DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

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 fluid 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, specifically hydroxyethyl starch (HES), has been associated with an increased rate of renal insufficiency and failure requiring renal replacement therapy.**
  - ➢ **Hypertonic saline may have a benefit in the setting of damage control surgery with large volume hemorrhage, weighing a slight increase in renal failure with a large decrease in ARDS-related morbidity.**
- **Level 3**
  - ➢ **Colloids may have a secondary role in patients unresponsive to crystalloids or those who cannot tolerate large-volume crystalloid resuscitation.**
  - ➢ **Chloride-restrictive fluids may improve rates of renal failure and mortality and should be used preferentially as adjuncts to blood products and other therapies in cases of septic shock, burn injury, and hemorrhage.**

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.

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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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 or those with massive hemorrhage and damage control surgery. 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. Hypertonic saline appears to contribute to slight increases in renal failure, while significantly decreasing the amount of required fluid resuscitation and consequent ARDS related to interstitial fluid overload.

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 crystalloids; less volume is therefore required. Albumin is expensive (roughly 50 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). Previously, they have been found to be equivalent to albumin as a resuscitation fluid, and their use was discouraged due to their increased expense (13 times that of crystalloid), a dose-related coagulopathy (greatest with hetastarch), and occasional anaphylaxis (greatest with the dextrans). However, studies have demonstrated a significant increase in renal injury and failure requiring renal replacement therapy in some patients receiving hydroxyethyl starch (HES) compared to saline alone. Moreover, non-protein colloids can also interfere with antigen detection during cross matching of blood products. As such, the use of these products, most specifically HES, has been discouraged in the resuscitation of hypovolemic patients, except in the setting of battlefield resuscitation where their decreased weight and consequent ability to treat more patients with the same weight of resuscitation has been deemed an appropriate trade-off with their adverse effects.

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 questions are 1) whether colloids improve patient morbidity and mortality, 2) which patients benefit from colloid fluids either as adjuncts or primary resuscitation, and 3) whether the use of colloids 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 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. Additionally, the study also found that the ratio of crystalloid to colloid administration to achieve the same resuscitation endpoints was much less than previously thought, with a ratio of albumin to saline administration of 1:1.4, as compared to the previously accepted ratio of 1:3. 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 outside of a nationalized health service 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.

In 2009, Duchesne et al. published a 4 year retrospective review of trauma patients who required greater than 10 units of packed red blood cells and underwent damage control surgery (12). 188 patients were evaluated, with 76 patients receiving 50 mL/hr of 3% saline for an average of 48 hours during the damage control phase of care, compared with 112 resuscitated using isotonic crystalloid solutions (12). Comparing the two groups (hypertonic saline vs. isotonic saline) there were marked differences between average fluid requirements at 48 hours (1920mL vs. 8400mL), average urine output in the first 48 hours (4320 mL vs. 1940 mL), mean ICU length of stay (8 vs. 10 days), prevalence of acute respiratory distress syndrome (4.0% vs. 13.4%), sepsis (6.6% vs. 15.2%), multi-system organ failure (2.6% vs. 16.1%), and 30-day mortality (5.3% vs. 15.2%, with no significant difference in the expected renal failure prevalence (5.3% vs. 3.6%). While the limitation of selection bias is inherent in this retrospective study, its dual-institutional finding of improved patient outcomes warrants further study and consideration in clinical management.

A 2012 study from Australia evaluated the association between kidney injury in critically ill patients and their receipt of chloride-liberal and chloride-restrictive IV fluid administration (13). A pilot study was performed restricting the use of chloride-liberal IV fluids, with 6 months of data collected prior to an educational period, a 6 month phase out period, and then 6 months of data collection with only chloride-restrictive IV fluids available except for specific electrolyte abnormalities, traumatic brain injury or cerebral edema. They found that the chloride-restrictive group had significantly decreased incidence of acute kidney injury and use of renal replacement therapy, though no differences in hospital mortality, hospital or ICU length of stay, or need for renal replacement therapy post-discharge. Two significant confounders were the elimination of

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gelatin containing fluids simultaneously, and the particular focus on usage of fluid during the study period, both of which could affect renal function.

In 2013, the CRISTAL study evaluated the effects of colloid resuscitation versus crystalloid resuscitation in patients with hypovolemic shock in a randomized controlled prospective study (14). The two groups were stratified and outcomes were analyzed, including mechanical ventilation days, need for vasopressor therapy, ICU and hospital stay, and organ failure. The two groups were similar in injury severity score and ICU admission type. Neither 28-day mortality nor length of ICU stay were statistically different between each group. There was a reduction in 90-day mortality which was slightly lower in patients stratified to the colloid resuscitation group (RR 0.92, 95% CI 0.86 to 0.99, p = 0.03); however, the authors stated that these findings should be considered exploratory and require further evaluation. The study did find that patients who received crystalloid resuscitation were placed on mechanical ventilation earlier compared to patients receiving colloids only (mean 2.1 vs 1.8 days respectively, mean difference 0.30 [95% CI 0.09 to 0.48] days; p = 0.01). However, there was no statistical difference in need for renal replacement therapy, development of organ failure, or hospital length of stay between the two groups.

Non-protein colloids, including Hydroxyethyl starch (HES), had previously been found to be equivalent to albumin as a resuscitation fluid. However, according to the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), published in 2013, the use of HES was associated with a statistically increased rate of adverse events (5.3% vs 2.8%, p<0.001) (15). The researchers looked at the use of saline-only resuscitation versus HES/saline solutions (Voluven). Patients were randomized to each group, and outcome data, including 90-day mortality and all adverse events, were analyzed. Each group had similar characteristics and injury severity score. The 90-day mortality between each group was not statistically significant; however, the development of renal insufficiency and injury was statistically greater in the HES group (RR 0.91, p=0.007). Additionally, the need for renal-replacement therapy was statistically greater for patients receiving HES (RR 1.21, p=0.04). As the use of HES was not found to have any survival benefit when compared to saline only, and was associated with increased renal failure in these patients, its use has significantly decreased and has been discouraged in favor of saline or other colloid solutions, including albumin. The lone exception is in the setting of military settings where the decreased weight and volume required for resuscitation makes it more desirable than crystalloids when blood products are not available. (16).

In 2014, a large patient cohort study involving 360 US hospitals and nearly sixty thousand patients with sepsis was performed tracking the use of balanced (lactated ringers) vs. non-balanced isotonic fluid (most often normal saline) over 5 years from 2005 through 2010 (17). A propensity matched cohort of 6,370 patients was evaluated, and the receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs. 22.8%), with a noted decline in mortality directly related to the increased proportion of balanced solution received. No differences in acute renal failure or in-hospital or ICU length of stay was noted.

The most recent Cochrane Database Review (78 randomized controlled trials, including the SAFE study and CHEST study) published in 2013 reached a similar conclusion to previous database reviews, stating that “as colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.” (18). Additionally, they concluded that the use of HES was associated with worse outcomes, including increased mortality. Twenty-four trials compared albumin to crystalloid with a pooled RR of 1.01 (95% CI 0.93 to 1.10). Twenty-five studies compared HES with crystalloids (RR 1.1, 95% CI 1.02 to 1.19), 11 trials compared modified gelatin (RR 0.91, 95% CI 0.49 to 1.72), and 9 trials compared dextran (RR 1.24, 95% CI 0.94 to 1.65).

A systematic review published in 2017 on the use of hypertonic saline reviewed 25 studies comparing 3% saline (10 studies), 7.5% saline, (6 studies), and 5% saline (4 studies) in the setting of spinal anesthesia, general anesthesia, cardiac surgery, general ICU, healthy volunteers, and in other generalized settings (19). They noted that hypertonic saline increased hemodynamic parameters when compared to equal volumes of 0.9% saline, decreased fluid requirements, increased diuresis, and decreased hospital length of stay, readmission rate, and mortality rate. The expected difficulties with serum sodium and chloride abnormalities were not observed except occasionally in patients who were hypovolemic (such as in fasting

patients). They conclude that in select critically ill patients, while potentially causing temporary electrolyte abnormalities, using hypertonic saline may decrease ICU length of stay and mortality.

Based on the above cited trials and guidelines, the following general statements can be made:

- Crystalloids
  - ➢ Are generally as effective as albumin in post-operative patients
  - ➢ Should be balanced (lactated ringer) unless the clinical scenario specifically requires chloride rich solutions (damage control surgery, traumatic brain injury, electrolyte abnormalities, etc.)
  - ➢ Are the initial resuscitation fluid of choice for:
    - Hemorrhagic shock / traumatic injury (if blood products are not available)
    - Septic shock
    - Hepatic resection
    - Thermal injury
    - Dialysis induced hypotension
    -
- Non-protein colloids
  - ➢ Except in the case of military or disaster relief endeavors, non-protein colloids should be avoided due to increased risk of renal injury leading to need for renal replacement therapy.

- Albumin
  - ➢ Should be considered a second-line agent as an adjunct to decrease total infused volume
  - ➢ Does not provide benefits over crystalloid alone when used for intravascular expansion
  - ➢ Should not be titrated to maintain pre-determined levels
  - ➢ Should not be administered in combination with parenteral nutrition
  - ➢ May be useful in:
    - ➢ Elderly patients who cannot tolerate large volume resuscitation
    - ➢ Burn patients
    - ➢ 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

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