

American Thoracic Society Documents

Evidence-based Colloid Use in the Critically Ill: American Thoracic Society Consensus Statement

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INTRODUCTION

Critical care clinicians have the opportunity to choose among several intravenous solutions for fluid replacement. These fall into two broad categories: crystalloids and colloids. The fundamental physiologic difference between these two is that colloid solutions generate protein or colloid osmotic pressure (COP). The appropriate indications for use of either a crystalloid or a colloid solution have been debated for decades (1) and were highlighted by the publication of systematic reviews that conflict in their estimates of benefit or detriment attributable to colloids (2–5). On the basis of the inherent limitations of systematic reviews and meta-analyses, considerable criticism was directed at both the methods and conclusions of these studies (6–9).

Colloids have theoretical advantages according to Starling's Law (10), with greater volume expansion per unit infused and

maintenance of COP. Colloids can be distinguished as being synthetic (gelatins, dextrans, and starches) or nonsynthetic (derived from plasma, hereinafter referred to as albumin as the predominant available form). Each type is associated with several real or hypothetical risks. For example, synthetic colloids have been associated with coagulopathy (11), anaphylactoid reactions (12), and end-organ damage (13), whereas albumin is derived from pooled plasma collection, and thus carries the potential risk of infection (14). Low serum albumin levels have been associated with poor survival in critically ill patients (15), and hypoproteinemia is a licensed indication for albumin therapy. Intravenous solutions consume a substantial portion of pharmacy budgets, with crystalloids being less expensive than colloids, and albumin the most costly (16). Critical care physicians are one of the groups of physicians that most commonly prescribe colloids (17–19). In light of the high use of colloids in critical care, their potential for adverse effects, their relatively high cost, and the lack of consensus regarding their use, the mission of this working group was to review the evidence supporting use of colloids in specific clinical conditions, and to provide recommendations for future research opportunities, particularly when current knowledge is insufficient to make strong evidence-based recommendations for clinical use.

METHODS

This working group was formed under the auspices of the Critical Care Assembly of the American Thoracic Society. The goal was to critically review the literature related to natural and synthetic colloids with a particular focus on patients in medical, surgical, and cardiovascular intensive care units, excluding thermally injured and pediatric patients. We identified articles by performing a systematic search of MEDLINE and the Cochrane Library. We began this review by searching for relevant English language articles, using a uniformly adopted keyword base for consistency: albumins, colloids, dextrans, gelatin, hetastarch, isotonic solutions, plasma substitute. Retrieved articles were categorized according to the subcommittees described below, and additional references were identified using topic-specific keywords. This search included all references produced from 1996 to 2002, and by hand searching bibliographies of retrieved articles and additionally culled from the personal files of working group members. To ensure complete data review, a request for additional unpublished data was made to the producers of natural and synthetic colloids. No additional data were discovered. Specific evaluation of existing systematic reviews and metaanalyses was undertaken. These data were reviewed and discussed at meetings held in conjunction with the American Thoracic Society International Conferences in 2000 (Toronto, ON, Canada) and 2001 (San Francisco, CA) and the 21st International Symposium on Intensive Care and Emergency Medicine in 2001 (Brussels, Belgium).

The members of the Working Group were divided into three subcommittees: a basic science group for review of the cellular and biochemical aspects of colloids, a preclinical group charged with evaluating colloids in experimental models, and a clinical

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TABLE 1. GRADES OF EVIDENCE FOR THE QUALITY OF CLINICAL STUDY DESIGN*

Grade	Description
I	Evidence obtained from at least one properly randomized, controlled trial
II-A	Evidence obtained from well-designed controlled trials without randomization or randomized trials without blinding
II-B	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-C	Evidence obtained from multiple time series with or without intervention, uncontrolled cohort studies, and case series
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees
NR	Evidence not rated for clinically nonrelevant outcome

* The grades are adapted from those of the U.S. Preventive Services Task Force (20).

group to review colloid-specific patient outcomes and systematic reviews. Evidence was graded for a clinically important outcome according to a standard hierarchical schema (20) (see Table 1). Each subcommittee was charged with discussing and developing a position paper on one aspect of the problem. These position papers were presented to the entire committee for comments and discussion. When the committee reached agreement, specific modifications were made to the position papers. The following subcommittee reports are a product of this consensus process.

SUBCOMMITTEE I RESULTS: BASIC SCIENCE

In addition to restoring intravascular volume, the ideal colloid would favorably modulate the inflammatory processes that frequently characterize critical illnesses. These include increased vascular permeability and tissue edema formation, dysfunctional vasomotor control with disordered delivery of cellular nutrients, and rheologic changes characterized by increased neutrophil rolling, adherence, and activation.

Inflammatory/Anti-inflammatory Effects

Vascular permeability. The principal characteristics of colloids are summarized in Table 2. Under normal physiological conditions, there is a net movement of albumin from the intravascular to the interstitial space with recirculation to the vasculature via lymphatics. The rate of passage is dependent on the albumin concentrations of the two compartments, the permeability of the endothelium, and the electrical charge across the capillary wall (21). Albumin administration may directly influence vascular

integrity, by binding in the interstitial matrix and subendothelium and reducing permeability of these layers to large molecules (22–24). Alternatively, albumin may indirectly affect vascular permeability by binding to inflammatory mediators, such as arachidonic acid (25), or through free radical-scavenging capacities (26). Hydroxyethyl starch (HES) solutions also decrease endothelial cell activation and neutrophil adhesion *in vitro* (27), possibly by stabilization of the endothelial cell membrane or by forming a mechanical barrier over the endothelial cell surface.

The influence of albumin and synthetic colloids on microvascular integrity in the face of inflammation remains uncertain. Thus, increased vascular permeability induced by endotoxemia can be attenuated by hypertonic saline, with or without dextran (28). In an ischemia–reperfusion model, HES administration reduces capillary permeability and tissue edema formation compared with crystalloids, and decreases xanthine oxidase release after hepatoenteric ischemia–reperfusion (29). Further, hyperoncotic albumin may increase permeability and thus augment fluid flux across lung endothelial monolayers (30–32) and isolated perfused rat lungs (33), whereas iso-oncotic albumin maintains or reduces endothelial permeability (23, 34). These effects may relate more to molecular charge than to changes in COP (35). Moreover, endotoxemia-induced permeability of the mesenteric capillary bed is attenuated equally by resuscitation with albumin or crystalloid (36), suggesting that endothelial integrity may be favorably influenced by volume repletion regardless of changes in COP.

Neutrophil adhesion and activation. Combined crystalloid and colloid fluid replacement in animal models has been beneficial

TABLE 2. PHYSIOLOGICAL CHARACTERISTICS AND CLINICAL EFFECTS OF COMMONLY USED INTRAVENOUS SOLUTIONS

	Available Formulations								
	Albumin Solutions		Starches		Dextrans		Gelatins	Crystalloids	
	4%, 5%	20%, 25%	3%, 6%, 10% Hetastarch	10% Pentastarch	10% Dextran-40	3% Dextran-60, 6% Dextran-70	Succinylated and Cross-linked: 2.5%, 3%, 4% Urea-linked: 3.5%	Normal Saline	Ringer's Lactate
Molecular weight, average (kD)	69	69	450	280	40	70	30–35	0	0
Osmolality, mOsm/L	290	310	300–310	326	280–324	280–324	300–350	285–308	250–273
COP, mm Hg	20–30	70–100	23–50	23–50	20–60	20–60	25–42	0	0
Maximum volume expansion,* %	70–100	300–500	100–200	100–200	100–200	80–140	70–80	20–25	20–25
Duration of volume expansion, h	12–24	12–24	8–36	12–24	1–2	≤ 8–24	≤ 4–6	1–4	1–4
Plasmatic half-life, h	16–24	16–24	50	2–12	4–6	~12	~2–9	0.5	0.5
Potential for adverse reactions	+	+	++	++	+++	+++	++	+	+
Possible side effects	Allergic reactions	Allergic reactions	Renal dysfunction	Renal dysfunction	Anaphylactoid reactions	Anaphylactoid reactions	High calcium content (urea-linked forms)	Hyperchloremic metabolic acidosis	Hyperkalemia
	Transmitted infection	Transmitted infection	Coagulopathy	Coagulopathy	Allergic reactions	Allergic reactions	Anaphylactoid reactions		
			Pruritus	Pruritus	Interference with blood cross-matching	Interference with blood cross-matching			
			Anaphylactoid reactions	Anaphylactoid reactions					

Definition of abbreviation: COP = colloid osmotic pressure.

* Expressed as a percentage of administered volume.

for hepatic microvascular perfusion, prevention of reperfusion-induced leukocyte stasis/adherence, and attenuation of leukocyte-endothelial interaction (37, 38). In hemorrhagic shock, albumin administration reduces leukocyte rolling and adhesion compared with isotonic crystalloid (39). Albumin suppresses the respiratory burst of neutrophils in response to cytokines, including reversible inhibition of tumor necrosis factor α -induced neutrophil spreading (40). Moreover, neutrophil oxidative burst activity is markedly increased after incubation with synthetic colloids and crystalloids, with increased neutrophil CD18 expression that was not observed with albumin (41). However, the administration of albumin, gelatin, or HES showed no effect on *in vivo* adhesion or granulocyte activation (42).

Cell signaling. In the reduced state, albumin is the principal extracellular antioxidant and chiefly responsible for maintaining the redox state of plasma, via a single exposed thiol group (43, 44). Cell signaling may be altered by redox-sensitive regulation of transcription factor nuclear factor κ B (45). Albumin administration to critically ill patients increases plasma thiols, which persist after albumin clearance from the circulation, and thus may influence cellular signaling by thiol oxidative-reductive reactions (46, 47). Such redox influence may be beneficial or deleterious; a conceivably reduced inflammatory response attenuating the deleterious aspects of generalized inflammation while impairing the host immunologic resistance to infection. Moreover, free thiols are important in determining the DNA-binding activity of some transcription factors, including nuclear factor κ B (48), thereby potentially influencing cellular apoptosis. In addition, apoptosis may be affected by fluid resuscitation, with 6% hetastarch resulting in the highest degree of apoptosis, and the plasma component of whole blood the least (49).

Hemostatic Effects

Albumin has modest antithrombotic and anticoagulant effects, possibly because of its capacity to bind nitric oxide (NO) (50) and form *S*-nitrosothiols, thereby inhibiting the inactivation of NO and prolonging its antiplatelet effect. Starch solutions have clear antihemostatic effects (51), with lower molecular weight HES solutions having less effect on coagulation than higher molecular weight solutions (52). Using thromboelastography, *in vitro* studies suggest that gelatin solutions are less intrinsically anticoagulant than HES, whereas dextran-40 has the most potent effect (53).

Pharmacologic Interactions

Albumin functions as a circulating depot and transport molecule for a large number of substances, including transition metals, fatty acids, calcium, copper, thyroxine, bilirubin, NO, and amino acids. Ligands can compete for binding at a single site or may compete by altering the affinity of remote sites through conformational changes to the tertiary structure of the molecule. Competitive drug binding may displace one drug for another (e.g., warfarin, phenytoin), whereas highly albumin-bound pharmaceuticals may bind at separate sites and not displace each other (e.g., warfarin, diazepam). The effects of synthetic colloids on drug binding have not been explored in detail; hemodilution induced by HES may produce hypoalbuminemia and increase the free fraction of highly protein-bound drugs (54). Pharmaceutical ligands that have particular clinical significance because of their highly protein-bound state and low margins of safety are warfarin, phenytoin, nonsteroidal anti-inflammatory agents, and digoxin. In the critical care setting, midazolam, thiopental, and several antibiotics can be added to this list. The volume of distribution of albumin-bound drugs may increase in hypoalbuminemic states, thereby reducing their efficacy and/or altering their elimination.

SUBCOMMITTEE II RESULTS: PRECLINICAL MODELS

Colloid solutions are often used for hemodynamic goals in the intensive care unit (ICU), although effects on individual organs may be independent of cardiovascular performance. This section reviews the literature regarding experimental models of colloid use, with particular focus on the function of specific organs.

Cardiovascular

Colloid solutions are often chosen over crystalloids for use in resuscitation from shock. Experimental models of colloid administration demonstrate superiority in rapid resuscitation and restoration of tissue perfusion (39, 55–59). As expected, oncotic solutions achieve similar resuscitation goals with less than one-half the infusion volume of crystalloids (59–62). Albumin specifically reduces inflammatory cytokine expression after hemorrhagic shock (39, 62), and continued colloid administration in experimental sepsis reduces microvascular and parenchymal tissue injury (63). By comparison, crystalloid solutions promote adhesion molecule expression (64) and cellular apoptosis (41, 49, 65).

Pulmonary

The inverse relationship between plasma COP and transendothelial fluid flux is important to the maintenance of fluid balance in the lung and other organs. As expected on the basis of the Starling equation (10), hyperoncotic solutions reduce tissue-directed fluid flux and lung lymph flow by widening the oncotic pressure gradient in the lung (66). However, colloids may influence pulmonary capillary integrity independent of their oncotic effect. Endogenous albumin is an important regulator of endothelial barrier permeability to macromolecules (67). Albumin influences endothelial barrier function, perhaps in a concentration-dependent manner (23, 33, 34), and also by modulating molecular charge (68). Albumin resuscitation after hemorrhagic shock reduces pulmonary inflammation and lung edema (62), and during rodent sepsis attenuates subsequent lung injury by abrogating neutrophil sequestration (69).

COP may be less important than the efficiency of lung lymphatics in preventing pulmonary edema (70). This is particularly true in states of altered capillary permeability, such as sepsis or acute lung injury/acute respiratory distress syndrome (ALI/ARDS), in which the protein reflection coefficient is reduced and hydrostatic pressure is more important in affecting the accumulation of edema fluid in the extravascular compartments (71). However, the importance of COP as an edema-protective mechanism is clear: a 50% reduction in COP increases lymphatic flow by fourfold (72), and lung water accumulates more readily in hypoproteinemic dogs (73), particularly during crystalloid administration (74). However, the logical relationship between the plasma COP minus pulmonary capillary pressure gradient and the development of pulmonary edema has proven inconsistent (75, 76).

Central Nervous System

Resuscitation of the cerebral microcirculation may not parallel other organs because shock impairs cerebral autoregulation and disrupts the blood-brain barrier, and consequent cerebral edema may be aggravated by reductions in COP (77). Furthermore, drugs that improve blood rheology have theoretical value because viscosity and platelet aggregation play a pathogenic role in development of cerebral ischemia. However, the blood-brain barrier does not follow traditional Starling principles of fluid and solute exchange, and plasma osmolality may be more important than COP for modulating cerebral edema (78).

In rodent models of focal cerebral ischemia, albumin variably reduces cerebral edema (79–81) and consistently improves corti-

cal perfusion and reduces infarct volume compared with saline solutions (79–82). Albumin-mediated neuroprotection is apparent even 4 hours after brain injury (81), and may be mediated by nonhemodynamic, nononcotic mechanisms such as free radical scavenging or replenishment of neuronal polyunsaturated fatty acids (83, 84).

In experimental traumatic coma, isovolemic hemodilution with dextran compared with no hemodilution minimizes microvascular circulatory impairment and reduces infarct size (85). Brain edema is not consistently reduced by albumin administration in experimental traumatic brain injuries, although necrotic tissue volume and neurologic severity are improved (86, 87) with coincident improvements in cerebral metabolism (88).

Gastrointestinal

Experimental models used to study HES suggest effects beyond those attributable to oncotic pressure. HES used in extracorporeal circulation reduces intestinal edema compared with crystalloid both by maintenance of COP and by reducing microvascular permeability (89). Organ dysfunction after hepatoenteric ischemia–reperfusion is abrogated by HES more than by albumin through alterations in xanthine oxidase activity (29), and HES administration after laparotomy is associated with fewer peritoneal adhesions (90).

The immunologic and metabolic effects of synthetic colloids remain unclear. HES resuscitation is associated with increased immunosuppression and mortality (91, 92), yet has been found to reduce bacterial translocation and intraluminal overgrowth in experimental bowel obstruction (93). HES decreases phagocytic function and undergoes long-term deposition in the reticuloendothelial system partially by phagocytic uptake (92, 94). HES may be an important component of organ preservation solutions, with limited proteolysis in an isolated perfused rat liver model (95). Reduced hepatic synthetic function with *in vitro* exposure to bovine serum albumin and HES has been observed (96), although albumin and starches *in vivo* do not alter hepatic metabolism or induce histologic injury (97).

Renal

Analbuminemic rats are unable to deliver furosemide to the medullary and cortical thick ascending limb of Henle, rendering them insensitive to its action (98). This effect is mediated by the highly protein-bound nature of furosemide, such that administration of furosemide conjugated with albumin reproduces the normal diuretic response. Other preclinical evidence regarding colloids and renal physiology are lacking, although histologic renal tubular damage has been observed with experimental HES administration (99) and dialysates containing albumin enhance the clearance of unconjugated bilirubin compared with normal saline (100).

SUBCOMMITTEE III RESULTS: CLINICAL TRIALS AND SYSTEMATIC REVIEWS

Fluid resuscitation is one of the most common interventions for an intensivist, and thus may impact outcome for a variety of conditions. General albumin supplementation among ICU patients does not improve patient outcomes (101–103), and thus this section focuses on condition-specific colloid uses.

Cardiovascular/Shock States

In one of the largest prospective clinical studies to date, the SAFE (Saline versus Albumin Fluid Evaluation) trial randomized a heterogeneous group of 7,000 critically ill patients requir-

ing fluid resuscitation to receive iso-oncotic albumin or isotonic crystalloid. Overall, 28-day mortality was 21% and did not differ according to treatment assignment (104).

Septic shock. The hemodynamic manifestations of sepsis are among the most common and complex problems encountered in the ICU. The primary goal in patients with septic shock is rapid restoration of hemodynamic stability and microcirculatory tissue oxygen delivery (105, 106). When considered in combination with the primary goals of fluid therapy, there may be additional benefit to the solution that can be most rapidly administered. Colloids appear to possess these desirable characteristics because of their smaller volume of infusion and shorter time of administration (107), although other solutions may be more readily available in a given clinical environment (prehospital, emergency department, operating room, or intensive care unit).

Colloids maintain COP and produce plasma volume expansion with one-quarter to one-half the volume required for isotonic crystalloid solutions (1, 107, 108) (evidence grade NR; see Table 1). Albumin and synthetic colloids appear equivalent for these purposes (109). Iso-oncotic albumin infusion results in plasma volume expansion equal to the volume infused, with an equivalent expansion of the interstitial space; crystalloid solutions expand plasma volume by 25% of administered volume and produce a threefold increase in interstitial fluid volume (110) (evidence grade II-A [see Table 2]). Resuscitation with iso-oncotic albumin in septic shock may confer survival benefits (relative risk for death with albumin, 0.87; 95% confidence interval, 0.74–1.02), but results from this subgroup require prospective confirmation (104).

Perioperative shock states. CARDIOVASCULAR SURGERY. Clinical trials have compared various fluid regimens in cardiovascular surgery patients with conflicting results. Definitive conclusions from these studies are impossible because of improvements in surgical techniques, heterogeneous patient populations, and varied intravenous solutions. The timing of fluid administration further limits comparison, as some trials assessed intravenous fluids preoperatively or intraoperatively (111–116), whereas others limited their intervention to the postoperative period (117–127). Retrospective and cohort data comparing solutions used for cardiopulmonary bypass pump prime indicate a 20% reduction in the odds of death with albumin use compared with synthetic colloids (128), and an increase in bleeding events with starch compared with albumin, even when administered at doses that have been considered safe (11, 129) (II-B). Other studies have found no clinical difference in hemostasis, chest tube drainage, or requirement for blood transfusion when stratified by bypass prime fluid (130) (I). Although still inconclusive, greater postoperative bleeding with HES has been suggested by meta-analysis of the literature (131).

TRAUMA. Severe trauma may cause hemorrhagic shock, resulting in mortality rates exceeding 50%. Early fluid resuscitation has traditionally been used to avert shock and its attendant complications, yet clinical data suggest that definitive bleeding control is imperative before aggressive asanguineous resuscitation (132). Primary resuscitation using colloids requires one-quarter to one-half the infusion volume of crystalloids (II-A) (107, 133–137) and may reduce resuscitation time by up to 75%, depending on illness severity (II-A) (107). However, colloids have only inconsistently been shown to reduce subsequent organ dysfunction, such as ALI/ARDS (136–138, 140) (II-A). Studies of relevant pulmonary function are inconclusive (136–138, 140).

On the basis of a prospectively defined subset in the SAFE trial, crystalloids are the best choice for general resuscitation of trauma patients (relative risk for death with colloids, 1.36; 95% confidence interval, 0.99–1.86). This is particularly true among these patients when associated with traumatic brain injuries (col-

loid relative risk, 1.62; 95% confidence interval, 1.12–2.34), although these conclusions stem from a subset analysis (104). Secondary insults after major trauma may incite an inflammatory reaction with altered capillary permeability; intravenous fluid resuscitation in this phase should be guided by the same principles as in sepsis.

OTHER SURGICAL CONDITIONS. Studies comparing resuscitative fluids in noncardiovascular surgery are inconclusive. Investigations have included major abdominal (141–146), abdominal aortic (1, 147–153), orthopedic (154–157), and urologic surgeries (158, 159).

Pulmonary

Acute lung injury/acute respiratory distress syndrome. Sepsis is the leading cause of death in the ICU and the most common cause of ALI and ARDS, occurring in 30–40% of patients (160). The pulmonary edema that develops in ALI/ARDS results from alveolocapillary barrier dysfunction, although reduced COP may contribute to the generation and persistence of pulmonary edema (161). Both intravascular hydrostatic pressure and plasma COP may be manipulated by colloid or crystalloid administration, and the preponderance of data supports exaggerated edema formation in states of reduced COP, particularly if hydrostatic pressures rise above normal (63, 162–166).

As in sepsis, varying recommendations have emerged over the past 25 years regarding appropriate fluid management in patients with ALI/ARDS (167, 168), although no definitive evidence supports a given fluid to improve relevant clinical outcomes. Early studies of critically ill patients with acute hypoxemic respiratory failure reported inconsistent physiologic improvements (136, 169) (NR). In patients with established pulmonary insufficiency, intrapulmonary shunt was significantly improved with albumin administration (170) (NR). Hypoproteinemic patients with established ALI treated with a combination of albumin and furosemide achieved significant diuresis and weight loss with concomitant 40% improvements in oxygenation and sustained improvements in hemodynamic stability (171) (NR). Independent of colloid administration, management of patients with ALI/ARDS by means of a fluid restrictive strategy may benefit both hydrostatic and oncotic pressures and has been shown to reduce the extravascular lung water content while shortening the duration of mechanical ventilation (9 versus 28 days) and producing trends toward reduced ICU length of stay and mortality (172) (II-A).

Central Nervous System

Ischemic brain injury. Several clinical studies have investigated the use of colloids to achieve hemodilution after acute ischemic stroke (173–185). Initial dextran trials reported improvements in disability and survival (186), although subsequent large trials have failed to confirm these benefits (181, 182) (I). Similar purported benefits with starch solutions have not been confirmed, with one trial terminated early for worse outcomes in patients randomized to receive HES (184, 187, 188) (I). In a large randomized comparison of normovolemia, achieved with crystalloid, versus normovolemia with hemodilution, via phlebotomy and albumin, mortality and functional outcomes were not different between the two groups (189) (I). In subgroup analyses, initially euvolemic patients had improved survival and functional independence with albumin hemodilution, whereas volume-contracted patients were best improved with normovolemia via crystalloids. While hemodilution decreases viscosity and optimizes circulatory volume, it may impair tissue oxygen delivery in hypovolemic patients. A systematic review of randomized trials in hemodilution for acute ischemic stroke reported no benefit (190).

Subarachnoid hemorrhage. Cerebral blood flow (CBF) is reduced after subarachnoid hemorrhage and can result in ischemia

from cerebral vasospasm. If CBF is volume dependent only under hypovolemic conditions, albumin-induced reductions in natriuresis may limit the intravenous fluid required to achieve normovolemia (191) (NR). However, in asymptomatic patients with a ruptured cerebral aneurysm, volume expansion with albumin did not increase CBF or reduce symptomatic vasospasm (192) (II-C). Uncontrolled case series suggest that hypervolemic therapy, often achieved with colloids, can reverse ischemic deficits in symptomatic patients (193–196) (II-C). However, in a trial in which patients with subarachnoid hemorrhage received albumin, and normovolemia was compared with hypervolemia, there was no difference in CBF or the incidence of cerebral vasospasm (197) (II-A).

Nephrology

Acute renal failure. The development of acute tubular necrosis is associated with reductions in renal blood flow, although volume expansion does not linearly increase glomerular filtration or consistently improve renal function (198). Albumin administration to patients with hypovolemia related to vascular leak after interleukin-2 therapy reduces oliguria compared with crystalloids (199) (II-A). The finding that resuscitation of sepsis patients with HES increases the risk of acute renal failure by 2.6 times, compared with patients receiving gelatin, is complicated by infusion volume differences between groups (200) (II-A). Septic patients with acute renal failure are poorly tolerant of fluid removal during dialysis and frequently experience hemodynamic deterioration related to abnormal vascular resistance (201). In patients with severe sepsis requiring hemodialysis, albumin priming of the dialysis circuit results in more stable hemodynamics and increases filtration volume by 45 to 60% (202) (II-A).

Cirrhosis-related abnormalities in renal function are related to circulatory dysfunction with a reduction in systemic vascular resistance and renal vasoconstriction. Administration of albumin has a favorable effect on renal blood flow and glomerular filtration rate only in patients with early renal dysfunction (203). The failure of fluid resuscitation in hepatorenal syndrome may relate to the inability to expand effective blood volume because of splanchnic vasodilation (204), although therapeutic colloid use for hepatorenal syndrome has not been adequately tested.

Chronic renal failure. Chronic renal failure with oliguria or anuria complicates fluid management during critical illnesses, particularly when cardiac disease coexists (205). Dialysis-related hypotension likely occurs more frequently in ICU patients than the 20–30% incidence observed in ambulatory dialysis patients (206), and intradialytic hypotension may result in the administration of volume expanders and vasopressors, thus hindering the goals of fluid and electrolyte removal necessary for optimal patient management (207). In ambulatory patients experiencing intradialytic hypotension, both albumin and HES successfully restore intravascular volume and prevent subsequent hemodynamic compromise compared with hypertonic or isotonic crystalloid solutions (208, 209) (II-A). The logical extrapolation of these results to critically ill patients requires confirmation in clinical trials.

Gastroenterology/Hepatology

Gastrointestinal bleeding. No studies have examined outcome differences when comparing intravenous fluid preparations in patients with nonsurgical bleeding, such as gastrointestinal hemorrhage. In these patients, control of bleeding and replacement of lost intravascular volume (often with red blood cells or fresh frozen plasma) is paramount, with selection of crystalloid or colloid solutions based on other criteria.

Mesenteric ischemia. Human studies comparing resuscitation fluids with respect to gut blood flow are limited. Experimental

reductions in cardiac index and hepatic blood flow induced by phlebotomy are rapidly corrected by albumin resuscitation, whereas crystalloids require double the volume (210). In septic patients, all colloids improve hemodynamics, although HES may prevent mesenteric ischemia better than crystalloids (211), and gelatins may increase mesenteric blood flow more than starch solutions (212, 213) (NR). Protocolized hemodynamic care incorporating HES after cardiac surgery has been shown to significantly reduce the incidence of gut hypoperfusion (from 56 to 7%), while reducing complications and shortening hospital care by more than 3.5 days (214) (II-A).

Large-volume paracentesis. Large volume paracentesis for tense or diuretic refractory ascites has been associated with circulatory dysfunction characterized by increases in plasma renin activity—an effect best ameliorated by albumin infusion (215, 216). There is no direct relationship between large-volume paracentesis and death, although the rise in plasma renin has been associated with mortality (217). The addition of albumin to ascites management by large-volume paracentesis reduces the odds of subsequent renal failure by 90% (218) (II-A). Peritoneovenous shunting has been utilized in patients with refractory ascites, although serial large-volume paracenteses combined with albumin produce similar outcomes with fewer complications (219) (II-A). At present, consensus recommendations include volume expanders for large-volume paracentesis, particularly the use of 50 g of albumin for paracentesis greater than 5 L (220, 221). However, the data are inadequate to define the optimal albumin dose or the role of synthetic colloids.

Spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis is a common complication of cirrhosis, with high mortality (222). One-third of patients will develop renal failure, which is associated with the worst prognosis for survival (223). For cirrhotic patients who develop spontaneous bacterial peritonitis, the combination of albumin and antibiotic therapy is superior to antibiotic therapy alone, reducing the risk of both renal impairment and mortality by approximately two-thirds (224) (II-A).

Meta-analyses and Systematic Reviews

Twelve metaanalyses have addressed the issue of colloid administration and morbidity or mortality in critically ill patients: nine

of these are published in a peer-reviewed format (2–5, 225–229) and three are recurrent updates from the Cochrane Library (230–232) (*see* Table 3). These reports are split between those that suggest harm associated with colloids (2, 3, 225, 229, 230), and those that find no difference in outcome (4, 5, 226, 233). Further complicating the analyses is the heterogeneity that is present across the studies, reflected in the finding that colloids may benefit certain subgroups, often representing conflicting point estimates from the overall analysis (2, 225, 228). Critiques of these meta-analyses have addressed the methods of the trials they summarize (modest quality, noncontemporary fluid protocols) and the methods of pooling the results of these trials (given different short- and long-term trial objectives and the heterogeneity of fluid protocols). In addition, the biological plausibility for harm associated with colloids is lacking, having been specifically examined in one review (4).

Meta-analyses are frequently cited as the highest level of evidence, although discordance with randomized, controlled trials may occur in as many as 25% of reviews (234). There is only moderate agreement for the estimates of effect between meta-analyses and well-conducted, controlled trials of adequate power, yielding positive and negative predictive values less than 70% (235). Furthermore, the analytic strategies used in the systematic reviews that suggested a harmful effect of colloids may produce more discrepancies than other analytic approaches (236). Overall, the underlying trials represent substantial heterogeneity with temporal differences in design and outcome. Different analytic strategies may improve the precision of an estimate, although in the presence of considerable heterogeneity a single summary measure cannot adequately describe the data (237). Thus, the design, study selection, and methods of analysis may affect the results of meta-analysis to an equal degree as the data themselves (234). Although these meta-analyses raise questions about the safety of colloids, the aforementioned SAFE trial allays many concerns for exaggerated mortality, at least for albumin use in most critically ill patients (104).

CONCLUSIONS

Colloids have rarely been studied in trials designed to determine clinical outcome benefits. The SAFE trial is a notable exception,

TABLE 3. SYSTEMATIC REVIEWS THAT HAVE EVALUATED THE USE OF COLLOIDS IN CRITICALLY ILL PATIENTS

Author (Reference No.)	Patient Population	No. of Trials (Patients)	Result
Velanovich (225)	Trauma and nontrauma	8 (826)	Colloid mortality, +5.7%
Bisonni and coworkers (226)	Heterogeneous, seriously ill	7 (354)	Colloid mortality, +7.9%
Wade and coworkers (228)	Neurologic trauma	6 (223)	HSD mortality, –11.0%
Wade and coworkers (227)	Trauma	13 (1,233)	Mortality RR, 0.47 (95% CI, 0.99–0.22)
Schierhout and Roberts (2)	Heterogeneous, seriously ill	19 (1,315)	Mortality RR, 1.19 (95% CI, 0.98–1.45)
Subgroup:	Trauma	6 (636)	RR, 1.30 (0.95–1.77)
	Surgery	7 (191)	RR, 0.55 (0.18–1.65)
	Burns	4 (416)	RR, 1.21 (0.88–1.66)
Cochrane Injuries Group (3)	Heterogeneous, seriously ill	24 (1,204)	Mortality RR, 1.68 (95% CI, 1.26–2.23)
Subgroup:	Hypovolemia	13 (534)	RR, 1.46 (0.97–2.22)
	Thermal injury	3 (163)	RR, 2.40 (1.11–5.19)
	Hypoalbuminemia	8 (507)	RR, 1.69 (1.07–2.67)
Choi and coworkers (4)	Heterogeneous, seriously ill	17 (814)	Mortality RR, 1.16 (95% CI, 0.85–1.59)
Subgroup:	Nontrauma	10 (430)	RR, 1.02 (0.74–1.43)
	Trauma	5 (302)	RR, 2.56 (1.12–5.88)
Wilkes and Navickis (5)	Heterogeneous, seriously ill	42 (2,958)	Mortality RR, 1.11 (95% CI, 0.95–1.28)
Subgroup:	Surgery or trauma	20 (1,339)	RR, 1.12 (0.85–1.46)
	Thermal injury	4 (197)	RR, 1.76 (0.97–3.17)
	Hypoalbuminemia	4 (357)	RR, 1.59 (0.91–2.78)
	Ascites	4 (373)	RR, 0.93 (0.67–1.28)
Wilkes and coworkers (229)	Cardiac surgery	16 (653)	SMD, –0.24 (–0.40 to –0.08)

Definition of abbreviations: HSD = hypertonic saline with dextran; RR = relative risk of mortality with colloid exposure; SMD = standardized mean difference (in postoperative bleeding).

supporting a neutral mortality influence of colloids in a general ICU population. From the data reviewed by this group, colloids are superior resuscitative agents and are important adjuncts in the therapy of dialysis-related hypotension and in the management of ascites requiring paracenteses. Their role in certain forms of brain injury and in spontaneous bacterial peritonitis requires further study and confirmation. Given the inadequate clinical trial data and wide confidence intervals in the meta-analyses, further investigation is needed in many areas of intensive care colloid use. In particular, outcome-centered trials are needed in septic shock, renal failure, ALI/ARDS, and certain forms of brain injury.

Although cost cannot be evaluated from the available data, colloids have invariably greater acquisition costs. Given the cost-conscious nature of medical practice and the lack of clear evidence favoring colloid use in many critical care conditions, enthusiasm for colloid use outside the specific conditions discussed in this Working Group Report is limited. As part of future clinical outcome trials, integrated pharmacoeconomic analyses should be included.

Summary Points

1. Colloids have various nononcotic properties that may influence vascular integrity, inflammation, and pharmacokinetics, although the clinical relevance of these properties has not been elucidated (NR).
2. All colloids affect the coagulation system, with dextran and starch solutions having the most potent antithrombotic effects (II-A).
3. HES may be deposited in the reticuloendothelial tissues for prolonged periods; the clinical significance of this is unknown (II-C).
4. Colloids restore intravascular volume and tissue perfusion more rapidly than crystalloids in all shock states, regardless of vascular permeability (II-A).
5. There is conflicting evidence that HES increases the risk of bleeding after cardiopulmonary bypass surgery (I).
6. Although hydrostatic pressure is more important than COP for accumulation of pulmonary edema, colloid administration reduces tissue edema and may ameliorate pulmonary edema as a consequence of shock resuscitation (II-A).
7. There is no evidence of a benefit of colloids in treating ischemic brain injury (I) or subarachnoid hemorrhage (II-A). Colloids may adversely impact survival in traumatic brain injury (I).
8. HES administration may increase the risk of acute renal failure in patients with sepsis (II-A).
9. Treatment of dialysis-related hypotension with colloids is superior to crystalloids for chronic dialysis patients; presumably, colloids are similarly superior for acutely ill patients (II-A).
10. Colloids are superior to crystalloids in intravascular volume replacement with large-volume paracentesis (II-A) and as adjunctive therapy to antibiotics in treating spontaneous bacterial peritonitis (II-A).
11. Meta-analyses of critical care colloid use are conflicting because of entry trial heterogeneity and varied analytic techniques, and a large prospective trial suggests a neutral influence of colloids on clinical outcomes.

Therapeutic Implications

1. Crystalloids should be administered first in nonhemorrhagic shock resuscitation (III).
2. Hydroxyethyl starch solutions should be used with caution

in cardiopulmonary bypass (meta-analysis) and in patients with sepsis (II-A).

3. Colloids should be avoided or used with caution in patients with traumatic brain injury (I).
4. Fluid restriction is appropriate for patients with hemodynamically stable ALI/ARDS (II-A); the combination of colloids and diuretics may be considered in patients with hypo-oncotic ALI/ARDS (III).
5. Colloids are preferred for treating dialysis-associated hypotension and in maintaining hemodynamics to achieve dialysis goals (II-A).
6. Hyperoncotic albumin should be administered in conjunction with large-volume paracentesis for diuretic-refractory ascites (II-A).
7. Albumin may be administered in conjunction with antimicrobial therapy to patients with spontaneous bacterial peritonitis (II-A).

Future Investigations

1. Clinical trials are needed to determine the clinical significance of basic science properties specific to individual colloids, such as modulation of vascular permeability and systemic inflammation.
2. Outcomes-centered clinical trials powered to discern a mortality benefit for colloid resuscitation in septic shock and/or hemorrhagic shock are needed, with integrated pharmacoeconomic analyses.
3. Adequately powered prospective trials are necessary to determine the risk of bleeding after cardiopulmonary bypass surgery for HES compared with albumin and with crystalloid solutions.
4. Well-designed clinical trials are required to evaluate both the clinical outcomes effects and physiologic effects of colloids and crystalloids relevant to individual organ function, including lung fluid balance in patients at risk for or with established ALI/ARDS.

This Consensus Conference Statement was prepared by an ad hoc subcommittee of the American Thoracic Society Critical Care Assembly. Members of this subcommittee are as follows:

Chairs: GREG S. MARTIN, M.D., M.Sc., Emory University, Atlanta, GA

MICHAEL A. MATTHAY, M.D., University of California at San Francisco, San Francisco, CA

Subcommittee sections:

Basic Science: EDWARD R. ABRAHAM, M.D., University of Colorado, Denver, CO

TIMOTHY W. EVANS, M.D., Ph.D., Royal Brompton Hospital, London, UK (Section head)

GEORGE M. MATUSCHAK, M.D., St. Louis University, St. Louis, MO

ARTHUR S. SLUTSKY, M.D., University of Toronto, Toronto, ON, Canada

Preclinical: JAHAR BHATTACHARYA, M.D., D.Phil., Columbia University, New York, NY

R. PHILIP DELLINGER, M.D., Robert Wood Johnson Medical School, Camden, NJ

JANE E. DEMATTE, M.D. (Section head), Northwestern University, Chicago, IL

MICHAEL A. MATTHAY, M.D., University of California at San Francisco, San Francisco, CA

WILLIAM J. SIBBALD, M.D., University of Toronto, Toronto, ON, Canada

Clinical: GORDON R. BERNARD, M.D., Vanderbilt University, Nashville, TN

DEBORAH J. COOK, M.D., M.Sc., McMaster University, Hamilton, ON, Canada

MARC DUBOIS, M.D., University of Montreal, Montreal, PQ, Canada

GREG S. MARTIN, M.D., M.Sc., Emory University, Atlanta, GA

THOMAS E. STEWART, M.D. (Section head), University of Toronto, Toronto, ON, Canada

JEAN-LOUIS VINCENT, M.D., Ph.D., Erasme University Hospital, Brussels, Belgium

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