Clinical question.

In infants and children with any type of shock (P), does the use of any specific resuscitation fluid or combination of fluids [eg: isotonic crystalloid, colloid, hypertonic saline, blood products] (I) when compared with standard care (C) improve patient outcome (hemodynamics, survival) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet: new topic

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No relevant conflicts of interest

Search strategy (including electronic databases searched).

- PubMed: Search query

- OvidMed: Search query

- Embase

- Cochrane Database
  Shock

- AHA EndNote Master Library
  Shock

References of pulled articles were also searched

- State inclusion and exclusion criteria

  Included: studies reporting outcome measures (haemodynamic parameters, survival, morbidity), hypovolemic or septic shock, all types of intravenous/intravenous fluid. Human (infant, child, adolescent) studies

  Excluded: case reports, animal studies, studies which do not describe or compare different specific types of fluid. Reviews included only for identifying primary studies.

  Studies not in peer-reviewed journals or in abstract form only were excluded

Papers returned by initial query

2202 “shock OR resuscitation AND fluid therapy” Pubmed and Ovid searches

99 filtered by: infant OR child OR adolescent

12 meeting criteria for detailed review, 6 additional papers identified through search of citations

3 of 5 Cochrane reviews included (2 were earlier versions of later Cochrane reviews)

- Number of articles/sources meeting criteria for further review

16 Papers selected for detailed review based on study description/design information available in abstract and criteria noted above
### Summary of evidence

#### Evidence Supporting Clinical Question: For Crystalloids (Against Colloids)

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<td>Myburgh SAFE-TBI 2007, C</td>
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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*

#### Evidence Neutral to Clinical question: No Difference between Crystalloids and Colloids

| Good | Wills 2005 E | | | Choi 1999 C  
|------|-------------|---|---| Finfer SAFE 2004 C |

| Fair | Dung 1999 E  
| Upadhyay, 2005 C, E  
| Ngo 2001 C, E |

| Poor | Bowser-Wallace 1986 E  
| Maitland 2003 C, E |

| | Cocks 1998 C, E |

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
Evidence Opposing Clinical Question: Against Crystalloids (For Colloids)

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Level of evidence

A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint
B = Survival of event  D = Intact neurological survival  Italics = Animal studies

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

CRYSTALLOIDS VERSUS COLLOIDS AS THE RESUSCITATIVE FLUID OF CHOICE

The majority of studies were supportive of crystalloids over colloids as the resuscitative fluid of choice in patients with shock. There were 6 studies (1 was a subgroup of a larger study) supporting crystalloids, 10 studies that were neutral and only 1 study that favored colloids over crystalloids.

There were 8 pediatric studies: 7 studies were neutral (LOE 1 or RCTs: Dung 1999; Ngo 2001, Upadhyay 2005, Willis 2005), LOE 2 Bowser-Wallace 1986, LOE 2 Maitland 2003, LOE 4 Cocks and only 1 study (Maitland 2005) (LOE 1) against crystalloids.

The Willis 2005 study (LOE 1) was a level 1 large blinded RCT of pediatric patients with dengue shock syndrome (good evidence) comparing crystalloids (Ringer’s lactate) and colloids (dextran and starch) found no difference in primary outcome (need for rescue colloid). The secondary outcome measures were: time to achieve cardiovascular stability, volume of rescue colloid, total IV fluid needed, pattern of change in hematocrit, and number of hospital days. Although there was less rapid improvement in the hematocrit and a marginally longer time to initial recovery with normal saline than dextran 70 or 6% hydroxyethyl starch, there were no differences in other treatment measures. Bleeding manifestations, coagulation derangements, and severity of fluid overload were similar. Eight percent (15/193) of the patients receiving dextran had severe reactions (transient high fever and rigors without cardiovascular compromise). This study favors crystalloids because of adverse effects with colloids.

In the Upadhyay 2005 study (LOE 1), both normal saline and gelatin were equally effective as resuscitation fluid.

In the Dung 1999 study, there were no significant differences between the crystalloids and colloids in clinical parameters: hours in shock, number of shock episodes, need for further crystalloid infusions, need for further colloid infusions; although colloids more rapidly (within 2 hours) restored hemodynamic parameters: (e.g. normalization of hematocrit, blood pressure). The clinical significance of the hemodynamic parameters is uncertain given the good final results for all children.

The Ngo 2007 study (LOE 1) determined “there was no clear advantage to using any of the 4 fluids (dextran, gelatin, lactated Ringer’s, and normal saline)”. All the children survived. The longest recovery times (measured by improvement in pulse pressure recovery rate) were in the lactated ringer’s group. However,
although there may be a difference in the pulse rates after one hour as a measure of recovery time, it is likely that this has no real clinical significance. This study had a problem in that there was an unequal distribution of the more severely ill patients with patients in the dextran group having the fewest severely ill patients.

It should be noted that in two studies (Ngo, Dung), initial changes in the early time frame (in 1, 2 or 3 hours) in hemodynamics (such as pulse rate or hematocrit normalization) improved with both crystalloids and colloids although the improvement may have been slightly better (such as a greater decrease in pulse at 2 hours) with colloids but there were no difference in terms of mortality, or complications (such as pulmonary edema), etc. Both crystalloids and colloids improved hemodynamics with colloids doing it slightly faster in some studies but this did not play a role in the patient’s eventual outcome or in clinically significant measures such as complications, length of hospital stay, etc.

In the one pediatric study favoring colloids (Maitland 2005- LOE 1) the quality of evidence was poor and there were several methodological problems with the study. The limitations of this study included: the study was confounded. The groups were unequal in terms of severity with a greater number of severely ill patients in the normal saline group. The normal saline group had a higher incidence of hypotension, seizures, and hypoglycemia. There were four patients who had elevated salicylate levels which may have contributed to the acidosis in some patients. The cause of death was attributed to “brain swelling” but the intracranial pressure was not monitored and no autopsies were done. This was a single center with a small number of patients and nonblinded (open label) study. There was no difference in the primary outcome measure: a reduction in base deficit at 8 hours between the crystalloid or colloid groups but there was a significant decreased mortality for patients receiving albumin (3.6% =2/56) compared to the normal saline group (18% = 11/61) (p=0.013).

In the Maitland 2003 study (LOE 2), “there were no clear differences in response between the albumin and saline groups.” There were 2 other pediatric studies (Bowser-Wallace 1986 –LOE 2, and Cox 1998- LOE 4) that were neutral.

The Boluyt study (LOE 5) was a pediatric clinical practice guideline that was derived as a systematic review based on 3 adult systematic reviews, 2 pediatric RCTs, and one very large blinded adult RCT with 6997 patients so this was considered a level 5. The recommendation was “in neonates and infants with hypovolemia the first choice fluid for resuscitation should be isotonic saline.”

In the So 1996 study (LOE 5) of preterm infants, there were no differences in need for inotropic support, death, or chronic lung disease between isotonic saline and albumin. However, isotonic saline had the advantage of causing less fluid retention and weight gain.

There were 5 systematic reviews of crystalloids versus colloids in adult patients, all were LOE 5, (3 were Cochrane reviews: Perel 2009, Alderson 2004, Bunn 2008) the others were: Schierhout, Choi). Two other Cochrane reviews (Roberts 2004, Cochrane – BMJ 1998), were earlier versions of later studies. There were 2 other studies that compared various colloids, one was a Cochrane review (Bunn 2008), the other (Boldt 1993) was not a Cochrane review. The Bunn review compared various colloid solutions and the Boldt compared 2 colloid solutions (hydroxyethyl starch and albumin).

Of the reviews comparing crystalloids with colloids, all were LOE 5 (2 Cochrane: Alderson 2004, Perel 2007, and the Schierhout and Choi metanalyses). All looked at mortality and were all for crystalloids over colloids (Choi trauma subgroup for crystalloids) except Choi overall neutral. The Schierhout metanalysis found the risk of death was 24% in the colloid group and 20% in the crystalloid giving an absolute risk of mortality for resuscitation with colloids of 4%. The one neutral metanalysis (Choi) found “no apparent difference in pulmonary edema, mortality, or length of stay between isotonic crystalloid and colloid. resuscitation.”(Level 5, Level of evidence- good, Neutral) But in the subgroup of trauma patients in the Choi study, crystalloids are favored: “Crystalloid resuscitation is associated with a lower mortality in trauma patients”

Two large excellent studies in adult patients (from the SAFE study investigators) are included. The Safe Study in 2004 (Finfer) compared albumin and saline for fluid resuscitation in 6997 adults in the intensive care unit. This was a prospective, blinded, multicenter randomized controlled trial involving16 ICUs in academic tertiary care hospitals. There was no difference in 28 day mortality, patients with new single-organ failure, multiple organ failure, or in number of ICU days between the normal saline and the albumin groups. (Level 5, Quality of Evidence- good, Neutral).
The SAFE –TBI study 2007 (Myburgh) compared the use of saline or albumin for fluid resuscitation in adults with traumatic brain injury. This was a post hoc follow-up study of patients with TBI who were enrolled in the SAFE study. At 24 months 33.2% (71/214) of the patients in the albumin group died compared with 20.4% (42/206) in the saline group, p< 0.001. “Fluid resuscitation with albumin was associated with higher mortality rates than with saline.” (Level 5, Quality of Evidence- good, Favors crystalloids).

INTRODUCTION

Shock is inadequate tissue perfusion due to an imbalance between the delivery of oxygen and substrate to the tissues and cellular demands. The insufficient supply of oxygen and substrates to the tissues leads to the stimulation of various autonomic responses intended to maintain perfusion pressure to the vital organs. However, if these responses are inadequate, cellular injury occurs with the production and release of inflammatory mediators. These mediators, in turn, further worsen tissue perfusion by initiating functional and structural changes in the microcirculation. A vicious cycle then results. Cellular injury results in the maldistribution of blood flow causing further impairment of cellular perfusion, leading to multiple organ failure and eventually, the death of the patient, if the cycle is not broken and adequate tissue perfusion restored to maintain cellular viability.

Fluid resuscitation is the mainstay of therapy for all forms of shock. Volume therapy is the “C” for circulation in the ABCDE principles of shock resuscitation: A = Airway: establish an airway, B = Breathing: maintain breathing or ventilation, C = Circulation: restore then maintain optimal circulation (and thereby, perfusion) D = Delivery: attain adequate oxygen delivery, E = End Points: accomplish the endpoints of resuscitation. The goal of fluid resuscitation is to restore the intravascular volume relative to the vascular space and optimize ventricular preload with the end result of reestablishing sufficient oxygen and substrate delivery to the tissues. Fluid resuscitation is essential in the therapy of all forms of shock, even cardiogenic shock, although in this situation a more cautious approach with smaller boluses and a lesser total fluid volumes may be indicated.

TYPES OF REUSCITATION SOLUTIONS

CRYSTALLOIDS

The crystalloid solutions are hypo-oncotic solutions since they do not contain the large protein molecules found in the plasma. Therefore, when crystalloid solutions are given, part of the administered crystalloid solution will move into the extravascular space in an amount corresponding to the relative size of the intravascular and interstitial fluid compartments. When isotonic crystalloid is given, the maximal amount of fluid remaining in the intravascular space is only 30%. Thus, the algorithm used is: if X amount of blood is lost, then 3 times X is necessary to restore the intravascular volume since approximately 70% of the administered fluid shifts into the interstitial space. Regarding the specific crystalloid, there are several considerations. Lactated ringer’s solution may increase lactic acidosis if administered in large amounts and increases the release of cytokines, while normal saline worsens the intracellular depletion of potassium and produces hyperchloremic acidosis. Infusions of large amounts of either crystalloid results in a greater activation of neutrophils.

Normal saline (NS), lactated ringer’s solution (LRS), and ringer’s acetate are the three types of isotonic crystalloids that are available. (Table 1) There is no conclusive data documenting a definitive advantage of one crystalloid (e.g normal saline or lactated ringer’s solution) over the other, although in one of the studies (Nhan 2001), normal saline was preferred over lactated ringer’s solution.

COLOIDS

Colloids contain larger molecular weight particles so they have an oncotic pressure that is similar to that of normal plasma proteins. Because of their higher molecular weight, colloids would be expected to stay in the intravascular space and replace any lost plasma proteins. At
least theoretically, colloids would have fewer adverse effects, e.g. less incidence of pulmonary edema with diminished oxygen diffusion, and be more effective in restoring the circulating volume than crystalloids. In reality, in disease states including shock or sepsis, vascular permeability is increased, which allows these larger colloid molecules to leak into the extravascular space.

The clinically available colloid solutions comprise a heterogeneous collection of substances. They include albumin in various concentrations: 4%, 5%, and 25%; dextran in several solutions: dextran (the 10% solution or dextran-40 has a molecular weight of 40 kDa, the 6% solution or dextran-70 has a molecular weight of 70 kDa), hetastarch: 6% hydroxyethyl starch concentration, gelatin, and fresh frozen plasma. More recently, hypertonic solutions have also been used; either saline (7.0 to 7.5% NaCl) or saline and dextran (7.5% saline and 6% dextran-70). (Table 1) Studies including a pediatric study that compared hydroxyethyl starch and albumin) and a Cochrane review (Bunn F) that compared different colloids (albumin, purified protein fraction, hydroxyethyl starch, gelatin, and dextran.) found no evidence that any one colloid solution was more effective or safe than any other.

OTHER RESUSCITATION FLUIDS

Oxygen-carrying resuscitation fluids are either hemoglobin-based oxygen carriers or fluorocarbon-based oxygen carriers have been proposed and are being studied as products that may be able to serve as a substitute for blood transfusions. At present, however, there is no currently available product that is approved or been well documented to be safe, effective, and have the ability to be used for large volume resuscitation

FLUID THERAPY

Aggressive fluid therapy is the primary treatment for any condition characterized by decreased intravascular volume with concomitant tissue hypoperfusion and multiple organ system dysfunction, and provides benefits in other types of shock with relative hypovolemia, as well as being necessary in various conditions characterized by loss of plasma fluid and electrolytes such as dehydration and burns.

Given that volume expansion is the cornerstone of therapy for shock, the question then arises: “What is the preferred fluid in the treatment of shock?” This has become “the crystalloid versus colloid” controversy.

TABLE 1: SPECIFIC FLUIDS USED FOR RESUSCITATION

Crystalloids (isotonic fluids)
- Normal saline (NS)
- Lactated ringer’s solution (LRS)
- Ringer’s acetate

Colloids
- Albumin (4%, 5%, 25% concentrations)
- Dextran (Dextran-40 is a 10% solution, molecular weight =40 kDa, Dextran-70 is a 6% solution, molecular weight = 70 kDa)
- Gelatin
- Hetastarch (6% hydroxyethyl starch concentration)
- Fresh-frozen plasma

Hypertonic solutions
- Saline (7.0% to 7.5 % NaCl)
- Saline and dextran (7.5% NaCl and 6% Dextran-70)
Acknowledgements:

Citation List


Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality
Metaanalysis of randomized controlled trials
Limitations: The SAFE study was included in this metaanalysis so this is not an entirely independent additional study.


Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality
Metaanalysis of randomized controlled trials
Limitations: This is an older metaanalysis of the Alderson study
Adult studies included in the analysis.

PEDIATRIC STUDY

This metanalysis is not part of the evidentiary table but was included since it documents that there is no advantage of one colloid compared with any other colloid (See discussion)


Evidence: For crystalloid (Against Colloids)
Level of Evidence: 5
Quality of Evidence: good
Outcome: Death, pulmonary edema, number of days in hospital, chronic lung disease, intraventricular hemorrhage
This guideline was based on a high quality systematic review that included 3 pediatric RCTs, 1 large adult RCT, and 6 systematic reviews. 
Limitations: Included an adult study, was a systematic review

OBJECTIVES: To compare two different fluids: hypertonic lactated saline v. Ringer’s lactate-colloid in severely burned children 

Evidence: Neutral: Because of no differences in outcome measures. 
Level of Evidence: 2 
Quality of Evidence: poor 
Outcome: weight gain, urine output, hematocrit, BP, blood tests, also cost 
Small prospective nonblinded not randomized comparative trial in pediatric patients 
Limitations: Small N, not truly randomized, not blinded, default to colloid group based on prearrival infusion volumes suggests that the patient groups may not have been equivalent, cardiovascular shock poorly defined, no isotonic crystalloid group, indirect outcome measures, not a true comparison of colloid vs. isotonic crystalloid, instead compared colloid with hypertonic crystalloid

This metanalysis is not part of the evidentiary table but was included since it documents that there is no advantage of one colloid compared with any other colloid (See discussion)


Evidence: Neutral 
For crystalloids (Against colloids) for subgroup of trauma patients 
Level of Evidence: 5 
Quality of Evidence: Good 
Outcome: Pulmonary edema, mortality, length of stay 
Metanalysis of randomized controlled trials in adults


Evidence: Neutral: Because of no differences in outcome measures. 
Level of Evidence: 2 
Quality of Evidence: poor 
Outcome: survival to discharge, rate of ARDS, Small prospective nonblinded not randomized comparative trial in pediatric patients 
Limitations: Small N, not truly randomized, not blinded, default to colloid group based on prearrival infusion volumes suggests that the patient groups may not have been equivalent, cardiovascular shock poorly defined, no isotonic crystalloid group, indirect outcome measures, retrospective, missing data on 6
patients, patients with smoke inhalation included with burn patients suggests heterogeneous groups, not a true comparison of colloid vs. isotonic crystalloid since one group got a mixture of crystalloid and colloid vs. colloid


Evidence: Neutral (No difference between crystalloids and colloids)
Level of Evidence: 1
Quality of Evidence: fair
Outcome: requirement for further colloid, requirement for further crystalloid, incidence of reshock, hours in shock, complications (volume overload, bleeding tendencies) over time.
Prospective blinded randomized controlled trial of crystalloids vs colloids in dengue shock syndrome in pediatric patients
Limitations: Interventions were only for the first 2 hours of fluid therapy so may question if this truly had an impact, all children survived so uncertain if the outcome measures has clinical significance, the magnitude of difference detected was of limited clinical significance, the study had low power, Dengue shock syndrome is likely different physiologically from other types of shock


Evidence: Neutral
Level of evidence: 5
Quality of evidence: good
Outcome: mortality
Prospective double-blind, randomized controlled multicenter trial of adults patients in the ICU randomly assigned to either albumin or normal saline for all fluid resuscitation


Evidence: Neutral
Level of Evidence: 2
Quality of Evidence: fair
Outcome: Clinical, hemodynamic, and laboratory parameters, complications (volume overload, cerebral edema)
Prospective, nonblinded, comparative trial of saline vs albumin in children with severe malaria.
Limitations: Note: not truly randomized since treatment given (saline vs albumin) was allocated based on date, also not blinded, was quasi-randomized. There is also a possibility that some the patients had shock from causes other than malaria since “falciparum parasitemia is present in over 30% of the children in that community” which raises the possibility that parasites in the blood may occur when there the individual is not having a bout of malaria, although this is unlikely.


Evidence: Against crystalloids
Level of evidence: 1
Quality of evidence: poor
Outcome: reduction in base deficit, mortality
This is a prospective open-label RCT in a pediatric population with severe malaria and acidosis showing no difference in base deficit but a significant difference in mortality.
Limitations: Several methodological issues with this study: 1. "In the severe acidosis group, hypotension, seizures, and hypoglycemia were all slightly more common among those assigned to receive saline than albumin" so this study was confounded.
2. "Salicylate ingestion was suspected in 87 patients of which 73 had an unrecordablesalicylate level; of the rest, only 4 had a salicylate ingestion of any potential clinical significance (> 10 mg/dl). They did not note which group these patients were in.
3. They presumed the cause of death was “brain swelling” but did not monitor the intracranial pressure or do autopsies on the children who died.
4. There is the possibility of some patients not having malaria and having another etiology for their acidosis and anemia. The parasitemia in some patients may have been an incidental finding. In this region of Kenya, > 30% of the children have parasitemia. They used a clinical case definition. The entry criteria were clinical features of “prostration, coma, or respiratory distress” and the presence of falciparum parasitemia.


Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: good
Outcome: mortality
Post hoc follow-up study of adult patients with traumatic brain injury, original study was a prospective double-blind, randomized, controlled multi-center trial of adult trauma patients randomly assigned to either albumin or normal saline for all fluid resuscitation in the ICU


Evidence: Neutral: In the majority of patients because of no difference in mortality and more complications with colloids. Of the crystalloids, NS is preferred over LRS.
Level of Evidence: 1
Quality of Evidence: fair (due to unequal distribution of severely ill patients)
Outcome: mortality, complications, hemodynamic parameters (such as initial PP recovery time, reshock, time to first reshock, total volume dextran required, drop in Hct, total IV fluids)
Prospective blinded randomized controlled trial in dengue shock syndrome in pediatric patients.
Limitations: Unequal numbers of severely ill patients in the various groups so this study has a methodological problem because of confounding. The low numbers of patients in grade 4 DSS although for no power to determine difference in this group. The outcomes are interim treatment points and not measures of survival or quality of survival and thus, they may not be of clinical significance. Since all the children survived, there is no power to determine survival effect.

Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality
Metanalysis of randomized controlled trials
This is the largest and most current metanalysis on colloids vs. crystalloids.
limitations: Adult studies were included in the analysis.

14.B. This is an earlier version of the above Perel Cochrane review.

Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality
Metanalysis of randomized controlled trials and quasi-randomized trials


Evidence: For crystalloids (Against colloids)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality
Metanalysis of randomized controlled trials and quasi-randomized trials


Evidence: For crystalloids (Against colloids)
Level of evidence: 5
Quality of evidence: good
Outcome: Primary outcomes: death, chronic lung disease, number of infants requiring inotropic support.
Secondary outcomes: need for additional doses of volume expander, mean percentage weight gain at 24 hours and 48 hours.
This is a prospective, open label, randomized controlled trial in preterm infants with hypotension.
Limitations: study in neonates

Evidence: Neutral (No difference between Crystalloids and Colloids)
Level of Evidence: 1
Quality of Evidence: fair
Outcome: hemodynamic stability, incidence of organ dysfunction, mortality
Nonblinded prospective randomized controlled trial of septic shock in pediatric patients
This is an open label RCT in a pediatric population with septic shock showing no significant differences in mortality or other outcome measures (hemodynamic stability, need for pressors) between isotonic fluid (normal saline) or colloids (polymer from degraded gelatin). Limitations: Unblinded, underpowered for survival outcome.


Evidence: Neutral: Because of no differences in overall treatment response and more adverse reactions associated with colloids (e.g. dextran)
Of the colloids, starch preferred because of more adverse reactions with dextran.
Level of Evidence: 1
Quality of Evidence: good
Outcome: requirement for rescue colloid, adverse reactions
Large prospective blinded randomized controlled trial of crystalloids vs colloids in dengue shock syndrome in pediatric patients
Limitations: Is DSS different in pathophysiology from other types of shock?