FLUID RESUSCITATION

SUMMARY
The decision as to whether to use crystalloid versus colloid as the primary resuscitation fluid in the critically ill has long been a subject of debate. Two previous meta-analyses of the numerous prospective, clinical trials in this area suggested that colloid resuscitation may be associated with increased patient mortality. A large multicenter, randomized, double-blind trial, however, documented the safety of colloid-based resuscitation using albumin, but failed to demonstrate either an economic or survival benefit to such therapy.

RECOMMENDATIONS

- **Level 1**
  - Despite equivalent efficacy, crystalloids are the resuscitation fluids of choice given the lack of survival benefit and increased cost associated with albumin.
  - Albumin is contraindicated in the initial resuscitation of the traumatically injured.
  - Albumin should be avoided in patients with severe traumatic brain injury (Glasgow Coma Score (GCS) ≤ 8).

- **Level 2**
  - Non-protein colloids are preferred over albumin based on economic considerations.

- **Level 3**
  - Colloids may have a secondary role in patients unresponsive to crystalloids or those who cannot tolerate large-volume crystalloid resuscitation.

INTRODUCTION
Critically ill patients frequently demonstrate evidence of inadequate tissue perfusion manifested by anaerobic metabolism and lactic acidosis. The primary resuscitation goal in such patients is to restore tissue perfusion / cellular oxygenation and maintain end-organ function through volume resuscitation. The optimal resuscitation fluid, however, remains a subject of debate.

Crystalloids
Crystalloids may be classified as hypotonic, isotonic, or hypertonic. For purposes of resuscitation, only the isotonic and hypertonic fluids are of use as hypotonic fluids (such as 5% dextrose in water and ½ normal saline) do not remain intravascular. Isotonic fluids (such as lactated Ringer's and normal saline) form the backbone of crystalloid resuscitation. Hypertonic fluids (such as 3%, 6%, or 7.5% normal saline) may have a role in specific patient populations such those with traumatic brain injury. Crystalloids have the advantage of being inexpensive and readily available. They resuscitate both the intravascular and interstitial space, and promote urinary output. Disadvantages include edema formation in patients with capillary permeability and the need for increased volumes to achieve equivalent resuscitation to colloids.

EVIDENCE DEFINITIONS

- **Class I**: Prospective randomized controlled trial.
- **Class II**: Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III**: Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment**: A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1**: Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2**: Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3**: Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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Colloids
Colloids may be divided into protein and non-protein colloids. The protein colloids include human serum albumin (5% and 25%) and gelatin solutions (Plasmagel, Haemacell, Gellifundol). The latter are not currently available in the US and will therefore not be addressed further. Albumin has the advantage of remaining intravascular longer than the crystalloids; less volume is therefore required. Albumin is expensive (65 times that of an equivalent volume of crystalloid) and does not restore the interstitial space. It can cause anaphylaxis in rare circumstances.

The non-protein colloids include the starches (6% hetastarch, 10% pentastarch) and the dextrans (dextran-40 in normal saline, dextran-70 in 5% dextrose in water). They have been found to be equivalent to albumin as a resuscitation fluid. Their primary drawbacks are their expense (13 times that of crystalloid), a dose-related coagulopathy (greatest with hetastarch), and occasional anaphylaxis (greatest with the dextrans). There have also been reports that these starch molecules may adversely affect renal function by causing tubular injury. Non-protein colloids can also interfere with antigen detection during cross matching of blood products. Newer preparations are on the horizon which may alleviate some of the above concerns.

There is no debate that 1) colloids remain intravascular longer than crystalloids, 2) colloids expand plasma volume to a greater extent, and 3) crystalloids are more likely to cause edema formation. The real question is whether colloids improve patient morbidity and mortality and whether their use is worth the added expense.

LITERATURE REVIEW
Several meta-analyses of prospective, randomized clinical trials evaluating the use of crystalloids vs. colloids in critical care resuscitation were performed in the 1990's (1-4). Each demonstrated a survival advantage to patients resuscitated with crystalloids, especially in the traumatically injured. These studies (including two performed by the Cochrane Group) consistently concluded that there is no advantage to colloid resuscitation and that crystalloids are the resuscitation fluid of choice, especially in patients following trauma, sepsis, acute respiratory distress syndrome (ARDS), or increased capillary permeability. The potential for increased mortality (4-6%) in these studies among patients resuscitated with albumin led several authors to call for a review of its use by the FDA. Interestingly following the meta-analyses published by Schierhout and Roberts in the British Medical Journal in 1998, use of albumin solutions in the United Kingdom reportedly decreased by at least 40%.

The vigorous outcry that followed the Cochrane meta-analyses prompted several additional studies. In 2001, Wilkes and Navickis performed a rather large and comprehensive meta-analysis concerning the use of albumin versus crystalloid in critically ill patients (5). They evaluated 55 studies including 3504 randomized patients (27 studies with 1504 surgical/trauma patients). The pooled relative risk of death for all patients was 1.11 (95% CI, 0.95-1.28) and for surgery and trauma patients was 1.12 (95% CI, 0.85-1.46). Although no statistically significant increase in mortality was seen, the point estimate indicates an increase in relative risk of death of more than 10% for surgical and trauma patients.

In 2003, Rizoli et al. published an excellent review of some of the larger meta-analyses and of the methodology used in these studies themselves (6). They concluded that “even when all limitations and nuances of interpretation are considered, one piece of evidence that comes out is that trauma patients should probably continue to be resuscitated with crystalloids.” They stressed that the results of these meta-analyses should, in the very least, be “hypothesis generating” and should fuel further, larger, randomized controlled trials. Another such critical appraisal can be found in an editorial by Cook and Guyatt (7). Many other reviews have recently been published on this subject as well (8,9).

In 2004, the SAFE Study Investigators published a very large (~7000 patient) multicenter, randomized, double-blind trial comparing 4% albumin (n=3497) to normal saline (n=3500) for intravascular-fluid resuscitation (10). This study found no difference in mortality, ICU or hospital days, days of mechanical ventilation, or days of renal-replacement therapy. It was noted that patients who were resuscitated with albumin received less overall fluid. Subgroup analysis noted that the relative risk of death among trauma
patients in the albumin group was 1.36 compared to the saline group. Among traumatically injured patients without head injury there was no difference in mortality. The group concluded that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of patients in the ICU. Performed in the setting of a national health service (Australia and New Zealand), no economic analysis was completed. While the SAFE Study authors purport that this study demonstrates that albumin should be utilized as a resuscitation fluid, the lack of a survival benefit of albumin and the significant economic burden associated with its use suggests that albumin should be reserved for specific, limited indications.

The SAFE Study authors subsequently performed a post hoc analysis of their data to confirm the suggestion that albumin is associated with a higher mortality rate in patients with traumatic brain injury (TBI) (11). At 24 months post-study, 33.2% of albumin patients had died vs. 20.4% of crystalloid patients (relative risk 1.63; 95% confidence interval 1.17 to 2.26; p=0.003). The relative risk was 1.88 for patients with a Glasgow Coma Score (GCS) of 3-8 (95% confidence interval 1.31 to 2.70; p<0.001) and 0.74 for patients with a GCS of 9-12 (95% confidence interval 0.31 to 1.79; p=0.50). The authors concluded that resuscitation with albumin is associated with a higher mortality rate among patients with severe TBI.

The most recent Cochrane Database Review (46 randomized controlled trials, SAFE study included) on the subject concluded that “As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of randomized controlled trials.” (12,13). Twenty trials compared albumin to crystalloid with a pooled RR of 1.02 (95% CI 0.93 to 1.11). Ten trials did the same for Hydroxyethyl starch (RR = 1.16, 95% CI 0.68 to 1.96) and 9 trials for Dextran (RR = 1.24 (95% CI 0.94 to 1.65).

Several excellent review articles and consensus statements on this issue have previously been published (14-16). From these documents, and the above cited trials, the following general statements can be made:

- **Crystalloids**
  - Are as effective as albumin in post-operative patients
  - Are the initial resuscitation fluid of choice for:
    - Hemorrhagic shock / traumatic injury
    - Septic shock
    - Hepatic resection
  - Thermal injury
  - Cardiac surgery
  - Dialysis induced hypotension

- **Non-protein colloids**
  - Should be used as second-line agents in patients who do not respond to crystalloid
  - May be used in the presence of capillary leak with pulmonary or peripheral edema
  - Are favored over albumin due to their lower cost

- **Albumin**
  - Should be considered a third-line agent
  - Does not provide benefits over crystalloid alone when used for intravascular expansion
  - Titrated to maintain pre-determined levels is not supported by the literature
  - Is contraindicated in the first 24 hours post-burn, but may have a role in severe burns (>50%TBSA) after the first 24 hours
  - Administered in combination with parenteral nutrition does not provide benefit
  - May be useful in:
    - Elderly patients who cannot tolerate large volume resuscitation
    - Following paracentesis of greater than 4 L
    - Severe diarrhea and albumin <2 g/dl
    - Nephrotic syndrome
    - Liver transplant patients with albumin < 2.5 g/dl
    - Following plasmapheresis
REFERENCES