecular weight 200kD, degree of substitution 0.60-0.66 (n = 15).</li> <li>4. 6% HES: molecular weight 450kD, degree of substitution 0.7 (n = 15).</li> </ol>
Outcomes	Deaths not stated but 'all' patients discharged 10-14 days after surgery; therefore no deaths. Central venous pressure. Urine output. Blood osmolality. Urine osmolality.
Notes	Follow up two days.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Eleftheriadis 1995**

Methods	Patients "randomizedly distributed". Blinding not mentioned. Unable to assess loss to follow up.
Participants	Participants were undergoing coronary artery bypass surgery.
Interventions	<ol style="list-style-type: none"> <li>1. 6% hydroxyethyl starch.</li> <li>2. 3.5% gelatin.</li> <li>3. Ringer's lactate.</li> </ol> Allocated fluid was used in the post-operative period only guided by mean arterial pressure.
Outcomes	Deaths were not reported. Haemodynamic variables.
Notes	Follow up period unspecified.

Eleftheriadis 1995 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Ernest 1999

Methods	Randomised controlled trial, allocation concealment not described. No blinding. No loss to follow up mentioned.	
Participants	Patients with a clinical diagnosis of sepsis.	
Interventions	1. 5% albumin (n = 9). 2. 0.9% saline (n = 9). Volume of infusion guided by PAWP.	
Outcomes	Haemodynamic variables and volume measurements. Deaths not reported.	
Notes	Follow up to immediately after infusion.	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Evans 1996

Methods	Quasi-randomised trial (allocation by day of the week). Blinding not mentioned. No loss to follow up.	
Participants	Aged 16 or more, admitted with trauma to an emergency centre within 2 hours after injury, only crystalloid as a pre-hospital infusion. Excluded if had underlying illness likely to affect clotting.	
Interventions	1. IV haemaccel (n = 11). 2. IV Ringer's lactate (n = 14). Fluid was used until vital signs were stable.	
Outcomes	Deaths from author. Clotting variables.	

Evans 1996 (Continued)

Notes	Follow up period unspecified.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	No	Inadequate

Evans 2003

Methods	Randomised controlled trial. Allocation concealment not reported. Blinding methods not reported. Loss to follow up not reported.	
Participants	55 patients undergoing primary unilateral total hip replacement. Exclusion criteria were pre-existing defect in platelet function or on aspirin that could not be stopped for 2 weeks prior to the operation.	
Interventions	<ol style="list-style-type: none"> <li>1. 4.5% Albumin (n = 13).</li> <li>2. Gelofusine (n = 14).</li> <li>3. Haemaccel (n = 14).</li> <li>4. 0.9% Saline (n = 14).</li> </ol>	
Outcomes	Haemostatic parameters. Death not reported.	
Notes	Length of follow up not reported but all outcomes were in-hospital.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

Fries 2004

Methods	Randomised controlled trial. (Patients "randomly" received crystalloid or colloids.) Method of allocation concealment not reported. Blinding not reported. Loss to follow up not reported.	
Participants	60 patients undergoing knee replacement surgery. Exclusion criteria were contraindication for regional anaesthesia, known allergies or haemostatic disorders.	

**Fries 2004** (Continued)

Interventions	1. HES (n = 20). 2. Modified gelatin (n = 20). 3. Ringer's solution (n = 20). Groups 1 and 2 also received a basis of Ringer's solution infusion.	
Outcomes	Coagulation parameters. Death not reported.	
Notes	Length of follow up not reported but all outcomes were in-hospital measures.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Gallagher 1985**

Methods	Randomised controlled trial. Method of allocation concealment not described. Author contacted - allocation concealment by computerised system - patient details were entered before treatment assignment was revealed. Blinding not mentioned. No loss to follow up.	
Participants	Patients after coronary artery bypass graft surgery. Exclusions: patients with significant left main coronary artery stenosis, poor left ventricular function or poor pulmonary function.	
Interventions	1. IV 5% albumin (n = 5). 2. IV 6% hydroxyethyl starch (n = 5). 3. IV Ringer's lactate (n = 5). Fluid used from admission to intensive care post op, guided by PAWP. RBC given if needed. Five patients received 5% albumin. Five patients received lactated Ringer's.	
Outcomes	Deaths were not reported. Author contacted and confirmed that there were no deaths in any group. Haemodynamic data.	
Notes	Follow up to 1 day.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Adequate

**Goodwin 1983**

Methods	Randomised controlled trial - assigned by "random numbers table". Method of allocation concealment unclear. Blinding not mentioned. No loss to follow up.
Participants	79 previously healthy young adults admitted with burns. No exclusion criteria reported.
Interventions	1. 2.5% albumin in Ringer's lactate (n = 40). 2. Ringer's lactate (n = 39). Fluids on day 1 guided by haemodynamic variable. On day 2, given at 0.3-0.5ml/kg/%burn, then 5% dextrose.
Outcomes	Deaths reported. Lung water in some. Infections.
Notes	Follow up to discharge from hospital.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Grundmann 1982**

Methods	Randomised controlled trial. Method of allocation concealment unclear. Blinding not mentioned. No loss to follow up.
Participants	20 people undergoing partial gastrectomy. The average age was 50 years (range 19-84). No exclusion criteria reported.
Interventions	1. Colloid group received human albumin solution (n = 14). 2. Details of crystalloid were not reported (n = 6). Allocated fluid was continued for 4 days after operation.
Outcomes	Deaths reported. Volumes of fluid given. Haemodynamic variables.
Notes	Follow up to discharge from hospital.

***Risk of bias***

**Grundmann 1982** (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Guo 2003**

Methods	Randomised controlled trial. Allocation concealment not reported. Blinding not reported. No loss to follow up reported.
Participants	42 patients undergoing elective cytoreductive surgery for ovarian cancer. Exclusion criteria included: preoperative anaemia, allergic response to HES or perioperative administration of cardiovascular agents. 2 patients randomised but excluded because of use of cardiovascular agents.
Interventions	1. Ringer's Lactate (n = 20). 2. 6% HES (n = 20).
Outcomes	Splanchnic perfusion. Death not reported but in results authors mentioned that "all patients were discharged."
Notes	Follow up to discharge from hospital.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Hall 1978**

Methods	Quasi-randomised controlled trial (participants were stratified by age, extent of burn and aetiology, and then allocated by alternation). Blinding not mentioned. No loss to follow up.
Participants	Burns covering more than 10% of the body surface (for children), and more than 15% of the body surface (for adults). No exclusions mentioned.
Interventions	1. 120ml/%burn IV 6% Dextran 70 in 0.9% saline over 48 hrs plus oral water or IV 5% dextrose for 'metabolic requirements' (n = 86). 2. 4ml/kg/%burn IV Ringer's lactate over 24 hrs, then 10% of initial body weight of fluid over 24 hrs plus oral water (n = 86).

**Hall 1978** (Continued)

Outcomes	Death. Fluid given, haemodynamic variables.	
Notes	Follow up to discharge from hospital.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	No	Inadequate

**Hartmann 1993**

Methods	Randomised controlled trial (method of allocation unclear). Blinding not mentioned. No loss to follow up.	
Participants	Adults undergoing major abdominal surgery. Exclusions: cardiorespiratory dysfunction, uraemia, diabetes, taking steroids, anticoagulants or diuretics.	
Interventions	<ol style="list-style-type: none"> <li>1. IV Dextran 70 in saline (concentration not given) with 2.5% dextrose (n = 15).</li> <li>2. IV saline (concentration not given) with 2.5% dextrose (n = 14).</li> </ol> Both groups given red cells, plasma, Dextran 70 and crystalloids during the operation as decided by the clinician. Post-operative fluids according to the trial group guided by tissue oxygen tension to the end of resuscitation.	
Outcomes	Death not reported. Fluid given, haemodynamic variables.	
Notes	Follow up to 7 days.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Jelenko 1978**

Methods	Randomised controlled trial, method of allocation concealment unclear. Blinding not mentioned. No loss to follow up.	
Participants	19 people with burns covering more than 20% of body surface.	

**Jelenko 1978** (Continued)

Interventions	<ol style="list-style-type: none"> <li>1. 12.5% albumin in hypertonic saline (240MeQ Na+, 120 MeQ chloride, 120 MeQ lactate), (n = 7).</li> <li>2. Hypertonic saline (240MeQ Na+, 120 MeQ chloride, 120 MeQ lactate). (n = 5).</li> <li>3. Ringer's lactate (n = 7).</li> </ol> Allocated fluid was used, guided by haemodynamic variables, to the end of resuscitation.	
Outcomes	Deaths reported. Haemodynamic variables.	
Notes	Follow up to end of resuscitation.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Karanko 1987**

Methods	Randomised controlled trial. Description of allocation procedure unclear. Blinding not mentioned. No loss to follow up.	
Participants	32 adult men scheduled for coronary artery bypass surgery. Exclusions: left ventricular ejection fraction under 40%, abnormal lung function.	
Interventions	<ol style="list-style-type: none"> <li>1. Colloid group received 6% dextran 70 (n = 14).</li> <li>2. Ringer's lactate (n = 18).</li> </ol> Allocated fluid was used to the end of resuscitation.	
Outcomes	Deaths reported. Haemodynamic variables. Lung water.	
Notes	Follow up 2 weeks.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Lang 2001**

Methods	Randomised controlled trial, using a closed-envelope system.
Participants	42 patients scheduled for elective major abdominal surgery.
Interventions	1. Lactated Ringer's (n = 21). 2. 6% HES, molecular weight 139kD, degree of substitution 0.4 (n = 21).
Outcomes	Deaths. Haemodynamics and laboratory data. Tissue oxygenation. Volume input and output.
Notes	Follow up period unclear.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate

**Lang 2003**

Methods	Randomised controlled trial. Allocation concealment not clearly reported ("Closed envelope system"). Blinding method not reported ("...treatment in the ICU was performed by physicians who were blinded to the study").
Participants	36 patients undergoing elective major abdominal surgery. Exclusion criteria included: myocardial failure, renal insufficiency, severe pulmonary disease, liver dysfunction, diabetes mellitus, steroid therapy, pre-existing viral or bacterial infection and known allergic reactions to starch preparations.
Interventions	1. 6% HES (n = 18). 2. Ringer's Lactate (n = 18). Additional crystalloid solutions were supplied to equalize insensible fluid loss or as a solvent for drugs in group 1.
Outcomes	Pro- and anti-inflammatory cytokines. All patients survived.
Notes	Length of follow up not reported but all outcomes were in-hospital measures.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Ley 1990**

Methods	Randomised controlled trial. Method of allocation concealment unclear. Assessment of chest x-ray blinded. No loss to follow up.	
Participants	21 people undergoing coronary artery bypass grafting or valve surgery.	
Interventions	1. 6% hetastarch up to 1.5L then 5% plasma protein fraction (n = 11). 2. 0.9% saline (n = 10). Allocated fluid was used for post-operative fluid resuscitation.	
Outcomes	Deaths were not reported. Pulmonary and peripheral oedema. Haemodynamic variables.	
Notes	Follow up to discharge.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Lowe 1977**

Methods	Randomised controlled trial, allocation by sealed envelopes. Blinding not mentioned. No loss to follow up.	
Participants	Participants with serious trauma.	
Interventions	1. 25% albumin in Ringer's lactate (n = 77). 2. Ringer's lactate (n = 94). Allocated fluid was used throughout the pre- and intra-operative period.	
Outcomes	Deaths reported.	
Notes	Follow up to 5 days post-operatively. Data on the 30 participants with chest injuries who were left out of the Lowe 1977 report, but included in Moss 1981, have been included in the meta-analysis.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Lucas 1978**

Methods	Randomised controlled trial. Randomisation was based on the last digit of each patient's case number.
Participants	52 seriously injured patients.
Interventions	1. Standard resuscitation regimen ('balanced electrolyte', blood, fresh frozen plasma) plus salt poor albumin, maximum 150g during surgery and 150g per day for the next 5 days (n = 27). 2. Standard resuscitation regimen as above (n = 25).
Outcomes	Deaths reported in some patients.
Notes	In the final report of 94 randomised patients deaths were not reported. However, in this preliminary report of 52 injured patients deaths were reported.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	No	Inadequate

**Maitland 2005**

Methods	Randomised controlled trial. Open label. Random allocation was assigned by the use of sealed cards. No loss to follow up.
Participants	159 children with severe malaria and metabolic acidosis. Exclusion criteria included pulmonary oedema, oedematous malnutrition or papilledema.
Interventions	Severe acidosis 1. 4.5% Albumin (n = 23). 2. 0.9% Saline (n = 26). Moderate acidosis 1. 4.5% Albumin (n = 33). 2. 0.9% Saline (n = 35). 3. Control (n = 33).
Outcomes	Reduction in base deficit. Neurological sequelae. Death reported.
Notes	Length of follow up not reported but all outcomes were in-hospital measures.

***Risk of bias***

Item	Authors' judgement	Description
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**Maitland 2005** (Continued)

Allocation concealment?	Unclear	Unclear
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**Mattox 1991**

Methods	Quasi-randomised, allocation by alternation. Double-blind. 2 patients excluded from the analysis as code of fluid lost.
Participants	Participants were pre-hospital trauma victims attended to by emergency personnel within an hour of injury, who had systolic blood pressure of 90 mmHg or less and were 16 years or older. 72% of participants had sustained penetrating trauma.
Interventions	1. 250 mL Dextran-70 in 7.5% NaCl (n = 211). 2. 250 mL Ringer's lactate, saline or plasmalyte (n = 211). Allocated fluid was for initial pre-hospital resuscitation only.
Outcomes	Deaths reported.
Notes	Follow up to hospital discharge or transfer.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	No	Inadequate

**Mazher 1998**

Methods	Patients 'randomized'. Blinding of care givers by use of pharmacy prepared solutions. No loss to follow up.
Participants	Patients undergoing elective coronary artery surgery. Exclusions: age over 75, ejection fraction under 35%, creatinine over 135umol/L, ACE inhibitors.
Interventions	1. 5mL/kg polygeline (n = 10). 2. 5mL/kg 7.2% saline (n = 10). Allocated fluid given post-op over one hour. All patients subsequently receive polygeline and red blood cells.
Outcomes	Haemodynamic variables. Death.
Notes	Follow up to discharge from intensive care.

**Risk of bias**

**Mazher 1998** (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**McNulty 1993**

Methods	Randomised controlled trial. Method of allocation concealment not described. Blinding not mentioned. No loss to follow up.
Participants	Patients following elective cardiopulmonary bypass.
Interventions	1. 5% albumin and cell-saved blood (n = 14). 2. Plasmalyte and cell-saved blood (n = 14). Allocated fluid used as part of fluid volume replacement.
Outcomes	Deaths not reported. Study was designed to look at the effect of protein infusion on the accuracy of a haematocrit measuring device.
Notes	Length of follow up unspecified.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Metildi 1984**

Methods	Randomised controlled trial. Blinding not mentioned. No loss to follow up.
Participants	Participants were admissions to an intensive care and a trauma unit with adult respiratory distress syndrome and established pulmonary failure. Included both trauma and non-trauma patients.
Interventions	1. 5% salt-poor albumin (n = 20). 2. Ringer's lactate (n = 26). Allocated fluid was used throughout resuscitation, and if an operation was required the allocated fluid was used for volume replacement before and during the operation.
Outcomes	Deaths reported. Haemodynamic variables.
Notes	Follow up to discharge.

**Metildi 1984** (Continued)

<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Modig 1983**

Methods	Quasi-randomised controlled trial, allocation by admission date. Blinding not mentioned. No loss to follow up.
Participants	Participants were trauma admissions to an emergency department with a systolic blood pressure of less than 70mmHg. Age range was 20-58 years.
Interventions	1. Dextran-70 in Ringer's lactate (n = 12). 2. Ringer's lactate (n = 11). Allocated fluids were given as the initial resuscitation fluid on admission to the emergency department, and continued as needed until after the 6th day when major reconstructive surgery was undertaken.
Outcomes	Deaths reported. Development of respiratory distress syndrome.
Notes	Follow up to definitive reconstructive surgery.

<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	No	Inadequate

**Moretti 2003**

Methods	Randomised controlled trial. Allocation concealment method not clearly reported ("Patients randomized...by using a closed-envelope technique"). Blinding method not clearly reported ("Researchers were unaware of the patient's randomization"). No loss to follow up.
Participants	90 adult patients undergoing major elective general, gynaecological, orthopedic or urologic surgery with an anticipated blood loss > 500 ml. Exclusion criteria included age < 16 years, coagulopathy, renal or hepatic dysfunction and congestive heart failure.
Interventions	1. Hetastarch-Normal Saline (n = 30). 2. Hetastarch-Balanced Salt (n = 30). 3. Ringer's Lactate (n = 30).

**Moretti 2003** (Continued)

Outcomes	Postoperative nausea and vomiting. Death not reported.	
Notes	Follow up to discharge.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Nagy 1993**

Methods	Randomised controlled trial, contact with author showed it was an open label study. Blinding not mentioned. No loss to follow up.	
Participants	Participants were adult admissions to a trauma unit, with measurable systolic blood pressure less than 90 mmHg.	
Interventions	<ol style="list-style-type: none"> <li>1. Pentastarch in 0.9% NaCl (n = 21).</li> <li>2. Ringer's lactate (n = 20).</li> </ol> Allocated fluid was used throughout resuscitation with the exception that colloid patients received a maximum 4L of pentastarch, after which Ringer's lactate was given.	
Outcomes	Deaths were not reported. Haemodynamic variables.	
Notes	Follow up to discharge.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	No	Inadequate

**Ngo 2001**

Methods	Randomised controlled trial, opaque envelopes containing only treatment pack number.	
Participants	230 children with dengue shock syndrome.	
Interventions	<ol style="list-style-type: none"> <li>1. Dextran 70 (n = 55).</li> <li>2. 3% gelatin (n = 56).</li> <li>3. Lactated Ringer's (n = 55).</li> </ol>	

**Ngo 2001** (Continued)

	4. 'Normal' saline (n = 56).	
Outcomes	Initial pulse recovery time. Occurrence of timing and subsequent episodes of shock. Fall in haematocrit. Volume of fluid administered till recovery. Complications. And noted that there were no deaths in any group	
Notes	Follow up period unclear.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Adequate

**Nielsen 1985**

Methods	Randomised controlled trial. Method of allocation concealment not described. Blinding not mentioned. No loss to follow up.	
Participants	26 patients admitted for reconstructive surgery of the abdominal aorta.	
Interventions	1. Whole blood, crystalloid plus 80g albumin on the day of the operation, and 20g per day for the next 3 days. Albumin given as 100mL 20% human albumin solution (n = 13). 2. Whole blood and crystalloid, type not specified (n = 13).	
Outcomes	Deaths not reported. Author when contacted confirmed that there were no deaths in either group.	
Notes	Length of follow up 4 days.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Pockaj 1994**

Methods	Randomised controlled trial, allocation concealment unclear. Blinding not mentioned. Loss to follow up 18/54 in colloid group, 13/53 in saline group.	
Participants	Participants required fluid resuscitation as a result of vascular leak syndrome associated with Interleukin-2 therapy for metastatic cancer.	
Interventions	<ol style="list-style-type: none"> <li>250 mL boluses of 5% albumin in saline (n = 36 reported).</li> <li>250 mL boluses of 0.9% normal saline (n = 40 reported).</li> </ol> Boluses guided by haemodynamic variables. Both groups also received 0.45% saline with 10mmol/L KCl.	
Outcomes	Deaths. Toxic effects of chemotherapy. Haemodynamic variables.	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Prien 1990**

Methods	Randomised controlled trial. Blinding not mentioned. No loss to follow up.	
Participants	Participants were undergoing modified Whipple's operation.	
Interventions	<ol style="list-style-type: none"> <li>10% hydroxyethyl starch in 0.9% saline plus plasma protein fraction if requirements &gt; 20mL/kg (n = 6).</li> <li>20% human albumin solution (n = 6).</li> <li>Ringer's lactate.</li> </ol> Allocated fluid was administered intra-operatively only.	
Outcomes	Deaths. Intestinal oedema formation.	
Notes	Follow up period was unspecified.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Rackow 1983**

Methods	Randomised controlled trial, allocation concealment unclear. Blinding not mentioned. No loss to follow up.
Participants	Participants were aged 54 to 97, and had any one of the following pre-determined indicators of shock: systolic blood pressure of 90 mmHg or less, a cardiac index of less than 2.2 L./min.m <sup>2</sup> , a serum arterial lactate greater than 18mg/dl and WP less than 15mmHg.
Interventions	1. 6% hydroxyethyl starch (n = 9). 2. 5% albumin (n = 9). 3. 0.9% saline (n = 8). Allocated fluid was given as needed until the end of resuscitation.
Outcomes	Deaths reported. Fluid balance.
Notes	Follow up to discharge from hospital.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Rocha e Silva 1994**

Methods	Randomised controlled trial.
Participants	Participants were admissions to the emergency room, with a systolic blood pressure of 90 mmHg or less and were 16 years of age or older.
Interventions	Colloid group received 6% dextran-70 in 7.5% NaCl; crystalloid group received Ringer's lactate. Allocated fluid was used for the first intravenous infusion only.
Outcomes	Death was the main outcome measure, but the data are unpublished.
Notes	Follow up to 30 days. By April 1994, 125 patients had been entered into the study.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**SAFE 2004**

Methods	Randomised controlled trial. Randomisation by minimisation algorithm accessed through secure website.
Participants	Patients aged 18 years and above admitted to closed multidisciplinary intensive care units in 16 tertiary hospitals in Australia over 19-month period.
Interventions	1. 4% albumin (Albumex, CSL) (n = 3499). 2. Normal saline (n = 3501).
Outcomes	Death. Patients with new single or multiple-organ failure. Mean number of days: in ICU, in hospital, on mechanical ventilation, on renal replacement therapy.
Notes	Follow up to 28 days.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate

**Shah 1977**

Methods	Randomised controlled trial. Allocation by sealed envelope. Blinding not mentioned. No loss to follow up.
Participants	Patients with severe, multiple trauma and a systolic blood pressure of less than 90mmHg. All patients were adults and both sexes were included.
Interventions	1. 5% salt-poor albumin in Ringer's lactate (n = 9). 2. Ringer's lactate (n = 11). Volume infused guided by physiological parameters.
Outcomes	Death reported. Haemodynamic variables.
Notes	Length of follow up not stated.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Shires 1983**

Methods	Patients 'assigned randomly'. Blinding not mentioned. No loss to follow up.
Participants	People undergoing aortic reconstruction surgery. No exclusion criteria mentioned.
Interventions	1. Plasmanate (n = 9). 2. Ringer's lactate (n = 9). Allocated fluid used guided by haemodynamic variables until the first postoperative morning. All patients then received 0.45% saline.
Outcomes	Lung water. Haemodynamic variables. Death.
Notes	Follow up to two days post-op.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Sirieix 1999**

Methods	Patients "randomly assigned". Blinding not described. Two patients excluded after randomisation due to arrhythmias on giving the fluid (both in hypertonic saline group).
Participants	Patients undergoing mitral valve repair. Exclusions: LVEF < 0.4, systolic PAP > 50mmHg, coagulation disorders, creatinine >150mmol/L, electrolyte imbalance, diabetes, previous atrial fibrillation lasting > 1 year.
Interventions	1. 250mL 7.2% hypertonic saline, 6%HES (n = 8). 2. 250mL 7.2% hypertonic saline (n = 10). 3. 250mL 6% HES (n = 8). Fluid given over 15mins, 1 hour after admission to post-op intensive care.
Outcomes	Haemodynamic variables. Deaths reported. Side effects (2 had severe hypotension in group 2 and 1 in group 1; arrhythmias in 1 patient in group 1, 3 in group 2 and 1 in group 3).
Notes	Follow up to discharge from hospital (all within 10 days).

***Risk of bias***

Siriex 1999 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Skillman 1975

Methods	Randomised controlled trial, allocation concealment unclear. Blinding not mentioned. No loss to follow up.
Participants	Participants were undergoing elective abdominal reconstructive surgery.
Interventions	1. 25% salt-poor albumin 1g/kg and 5% albumin 1L (n = 7). 2. Ringer's lactate. Allocated fluid was given intra-operatively. All patients received crystalloids only for pre-loading before surgery.
Outcomes	Deaths were not reported.
Notes	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Tollofsrud 1995

Methods	Randomised controlled trial, allocation by sealed envelopes. Blinding not mentioned. No loss to follow up.
Participants	Participants were adult patients in need of volume replacement during and after coronary artery bypass surgery.
Interventions	1. Haemaccel (n = 10). 2. Dextran 70 (n = 10). 3. Albumin 40 (n = 10). 4. Ringer's lactate (n = 10). Allocated fluid was used throughout resuscitation.
Outcomes	Deaths reported. Fluid balance.
Notes	Follow up to 48 hours.

**Tollofsrud 1995** (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Tollofsrud 1998**

Methods	Randomised controlled trial, allocation by sealed envelope. Described as double blind, no loss to follow up mentioned.	
Participants	Patients with three vessel coronary artery disease undergoing elective coronary artery surgery. Exclusions: LVEF < 0.4, ventricular aneurysm, significant arrhythmia, diabetes, renal failure, lung disease.	
Interventions	<ol style="list-style-type: none"> <li>1. 4mL/kg of 75mg/mL hypertonic saline in dextran 70 60mg/mL over 30 mins (n = 10).</li> <li>2. Same volume and rate of isotonic saline (n = 10).</li> </ol> Fluid given just after surgery while still in operating theatre. Ringer's lactate for additional fluid.	
Outcomes	Fluid balance. Haemodynamic variables. Deaths not reported.	
Notes	Follow up to 48 hours.	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

**Upadhyay 2004**

Methods	Open label randomised trial. Allocation by sealed envelope. No loss to follow up mentioned.	
Participants	60 patients with septic shock aged 1 month to 12 years. Exclusion criteria: age less than one month, multiorgan failure and immunodeficiency states.	
Interventions	<ol style="list-style-type: none"> <li>1. Normal saline (n = 31).</li> <li>2. Polymer from degraded gelatin in saline (gelatin) (n = 29).</li> </ol>	
Outcomes	Haemodynamic data. Death reported.	
Notes	Length of follow up not reported but all outcomes were in-hospital measures.	

Upadhyay 2004 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Vassar 1990

Methods	Randomised controlled trial, allocation concealment unclear. Double blind study (solutions prepared in identical containers). No loss to follow up.	
Participants	Participants were emergency department admissions with trauma and a systolic blood pressure below 80mmHg and were 18 years or older. Pregnant women and people with preexisting cardiac, hepatic or renal disease were excluded.	
Interventions	<ol style="list-style-type: none"> <li>1. 6% dextran 70 in 7.5% saline (n = 23).</li> <li>2. Ringer's lactate (n = 24).</li> </ol> Allocated fluids were given as the initial resuscitation in the emergency department. Additional isotonic crystalloids (Ringer's lactate) were given as needed.	
Outcomes	Deaths reported. Haemodynamic variables.	
Notes	Follow up to hospital discharge.	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Vassar 1991

Methods	Randomised controlled trial, allocation by randomised sequence of coded containers. Double blind study. No loss to follow up.	
Participants	Participants were pre-hospital trauma cases undergoing helicopter transport to an emergency centre, with a systolic blood pressure of 100mmHg or less and were 18 years or older. Exclusions: preexisting cardiac renal, hepatic or neurological disease. Peripheral oedema.	
Interventions	<ol style="list-style-type: none"> <li>1. 4.2% dextran 70 in 7.5% saline or 6% dextran 70 in 7.5% saline (n = 83).</li> <li>2. Ringer's lactate (n = 83).</li> </ol> Fluids were given as the initial resuscitation fluid in the pre-hospital setting. Supplemental isotonic fluids were given at the discretion of the flight nurses.	

Vassar 1991 (Continued)

Outcomes	Deaths reported. Haemodynamic variables.	
Notes	Follow up to discharge. Allocation was to 4.2% dextran-70; to 6% dextran-70; or to crystalloid; for the calculation of the summary effect measure, the two dextran groups are combined.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Adequate

Vassar 1993a

Methods	Randomised controlled blind trial, allocation concealed by random sequence of identical containers. Double blind study. 36 people excluded post randomisation as deemed not to have met eligibility criteria. No loss to follow up.	
Participants	Participants, who were undergoing ambulance transport to an emergency centre, had systolic blood pressure 90 mmHg or less, and were 18 years or older. Exclusions: asystolic, undergoing CPR, lack sinus complex on ECG, more than 2 hours after trauma, pregnant, preexisting seizures, bleeding disorder, hepatic, cardiac or renal disease.	
Interventions	<ol style="list-style-type: none"> <li>1. 6% dextran 70 in 7.5% saline (n = 89).</li> <li>2. 7.5% saline (n = 85).</li> <li>3. 0.9% saline (n = 84).</li> </ol> Participants received 250mL of the allocated fluid in the pre-hospital setting. Additional isotonic crystalloids were given as needed.	
Outcomes	Deaths reported. Haemodynamic variables. Trauma scores.	
Notes	Follow up was to discharge from hospital.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Adequate

**Vassar 1993b**

Methods	Randomised controlled trial, allocation concealed by sequential use of coded identical containers. Double blind study. 39/233 patients excluded as deemed not to meet eligibility criteria, unclear from which groups.
Participants	Participants were pre-hospital trauma cases undergoing helicopter transport to an emergency centre, had a systolic blood pressure of 100mmHg or less and were 18 years or older. Exclusions: asystolic, undergoing CPR, lack sinus complex on ECG, more than 2 hours after trauma, pregnant, preexisting seizures, bleeding disorder, hepatic, cardiac or renal disease.
Interventions	<ol style="list-style-type: none"> <li>1. 12% dextran 70 in 7.5% saline (n = 49).</li> <li>2. 6% dextran 70 in 7.5% saline (n = 50).</li> <li>3. 7.5% saline (n = 50).</li> <li>4. Ringer's lactate (n = 45).</li> </ol> Participants received 250mL of the allocated fluid in the pre-hospital setting. Additional isotonic crystalloids were given as needed.
Outcomes	Deaths reported. Haemodynamic variables. Trauma scores and neurological outcome scores.
Notes	Follow up to hospital discharge.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate

**Verheij 2006**

Methods	Randomised controlled trial. Allocation concealment by "the sealed envelope method". Blinding method not reported. No loss to follow up.
Participants	67 patients with presumed hypovolemia after cardiac and major vascular surgery. Exclusion criteria; age > 79 years and known anaphylactoid reaction to colloids.
Interventions	<ol style="list-style-type: none"> <li>1. Saline (n = 16).</li> <li>2. Gelatin (n = 16).</li> <li>3. HES (n = 16).</li> <li>4. Albumin (n = 16).</li> </ol>
Outcomes	Haemodynamic data. Death not reported.
Notes	Length of follow up not reported but all outcomes were in-hospital measures.

Verheij 2006 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Virgilio 1979

Methods	Allocation "by random number". Blinding not mentioned. No loss to follow up.
Participants	Participants were undergoing abdominal aortic surgery.
Interventions	1. 5% albumin (n = 15). 2. Ringer's lactate (n = 14). Allocated fluid was used during operation for maintenance of pre-defined physiological parameters, and the resuscitation was continued with the allocated fluid until the day following the operation. This was followed by 5% dextrose in half-normal saline, with potassium chloride as needed.
Outcomes	Deaths reported.
Notes	Follow up two and a half weeks.

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Wahba 1996

Methods	Patients "randomly allocated". Blinding not mentioned. Two patients excluded as they required reoperation for bleeding.
Participants	22 adult patients in need of volume replacement following coronary artery bypass surgery. Exclusions: abnormal left ventricular function, platelet active medication or heparin.
Interventions	1. Haemaccel (n = 10). 2. Ringer's lactate (n = 10). Allocated fluid was used from the time of admission to intensive care following operation, to the end of resuscitation.
Outcomes	Deaths reported. Pulmonary oedema.

Wahba 1996 (Continued)

Notes	Follow up to discharge.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

Wills 2005

Methods	Randomised controlled study. Allocation concealed by specially prepared cardboard containers. Method of blinding not mentioned. No loss to follow up.	
Participants	512 children with Dengue shock syndrome aged 2 to 15 years.	
Interventions	Children with immoderately severe shock were randomised to the three interventions: 1. Ringer's lactate (n = 128). 2. 6 percent dextran 70 (n = 126). 3. 6 percent hydroxyethyl starch 200/0.5 (n = 129). Children with severe shock were randomized only to either of the two colloids interventions: 1. 6 percent dextran 70 (n = 67). 2. 6 percent hydroxyethyl starch 200/0.5 (n = 62).	
Outcomes	Requirement for supplemental intervention with rescue colloid. Time taken to achieve initial cardiovascular stability. Time taken to achieve sustained cardiovascular stability. Volume required. Change in the Hematocrit. Days in hospital. One death reported but not specified in which group.	
Notes	Length of follow up not clear.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Adequate

**Woittiez 1997**

Methods	Randomised controlled trial, allocation concealment by sealed opaque envelopes. No information on blinding or loss to follow up.	
Participants	60 patients who had developed hypoalbuminaemia (< 20g/l) after major surgery. 2 patients died after randomisation and before treatment started. They were excluded from the analysis.	
Interventions	<ol style="list-style-type: none"> <li>1. saline (500ml/24 hr) (n = 16).</li> <li>2. albumin 20% (300 ml/24h) (n = 15).</li> <li>3. HES 10% (500ml/24h) for 3 days (n = 27).</li> </ol> Aim was to restore colloid osmotic pressure.	
Outcomes	Changes in fluid balance, serum albumin, COP and clinical signs of oedema were followed daily. Death rates supplied by the author.	
Notes	Length of follow up unspecified.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Wu 2001**

Methods	Randomised controlled trial. No details given of randomisation method.	
Participants	41 adolescent or adult patients in emergency room suffering from shock.	
Interventions	<ol style="list-style-type: none"> <li>1. 4% modified fluid gelatin: succinated gelatin 40g/L, sodium chloride 7g/L, sodium hydroxide 1.36g/L (n = 18).</li> <li>2. Lactated Ringer's (n = 16).</li> </ol>	
Outcomes	Death. Haemodynamic variables.	
Notes	Not intention-to-treat: five patients who received blood transfusion and two who had surgery within the first hour of resuscitation were dropped from the analysis. Length of follow up not clear.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Younes 1992**

Methods	Randomised “in a double blind fashion”. Blinding by use of similar bottles. No loss to follow up.	
Participants	Participants were emergency department admissions, who had a systolic blood pressure of less than 80mmHg and were 19 years and older. Exclusions: pregnant, preexisting cardiac or metabolic disease.	
Interventions	<ol style="list-style-type: none"> <li>1. 6% dextran 70 in 7.5% saline (n = 35).</li> <li>2. 7.5% saline (n = 35).</li> <li>3. 0.9% saline (n = 35).</li> </ol> Allocated fluid was for initial bolus of 250mL, followed by isotonic crystalloids as needed.	
Outcomes	Deaths reported. Fluid balance.	
Notes	Follow up to discharge from hospital.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Younes 1994**

Methods	Trial conducted in a “double blind randomised fashion”. Blinding by use of coded, identical containers.	
Participants	Participants were trauma admissions to the emergency room requiring treatment for haemorrhagic hypovolaemia; all were over 15 years old. Exclusions: pregnant, cardiac or renal failure, cardiac arrest on arrival.	
Interventions	<ol style="list-style-type: none"> <li>1. 6% dextran 70 in 7.5% saline (n = 101).</li> <li>2. 0.9% saline (n = 111).</li> </ol> Allocated fluid was for the first intravenous infusion only.	
Outcomes	Deaths reported. Complications.	
Notes	Follow up period was 30 days.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Younes 1998**

Methods	Randomised controlled trial, allocation by sealed envelope. Blinding not mentioned, no apparent loss to follow up.	
Participants	Trauma patients with systolic blood pressure <90mmHg admitted to the emergency room, with no previous treatment.	
Interventions	<ol style="list-style-type: none"> <li>1. 10% pentastarch (n = 12).</li> <li>2. 0.9% saline (n = 11).</li> </ol> Fluid given in 250mL boluses until systolic blood pressure > 100mmHg.	
Outcomes	Deaths reported. No complications reported in either group.	
Notes	Follow up to 24 hours.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Zetterstrom 1981a**

Methods	The patients were randomly divided into two groups. Allocation concealment was by sealed opaque envelopes (information supplied by author). Blinding not mentioned. No loss to follow up.	
Participants	Adult patients undergoing elective major abdominal surgery.	
Interventions	<ol style="list-style-type: none"> <li>1. Standard volume replacement regimen (1L Dextran 70 then up to 4 units of RBC with electrolyte, then whole blood or RBC with plasma; post-op patients were given crystalloids and whole blood) plus 20% human albumin solution 100ml at end of operation, 200-300ml on same day, then 200ml on first post-op day, then 100ml for next 3 days (n = 15).</li> <li>2. Standard volume replacement regimen as above (n = 15).</li> </ol>	
Outcomes	Deaths reported. Haemodynamic variables.	
Notes	Length of follow up unspecified.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Unclear

**Zetterstrom 1981b**

Methods	The patients were randomly divided into two groups. Allocation concealment was by sealed opaque envelopes (information supplied by author). Blinding not mentioned. No loss to follow up.
Participants	18 patients who had undergone elective abdominal aortic surgery. No exclusions mentioned.
Interventions	1. 5% human albumin solution (n = 9). 2. Ringer's lactate solution (n = 9). Administration guided by pulmonary arterial occlusion pressure.
Outcomes	Deaths reported. Haemodynamic variables.
Notes	Follow up to discharge from hospital.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

COP = colloid osmotic pressure  
HES = hydroxyethylstarch  
LVEDP = left ventricular end diastolic pressure  
LVEF = left ventricular ejection fraction  
PAP = pulmonary artery pressure  
PAWP = pulmonary artery wedge pressure  
RBC = red blood cells  
WP = wedge pressure

**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Artru 1989	Intervention to control intracranial pressure not directed at fluid resuscitation.
Bocanegra 1966	This study contained two quasi-randomised comparisons of colloid with glucose and plasma/saline with saline. In both studies, the control solution was only given IV if the patient was in coma or shock. It was therefore not a reasonable comparison of colloid and crystalloid.
Boldt 1996	All groups received some colloid.

(Continued)

Boldt 2007	Comparison was not between colloids and crystalloids, rather two different colloid solutions.
Bothner 1998	Participants were having minor elective surgery, therefore not considered to be critically ill.
Breheme 1993	Intervention directed at haemodilution, not at volume replacement.
Bueno R 2004	The participants had elective surgery.
Chin 2006	Participants were undergoing elective surgery, therefore not considered to be critically ill.
Golub 1994	Albumin given solely as a nutritional supplement.
Goslinga 1992	Intervention directed at haemodilution, not volume replacement.
Green 2008	Article is a review.
Greenhalgh 1995	Intervention directed at the maintenance of serum albumin levels, not for volume replacement.
Hauser 1980	Cross-over trial.
Ko 2007	Comparison of crystalloids and colloids as preloading solutions.
Krasheninnikov 2007	Not a randomised controlled trial.
Lagonidis 1995	Intervention was pre-loading for coronary artery bypass surgery.
Lobo 2008	Experiment conducted on rabbits.
Marhofer 1999	Trial of fluid for preloading before spinal anaesthesia.
Mittermayr 2007	Patients were undergoing elective surgery.
Mittermayr 2008	Outcome was the change in concentration of tissue-type plasminogen activator.
Niemi 2008	Solutions were used for pump priming.
Nilsson 1980	Albumin given as a nutritional supplement.
Oliviera 2002	The participants had sepsis.
Paton-Gay 2007	The outcome was non-relevant to comparing crystalloids and colloids.
Paul 2003	The participants had elective surgery.
Rehm 2001	Two colloids (albumin and hetastarch) compared.
Steinberg 1989	Cross-over trial.

(Continued)

Tiryakioglu 2008	Patients were undergoing elective surgery and not considered critically ill. Also, the solutions were used as priming solutions.
Tseng 2008	Crystalloid and colloid treatment was not randomised.
Valetova 2007	Patients were randomised depending upon their treatment not prior to treatment.
Vercueil 2006	Article is a review.
Wilkes 2001	One group received saline plus hetastarch; the other received 'balanced' fluid plus hetastarch. Thus, each group received both a colloid and a crystalloid. This conflicts with the purpose our review which compares patients who had one of these with patients who had the other.
Woods 1993	This quasi-randomised trial looked at albumin supplementation in post operative patients, with the aim of maintaining the serum albumin. Since the main aim of giving albumin was not to replace volume, the study was excluded.

## DATA AND ANALYSES

### Comparison 1. colloid versus crystalloid (add-on colloid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 deaths	47		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 albumin or PPF	23	7754	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.10]
1.2 hydroxyethyl starch	17	1172	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.96, 1.44]
1.3 modified gelatin	11	506	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.49, 1.72]
1.4 dextran	9	834	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.94, 1.65]

### Comparison 2. colloid and hypertonic crystalloid versus isotonic crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 deaths	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 albumin or PPF	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.06, 4.33]
1.2 hydroxyethyl starch	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 modified gelatin	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 dextran	8	1283	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.05]

### Comparison 3. colloid versus hypertonic crystalloid

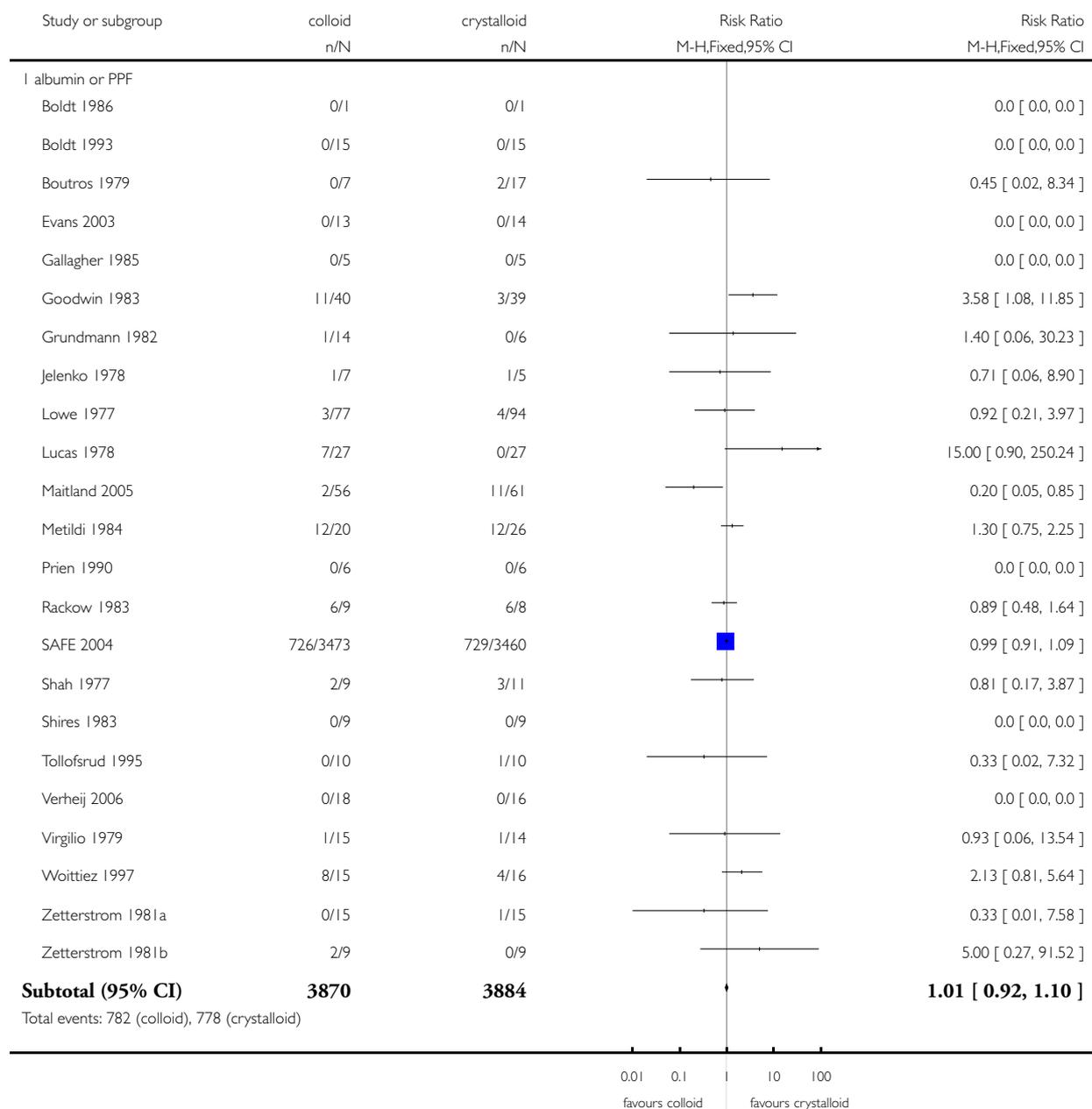
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 deaths	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 albumin or PPF	1	38	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.39, 126.92]
1.2 hydroxyethyl starch	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 modified gelatin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 dextran	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

### Analysis 1.1. Comparison 1 colloid versus crystalloid (add-on colloid), Outcome 1 deaths.

Review: Colloids versus crystalloids for fluid resuscitation in critically ill patients

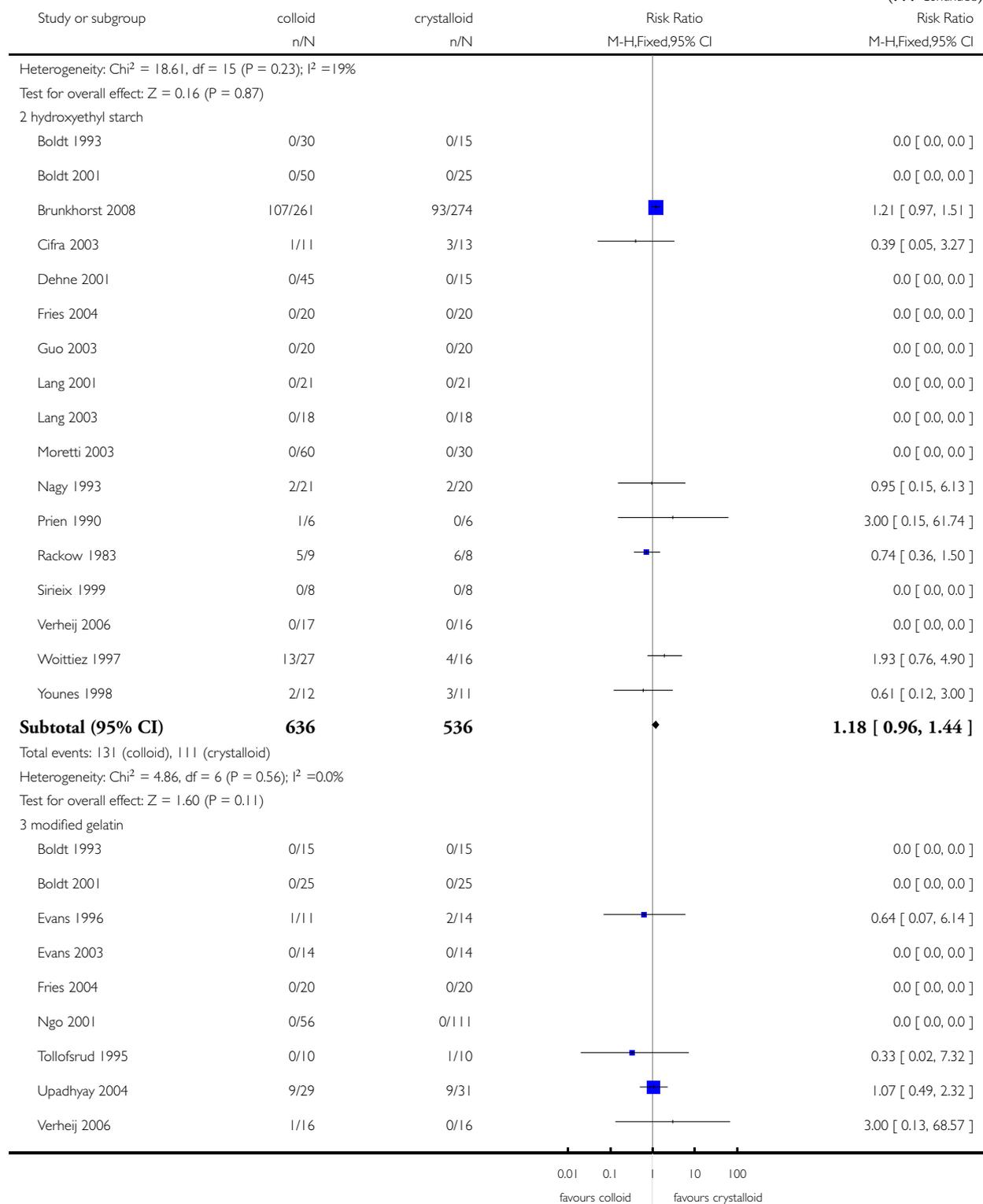
Comparison: 1 colloid versus crystalloid (add-on colloid)

Outcome: 1 deaths



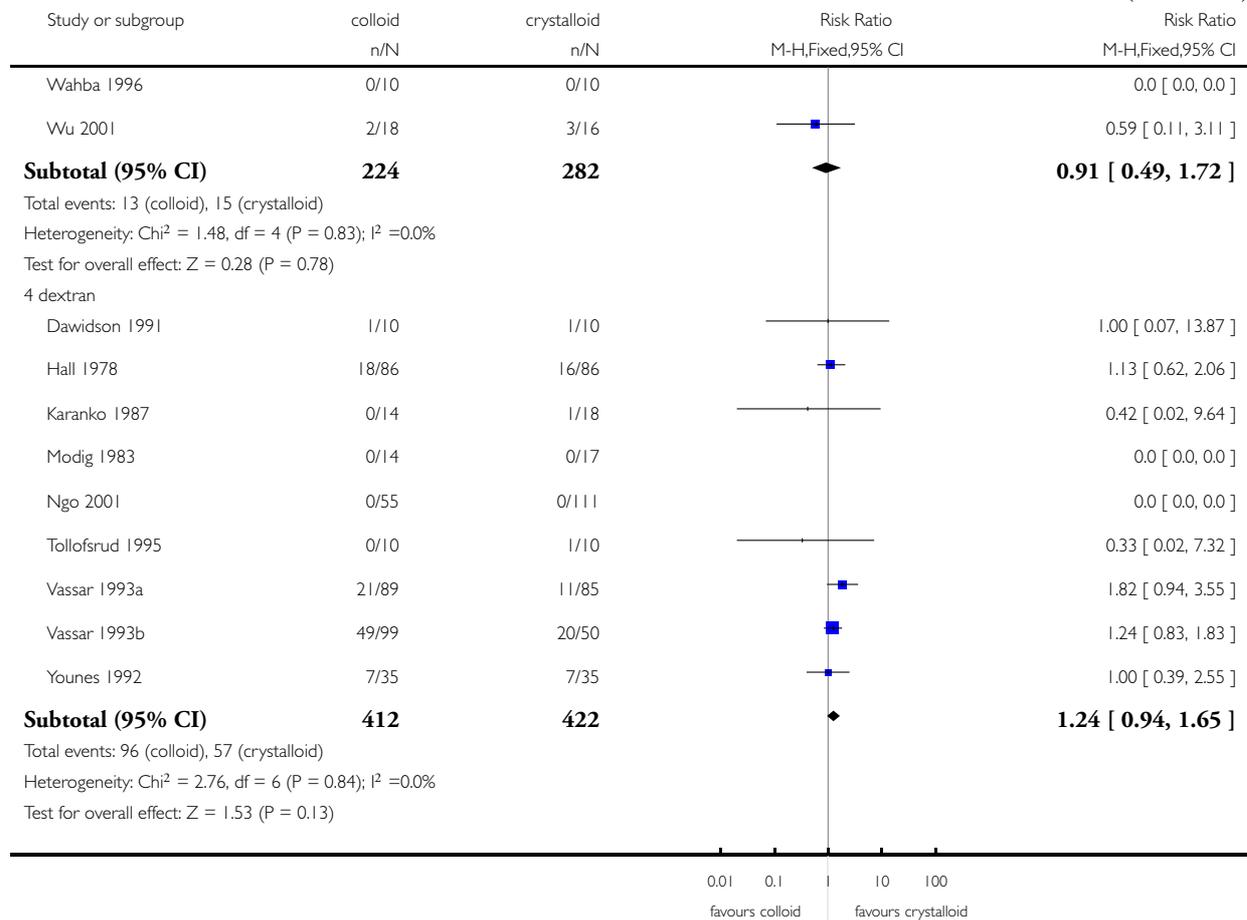
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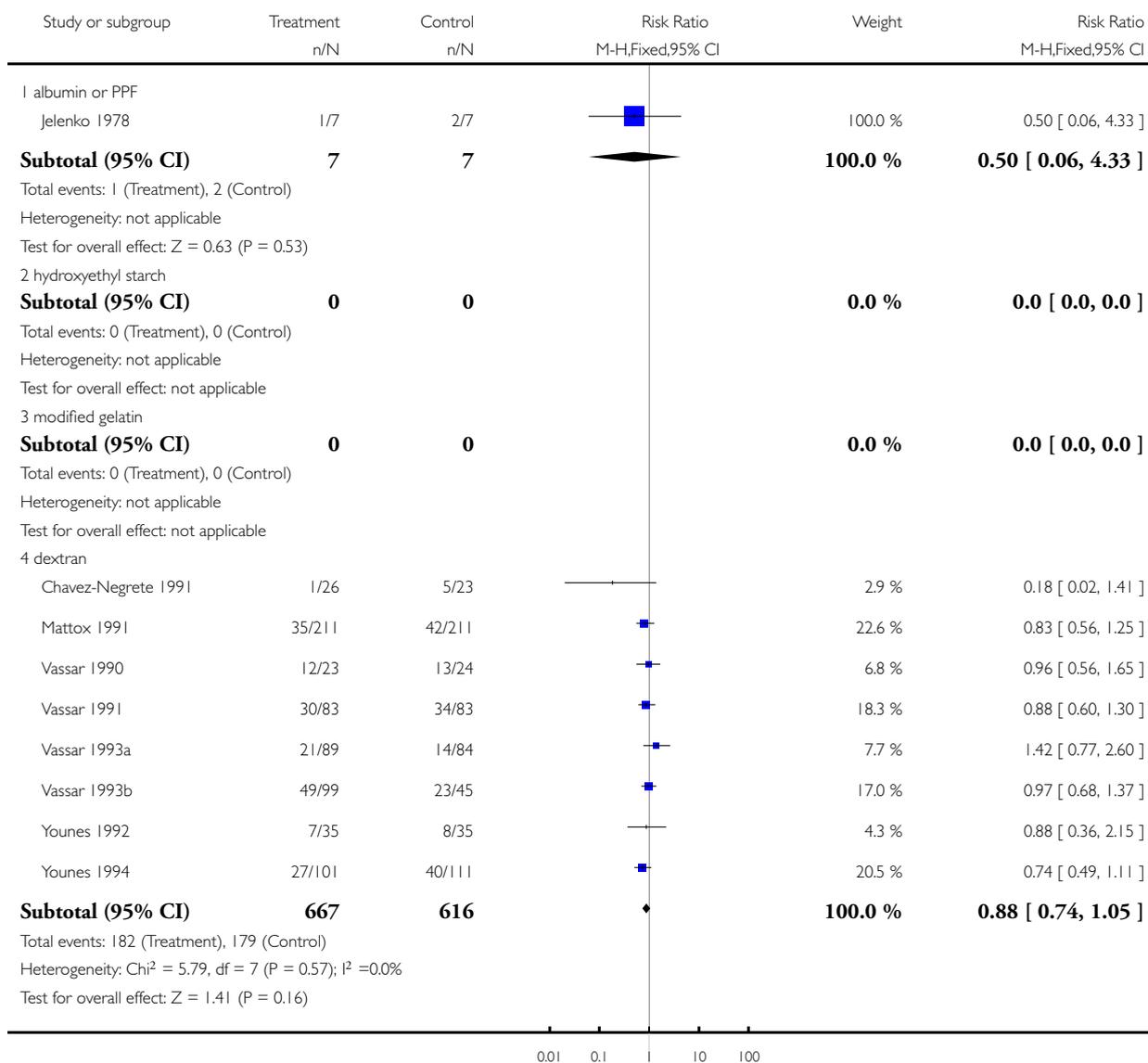


## Analysis 2.1. Comparison 2 colloid and hypertonic crystalloid versus isotonic crystalloid, Outcome 1 deaths.

Review: Colloids versus crystalloids for fluid resuscitation in critically ill patients

Comparison: 2 colloid and hypertonic crystalloid versus isotonic crystalloid

Outcome: 1 deaths

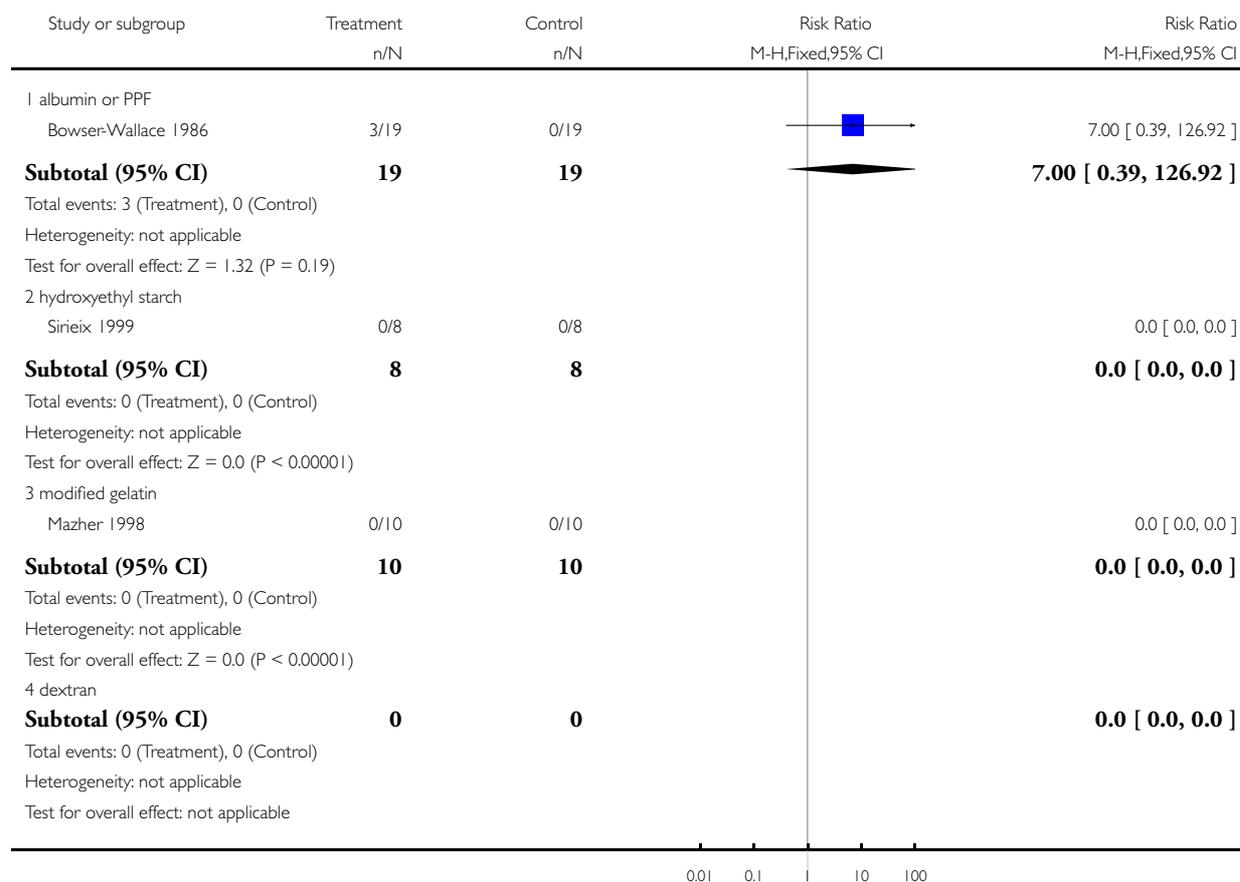


### Analysis 3.1. Comparison 3 colloid versus hypertonic crystalloid, Outcome 1 deaths.

Review: Colloids versus crystalloids for fluid resuscitation in critically ill patients

Comparison: 3 colloid versus hypertonic crystalloid

Outcome: 1 deaths



## APPENDICES

### Appendix I. Search strategy

Cochrane Injuries Group's Specialised Register (searched 30 Sept 2008), PubMed (searched 30 September; last three months), Controlled Trials metaRegister ([www.controlled-trials.com](http://www.controlled-trials.com)) (searched 30 Sept 2008)

colloid\* or hydrocolloid\* or crystalloid\*

#### MEDLINE 1950 to Sept 2008, EMBASE 1980 to Sept 2008

- 1.exp Fluid Therapy/
- 2.exp Rehydration Solutions/
- 3.exp Colloids/
- 4.exp Plasma Substitutes/
- 5.exp Plasma/
- 6.exp Serum/
- 7.exp Albumins/
- 8.exp Isotonic Solutions/
- 9.exp Hetastarch/
- 10.((fluid\$ or volume or plasma or rehydrat\$ or blood or oral) adj3 (replace\$ or therap\$ or substitut\$ or restorat\$ or resuscitat\$ or rehydrat\$)).ab,ti.
- 11.((fluid\$ or volume or plasma or rehydrat\$ or blood or oral) adj3 (challenge or perfusion or volume or intravenous or shock)).ti,ab.
- 12.(isotonic saline solution\$ or Blood substitute\$ or blood expander\$ or plasma volume expander\$ or volume expander\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 13.(colloid\$ or crystalloid\$ or albumin\$ or albumen\$ or plasma\$ or starch\$ or dextran\$ or gelofus\$ or hemaccel\$ or haemaccel\$ or hydrocolloid\$ or serum\$ or hetastarch or isotonic or ringer\$ or gelatin\$ or gentran\$ or pentastarch\$ or pentaspan\$ or hartman or sodium or potassium or salin\$ or hypertonic or hypotonic or hemodilution or haemodilution or ringer lactatae).ti.
- 14.or/1-13
- 15.randomi?ed.ab.
- 16.randomized controlled trial.pt.
- 17.controlled clinical trial.pt.
- 18.placebo.ab.
- 19.clinical trials as topic.sh.
- 20.randomly.ab.
- 21.trial.ti.
- 22.or/15-21
- 23.humans.sh.
- 24.22 and 23
- 25.14 and 24
- 26.colloid\* or hydrocolloid\* or crystalloid\*
- 27.exp Colloids/
- 28.26 or 27
- 29.25 and 28

#### ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to Sept 2008, ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to Sept 2008

Topic=(colloid\* or hydrocolloid\*) AND Topic=(crystalloid\*) AND Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial\* OR controlled clinical trial\* OR randomized controlled trial\*) NOT Topic=(animal model\* OR Animal\* OR Animal Experiment\* OR Animal disease model\* OR Laboratory Animal\*)

#### CENTRAL (The Cochrane Library Issue 3, 2008), National Research Register (to 2006, Issue 4)

#1MeSH descriptor Albumins explode all trees

#2MeSH descriptor Plasma Substitutes explode all trees

#3MeSH descriptor Plasma explode all trees  
 #4MeSH descriptor Plasma Volume explode all trees  
 #5MeSH descriptor Fluid Therapy explode all trees  
 #6MeSH descriptor Colloids explode all trees  
 #7(#1 OR #2 OR #3 OR #4 OR #5 OR #6)  
 #8(crystalloid\* or ringer\* or hartman\* or sodium\* or potassium\* or salin\*):ti or (crystalloid\* or ringer\* or hartman\* or sodium\* or potassium\* or salin\*):ab  
 #9Isotonic saline solution\* OR Blood substitute\* OR blood expander\* OR plasma volume expander\* OR volume expander\*  
 #10(colloid\* OR crystalloid\* OR albumin\* OR albumen\* OR plasma OR starch\* OR dextran\* OR gelofus\* OR hemaccel\* OR haemaccel\* OR OR serum OR hetastarch OR isotonic OR ringer\* OR gelatin\* OR gentran\* OR pentastarch\* OR pentaspan\* OR hartman OR sodium OR potassium OR saline):ti  
 #11(fluid\* OR volume OR plasma OR rehydrat\* OR blood OR oral) AND (replace\* OR therapy OR substitut\* OR restorat\* OR resuscitat\* OR rehydrat\*):ab  
 #12MeSH descriptor Rehydration Solutions explode all trees  
 #13MeSH descriptor Serum explode all trees  
 #14MeSH descriptor Isotonic Solutions explode all trees  
 #15MeSH descriptor Hetastarch explode all trees  
 #16(#1 OR #2 OR #2 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)  
 #17MeSH descriptor Colloids explode all trees  
 #18colloid\* OR crystalloid\* OR hydrocolloid\*  
 #19#17 OR #18  
 #20#16 AND #19

## WHAT'S NEW

Last assessed as up-to-date: 29 September 2008.

Date	Event	Description
10 February 2011	New citation required but conclusions have not changed	The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated ( <a href="#">Boldt 2009</a> ). As the editors who revealed this fabrication point out ( <a href="#">Reinhart 2011</a> ; <a href="#">Shafer 2011</a> ), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author ( <a href="#">Boldt 1986</a> , <a href="#">Boldt 1993</a> , <a href="#">Boldt 2001</a> , <a href="#">Lang 2001</a> , <a href="#">Lang 2003</a> ) on the conclusions of the review. The authors of the review have changed.

## HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 1997

Date	Event	Description
17 April 2009	New search has been performed	April 2009 An updated search for new trials was conducted in October 2008. One new study was included (Brunkhorst 2008). The analysis, results and discussion sections have been revised accordingly.
16 July 2008	Amended	Converted to new review format.
1 July 2007	New search has been performed	August 2007 An updated search for new trials was conducted in December 2006. Ten new studies were included (Evans 2003, Cifra 2003, Fries 2004, Guo 2003, Lang 2003, Maitland 2005, Moretti 2003, Upadhyay 2004, Verheij 2006, Wills 2005). The analysis, results and discussion sections have been revised accordingly.

## CONTRIBUTIONS OF AUTHORS

July 2007

PP and IR examined trials for inclusion or exclusion, reaching agreement by discussion. PP and IR extracted data from the new studies. PP amended the text of the review.

April 2009

IR and MP examined trials for inclusion or exclusion, reaching agreement by discussion. IR and MP extracted data from the new study. MP amended the text of the review. PP edited the final version.

February 2010

The Cochrane Injuries Group amended the text (Emma Sydenham, Managing Editor). Both authors agreed with the changes to the manuscript.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Institute of Child Health, University of London, UK.
- UK Cochrane Centre, NHS R&D Programme, UK.

### External sources

- NHS R&D Programme: Mother and Child Health, UK.
- Cochrane Review Incentive Scheme, Department of Health, UK.

## NOTES

The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated ([Boldt 2009](#)). As the editors who revealed this fabrication point out ([Reinhart 2011](#); [Shafer 2011](#)), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author ([Boldt 1986](#), [Boldt 1993](#), [Boldt 2001](#), [Lang 2001](#), [Lang 2003](#)) on the conclusions of the review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Rehydration Solutions; Colloids [\*therapeutic use]; Critical Illness [\*therapy]; Fluid Therapy [\*methods]; Plasma Substitutes [\*therapeutic use]; Randomized Controlled Trials as Topic; Resuscitation [methods]

### MeSH check words

Humans