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## Human albumin solution for resuscitation and volume expansion in critically ill patients (Review)

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[Intervention Review]

# Human albumin solution for resuscitation and volume expansion in critically ill patients

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## ABSTRACT

### Background

Human albumin solutions are used for a range of medical and surgical problems. Licensed indications are the emergency treatment of shock and other conditions where restoration of blood volume is urgent, such as in burns and hypoproteinaemia. Human albumin solutions are more expensive than other colloids and crystalloids.

### Objectives

To quantify the effect on mortality of human albumin and plasma protein fraction (PPF) administration in the management of critically ill patients.

### Search methods

We searched the Cochrane Injuries Group Specialised Register (searched 31 May 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), MEDLINE (Ovid) (1948 to week 3 May 2011), EMBASE (Ovid) (1980 to Week 21 2011), CINAHL (EBSCO) (1982 to May 2011), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to May 2011), ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to May 2011), PubMed ([www.ncbi.nlm.nih.gov/sites/entrez/](http://www.ncbi.nlm.nih.gov/sites/entrez/)) (searched 10 June 2011, limit: last 60 days). Reference lists of trials and review articles were checked, and authors of identified trials were contacted.

### Selection criteria

Randomised controlled trials comparing albumin or PPF with no albumin or PPF or with a crystalloid solution in critically ill patients with hypovolaemia, burns or hypoalbuminaemia.

### Data collection and analysis

We collected data on the participants, albumin solution used, mortality at the end of follow up, and quality of allocation concealment. Analysis was stratified according to patient type.

## Main results

We found 38 trials meeting the inclusion criteria and reporting death as an outcome. There were 1,958 deaths among 10,842 trial participants.

For hypovolaemia, the relative risk of death following albumin administration was 1.02 (95% confidence interval (CI) 0.92 to 1.13). This estimate was heavily influenced by the results of the SAFE trial, which contributed 75.2% of the information (based on the weights in the meta-analysis). For burns, the relative risk was 2.93 (95% CI 1.28 to 6.72) and for hypoalbuminaemia the relative risk was 1.26 (95% CI 0.84 to 1.88). There was no substantial heterogeneity between the trials in the various categories ( $\text{Chi}^2 = 26.66$ ,  $\text{df} = 31$ ,  $P = 0.69$ ). The pooled relative risk of death with albumin administration was 1.05 (95% CI 0.95 to 1.16).

## Authors' conclusions

For patients with hypovolaemia, there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia. The possibility that there may be highly selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trials.

## PLAIN LANGUAGE SUMMARY

### What is the effect of giving human albumin compared to saline to replace lost blood in critically ill or injured people

Trauma, burns or surgery can cause people to lose large amounts of blood. Fluid replacement, giving fluids intravenously (into a vein), is used to help restore blood volume and hopefully reduce the risk of dying. Blood products (including human albumin), non-blood products or combinations can be used. This review of 38 trials found no evidence that albumin reduces the risk of dying. Albumin is very expensive, in which case it may be better to use cheaper alternatives such as saline for fluid replacement.

## BACKGROUND

In patients with acute and chronic illness, serum albumin concentration is inversely related to mortality risk. A systematic review of cohort studies meeting specified criteria estimated that, for each 2.5 g/L decrement in serum albumin concentration, the risk of death increases by between 24% and 56% (Goldwasser 1997). The association persists after adjusting for other known risk factors and pre-existing illness, suggesting a direct protective effect of the albumin molecule (Goldwasser 1997). Largely as a result of these observations, human albumin solutions are now used in the management of a diverse range of medical and surgical problems. Published indications for human albumin solution include the emergency treatment of shock and other conditions where restoration of blood volume is urgent, the acute management of burns, and clinical situations associated with hypoproteinaemia (ABPI 1998).

In comparison with other colloidal solutions and with crystalloid solutions, human albumin solutions are expensive (McClelland

1990). Volume for volume human albumin solution is twice as expensive as hydroxyethyl starch, and over 30 times more expensive than crystalloid solutions such as sodium chloride or Ringer's lactate. Because of the high cost and limited availability of human albumin, it is particularly important that its use should be restricted to the indications for which it has been shown to be effective. To assess the effectiveness and safety of human albumin solutions in the management of critically ill patients, particularly those with hypovolaemia from injury or surgery, burns and hypoproteinaemia, a systematic review of randomised controlled trials was conducted.

## OBJECTIVES

To quantify the effect on mortality of human albumin administration in the management of critically ill patients.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We sought to identify all randomised controlled trials of human albumin or plasma protein fraction (PPF) administration (albumin or PPF versus no albumin or PPF, or a crystalloid solution).

#### Types of participants

Critically ill patients with hypovolaemia, burns or hypoproteinaemia. Trials involving patients receiving pre-operative volume

loading or haemodilution, and trials of albumin administration during paracentesis, were excluded.

#### Types of interventions

Human albumin solution or plasma protein fraction (PPF).

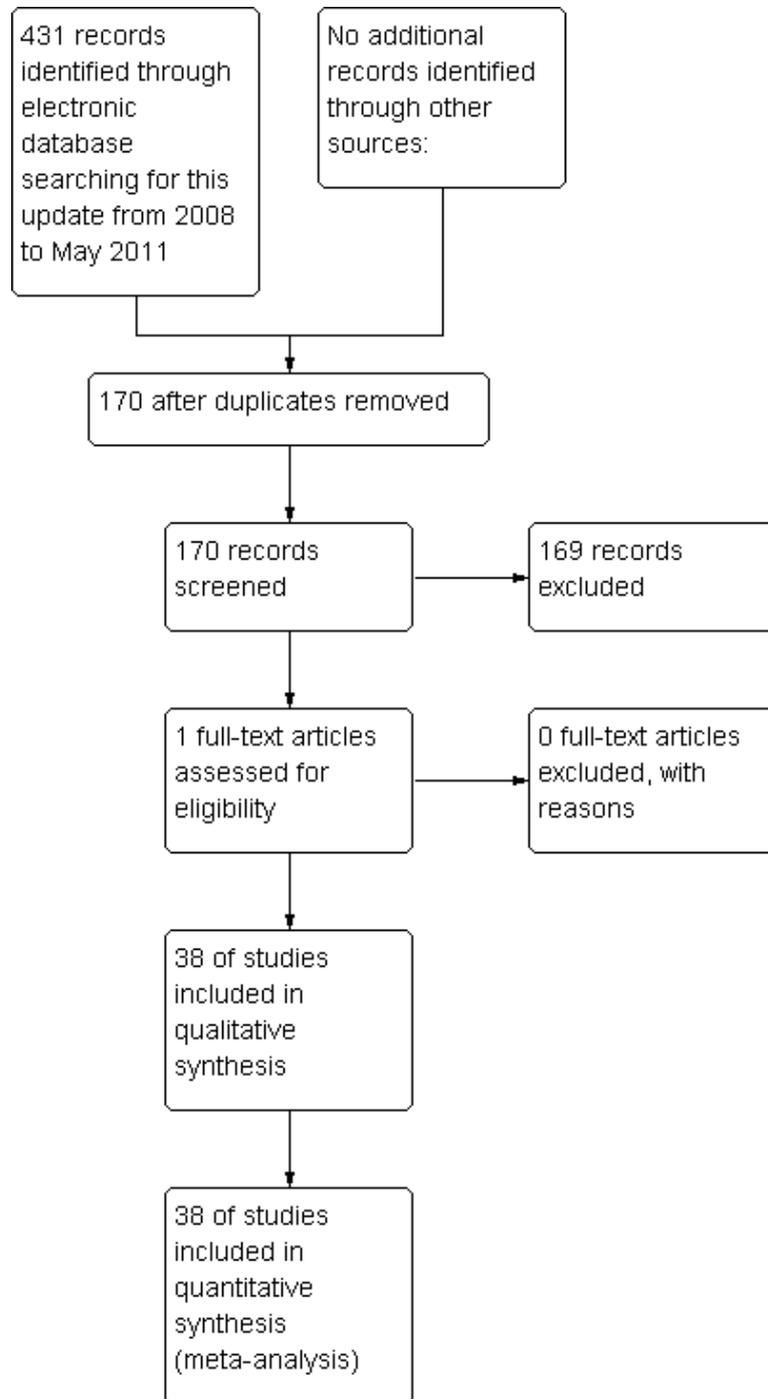
#### Types of outcome measures

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 latest search was carried out in May to June 2011 using the electronic databases listed below. See [Figure 1](#) for the study identification and selection process for this update.

Figure 1. PRISMA diagram: study identification and selection process-latest update only



Search strategies used for previous versions of this review can be obtained from the Trials Search Co-ordinator of the Cochrane Injuries Group.

### Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched May 31 2011);
- Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2011, Issue 2);
- MEDLINE(Ovid) (1948 to week 3 May 2011);
- Embase (Ovid) (1980 to Week 21 2011);
- CINAHL (EBSCO) (1982 to May 2011);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to May 2011);
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to May 2011);
- PubMed ([www.ncbi.nlm.nih.gov/sites/entrez/](http://www.ncbi.nlm.nih.gov/sites/entrez/)) (searched 10 June 2011, limit: last 60 days).

Full details of the latest search strategies can be found in [Appendix 1](#).

### Searching other resources

For the original searches, trials were identified using BIDS Index to Scientific and Technical Proceedings and by handsearching 29 international journals and the proceedings of several international meetings on fluid resuscitation. To identify unpublished trials we searched the register of the Medical Editors' Trial Amnesty, and contacted the Medical Directors of Bio Products Laboratory (Zenalb), Centeon Limited (Albuminar), and Alpha Therapeutic UK Limited (Albutein).

We have subsequently identified studies by examining reference lists of included studies and previously published reviews. We have also contacted authors of included studies to enquire about other published or unpublished studies that they may be aware of. We did not limit our searches by date, language or publication status.

### Data collection and analysis

One author scanned the titles and abstracts of reports identified by electronic searching to produce a list of possibly relevant reports. Two authors (PA and IR) then checked the list to determine which articles to retrieve in full. Disagreements were resolved by discussion.

The same two authors applied the selection criteria, again resolving disagreements by discussion. They both extracted data on study design, allocation concealment, participants, interventions and mortality. One author (IR) entered the data into Review Manager and the other (PA) checked it against his data extraction.

Where clarification on any aspect of a study was needed, one review author contacted the author of the trial.

Relative risks and 95% confidence intervals (CI) for mortality were calculated for each trial on an intention-to-treat basis. Heterogeneity between trials was tested using a Chi<sup>2</sup> test, where  $P \leq 0.05$  was taken to indicate significant heterogeneity. As long as statistical heterogeneity did not exist, for dichotomous data summary relative risks and 95% CIs were calculated using a fixed-effect model. In the event of statistical heterogeneity, if the source of heterogeneity could obviously be related to patient type, or allocation concealment, we stratified the analyses on that dimension.

## RESULTS

### Description of studies

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

A total of 38 randomised controlled trials were identified that met the study inclusion criteria. Mortality data were available either from the published report or on contact with the authors of 38 of these trials. The five trials for which mortality data could not be obtained (Ernest 1999; Ernest 2001; McNulty 1993; Oca 1999; Skillman 1975) included a total of 124 randomised patients, comprising 1.14% of the total number of randomised patients in all trials meeting the study inclusion criteria. One of the trials was an unpublished trial registered in the Medical Editors' Trial Amnesty (Woitiez 1998). Further details about this trial, including data on mortality, were obtained directly from the trialist. In six trials there were no deaths in either the intervention or comparison groups. An intention-to-treat analysis could not be done for nine of 50 patients in one study (Oca 2003) consequently mortality data is only presented for 41 patients. The trial by Lucas et al was reported in five publications. An early report gave the mortality data for 52 randomised patients, 27 allocated to receive albumin, 25 allocated to receive no albumin (Lucas 1978). Subsequent publications indicated that recruitment to the trial continued until 94 patients were randomised. Mortality data for all the 94 patients were not published, nor were they available on contact with the author. Consequently the outcome data for the 52 patients are presented. For the 32 included trials in which there were one or more deaths in either the intervention or control groups, allocation concealment involved a method that would be expected to reduce the risk of foreknowledge of treatment allocation (pharmacy controlled randomisation or serially numbered sealed opaque envelopes) in 20 trials, was unclear in eight trials, and inadequate in four trials.

## Risk of bias in included studies

[Bland 1973](#)

Randomised control trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment was not described.

[Bland 1976](#)

This study is reported as randomised but the method of allocating random numbers and method of allocation concealment are unknown.

[Boldt 1993](#)

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

[Boutros 1979](#)

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

[Brown 1988](#)

The random sequence was generated using random number tables. No allocation concealment.

[Cooper 2006](#)

Randomisation was accomplished with a computer-generated list and sequentially numbered sealed, opaque envelopes.

[Dubois 2006](#)

Eligible patients were randomised in a 1:1 ratio using sealed envelopes.

[Ernest 1999](#)

Randomisation was done by the hospital chart number (odd or even).

[Ernest 2001](#)

Randomisation was done by the hospital record number (odd or even).

[Foley 1990](#)

Patients were randomly assigned to either a treatment or non-treatment group by medical record number.

[Gallagher 1985](#)

Randomisation and allocation concealment were by computerised system.

[Golub 1994](#)

Random sequence was computer generated. Allocation concealment was by the use of sealed opaque envelopes.

[Goodwin 1983](#)

Randomisation was according to random number tables. The methods of allocation concealment were unknown.

[Greenhalgh 1995](#)

Randomisation scheme controlled by the pharmacy.

[Greenough 1993](#)

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

[Grundmann 1982](#)

The study is reported as prospectively randomised, but the methods of randomisation and allocation concealment are unknown.

[Jelenko 1978](#)

The study is reported as randomised but the method of randomi-

sation and allocation concealment are unknown.

[Kanarek 1992](#)

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

[Lowe 1977](#)

The method of allocating random numbers is unknown. Sealed envelopes were used to ensure allocation concealment.

[Lucas 1978](#)

Allocation was based on the last digit of each patient's case number. Ninety-four patients were randomised in total but the number of deaths was not reported in the final report. However, in a preliminary report, based on 52 of the randomised patients, deaths were reported.

[Maitland 2005](#)

Randomised control trial using a sealed card system.

[Maitland 2011](#)

Multicentre, open, randomised, controlled study. Sealed opaque envelopes were used to assist allocation concealment.

[McNulty 1993](#)

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

[Nielsen 1985](#)

This study is reported as randomised but the method of allocation concealment is not described.

[Nilsson 1980](#)

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

[Oca 1999](#)

Randomisation was done by sequentially numbered, sealed, opaque envelopes.

[Oca 2003](#)

Randomisation was accomplished by random number tables via sealed, serially numbered envelopes.

[Pockaj 1994](#)

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

[Prien 1990](#)

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

[Quinlan 2004](#)

Randomised double blind controlled trial.

[Rackow 1983](#)

Randomisation was according to a pre-determined randomisation schedule, but the methods and the allocation concealment are unknown.

[Rubin 1997](#)

Allocation concealment was by a sealed opaque envelope system in the hospital pharmacy.

[SAFE 2004](#)

Central randomisation accessed on the Internet through a secure website with use of a minimisation algorithm. Blinding was assured through the use of specially designed masking cartons and

specially designed and manufactured administration sets. The authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated.

[Shah 1977](#)

Randomised controlled trial. Allocation by sealed envelope.

[Skillman 1975](#)

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

[So 1997](#)

Randomised controlled trial. Allocation concealment was by computerised system.

[Tollofsrud 1995](#)

The method of generating random numbers is unknown. Allocation concealment was by sealed opaque envelopes.

[Virgilio 1979](#)

Randomisation was determined using random number tables. Methods of allocation concealment are unknown.

[Woittiez 1998](#)

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

[Wojtysiak 1992](#)

Randomisation was determined using random number tables. Allocation concealment was inadequate.

[Woods 1993](#)

Patients with even hospital numbers were allocated to the group receiving albumin, while those with odd hospital numbers were allocated to the group not receiving supplemental albumin.

[Zetterstrom 1981a](#)

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

[Zetterstrom 1981b](#)

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

## Effects of interventions

For hypovolaemia the pooled relative risk of death following albumin administration was 1.02 (95% confidence interval (CI) 0.92 to 1.13). This estimate was heavily influenced by the results of the SAFE trial which received 75.2% of the weight. For burns the relative risk was 2.93 (95% CI 1.28 to 6.72), and for hypoalbuminaemia the relative risk was 1.26 (95% CI 0.84 to 1.88). There was no substantial heterogeneity between the trials in the various categories ( $\text{Chi}^2 = 26.66$ ,  $\text{df} = 31$ ,  $P = 0.69$ ). The pooled relative risk of death with albumin administration was 1.05 (95% CI 0.95 to 1.16).

## DISCUSSION

Because many of the trials included in this meta-analysis are small and many are poorly concealed, the results must be interpreted

with caution. The SAFE trial, however, is a notable exception. The SAFE trial included a total of 6997 randomised participants, allocation was well concealed, the use of a minimisation algorithm helped to ensure that baseline characteristics were well balanced, vigorous attempts were made to ensure that the participating clinicians were blind to the type of fluid that was administered, and an intention-to-treat analysis was undertaken. The SAFE trial provided no evidence that albumin reduced mortality in patients with hypovolaemia, although the possibility of a modest benefit or harm could not be excluded.

This systematic review was first updated in November 2001. At that time, one additional trial was identified and included ([Bland 1973](#)). This trial compared albumin and dextrose infusions in new-born infants with low cord serum protein levels who were considered to be at risk of respiratory distress. This trial meets the eligibility criteria for the review (hypoproteinaemia) but had been overlooked in the original search. However, the inclusion of this trial does not change the conclusions of the review. The latest update of this review (July 2011) includes one further recently published trial that meets the inclusion criteria ([Maitland 2011](#)); it does not change the conclusions of the review.

## Summary of main results

There is no evidence that albumin reduces mortality in patients with hypovolaemia, burns or hypoproteinaemia. For patients with burns or hypoproteinaemia, there is a suggestion that albumin administration may increase mortality.

Mortality was selected as the outcome measure in this systematic review for several reasons. In the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients, and data on death are reported in nearly all studies. Furthermore, one might expect that mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes. The use of a pathophysiological end-point as a surrogate for an adverse outcome assumes a direct relationship between the two, an assumption that may sometimes be inappropriate. Finally, when trials collect data on a number of physiological end-points, there is the potential for bias due to the selective publication of end-points showing striking treatment effects. Because we obtained mortality data for all but four of the included trials, the likelihood of bias due to selective publication of trial outcomes is minimal.

## Potential biases in the review process

Although publication bias is a potent threat to the validity of systematic reviews, it is unlikely to have had an important impact in this study. There was no evidence of funnel plot asymmetry on visual inspection. In some of the trials included in this review,

allocation concealment was inadequate or was unclear. As a result, it is possible that more severely ill patients were preferentially allocated to the albumin treated group, which may account for the increased mortality risk in this group. Nevertheless, when the analyses were repeated, including only those trials in which allocation concealment involved a method that would be expected to reduce the risk of foreknowledge of treatment allocation, the point estimates were little different.

## AUTHORS' CONCLUSIONS

### Implications for practice

For patients with hypovolaemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia and there is a suggestion that albumin may increase the risk of death.

### Implications for research

The possibility that there may be highly selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of

albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trials.

## ACKNOWLEDGEMENTS

We thank the Intensive Care National Audit & Research Centre in London for help with identifying trials for this review and for their extensive handsearching activities. We are grateful to AJ Woittiez for providing unpublished trial data from the trial that was registered in the Medical Editors' Trial Amnesty. We thank Elizabeth Bryant, Information Officer at Centeon Limited, and Martin O'Fobve at Bio Products Limited, for searching their databases for albumin trials. We thank Anne Greenough for re-examining individual patient records in order to provide data on mortality. We are also grateful to Peter Sandercock for his assistance in the editorial process. Thanks also to Carol Lefebvre of the UK Cochrane Centre, for the original search strategy and for conducting the original database searches. Subsequent searches were conducted by the Injuries Group Trials Search Co-ordinator.

2011 update: The authors wish to thank Alain Li Wan Po and Leah Li for their contribution to the original version of the review and updates to 2011.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Bland 1973

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment not fully described   |
| Participants  | Newborn infants considered at high risk for developing respiratory distress. Those with a cord serum protein level less than 4.6g/100ml and at least one of the following; birthweight less than 2500g, gestational age less than 37 weeks, arterial pH less than 7.25 |
| Interventions | 1) Intervention (n=50) received 8ml/kg 25% salt poor albumin.<br>2) Control group (n=50) received 8ml/kg 5% dextrose in water  |
| Outcomes      | Deaths reported within 28 days.  |
| Notes         |  |

#### Bland 1976

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Method of allocation concealment not fully described   |
| Participants  | Premature infants (less than 37 weeks gestation), with hypoproteinaemia (cord serum total protein of 4.6g/100ml or less)        |
| Interventions | 1) Intervention group (n=14) received 8ml/kg salt-poor albumin.<br>2) Comparison group (n=13) received 8ml/kg glucose in water. |
| Outcomes      | Deaths reported.  |
| Notes         | Length of follow-up unspecified.  |

#### Boldt 1993

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described in published report. Authors were contacted and confirmed the use of sealed opaque envelopes |
| Participants  | Men undergoing elective aortocoronary bypass grafting, who had a pulmonary capillary wedge pressure of less than 5mmHg after induction of anaesthesia                    |
| Interventions | 1) Intervention (n=15): Albumin 5%.<br>2) Control (n=15): No additional volume.  |
| Outcomes      | Deaths not reported.<br>Authors were contacted and confirmed that there were no deaths in the albumin nor the control group  |

**Boldt 1993** (Continued)

|   |                           |                              |
|---|---------------------------|------------------------------|
| Notes                                   | Follow-up to 1 day.       |                              |
| <b>Risk of bias</b>                     |                           |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b> | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk                  |                              |

**Boutros 1979**

|               |  |  |
|---------------|--|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not fully described  |  |
| Participants  | Participants were undergoing major operative procedures on the abdominal aorta   |  |
| Interventions | 1) Intervention group (n=7) received albumin in 5% dextrose.<br>2) Control group (n=17) received 5% dextrose in lactated Ringers and 5% dextrose in 0.45 NaCl. Allocated fluids were used on admission to ICU, following surgery |  |
| Outcomes      | Deaths reported.   |  |
| Notes         | Follow-up to 48 hours after the end of the operation.  |  |

**Brown 1988**

|   |  |                              |
|---|--|------------------------------|
| Methods                                 | Randomised controlled trial. Patients entered into the study were assigned to one of two treatment groups by a table of random numbers. Method of allocation concealment not described. Author contacted - no allocation concealment |                              |
| Participants                            | All patients who required central TPN and had hypoalbuminaemia (serum albumin concentration below 3.0g/dl). Patients who were thermally injured, had nephrotic syndrome or required protein restriction were excluded                |                              |
| Interventions                           | 1) The intervention group received central TPN plus normal serum albumin (n=33).<br>2) The control group (n=34) received central TPN alone.  |                              |
| Outcomes                                | Deaths reported.   |                              |
| Notes                                   | Follow-up to discharge.  |                              |
| <b>Risk of bias</b>                     |  |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>  | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | High risk  |                              |

**Cooper 2006**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial, not blinded.   |
| Participants  | Eligible adults over 15 years old suffering from thermal injury not more than 12 hours before enrolment           |
| Interventions | 1) Intervention (n=19) received 5% albumin plus Ringer's lactate.<br>2) Control (n=23) received Ringer's lactate. |
| Outcomes      | Multiple Organ Dysfunction Score (MODS) and deaths reported.  |
| Notes         |   |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement  |
|---|--------------------|--|
| Allocation concealment (selection bias) | Low risk           | "Patients were allocated to study groups with stratified randomization with a computer-generated randomization list and sequentially numbered sealed, opaque envelopes. Randomization was stratified by center..." p. 81 |

**Dubois 2006**

|               |  |
|---------------|--|
| Methods       | Prospective, controlled, randomized, open, single centre study   |
| Participants  | All patients admitted to the hospital ICU with serum albumin less than or equal to 30g/L. Exclusion criteria were expected length of stay <72 hrs., life expectancy <3 months or a do not resuscitate order, albumin administration in the preceding 24 hrs. or evidence of fluid overload |
| Interventions | 1) Intervention (n=50) received 300 mL of 20% albumin solution on day 1 and 200 mL on subsequent days when serum albumin concentration was lower than 31 g/L.<br>2) Control (n=50) received Ringer's Lactate.  |
| Outcomes      | Effect of albumin on organ function as assessed by a delta Sequential Organ Failure Assessment score. Deaths not reported  |
| Notes         |  |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Allocation concealment (selection bias) | Low risk           | "Eligible patients were randomized in a 1:1 ratio using sealed envelopes. When a patient was assigned to one group, he or she remained in that group whether or not he or |

Dubois 2006 (Continued)

|  |                                      |
|--|--------------------------------------|
|  | she received the planned treatment.” |
|--|--------------------------------------|

**Ernest 1999**

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial, not blinded.  |
| Participants  | 18 septic, critically ill patients where a fluid infusion was clinically indicated |
| Interventions | 1) 5% albumin (n=9).<br>2) normal saline (n=9).                                    |
| Outcomes      | Information on death not collected.  |
| Notes         | Follow up for about an hour after infusion.  |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | High risk          |                       |

**Ernest 2001**

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial, not blinded.                        |
| Participants  | 40 postoperative cardiac surgical patients.                      |
| Interventions | 1) 5% albumin (n=23).<br>2) normal saline (n=17).                |
| Outcomes      | Information on death not collected.                              |
| Notes         | Follow up for 40 minutes after infusion. Trial conducted in 1992 |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | High risk          |                       |

**Foley 1990**

|   |   |                              |
|---|---|------------------------------|
| Methods                                 | Patients were randomly assigned to either a treatment or non-treatment group by medical record number   |                              |
| Participants                            | Hypoalbuminaemic (serum albumin <25g/L) critically ill patients. Potential subjects with Child's class C cirrhosis were excluded  |                              |
| Interventions                           | 1) The treatment group (n=18) received 25-50g per day of 25% albumin in addition to full nutritional support with parenteral nutrition. Albumin administration was continued daily until serum albumin levels exceeded 25 g/L after which patients received additional albumin as needed to keep the albumin level at 25 g/L or higher.<br>2) The non treatment group (n=22) received no exogenous concentrated albumin |                              |
| Outcomes                                | Deaths reported.  |                              |
| Notes                                   | Follow up to discharge.   |                              |
| <b><i>Risk of bias</i></b>              |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | High risk   |                              |

**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 |                              |
| Participants                            | Patients after coronary artery bypass graft surgery.  |                              |
| Interventions                           | 1) Treatment group received 5% albumin (n=5).<br>2) The control group received lactated Ringers (n=5).  |                              |
| Outcomes                                | Deaths were not reported. Author contacted and confirmed that there were no deaths in either group  |                              |
| Notes                                   | Follow-up to 1 day.   |                              |
| <b><i>Risk of bias</i></b>              |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

**Golub 1994**

|               |  |
|---------------|--|
| Methods       | Computer randomisation - method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by the use of sealed opaque envelopes  |
| Participants  | Patients in the surgical intensive care unit of a community hospital with circulating albumin concentrations of <3.0g/dL   |
| Interventions | 1) The treatment group (n=116) received 37.5g/day of albumin until the circulating albumin concentration increased to 3.0g/dL.<br>2) The control group received no supplemental albumin.<br>Both groups received standard nutritional support. |
| Outcomes      | Deaths reported.   |
| Notes         | Follow-up to discharge.  |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

**Goodwin 1983**

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described  |
| Participants  | 79 thermally injured patients. No other inclusion criteria were reported. All of the participants were previously healthy young adults   |
| Interventions | 1) The treatment group (n=40) group received 2.5% albumin in Ringer's lactate.<br>2) The control group (n=39) Ringers lactate. Allocated fluid was used throughout resuscitation |
| Outcomes      | Deaths reported.   |
| Notes         | Follow-up to discharge.  |

**Greenhalgh 1995**

|               |  |
|---------------|--|
| Methods       | Method of random allocation not described. Author contacted and confirmed the use of a randomisation scheme controlled by the pharmacy   |
| Participants  | Patients aged 18 years or younger with acute burns.  |
| Interventions | 1) High albumin group (n=34): Patients were supplemented with human albumin to maintain serum levels between 2.5 and 3.5g/dL. Albumin was supplied as a continuous drip of 25% human albumin at a rate of 3-10mL/hour. Supplementation was discontinued if serum albumin levels remained >2.5 g/dL without supplementation or if intravenous support was discontinued. |

**Greenhalgh 1995** (Continued)

|   |   |                              |
|---|---|------------------------------|
|   | 2) Low albumin group (n=36): Patients were not given albumin supplementation unless levels dropped <1.5 g/dL. During burn shock, patients were allowed to receive albumin if they had levels <2.0 g/dL and were receiving >4 mL/Kg/% burn fluid resuscitation |                              |
| Outcomes                                | Deaths reported.  |                              |
| Notes                                   | Follow-up to discharge.   |                              |
| <b>Risk of bias</b>                     |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

**Greenough 1993**

|   |   |                              |
|---|---|------------------------------|
| Methods                                 | Randomised controlled trial. Allocation concealment by sealed opaque envelopes  |                              |
| Participants                            | Infants between 24 and 34 weeks gestational age, who were ventilator dependent, and had a serum albumin level of less than or equal to 30g/l            |                              |
| Interventions                           | 1) Intervention group (n=20) received 5ml/kg 20% salt-poor human albumin.<br>2) Control group (n=20) received 5ml/kg of the infant's maintenance fluids |                              |
| Outcomes                                | Deaths were not reported. Author contacted and provided data on deaths  |                              |
| Notes                                   | Follow-up to 24 hours after infusion.   |                              |
| <b>Risk of bias</b>                     |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

**Grundmann 1982**

|               |   |  |
|---------------|---|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not fully described   |  |
| Participants  | Participants were undergoing partial gastrectomy. The average age was 50 years (range 19-84)  |  |
| Interventions | 1) Intervention group (n=14) group received human albumin.<br>2) Control group (n=6) details of crystalloid were not reported.<br>Allocated fluid was continued for 4 days after operation. |  |
| Outcomes      | Deaths reported.  |  |

**Grundmann 1982** (Continued)

|       |                         |
|-------|-------------------------|
| Notes | Follow-up to discharge. |
|-------|-------------------------|

**Jelenko 1978**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Method of allocation concealment not described   |
| Participants  | Participants had burns covering more than 20% of body surface   |
| Interventions | 1) Intervention group (n=7) received albumin in hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate, 3.5 torr/liter);<br>2) Control group (n=7) received hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate). Allocated fluid was used to the end of resuscitation |
| Outcomes      | Deaths reported.  |
| Notes         | Follow-up to 5 days.  |

**Kanarek 1992**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Allocation concealment by sealed opaque envelopes                                      |
| Participants  | Sick premature newborn infants whose serum albumin was less than 3g/dL  |
| Interventions | 1) Intervention group (n=12) received TPN with added albumin.<br>2) Control group (n=12) received no added albumin. |
| Outcomes      | Deaths reported.  |
| Notes         | Length of follow-up unspecified.  |

**Risk of bias**

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

**Lowe 1977**

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. The solutions were randomised by opening a sealed envelope containing a card denoting the appropriate fluid   |
| Participants  | Participants were undergoing emergency laparotomy for acute abdominal trauma   |
| Interventions | 1) Intervention group (n=57) received 50g albumin in 200ml in Ringers lactate;<br>2) Crystalloid group (n=84) received Ringer's lactate. Allocated fluid was used throughout the pre- and intra-operative period |

**Lowe 1977** (Continued)

|   |   |                              |
|---|---|------------------------------|
| 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>Risk of bias</b>                     |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

**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) Intervention group (n=27) received supplemental salt-poor albumin totaling a maximum of 150g during operation and 150g per day over the next five days.<br>2) Control group (n=25) received standard resuscitation regimen but no supplemental albumin |                              |
| Outcomes                                | Deaths reported.  |                              |
| 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   |                              |
| <b>Risk of bias</b>                     |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | High risk   |                              |

**Maitland 2005**

|               |  |  |
|---------------|--|--|
| Methods       | Unblinded, randomised, controlled trial.   |  |
| Participants  | Kenyan children older than 2 months with symptomatic severe malarial anaemia (haemoglobin less than 5g/dl)   |  |
| Interventions | 1) Intervention (n=23) received 4.5% albumin.<br>2) Intervention (n=20) received 0.9% saline.<br>3) Control (n=18) received only maintenance (rescue emergency intervention when required) |  |

**Maitland 2005** (Continued)

|   |   |   |
|---|---|---|
| Outcomes                                | Change in perfusion rates. Deaths not reported. |   |
| Notes                                   |   |   |
| <b>Risk of bias</b>                     |   |   |
| <b>Bias</b>                             | <b>Authors' judgement</b>                       | <b>Support for judgement</b>  |
| Allocation concealment (selection bias) | Low risk  | “On admission to the HDU, children were randomly assigned to PTM with one of the three treatments using sealed card system. The sealed cards were available 24h/day; either the admitting doctor or nurse assigned the therapy at admission based on laboratory results or, in an emergency, on clinical suspicion.” p. 128 |

**Maitland 2011**

|   |  |  |
|---|--|--|
| Methods                                 | Multicentre open, randomised, controlled study   |  |
| Participants                            | Children (n=3170) aged between 60 days and twelve years of age, with severe febrile illness, randomly assigned within two strata (stratum A was children with severe febrile illness and impaired perfusion but without severe hypotension - stratum B was children with severe hypotension) |  |
| Interventions                           | Children were randomly allocated to rapid volume replacement over the course of 1 hour with either:<br>1) 20 ml 5% Human Albumin solution per kg body weight (n=1063)<br>2) 20 ml 0.9% Saline solution per kg body weight (n=1063)   |  |
| Outcomes                                | Mortality at 4 weeks after randomisation   |  |
| Notes                                   | Children (n=1044) assigned to no treatment were not included in the analysis   |  |
| <b>Risk of bias</b>                     |  |  |
| <b>Bias</b>                             | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Allocation concealment (selection bias) | Low risk   | Trial numbers kept inside opaque, sealed envelopes. Opened in numerical order by clinician |

**McNulty 1993**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Method of allocation concealment not described                                 |
| Participants  | 28 Patients following elective cardiopulmonary bypass.  |
| Interventions | 1) Intervention group (n=14) received 5% albumin.<br>2) Control group (n=14) received isotonic crystalloid. |
| Outcomes      | Deaths not reported.  |
| Notes         | Length of follow-up unspecified.  |

**Myburgh 2007**

|               |  |
|---------------|--|
| Methods       | A double blind, randomised, controlled <a href="#">SAFE 2004</a> trial. "Randomization was stratified by a diagnosis of trauma (defined as injury to the body caused by mechanical forces, excluding burns)." p. 875 |
| Participants  | 460 patients with traumatic brain injuries.  |
| Interventions | 1) Intervention (n=231) received 4% albumin.<br>2) Control (n=229) received normal saline.   |
| Outcomes      | Mortality rate at 28 days.   |
| Notes         |  |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Allocation concealment (selection bias) | Low risk           | "Randomization was carried out centrally with the use of a minimization algorithm, and the service was accessed on the Internet through a secure Web site." <a href="#">SAFE 2004</a> p. 2248 |

**Nielsen 1985**

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described  |
| Participants  | Patients admitted for reconstructive surgery of the abdominal aorta. Twenty six patients were randomised   |
| Interventions | 1) Intervention (n=13): 80 g of albumin administered in units of 100 ml 20% human serum albumin on the day of the operation and 20 g albumin daily on the following three postoperative days.<br>2) Control group (n=13): no supplemental albumin. |
| Outcomes      | Deaths not reported. Author when contacted confirmed that there were no deaths in either group   |

**Nielsen 1985** (Continued)

|       |                   |
|-------|-------------------|
| Notes | Follow-up 4 days. |
|-------|-------------------|

**Nilsson 1980**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Allocation concealment by sealed opaque envelopes  |
| Participants  | Patients with colorectal cancer undergoing elective surgery with resection of the tumour and primary anastomosis  |
| Interventions | 1) Intervention group (n=29) received 20-25g per day of albumin (as 5% albumin or 20% albumin) for three days, starting on the day after the operation.<br>2) Control group (n=30) received no albumin. |
| Outcomes      | Deaths reported.  |
| Notes         | Follow up to discharge.   |

**Risk of bias**

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

**Oca 1999**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Allocation concealment was by the use of sealed opaque sequentially numbered envelopes. Information obtained on contact with the author  |
| Participants  | 24 neonates being treated for hypotension. Hypotension was defined as an oscilometric mean arterial blood pressure <30 mmHg for at least 30 minutes. Exclusion criteria consisted of proven sepsis, life-threatening congenital abnormalities, congenital hear disease, unresolved thoracic air leak, insulin-requiring maternal diabetes mellitus or treatment with high-frequency ventilation |
| Interventions | 1) 5% albumin (n=11).<br>2) normal saline (n=13).   |
| Outcomes      | Mean arterial blood pressure.   |
| Notes         | Follow-up to discharge.   |

**Risk of bias**

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

**Oca 2003**

|               |   |
|---------------|---|
| Methods       | Randomised, unblinded, controlled trial.  |
| Participants  | Newborn infants who were <24 hours old and were admitted to the ICU to receive one of two solutions for volume expansion. 41 infants were included in the trial |
| Interventions | 1) Intervention (n=21) received 4% albumin.<br>2) Control (n=20) received normal saline.  |
| Outcomes      | Magnitude of change in mean arterial blood pressure.  |
| Notes         |   |

***Risk of bias***

| Bias                                    | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Allocation concealment (selection bias) | Low risk           | "Randomization was accomplished by random number tables via sealed, serially numbered envelopes" p. 474 |

**Pockaj 1994**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Method of allocation concealment not described   |
| Participants  | Participants required fluid resuscitation as a result of vascular leak syndrome associated with Interleukin-2 therapy for metastatic cancer |
| Interventions | 1) Intervention group (n=54) received 5% albumin n 154meq/L NaCl;<br>2) Control group (n=53) received 0.9% normal saline with 154Meq/L NaCl |
| Outcomes      | Deaths reported.  |
| Notes         | Length of follow-up unspecified.  |

**Prien 1990**

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Method of allocation concealment not described   |
| Participants  | Patients undergoing hemipancreato-duodenectomy (Whipple's operation)  |
| Interventions | 1) Intervention group (n=6) received 20% human albumin to maintain central venous pressure at the pre-operative level.<br>2) Control group (n=6) received Ringer's lactate. |
| Outcomes      | Deaths reported.  |
| Notes         | Length of follow-up unspecified.  |

**Quinlan 2004**

|   |   |   |
|---|---|---|
| Methods                                 | Prospective, randomised, placebo-controlled study.  |   |
| Participants                            | Patients meeting the American European Consensus criteria for acute lung injury   |   |
| Interventions                           | 1) Intervention (n=10) received albumin (25g of a 25% solution) every 8 hrs for a total of nine doses.<br>2) Control (n=10) received normal saline administered in identical fashion and volume |   |
| Outcomes                                | Deaths noted.   |   |
| Notes                                   |   |   |
| <b><i>Risk of bias</i></b>              |   |   |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Allocation concealment (selection bias) | Unclear risk  | "Patients were randomized to receive 25g of human albumin every 8 hrs or a placebo (normal saline, administered in a double-blind fashion and targeted to normalization of serum total protein." p. 755 - 756 |

**Rackow 1983**

|               |  |  |
|---------------|--|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described  |  |
| Participants  | Participants were above 18 years of age, and had any one of the following pre-determined indicators of shock: systolic blood pressure of 90mmHg or less, a cardiac index of less than 2.2L./min.m <sup>2</sup> , a serum arterial lactate greater than 18mg/dl and WP less than 15mmHg |  |
| Interventions | 1) Intervention group ( n= 9) received 5% albumin.<br>2) Control group (n=8) received 0.9% NaCl. Allocated fluid was given as needed until the end of resuscitation  |  |
| Outcomes      | Deaths reported.   |  |
| Notes         | Follow-up to discharge.  |  |

**Rubin 1997**

|               |  |  |
|---------------|--|--|
| Methods       | Patients were randomised using "a closed envelope system in the pharmacy"  |  |
| Participants  | Patients with hypoalbuminaemia (<2.5g/dL) who required TPN for at least six days, were not pregnant or under age, and did not have metastatic cancer, cirrhosis, or nephrotic syndrome |  |
| Interventions | 1) Intervention group (n=16) 25g on normal serum albumin.<br>2) Control group (n=15) 100 mL of normal saline placebo over a 1 hour period daily  |  |

**Rubin 1997** (Continued)

|   |                           |                              |
|---|---------------------------|------------------------------|
| Outcomes                                | Deaths reported.          |                              |
| Notes                                   | Follow-up to discharge.   |                              |
| <b>Risk of bias</b>                     |                           |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b> | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk                  |                              |

**SAFE 2004**

|   |  |  |
|---|--|--|
| Methods                                 | Central randomisation accessed on the Internet through a secure website with use of a minimisation algorithm. Blinding was assured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated |  |
| Participants                            | Patients 18 years of age or older admitted to ICU who the treating clinician judged to require fluid administration to maintain or increase intravascular volume, with this decision supported by the fulfilment of at least one objective criterion. Patients admitted after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded        |  |
| Interventions                           | 1) 4% Albumin or<br>2) Normal saline<br>The allocated study treatment was used for all fluid resuscitation in the ICU until death or discharge or until 28 days after randomisation. The treating clinicians determined the amount and rate of fluid administration according to each patient's clinical status and response to treatment                                      |  |
| Outcomes                                | Deaths reported.   |  |
| Notes                                   | 28 day mortality.  |  |
| <b>Risk of bias</b>                     |  |  |
| <b>Bias</b>                             | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Allocation concealment (selection bias) | Low risk   | "Randomization was carried out centrally with the use of a minimization algorithm and the service was accessed on the Internet through a secure Web site." p. 2248 |

**Shah 1977**

|   |   |                              |
|---|---|------------------------------|
| Methods                                 | Randomised controlled trial, allocation by sealed envelope.   |                              |
| 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) Intervention group (n=9) 5% salt-poor albumin in Ringers lactate.<br>2) Control group (n=11) Ringer's lactate for resuscitation, volume infused guided by physiological parameters |                              |
| Outcomes                                | Death reported.   |                              |
| Notes                                   | Length of follow-up not stated.   |                              |
| <b><i>Risk of bias</i></b>              |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

**Skillman 1975**

|               |   |  |
|---------------|---|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described   |  |
| Participants  | Participants were undergoing elective abdominal reconstructive surgery  |  |
| Interventions | 1) Intervention group received 25% concentrated salt-poor albumin and 5% albumin in saline.<br>2) Control group received Ringer's lactate with 5% dextrose. Allocated fluid was given intra-operatively. All patients received crystalloids only for pre-loading before surgery |  |
| Outcomes      | Deaths were not reported. Author could not be contacted.  |  |
| Notes         | Follow-up to 1 day.   |  |

**So 1997**

|               |   |  |
|---------------|---|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by computer randomisation. Details of patient were entered before group allocation revealed |  |
| Participants  | Pre-term infants weighing 540 to 1959g at birth, with gestational ages of 23 to 34 weeks, who developed hypotension within the first two hours of life  |  |
| Interventions | 1) Intervention group (n=32) were given 5% albumin at a dose of 10mg/Kg by slow intravenous infusion over 30 minutes.<br>2) Control group (n=31) were given 0.9%NaCl at a dose of 10mg/kg by slow intravenous infusion over 30 minutes  |  |

So 1997 (Continued)

|   |                           |                              |
|---|---------------------------|------------------------------|
| Outcomes                                | Deaths reported.          |                              |
| Notes                                   | Follow up to discharge.   |                              |
| <b>Risk of bias</b>                     |                           |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b> | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk                  |                              |

Tollofsrud 1995

|   |   |                              |
|---|---|------------------------------|
| Methods                                 | Randomised controlled trial. Allocation concealment by sealed opaque envelopes  |                              |
| Participants                            | Patients undergoing elective coronary artery bypass surgery. Patients with left ventricular ejection fraction less than 40%, valvular heart disease, ventricular aneurysm, arrhythmia, diabetes mellitus, renal failure or lung disease were excluded |                              |
| Interventions                           | 1) Intervention group (n=10) received albumin 40mg/ml whenever fluid was required to stabilise haemodynamics.<br>2) Control group (n=10) received Ringers acetate.  |                              |
| Outcomes                                | Deaths reported.  |                              |
| Notes                                   | Follow-up to 48 hours.  |                              |
| <b>Risk of bias</b>                     |   |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>   | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | Low risk  |                              |

Virgilio 1979

|               |  |  |
|---------------|--|--|
| Methods       | Randomised controlled trial. Method of allocation concealment not described  |  |
| Participants  | Participants were undergoing abdominal aortic surgery.   |  |
| Interventions | 1) Intervention group (n=15) received 5% albumin in Ringer's lactate<br>2) Control group (n=14) received Ringers lactate. 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.   |  |

Virgilio 1979 (Continued)

|       |                               |
|-------|-------------------------------|
| Notes | Follow-up 2 and a half weeks. |
|-------|-------------------------------|

Woittiez 1998

|               |   |
|---------------|---|
| Methods       | Randomised controlled trial. Allocation concealment by sealed opaque envelopes                    |
| Participants  | Post-operative intensive care patients.   |
| Interventions | 1) Intervention group (n=15) received 20% albumin.<br>2) Control group (n=16) received 0.9% NaCl. |
| Outcomes      | Unpublished data on deaths were provided by the trialist.   |
| Notes         | Length of follow-up unspecified.  |

*Risk of bias*

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

Wojtysiak 1992

|               |  |
|---------------|--|
| Methods       | Randomised controlled trial. Table of random numbers was used to generate the random sequence. Method of allocation concealment not described in published report. The author was contacted and indicated that there was inadequate allocation concealment |
| Participants  | Patients between the ages of 18 and 75 years who were to receive parenteral nutrition and had a serum albumin concentration <3.0 g/dL. Patients were excluded if they had renal impairment, liver impairment or were haemodynamically unstable             |
| Interventions | 1) Intervention group (n= 15) had 25g of human albumin added to each litre of parenteral nutrition.<br>2) Control group (n=15) had no supplemental albumin.  |
| Outcomes      | Deaths not reported in published report. Author when contacted confirmed that there were no deaths in either group   |
| Notes         | Follow-up to 5 days.   |

*Risk of bias*

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | High risk          |                       |

**Woods 1993**

|   |  |                              |
|---|--|------------------------------|
| Methods                                 | Randomised controlled trial. Patients with even hospital numbers were randomised to the group receiving albumin while those patients with odd hospital numbers were randomised to the group not receiving supplemental albumin |                              |
| Participants                            | Patients undergoing surgery for abdominal aortic aneurysm, aortoiliac or aortofemoral bypass   |                              |
| Interventions                           | 1) Intervention group (n=37): albumin was replaced to a level greater than or equal to 3.5 g/dL.<br>2) Control group (n=32): received no supplemental albumin.   |                              |
| Outcomes                                | Deaths reported.   |                              |
| Notes                                   | Follow-up to discharge.  |                              |
| <b><i>Risk of bias</i></b>              |  |                              |
| <b>Bias</b>                             | <b>Authors' judgement</b>  | <b>Support for judgement</b> |
| Allocation concealment (selection bias) | High risk  |                              |

**Zetterstrom 1981a**

|                            |  |                              |
|----------------------------|--|------------------------------|
| Methods                    | The patients were randomly divided into two groups. The method of allocation concealment is not described. Author was contacted and confirmed the use of sealed opaque envelopes   |                              |
| Participants               | Adult patients undergoing elective major abdominal surgery.  |                              |
| Interventions              | 1) Intervention group (n=15)<br>2) Control group (n=15)<br>A similar schedule of fluid therapy and blood replacement was followed in the intervention and control groups. However, the albumin group received a 20% solution of human albumin intravenously according to the following scheme:<br>At the end of the operation: 100ml.<br>Postoperatively on the day of the operation: 200-300 ml.<br>First day after the operation: 200 ml.<br>Following 3 days 100 ml each day. |                              |
| Outcomes                   | Deaths reported.   |                              |
| Notes                      | Length of follow-up unspecified.   |                              |
| <b><i>Risk of bias</i></b> |  |                              |
| <b>Bias</b>                | <b>Authors' judgement</b>  | <b>Support for judgement</b> |
|                            |  |                              |

**Zetterstrom 1981a** (Continued)

|   |          |  |
|---|----------|--|
| Allocation concealment (selection bias) | Low risk |  |
|---|----------|--|

**Zetterstrom 1981b**

|               |   |  |
|---------------|---|--|
| Methods       | Patients were randomly divided into two groups. Method of allocation concealment was not described. Author was contacted and confirmed the use of sealed opaque envelopes   |  |
| Participants  | Patients undergoing elective reconstruction of the abdominal aorta  |  |
| Interventions | 1) Intervention group (n=9)<br>2) Control group (n=9)<br>Postoperatively, the aim of fluid administration was to keep the pulmonary arterial occlusion pressure equal to the preoperative level. When lower values were recorded, the patients in the control group were given a balanced electrolyte solution of the Ringer type, whereas the albumin patients received a 5% solution of human albumin |  |
| Outcomes      | Deaths reported.  |  |
| Notes         | Length of follow-up unspecified.  |  |

**Risk of bias**

| Bias                                    | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Allocation concealment (selection bias) | Low risk           |                       |

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

| Study         | Reason for exclusion  |
|---------------|---|
| Artru 1989    | Intervention to control intracranial pressure not directed at fluid resuscitation   |
| Bellomo 2006  | Trial was subset of <a href="#">SAFE 2004</a> trial, thus offering no new data.   |
| Brehme 1993   | Intervention directed at haemodilution, not at volume replacement   |
| Carlson 1979  | Randomised controlled trial of pre-operative volume expansion during anaesthesia  |
| Fiorica 1991  | Not a randomised trial. The first 18 patients received standard maintenance crystalloid solution. The next 10 consecutive patients received 100g of a concentrated 25% albumin solution |
| Goslinga 1992 | Intervention directed at haemodilution, not volume replacement  |

(Continued)

|                |   |
|----------------|---|
| Grundmann 1985 | This was a randomised controlled trial of 220 patients, 106 were given albumin when their colloid osmotic pressure (COP) fell below 24 cm water and 114 were given albumin when their COP fell below 29 cm water. Patients were not randomised to albumin or no albumin, nor were they randomised to supplemental albumin versus normal amounts of albumin, rather, this was a trial of different criteria for albumin supplementation. It is unlikely therefore that the two arms of the trial were comparable and hence the trial is excluded |
| Grundmann 1986 | This was a randomised controlled trial to examine whether postoperative human albumin supply is justified in intensive care patients in the case that the colloid osmotic pressure decreases below 26 centimetres of water. The therapy group received human albumin only if the colloid osmotic pressure dropped below 26 cm water. The control group also received albumin but only for resuscitation of cardiac output and central venous pressure. The trial was excluded because both intervention and control groups received albumin     |
| Hauser 1980    | Cross-over trial.   |
| Lagonidis 1995 | Intervention was pre-loading for coronary artery bypass surgery   |
| Lennihan 2000  | Participants had suffered subarachnoid hemorrhage and therefore did not meet the inclusion criteria   |
| Magder 1999    | Participants were stable patients following cardiopulmonary bypass surgery and therefore did not meet the inclusion criteria  |
| Maitland 2005a | Trial was subset of <a href="#">SAFE 2004</a> trial, thus offering no new data.   |
| Martin 1999    | Intervention involved comparison of albumin with furosemide versus placebo therefore did not meet the inclusion criteria  |
| Metildi 1984   | 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 and therefore did not meet the inclusion criteria for the review   |
| Steinberg 1989 | Cross-over trial.   |
| Tomita 1994    | Randomised controlled trial of normal versus high oncotic pressure following head injury. Patients were not randomised to albumin or no albumin. Albumin and furosemide were used together to achieve high oncotic pressure   |

## DATA AND ANALYSES

### Comparison 1. Supplemental albumin

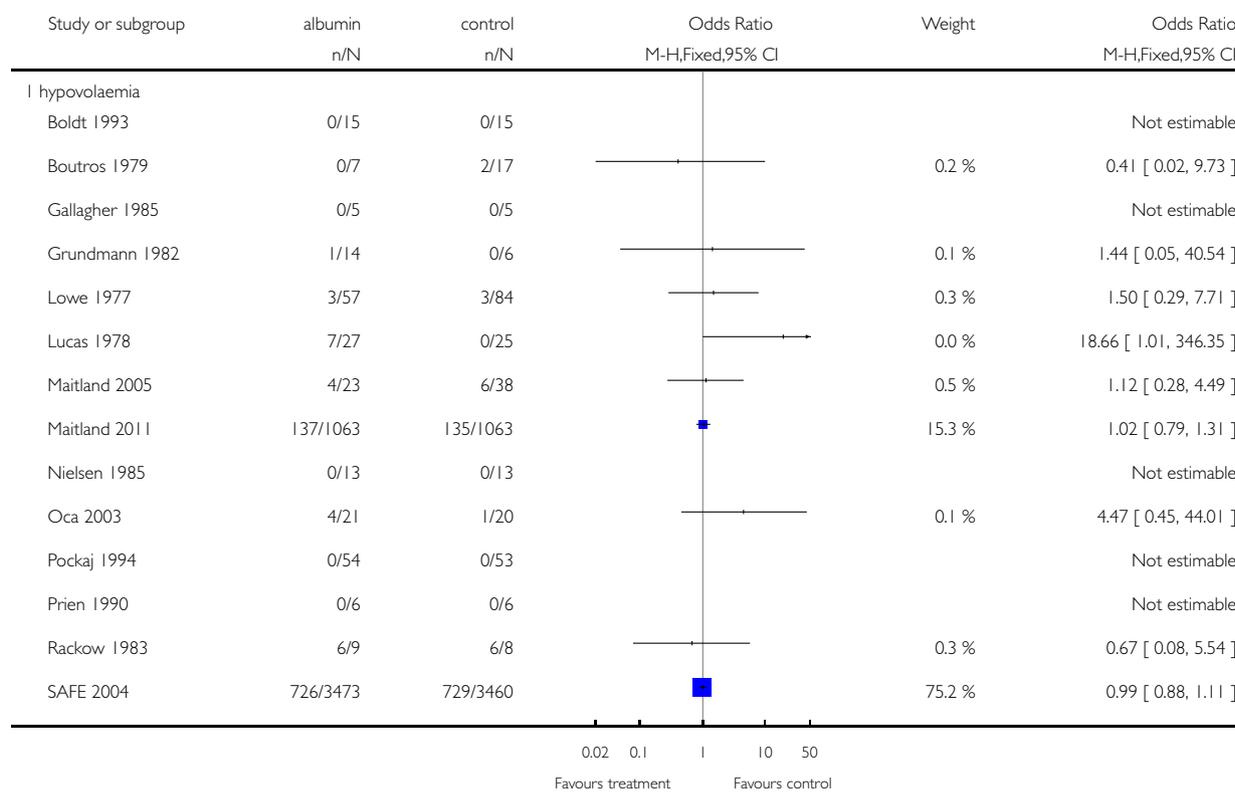
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method              | Effect size       |
|---------------------------|----------------|---------------------|---------------------------------|-------------------|
| 1 deaths                  | 38             | 10842               | Odds Ratio (M-H, Fixed, 95% CI) | 1.05 [0.95, 1.16] |
| 1.1 hypovolaemia          | 22             | 9880                | Odds Ratio (M-H, Fixed, 95% CI) | 1.02 [0.92, 1.13] |
| 1.2 burns                 | 4              | 205                 | Odds Ratio (M-H, Fixed, 95% CI) | 2.93 [1.28, 6.72] |
| 1.3 hypoalbuminaemia      | 12             | 757                 | Odds Ratio (M-H, Fixed, 95% CI) | 1.26 [0.84, 1.88] |

#### Analysis 1.1. Comparison 1 Supplemental albumin, Outcome 1 deaths.

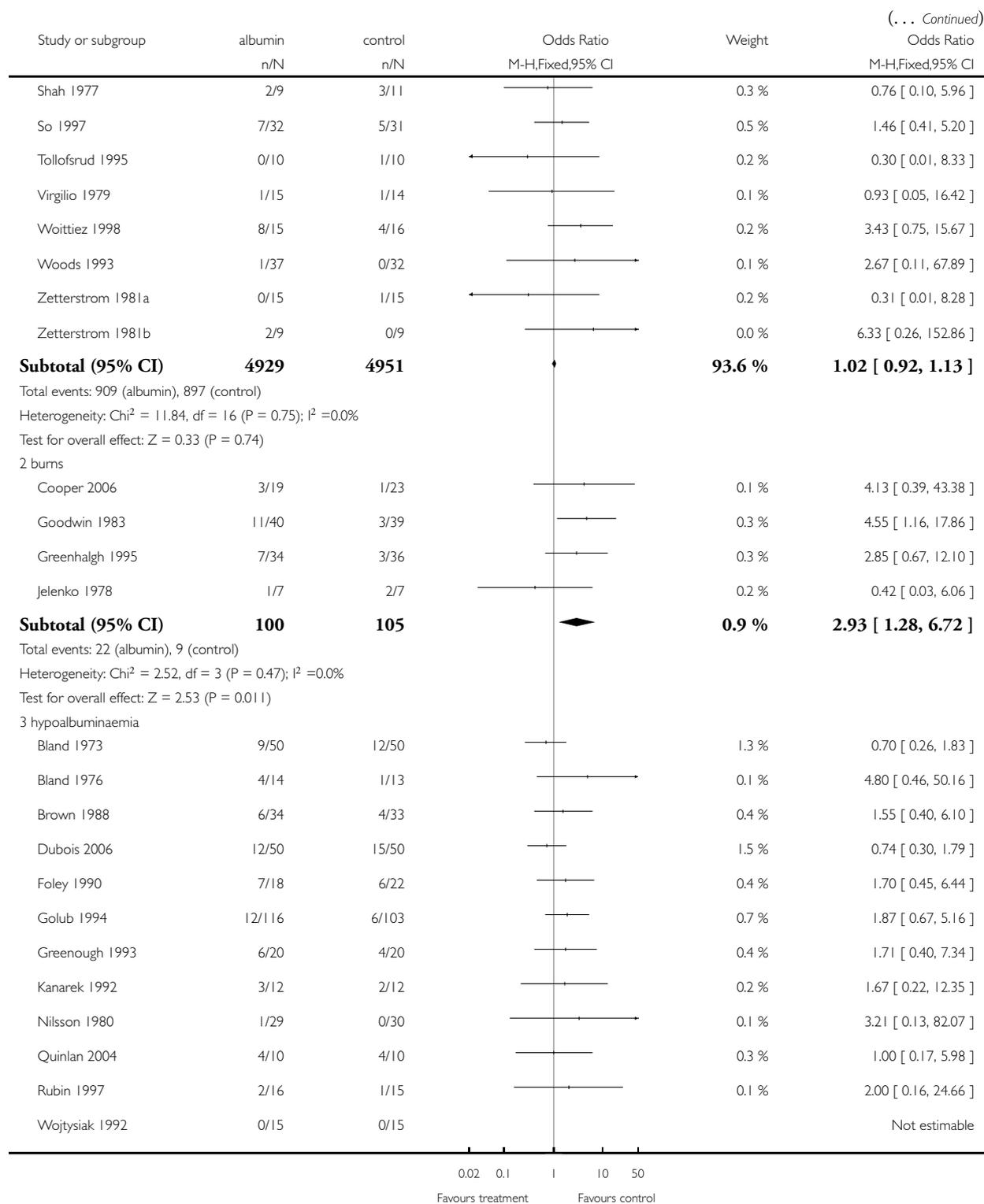
Review: Human albumin solution for resuscitation and volume expansion in critically ill patients

Comparison: 1 Supplemental albumin

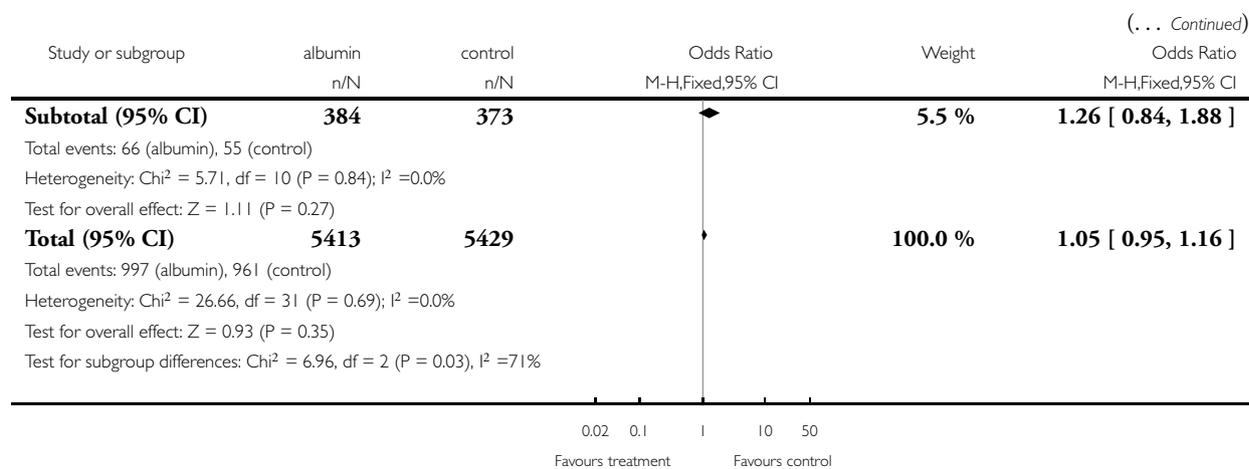
Outcome: 1 deaths



(Continued ...)



(Continued . . .)



## APPENDICES

### Appendix I. Search strategy

PubMed [[www.ncbi.nlm.nih.gov/sites/entrez/](http://www.ncbi.nlm.nih.gov/sites/entrez/)] (searched 10 June 2011 limit: last 60 days)

Cochrane Injuries Group Specialised Register (searched 31 May 2011)

- 1.fluid\* and (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)
- 2.rehydrate\* and (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)
- 3.volum\* and (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)
- 4.1 or 2 or 3
- 5.Albumin\*
- 6.4 and 5

Cochrane Central Register of Controlled Trials 2011, Issue 2 (The Cochrane Library)

#1MeSH descriptor Fluid Therapy explode all trees

#2fluid\*

#3((volume or rehydrat\*) near3 (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*))

#4(#1 OR #2 OR #3)

#5MeSH descriptor Albumins explode all trees

#6MeSH descriptor Serum Albumin explode all trees

#7albumin\*

#8(#5 OR #6 OR #7)

#9(#4 AND #8)

#10(#9), from 2008 to 2011

MEDLINE (Ovid) 1948 to Week 3 May 2011

1.exp Fluid Therapy/

2.fluid\*.ti,ab.

3.((volume or rehydrat\*) adj3 (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)).ti,ab.

Human albumin solution for resuscitation and volume expansion in critically ill patients (Review)

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4.1 or 2 or 3  
5.exp Albumins/  
6.exp Serum Albumin/  
7.albumin\*.mp.  
8.5 or 6 or 7  
9.4 and 8  
10.randomi?ed.ab,ti.  
11.randomized controlled trial.pt.  
12.controlled clinical trial.pt.  
13.placebo.ab.  
14.clinical trials as topic.sh.  
15.randomly.ab.  
16.trial.ti.  
17.10 or 11 or 12 or 13 or 14 or 15 or 16  
18.(animals not (humans and animals)).sh.  
19.17 not 18  
20.9 and 19  
21.(2008\* or 2009\* or 2010\* or 2011\*).ed.  
22.20 and 21

#### **EMBASE (Ovid) 1980 to Week 21 2011**

1.albumin\*.ab,ti.  
2.exp human serum albumin/  
3.exp recombinant human serum albumin/  
4.exp serum albumin/  
5.1 or 2 or 3 or 4  
6.exp fluid resuscitation/  
7.((volume or rehydrat\*) adj3 (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)).ti,ab.  
8.fluid\*.ti,ab.  
9.6 or 7 or 8  
10.5 and 9  
11.exp Randomized Controlled Trial/  
12.exp controlled clinical trial/  
13.randomi?ed.ab,ti.  
14.placebo.ab.  
15.\*Clinical Trial/  
16.randomly.ab.  
17.trial.ti.  
18.11 or 12 or 13 or 14 or 15 or 16 or 17  
19.exp animal/ not (exp human/ and exp animal/  
20.18 not 19  
21.10 and 20  
22.(2008\* or 2009\* or 2010\* or 2011\*).em.  
23.21 and 22

#### **CINAHL (EBSCO) 1982 to May 2011**

S1(MH "Fluid Therapy+")  
S2Fluid\*  
S3(volume or rehydrat\*) and (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)  
S4S1 or S2 or S3  
S5albumin\*  
S6(MH "Albumins+")  
S7(MH "Serum Albumin")

S8S5 or S6 or S7  
S9(MH "Clinical Trials+")  
S10 (MH "Randomized Controlled Trials")  
S11 S9 or S10  
S12 S4 and S8 and S12  
S13 S12 (2008-11)

**ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to May 2011, ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to May 2011**

1.Topic=((volume or rehydrat\*) same (solution\* or replac\* or therap\* or substitut\* or restorat\* or resuscitat\* or rehydrat\*)) OR Topic=(Fluid\*)  
2.Topic=(albumin\*)  
3.1 and 2  
4.Topic=((singl\* OR doubl\* OR trebl\* OR tripl\*) SAME (blind\* OR mask\*))  
5.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 Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)  
6.4 or 5  
7.Topic=(human\*)  
8.6 and 7  
9.3 and 8

## **F E E D B A C K**

### **Human albumin solution**

#### **Summary**

1. It would be helpful to state that this review was published in the BMJ in 1998, to summarise the subsequent correspondence in print and on the BMJ website, and to note the respects (if any) in which this Cochrane review differs from the BMJ publication.
2. It would be valuable to summarise the report of the Committee for Safety of Medicines (CSM) on this review in the Comments and Criticisms section, with a rejoinder by the authors.
3. Because mortality was not the primary endpoint in any of the trials reviewed, it would be useful to note the primary outcomes of each trial, under 'characteristics of included trials'.
4. It would be helpful if the number of participants in each arm of each reviewed trial appeared under 'characteristics of included trials.'

#### **Reply**

1. We agree that it is important to direct the reader to other published versions of the review and will ensure that readers are alerted to the BMJ publication. We do not think it is appropriate to summarise the correspondence in response to this review, as to do so would run the risk of misrepresenting the views of the correspondents. At the time of first publication the Cochrane review was identical to the review published in the BMJ. However, the Cochrane review will be regularly updated to take account of new information from randomised controlled trials.
2. The Cochrane Database of Systematic Reviews is an international database and for this reason we believe that it would be inappropriate to give undue emphasis to the deliberations of the British Committee on Safety of Medicines (CSM).
3. Mortality was recorded in all but two of the trials included in our systematic review. However, we have no information on whether this was considered by the trialist to be the primary endpoint and would be interested to hear where the author of the comment found this information. How does the author of the comment define a primary endpoint? The concept of a primary endpoint implies a selection within the mind of the trialist of the most important endpoint. We would also ask whether it is appropriate that a process

within the mind of a trialist should impact importantly on the estimation of the effect of albumin on mortality, and if so, what is the scientific basis for this.

4. We have included the number of participants in each arm of each reviewed trial in the section 'characteristics of included trials' as suggested.

### **Contributors**

Author of comments: Dr Andrew Herxheimer

Author of Responses: Ian Roberts

### **Human albumin solution**

#### **Summary**

I gather that a further trial - prompted by the review - is now planned and possibly underway in Australasia. If so, I think this should be mentioned, preferably with a link to a record for the trial on the meta-Register of Controlled Trials.

#### **Reply**

Details of this ongoing trial are now in the on-going studies section.

### **Contributors**

Author of comments: Ian Chalmers, UK

Author of response: Ian Roberts, UK

### **Human albumin solution**

#### **Summary**

Human albumin solution for resuscitation and volume expansion in critically ill patients

Summary of comment

1. In the hypovolaemia group, five randomised controlled trials were incorrectly included and should be deleted(1).
2. The Cochrane Albumin Review excluded or omitted extensive randomised controlled trials' evidence in the three categories of indications, namely, hypovolaemia, burns and hypoalbuminaemia(2) and this excluded and omitted evidence indicated that albumin may reduce rather than increase mortality.

(1) Horsey P Albumin and hypovolaemia - is the Cochrane evidence to be trusted? Lancet 2002 359 70-72

(2) Willkes MM and Navickis RJ Patient survival after human albumin administration: a meta-analysis of randomised controlled trials. Annals of Internal Medicine 2001 135 149-164

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

#### **Reply**

We are grateful to Dr Horsey for his thoughtful comments on our systematic review of albumin administration in critically ill patients. The comments were first made as a commentary in The Lancet (2002;359:70-72). Our response to these comments was published in the same issue (Lancet 2002:359:72-3). We are pleased that this discussion will now be available to readers of the Cochrane Library. Dr Horsey feels that some of the trials included under the category 'hypovolaemia' would be more appropriate in a different category. We accept that in some clinical situations hypovolaemia and hypoalbuminaemia co-exist so that deciding which category would be most appropriate is a matter for judgement. Also, as Dr Horesy points out, the relationship between hypovolaemia and low blood

pressure can be complicated, and the presence of the latter might not always signify the former. Nevertheless, our judgements about the categories were made without knowledge of the results of the trials and we are reluctant to change these post-hoc.

We are grateful to Dr Horsey for drawing our attention to the meta-analysis by Wilkes et al that was funded by the Plasma Protein Therapeutics Association. Because the inclusion criteria for the Cochrane Injuries Group Albumin Reviewer and the Wilkes reviews are different it does not follow that the two reviews should include the same trials.

We are pleased that our systematic review has stimulated so much interest from the intensive care community. However, it is a cause for concern that four years following the publication of our review, in which we concluded that there is no evidence that albumin administration reduced mortality in critically ill patients and a suggestion that it may increase mortality, that albumin continues to be used and promoted. Hopefully, the SAFE trial ([www.safestudy.net](http://www.safestudy.net)) will provide the evidence needed to resolve this issue.

### Contributors

Comment: Dr PJ Horsey

Reply: Professor Ian Roberts

### WHAT'S NEW

Last assessed as up-to-date: 2 August 2011.

| Date            | Event  | Description  |
|-----------------|--|--|
| 29 July 2011    | New citation required but conclusions have not changed | One new trial has been included, and the text has been amended accordingly. The conclusions remain the same. 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. One trial by Prof. Boldt is included in this review (Boldt 1993), but there were no deaths in the trial and so the data do not contribute to the results. The inclusion of the trial has no impact on the conclusions of the review. The authors of the review have changed. |
| 14 October 2008 | New search has been performed                          | Five new trials have been included in the review, and the analysis, results and discussion sections have been amended accordingly.   |

## HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 1998

| Date             | Event  | Description   |
|------------------|--|---|
| 9 June 2008      | Amended  | Converted to new review format.   |
| 20 August 2004   | New citation required and conclusions have changed | August 2004.<br>One new trial has been included (SAFE 2004) with the analysis, results and discussion amended accordingly   |
| 6 February 2002  | New search has been performed                      | February 2002.<br>An updated search for new trials was done in September 2002. One trial was found meeting the inclusion criteria but did not record data on mortality (Ernest 2001). Since the review was first published several new randomised control trials have been initiated. Details of these trials are given in the ongoing trials section |
| 19 November 1999 | Feedback has been incorporated                     | Feedback added.<br>Response to feedback added.  |

## CONTRIBUTIONS OF AUTHORS

For the original version of the review; Phil Alderson (UK Cochrane Centre) searched The Cochrane Central Register of Controlled Trials for relevant trials, extracted the data from the trials, and commented on the paper; Frances Bunn (London School of Hygiene & Tropical Medicine) searched the Cochrane Injuries Group Specialised Register for relevant trials, obtained copies of relevant papers, wrote to authors for further information on allocation concealment, and commented on the paper; Carol Lefebvre (UK Cochrane Centre) designed the original search strategies for The Cochrane Central Register of Controlled Trials and EMBASE, and searched these two databases for relevant trials; Leah Li (Institute of Child Health) did the funnel plot and the regression test of funnel plot asymmetry; Alain Li Wan Po (Centre for Evidence-Based Pharmacotherapy, University of Nottingham) helped to write the paper; Ian Roberts (London School of Hygiene & Tropical Medicine) designed the protocol, extracted data from the trials, contacted authors for unpublished data, and wrote the paper; Gillian Schierhout proposed the study hypothesis, and conducted preliminary searches of MEDLINE, EMBASE, and BIDS Index to Scientific and Technical Proceedings. For the 2008 update, Mia Pearson and Ian Roberts screened the search results, extracted data from the trials and updated the analysis, results and discussion sections of the review. For the 2011 update, Karen Blackhall updated the search for studies. Ian Roberts extracted data from the additional trial ([Maitland 2011](#)) and updated the analysis with Karen Blackhall.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Institute of Child Health, University College London, UK.

### External sources

- NHS Research and Development, UK.

## NOTES

Please note that this review was also published in the BMJ 1998;317:235-40 ([CIGAR 1998](#)).

August 2011:

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. One trial by Prof. Boldt is included in this review ([Boldt 1993](#)), but there were no deaths in the trial and so the data do not contribute to the results. The inclusion of the trial has no impact on the conclusions of the review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Blood Volume; Burns [blood; mortality; \*therapy]; Cause of Death; Critical Illness [mortality; therapy]; Hypoproteinemia [blood; mortality; \*therapy]; Hypovolemia [blood; mortality; \*therapy]; Plasma Substitutes [\*administration & dosage; adverse effects]; Randomized Controlled Trials as Topic; Serum Albumin [\*administration & dosage; adverse effects]

### MeSH check words

Humans