

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Home Subcommittee: PEDS
Author's Home Resuscitation Council: AHA	Date Submitted to Subcommittee: <u>May 29, 2004</u> ; Revised Aug 3, 2004; Nov 3, 2004

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity:

The fluid of choice for volume expansion is an isotonic crystalloid solution such as normal saline or Ringer's lactate (Class IIB, LOE 7). Administration of O-negative red blood cells may be indicated for replacement of large-volume blood loss (Class IIB, LOE 7). Albumin-containing solutions are less frequently used for initial volume expansion because of limited availability, risk of infectious disease, and an observed association with increased mortality.

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

An isotonic crystalloid solution, rather than an albumin-containing solution, is the fluid of choice for volume expansion in neonatal resuscitation.

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

The search strategy updated the review last conducted in 1999 (textword search terms: fluid therapy, shock; colloid; infusion, intravenous; blood volume; hypotension, albumin; resuscitation), with continuous surveillance of the literature for pertinent articles in the interim.

The update added a second large meta-analyses of adult, pediatric, and neonatal trials of fluid therapy; a large prospective trial in adult ICU patients; and an additional RCT in neonates, however, no data have yet been collected in a delivery room setting.

List electronic databases searched (at least MEDLINE (<http://igm.nlm.nih.gov/>) and hand searches of journals, review articles, and books.

Medline (Ovid), Cochrane Library - Substantive revision of the Cochrane Systematic Review was last made on November 26, 2001. This included addition of an RCT in neonates (Bland RD, Clarke TL, Harden LB, Meyer JL, Ries JP, Madden WA, Cras FW, Coyer WF, Bass JW. Early albumin infusion to infants at risk for respiratory distress. Arch Dis Child 1973; 48:800-805) in which albumin or dextrose solution was given to infants at risk for respiratory distress. Inclusion of this study, which fit the category of hypoproteinemia in the review, did not change the outcome of the analysis. The SAFE trial (Saline vs. Albumin Fluid Evaluation) in Australia and New Zealand, a multi-center randomized controlled trial of the effects of volume replacement with albumin compared to saline in critically ill adult patients, was recently completed. A randomized, double-blinded trial comparing saline versus albumin versus sham in an asphyxial model post CPR in newborn swine is nearing completion (PI: Myra Wyckoff, funding from NRP Research Grant Program).

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

Peer-reviewed manuscripts-no abstract-only studies; adult and pediatric data in meta-analyses

Pertinent abstract not yet published in peer-review form: Lynch SK, Stone CS, Graeber J, Mullett M, Polak MJ. Colloid vs. crystalloid fluid therapy for hypotension in neonates. *Pediatr Res* 2002; 51:384A.

Wyckoff MH, Garcia D, Perlman JM, Laptook AR. Randomized trial of volume infusion (VI) during resuscitation of asphyxiated neonatal piglets. *Pediatr Res* 2004; 55(4 part 2): 455A

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; End Note 4+ preferred as reference manager, though other reference databases acceptable.

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STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 2	Randomized clinical trials with smaller or less significant treatment effects
Level 3	<u>Prospective</u> , controlled, non-randomized, cohort studies
Level 4	<u>Historic</u> , non-randomized, cohort or case-control studies
Level 5	<u>Case series</u> : patients compiled in serial fashion, lacking a control group
Level 6	Animal studies or mechanical model studies
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design	Highly appropriate sample or model, randomized, proper controls	More than adequate design; minimally biased	Adequate, design, but possibly biased	Small or clearly biased population or model	Anecdotal, no controls, off target end-points
Methods	Outstanding accuracy, precision, and data collection in its class	More than adequate in its class	Adequate under the circumstances	Weakly defensible in its class, limited data or measures	Not defensible in its class, insufficient data or measures

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
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Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach
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Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

An isotonic crystalloid solution, rather than an albumin-containing solution, is the fluid of choice for volume expansion in neonatal resuscitation

Quality of Evidence	Excellent						Golden 1982E		
	Good	Emery 1992 BP So 1997 BP,R Oca 2003 BP						Rothmaie 1995 E	
	Fair							Huskisson 1992 E McClure 1991 E	
		1	2	3	4	5	6	7	8
Level of Evidence									

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival BP=blood pressure; R=respiratory status

Neutral or Opposing Evidence

An isotonic crystalloid solution, rather than an albumin-containing solution, is the fluid of choice for volume expansion in neonatal resuscitation

Quality of Evidence	Excellent		NNNITG 1996abE					Cochrane 1998 E Wilkes 2001E SAFE Study Investigators 2004 E	
	Good		Greenough 1993R,E			Bignall 1989BP, E		Ekblad 1992 E Lambert 1998 BP, E	
	Fair					Greenough 1988BP,E Barr 1977BP,R Lay 1980BP,E		Roberton 1997E Hope 1998E Cook 2001E	
		1	2	3	4	5	6	7	8
		Level of Evidence							

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival BP=blood pressure; R=respiratory status

META-ANALYSES: to provide a basis for Step 3

<p>Are there two or more Level 1 studies in Step 2D that support the proposal and are statistically significant at $p < 0.05$? No</p> <p>Do these supportive studies constitute at least one quarter of Level 1 clinical trials? No (If the answer to both questions is "yes", the null hypothesis is very likely to be false.)</p> <p>Do you think there are sufficient data to perform a formal meta-analysis? No</p> <p>Summarize core numeric data. <i>If you can provide a formal meta-analysis, attach the most critical tabulations, and cite the methodology used.</i></p>
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STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
<p>Class I <i>Definitely recommended.</i> Definitive, excellent evidence provides support.</p>	<ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness • Must be used in the intended manner for proper clinical indications. 	<ul style="list-style-type: none"> • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling

Class II: <i>Acceptable and useful</i>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Not yet confirmed definitively 	<ul style="list-style-type: none"> • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power • No evidence of harm
<ul style="list-style-type: none"> • <i>Class IIa: Acceptable and useful</i> Good evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered treatments of choice 	<ul style="list-style-type: none"> • Generally higher levels of evidence • Results are consistently positive
<ul style="list-style-type: none"> • <i>Class IIb: Acceptable and useful</i> Fair evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative treatments 	<ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results
Class III: <i>Not acceptable, not useful, may be harmful</i>	<ul style="list-style-type: none"> • Unacceptable • Not useful clinically • May be harmful. 	<ul style="list-style-type: none"> • No positive high level data • Some studies suggest or confirm harm.
Indeterminate	<ul style="list-style-type: none"> • Research just getting started. • Continuing area of research • No recommendations until further research 	<ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling

STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Intervention: Isotonic crystalloid is the preferred solution for volume expansion in neonatal resuscitation.

Final Class of recommendation: Class IIa-Acceptable & useful; good evidence

REVIEWER'S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Professor of Pediatrics, Neonatology

Past Co-chair, Neonatal Resuscitation Program Steering Committee (American Academy of Pediatrics) and liaison to the Pediatric Subcommittee, Emergency Cardiovascular Care Committee of the American Heart Association

Not directly involved in research in this area; no research funding or conflict of interest.

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. "Mismatches" refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers.

Two meta-analyses draw slightly different conclusions from similar data; both conclude that mortality risk is not decreased by albumin use (Cochrane 1998 and Wilkes 2001). The Cochrane analysis concludes that mortality risk may be increased by albumin administration. A large, prospective study powered for an endpoint of overall mortality at 28 days showed no difference in mortality between the albumin and normal saline groups (SAFE Study Investigators 2004). Data are lacking on newly born infants in the delivery room setting. Most available neonatal data are extrapolated from other settings and endpoints other than acute volume resuscitation. The latest randomized, controlled trial (Oca 2003) closely approximates the circumstances of the delivery room by enrolling acutely ill infants < 24 hours of age with hypotension on the basis of decreased intravascular volume.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Printed (paper) bibliography; and on diskette using a reference manager. It is recommended that the bibliography be printed in annotated format. This will include the article abstract and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Key figures or tables from evidence-based analysis

Full hard copies of most critical cited papers

Citation List

Citation Marker	Full Citation*
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Barr 1997	<p>1. Barr PA, Bailey PE, Sumners J, Cassady G. Relation between arterial blood pressure and blood volume and effect of infused albumin in sick preterm infants. <i>Pediatrics</i>. 1977;60:282-289.</p> <p>The relation between arterial blood pressure and blood volume was studied in 61 sick preterm infants (25-37 weeks), and the effect of infused salt-poor albumin (10% solution, 1.0 g/kg in 10 minutes) on blood pressure and blood gases in sick preterm infants was noted as well. Forty-two infants were studied within 12 hours of birth; half were hypotensive (MABP < 95th%ile for birth weight). Nineteen infants were studied after age 12 hours; 5 were hypotensive. There were no significant differences in plasma volume, hematocrit, and blood volume between normotensive and hypotensive infants. Blood pressure did increase at 15-60 minutes after albumin infusion; however the magnitude of the increase was small. Albumin infusion did not decrease the a/ADO₂. Thus, hypotensive infants are not, as a group, hypovolemic, and do not consistently benefit from volume expansion.</p> <p><i>LOE 5; Quality fair:</i></p> <p><i>Comments: The infants were treated for hypotension with rapid volume bolus at < 12 hours or > 12 hours of age. Hypotensive infants tended to be lighter and have lower Apgar scores.</i></p>
Bignall 1989	<p>2. Bignall S, Bailey PC, Bass CA, Cramb R, Rivers RPA, Wadsworth J. The cardiovascular and oncotic effects of albumin infusion in premature infants. <i>Early Human Development</i>. 1989;20:191-201.</p> <p>Twelve premature infants (24-32 weeks) received 18 doses of albumin (1.2 g/kg over 2h. as a 20% solution) when hypovolemia was suspected on clinical grounds (metabolic acidosis, toe-abdominal skin temperature difference > 2.5oC, hypotension, tachycardia > 160 beats/min, peripheral cyanosis). Blood volume increased by a median value of 15.5% and fell to preinfusion values by 3 h. post infusion in all but four cases. Albumin concentration and colloid osmotic pressure rose during infusion and remained raised even when blood volume had fallen to preinfusion levels. Blood pressure rose in 3 cases only and heart rate fell by > 5 beats/min in 6 cases. Blood pressure variability fell in the second hour of infusion, an effect which was independent of changes in lung inflation. No changes in blood gases or oxygenation occurred during infusion and no evidence of pulmonary edema was found.</p> <p><i>LOE 5; Quality good</i></p> <p><i>Comments: The extent of blood volume expansion was estimated by arterial hematocrit change. Marked interindividual variations in response to albumin infusion were noted.</i></p>
Cochrane 1998	<p>3. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. <i>BMJ</i>. 1998;317:235-240.</p> <p>OBJECTIVE: To quantify effect on mortality of administering human albumin or plasma protein fraction during management of critically ill patients. DESIGN: Systematic review of randomised controlled trials comparing administration of albumin or plasma protein fraction with no administration or with administration of crystalloid solution in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia. SUBJECTS: 30 randomised controlled trials including 1419 randomised patients. MAIN OUTCOME MEASURE: Mortality from all causes at end of follow up for each trial. RESULTS: For each patient category the risk of death in the albumin treated group was higher than in the comparison group. For hypovolaemia the relative risk of death after albumin administration was 1.46 (95% confidence interval 0.97 to 2.22), for burns the relative risk was 2.40 (1.11 to 5.19), and for hypoalbuminaemia it was 1.69 (1.07 to 2.67). Pooled relative risk of death with albumin administration was 1.68 (1.26 to 2.23). Pooled difference in the risk of death with albumin was 6% (95% confidence interval 3% to 9%) with a fixed effects model. These data suggest that for every 17 critically ill patients treated with albumin there is one additional death. CONCLUSIONS: There is no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia and a strong suggestion that it may increase mortality. These data suggest that use of human albumin in critically ill patients should be urgently reviewed and that it should not be used outside the context of rigorously conducted, randomised controlled trials.</p> <p><i>LOE 7; Quality excellent</i></p> <p><i>This systematic review of randomized controlled trials compared administration of albumin or plasma protein fraction with no administration or with administration of crystalloid solution in critically ill patients with hypovolemia, burns, or hypoalbuminemia. The main outcome measure examined was mortality from all causes at the end of the follow-up period for each trial. There was no evidence that albumin reduced mortality and a strong association with increased mortality. The</i></p>

Cook 2001	<p><i>reviewers suggest that albumin use be urgently examined and its use be restricted to rigorous, randomized controlled trials.</i></p> <p><i>Comments: Thirty randomized controlled trials were analyzed according to guidelines of the Cochrane collaboration. Six trials were excluded because of "no outcome" (no deaths) in either arm of the study. Only 4 of the remaining 24 trials dealt with newborn infants. Trials were pooled across three principal clinical settings: hypovolemia, burns, and hypoalbuminemia. Two randomized controlled trials involving albumin or plasma as volume expanders in neonates were not included in the meta-analysis (Emery 1992, NNNITG 1996a, 1996b).</i></p> <p>4. Cook D, Guyatt G. Colloid use for fluid resuscitation: evidence and spin. <i>Annals of Internal Medicine</i>. 2001;135:205-208.</p> <p><i>LOE 7 (editorial, analysis)</i></p>
Ekblad 1992	<p><i>The authors present a critique of the accompanying meta-analysis (Wilkes and Navickis 2001) and review the results of previous meta-analyses of fluid administration and mortality in seriously ill patients. They discuss the limitations and different interpretations of meta-analyses. The endpoints of short-term physiologic response, morbidity, and mortality are distinguished. Further well-designed clinical trials with current methodology and monitoring will resolve continuing controversies better than further meta-analyses.</i></p> <p>5. Ekblad H, Kero P, Korvenranta H. Renal function in preterm infants during the first five days of life: influence of maturation and early colloid treatment. <i>Biology of the Neonate</i>. 1992;61:308-317.</p>
Emery 1992	<p>Preterm infants < 30 weeks and 30-34 weeks gestation were randomly assigned to receive FFP 10 mL/kg on days 1-3 or no FFP. Effects were not long-lasting; there was no influence on creatinine clearance or mean arterial blood pressure over the first 5 days of life.</p> <p><i>LOE 7 (extrapolation from data collected for another purpose)</i></p> <p><i>Comments: Pertains to care of the newborn more than to acute resuscitation.</i></p> <p>6. Emery EF, Greenough A, Gamsu HR. Randomised controlled trial of colloid infusions in hypotensive preterm infants. <i>Archives of Disease in Childhood</i>. 1992;67:1185-1188.</p>
Golden 1982	<p>The study aim was to assess whether the amount of protein or the volume of colloid infusion accounts for the observed increase in blood pressure in hypotensive preterm infants. Sixty infants 24-36 wks were randomized to receive 5 mL/kg 20% albumin (1g/kg albumin), 15 mL/kg fresh frozen plasma (2g/kg protein or 0.75g/kg albumin), or 15 mL/kg 4.5% albumin (0.675 g/kg albumin). Infusions were given at 5mL/kg/hr. Infants were randomized when hypotensive (sys BP < 40 mmHg for 2 hours). The mean increase in BP one hour after completing the infusion was lowest in infants receiving 20% albumin (9%, 19%, 17% respectively). The volume infused, rather than albumin load relates to sustained BP increase.</p> <p><i>LOE 2, Quality good</i></p> <p><i>Comments: A single systolic BP level (<40 mmHg) was used to define hypotension across a broad range of gestational ages. Prolonged infusion is hypothesized to produce a sustained increase in oncotic pressure and less protein loss from the circulation due to a lower diffusion gradient.</i></p> <p>7. Golden SM, Steenbarger J, Monaghan P. Osmolality and oncotic pressure of volume expanding fluids for newborn administration. <i>Critical Care Medicine</i>. 1982;10:863-864.</p> <p>Resuscitation of the newborn frequently requires rapid expansion of the circulating volume and correction of metabolic acidosis and hypoglycemia. Solutions commonly used for resuscitation contain various concentrations of NaHCO₃, glucose, electrolytes, and albumin. We have demonstrated the wide range of osmolalities of solutions frequently available in nurseries and delivery rooms and the resultant osmolalities caused by the addition of NaHCO₃. We have also shown the in vitro concentration of albumin needed to equal full-term cord blood colloid osmotic pressure (COP).</p>
Greenough 1988	<p><i>LOE 6, Quality excellent</i></p> <p><i>Comment: This in vitro work adds support to the use of normal saline and Ringer's lactate as iso-osmolar fluids in resuscitation. It also demonstrates the dramatic increase in osmolality associated with addition of sodium bicarbonate.</i></p> <p>8. Greenough A, Greenall F, Gamsu HR. Immediate effects of albumin infusion in ill premature</p>

Greenough 1993	<p>neonates. Archives of Disease in Childhood. 1988;63:307-317.</p> <p>Ten normotensive premature infants (24 - 36 weeks) with idiopathic respiratory distress syndrome and albumin concentrations < 30 g/l were given 5 mL/kg of 20% salt poor albumin. Albumin concentrations 6 hours after infusion had increased significantly; these were associated with significant reduction in weight and improvement in urine output. There were not significant changes in blood pressure after the infusions.</p> <p><i>LOE 5, Quality fair</i></p> <p><i>Comments: Infants < 2 weeks age were eligible for the study; 5 of the infants were paralyzed before and during the study. Only spontaneous urine output was measured; decreased urine output occurred in 2 paralyzed patients; however these infants also lost weight.</i></p>
Hope 1998	<p>9. Greenough A, Emery EF, Hird MF, Gamsu HR. Randomised controlled trial of albumin infusion in ill preterm infants. European Journal of Pediatrics. 1993;152:157-159.</p> <p>Thirty intubated infants (25-34 weeks) were randomized to receive either 5 mL/kg of 20% albumin or 5 mL/kg of maintenance fluids, both as part of the total daily fluid requirement. All infants had an albumin level < 30 g/l; albumin infusion was associated with a significant increase in albumin level and significant reduction in weight. There was no significant change in peak inspiratory pressure following the infusions; FiO2 fell modestly in both groups. Albumin infusion in "hypoalbuminemic" sick preterm infants does not alter respiratory status.</p> <p><i>LOE 2 (negative results), Quality good</i></p> <p><i>Comments: Subjects were enrolled up to 7 days of age. Data from any infant who became hypotensive during the 12 hour period before randomization, or the 12 h. or 24 h. period after the infusion were excluded from analysis.</i></p>
Huskisson 1992	<p>10. Hope P. Pump up the volume? The routine early use of colloid in very preterm infants. Archives of Disease in Childhood Fetal and Neonatal Edition. 1998;78:F163-165.</p> <p>The author argues that volume expansion is being overutilized in preterm infants who present with slightly delayed capillary refill. Hypotension in preterm infants is difficult to define and probably not due to hypovolemia. Pressor support may be physiologically more appropriate treatment. Synthetic alternatives to colloid treatment in neonates should be further evaluated, and the role of physiologic crystalloid solutions should be acknowledged.</p> <p><i>LOE 7</i></p> <p><i>Comments: Call for further research on whom to treat, when, and with what fluid.</i></p>
Lambert 1998	<p>11. Huskisson L. Intravenous volume replacement: which fluid and why? Archives of Disease in Childhood. 1992;67:649-653.</p> <p>The author reviews the crystalloid/colloid controversy and details the composition and pharmacology of solutions available. The role of synthetic colloids remains to be evaluated in pediatric practice.</p> <p><i>LOE 7</i></p> <p><i>Comments: Review - pediatrics</i></p>
Lay 1980	<p>12. Lambert HJ, Baylis PH, Coulthard MG. Central-peripheral temperature difference, blood pressure, and arginine vasopressin in preterm neonates undergoing volume expansion. Archives of Disease in Childhood Fetal and Neonatal Edition. 1998;78:F43-45.</p> <p>An intravenous infusion of 4.5% albumin (20mL/kg) was given to 14 preterm infants and the effects on systolic blood pressure, central-peripheral temperature difference, and plasma arginine vasopressin (AVP) concentration was measured. Thirteen infants showed a rise in systolic blood pressure.</p> <p><i>LOE 7</i></p> <p><i>Comments: The authors conclude that clinical assessment of hypovolemia in preterm infants is poor. Infants were studied at 3 to 44 hours postnatal age. Central venous pressure was not measured. Only 6 infants showed a fall in plasma AVP, interpreted as evidence of hypovolemia improved by volume expansion. Closer scrutiny of indications for use of volume expanders and monitoring of response is encouraged.</i></p> <p>13. Lay KS, Bancalari E, Malkus H, Baker R, Strauss J. Acute effects of albumin infusion on blood</p>

<p>McClure 1991</p>	<p>volume and renal function in premature infants with respiratory distress syndrome. Journal of Pediatrics. 1980;97:619-623.</p> <p>Ten infants (28-36 weeks) received albumin 1 g/kg (25% solution) over a 10-minute period. Total serum protein, colloid osmotic pressure, and blood volume rose, while hematocrit fell from pre-infusion levels. Mean arterial blood pressure showed a smaller and less clear-cut increase. The results indicate that albumin infusion acutely increases blood volume and glomerular filtration in premature infants with RDS.</p> <p><i>LOE 5, Quality fair</i></p> <p><i>Comments: The effect of 25% albumin infusion on blood pressure is inconsistent.</i></p>
<p>NNNITG 1996 a</p>	<p>14. McClure G. The use of plasma in the neonatal period. Archives of Disease in Childhood. 1991;66:373-374.</p> <p>The uses of plasma and albumin solutions in the neonatal period are outlined.</p> <p><i>LOE 7</i></p> <p><i>Comments: A call for more research on postnatal volume expansion</i></p> <p>15. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. The Lancet. 1996;348:229-232.</p> <p>776 preterm infants less than 32 weeks gestation were randomized to receive, within 2 hours of birth, 20 mL/kg FFP followed by a further 10 mL/kg after 24 hours; or the same volumes of a gelatin-based plasma substitute; or maintenance infusion of glucose (control). All the surviving children underwent neurological and developmental assessment at the age of 2 years. The proportions dying (21.0%, 24.9%, 20.5%) and the proportions of survivors with a severe disability (11.3%, 11.2%, 14.1%) did not differ significantly between the randomized groups. The survivors had similar mean developmental quotients at 2 years age. The routine early use of intravascular volume expansion does not reduce death or disability in babies born at less than 32 weeks.</p> <p><i>LOE 2 (negative results); Quality excellent</i></p> <p><i>Comments: Volume expansion was given as soon as possible after randomization, within 2 hours of birth - not in the delivery room. Volume expansion was given prophylactically; there were no required indications for volume administration such as poor response to resuscitation, poor perfusion/delayed capillary refill, hypotension. The dose given was 20 mL/kg over 15 minutes. No data on blood pressure, heart rate, oxygenation are provided.</i></p> <p><i>The study does not directly address the use of volume expansion in immediate resuscitation, in response to indicators of hypovolemia.</i></p>
<p>NNNITG 1996 b</p>	<p>16. Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. European Journal of Pediatrics. 1996;155:580-588.</p> <p>776 preterm infants less than 32 weeks gestation were randomized to receive, within 2 hours of birth, 20 mL/kg FFP followed by a further 10 mL/kg after 24 hours; or the same volumes of a gelatin-based plasma substitute; or maintenance infusion of glucose (control). 43.0%, 37.5% and 42.3% of infants died or had documented at least a minor cerebral ultrasound abnormality before discharge. Those who died or developed a major scan abnormality (ventriculomegaly, parenchymal abnormality) were 22.7%, 27.0% and 23.3%.</p> <p><i>LOE 2 (negative results); Quality excellent</i></p> <p><i>Comments: Mortality among babies who never entered the trial was 45%, considerably higher than the mortality among those who participated in the trial (20%). However, 61 babies were judged too small or ill to justify randomization at birth (all died). Only 611 of the infants enrolled had a cranial ultrasound. Many babies received further supplementary colloid or blood outside the study protocol. 16% of the control group received at least 10 mL/kg blood or colloid later in the first day of life.</i></p> <p><i>Comment: The study does not directly address the use of volume expansion in immediate resuscitation, in response to indicators of hypovolemia. However, it does pertain to the overuse of volume expansion for presumed, but unproven hypovolemia ("poor perfusion").</i></p>
<p>Oca 2003</p>	<p>17. Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the</p>

	<p>treatment of neonatal hypotension. <i>Journal of Perinatology</i>. 2003;23:473-476.</p> <p>The study compared normal saline (NS) and 5% albumin (ALB) for treatment of hypotension in the acutely ill newborn infant. 41 term and preterm infants < 24 hour old were randomized to receive either NS or ALB for the indication of hypotension, defined as a sustained (>30 min) mean arterial pressure < 30 mmHg for infants <2500g or a MAP <40mmHg for those >2500g. The short-term outcome was resolution of hypotension for > 30 min. 21 infants received ALB and 20 received NS, 10mL/kg over 15 min, with the infusion repeated once if the infant failed to respond initially. Treatment was successful in 17/21 of infants in the ALB group and 17/20 infants in the NS group. Groups were equivalent in their rate of response and magnitude of change in MAP. 7 of 20 infants in NS group required a 2nd infusion and 3 required inotropic support; 9 of 21 infants in the ALB group required a 2nd infusion and 4 required inotropic support. The authors conclude that NS is as effective as ALB for the correction of acute hypotension and in light of its relatively low cost and availability, should be considered the initial treatment of choice in this setting.</p> <p><i>LOE 2 (small RCT, negative results, unblinded); Quality good</i></p>
Robertson 1997	<p><i>Comments: Randomization was adequate, however the study was not blinded. 9 patients were excluded following randomization and treatment; 4 because the baseline hematocrits were <40% and 5 because of institution of HFOV due to rapidly deteriorating respiratory status. Exclusion criteria included any clinical condition in which cardiac output was compromised (sepsis, heart disease, pneumothorax, HFOV). The outcome measure chosen was very short-term. The study was not adequately powered to assess long-term outcomes. The 5 deaths observed in the trial were all ELBW infants who died from complications of NEC (1 in NS group and 4 in ALB group).</i></p> <p>18. Robertson NRC. Use of albumin in neonatal resuscitation. <i>European Journal of Pediatrics</i>. 1997;156:428-431.</p>
Roithmaier 1995	<p>The author argues that albumin administration in the first hour of life in the resuscitation of asphyxiated, term babies is physiologically unsound.</p> <p><i>LOE 7</i></p> <p><i>Comments: Critical appraisal of indications for albumin</i></p>
SAFE Study Investigators	<p>19. Roithmaier A, Arlettaz R, Bauer K, Bucher HU, Krieger M, Duc G, Versmold HT. Randomized controlled trial of Ringer solution versus serum for partial exchange transfusion in neonatal polycythaemia. <i>European Journal of Pediatrics</i>. 1997;154:53-56.</p> <p>The authors examined whether crystalloid could be used instead of colloid for partial exchange transfusions in polycythemic neonates. Twenty term neonates were randomly assigned to partial exchange transfusion with a serum preparation (BISEKO) or Ringer solution. Plasma volume was measured with Evans blue dilution. Blood volume and red cell mass were calculated from plasma volume and venous hematocrit. More of the Ringer solution left the intravascular space within 4 hours after transfusion, as compared to the serum. However, there was no difference in hematocrit after exchange using Ringer's solution, as compared to serum.</p> <p><i>LOE 7</i></p> <p><i>Comment: Four hours after partial exchange transfusion, 36% of serum had left the intravascular space, as compared to 77% of the Ringer solution. The serum losses were highly variable and in some infants, much higher. Crystalloid solutions are 50-fold cheaper than serum products, carry no risk of anaphylactic reactions, and are not associated with risk of viral infection.</i></p> <p>20. The Saline versus Albumin Fluid Evaluation (SAFE) Study Investigators (Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, writing committee). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. <i>New England Journal of Medicine</i> 2004; 350:2247-2256.</p> <p>BACKGROUND: It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU. METHODS: We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization. RESULTS: Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups</p>

<p>So 1997</p>	<p>had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups (P=0.85). There were no significant differences between the groups in the mean (+/-SD) numbers of days spent in the ICU (6.5+/-6.6 in the albumin group and 6.2+/-6.2 in the saline group, P=0.44), days spent in the hospital (15.3+/-9.6 and 15.6+/-9.6, respectively; P=0.30), days of mechanical ventilation (4.5+/-6.1 and 4.3+/-5.7, respectively; P=0.74), or days of renal-replacement therapy (0.5+/-2.3 and 0.4+/-2.0, respectively; P=0.41). CONCLUSIONS: In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.</p> <p><i>LOE 7 (large RCT in adults - extrapolation); Quality excellent</i></p> <p><i>Comment: Patients who randomized to albumin received less study fluid than those assigned to saline, but a greater volume of packed red cells. There were no significant differences between the groups in the mean arterial pressure during the first four days of the study. Heart rate was slightly lower and CVP slightly higher in the albumin group during the first four days, but was not clinically significant. The authors conclude that "factors that may influence the choice of resuscitation fluid for a critically ill patient include the individual clinician's preference, the tolerability of the treatment, its safety, and its cost."</i></p>
<p>Wilkes 2001</p>	<p>21. So KW, Fok TF, Ng PC, Wong WW, Cheung KL. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Archives of Disease in Childhood. 1997;76:F43-46.</p> <p>63 preterm infants weighing 540 to 1950 grams (g.a. 23 to 34 weeks) who developed hypotension within the first 2 hours of life, were randomized to receive 10 mL/kg 5% albumin or isotonic saline. Inotropic support (dopamine) was given if the infants remained hypotensive after 3 infusions (30 mL/kg total). Subsequent doses of volume were given as 5% albumin on the basis of blood pressure. Outcome (BP and oxygenation status at 2,4,8,12,24,36 and 48 hours; interval between doses; no. of infants requiring inotropic support, no. who developed chronic lung disease) did not differ between the groups. The group who received albumin required significantly more volume expander to maintain normal blood pressure and had a higher mean percentage weight gain within the first 48 hours of life. The difference in weight gain persisted even when only those infants not requiring inotropic support or extra 5% albumin were compared. Isotonic saline is as effective as 5% albumin for treating hypotension in preterm infants, and it has the advantage of causing less fluid retention in the first 48 hours.</p> <p><i>LOE 2; Quality good</i></p> <p><i>Comments: Sample size was based on a 50% difference in failure rate between the two groups. No infants received fluid replacement or inotropic support during immediate postnatal resuscitation. There were no differences observed in NEC, PDA, BPD, ICH in the two groups.</i></p> <p>22. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. Annals of Internal Medicine. 2001;135:149-164.</p> <p>The authors conducted a meta-analysis of 55 randomized, controlled trials to test the hypothesis that albumin administration is not associated with excess mortality. A comprehensive search strategy identified 55 English and foreign language studies comparing albumin therapy with crystalloid therapy, no albumin, or lower doses of albumin. Trials involved surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other indications. For all trials the relative risk for death was 1.11 (95% CI 0.95 to 1.28). For high-risk neonates, relative risk was 1.19 (95% CI 0.78 to 1.81).</p> <p><i>LOE 7 (extrapolation of adult, pediatric, and neonatal data in meta-analysis); Quality excellent</i></p> <p><i>Comment: Inclusion criteria differ from those of the Cochrane systematic review. Meta-analysis was funded by the Plasma Protein Therapeutics Association.</i></p> <p>SUPPLEMENTAL REFERENCES</p> <p>Jardine L, Jenkins-Manning S, Davies M. Albumin infusion for low serum albumin in preterm newborn infants. Cochrane Database of Systematic Reviews 2004; 3:CD004208</p> <p>BACKGROUND: Intravenous albumin infusion to treat hypoalbuminaemia is used in intensive care nurseries. Hypoalbuminaemia occurs in a number of clinical situations</p>

including prematurity, the acutely unwell infant, respiratory distress syndrome (RDS), chronic lung disease (CLD), necrotising enterocolitis (NEC), intracranial haemorrhage, hydrops fetalis and oedema. Fluid overload is a potential side effect of albumin administration. Albumin is a blood product and therefore carries the potential risk of infection and adverse reactions. Albumin is also a scarce and expensive resource.

OBJECTIVES: The primary objective was to assess whether albumin infusions, in preterm neonates with low serum albumin, reduces mortality and morbidity. A secondary objective was to assess whether albumin infusion is associated with significant side effects.

SEARCH STRATEGY: Searches were made of MEDLINE from 1966 to April 2004, CINAHL from 1982 to April 2004 and the current Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library issue 1, 2004). Previous reviews (including cross references) and abstracts were also searched.

SELECTION CRITERIA: All randomised controlled trials in which individual patients were allocated to albumin infusion versus control were included. Cross-over studies were excluded. Quasi randomised trials were excluded. Participants were preterm infants who had hypoalbuminaemia. Types of interventions included albumin infusion versus placebo (e.g. crystalloid) or no treatment.

DATA COLLECTION AND ANALYSIS: The reviewers worked independently to search for trials for inclusion and to assess methodological quality. Studies were assessed using the following key criteria: blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome measurement.

MAIN RESULTS: Only two small studies were found for inclusion in this review and only one reported clinically relevant outcomes - it found no significant differences for our primary outcome measure of death (RR 1.5 [95% confidence interval 0.3 - 7.43]) or secondary outcome measures of intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis, bronchopulmonary dysplasia, duration of mechanical ventilation and duration of oxygen therapy.

REVIEWERS' CONCLUSIONS: There is a lack of evidence from randomised trials to determine whether the routine use of albumin infusion, in preterm neonates with low serum albumin, reduces mortality or morbidity, and no evidence to assess whether albumin infusion is associated with significant side effects. There is a need for good quality, double-blind randomised controlled trials to assess the safety and efficacy of albumin infusions in preterm neonates with low serum albumin.

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