Introduction

Fluids are the only known method of attenuating renal injury. Furthermore, fluid prescriptions whether for hydration, resuscitation or renal replacement therapy, must be tailored to the fluid and electrolyte, cardiovascular status and residual renal function of the patient. Different fluids have significantly different effects both on volume expansion as well as electrolyte and acid-base balance. While controversial, different fluids may even influence renal function differently. This ADQI workgroup has focused on fluids for prevention and management of acute kidney injury. We have reviewed the evidence and have made recommendations for clinical practice and future studies.

Fluids for Prevention of AKI

Prevention of AKI has significantly relied on fluid administration with or without an identified effective circulating volume deficit in concert with avoidance of nephrotoxic medications. Fluid administration serves to expand plasma volume, increase renal blood flow, and presumably glomerular filtration rate. Increased renal blood flow augments renal parenchymal oxygen delivery to support cellular metabolism while enhanced tubular filtration flushes potentially toxic elements out from the renal tubules. While these benefits of fluid administration should reduce or ameliorate AKI, some components of commonly used fluids may initiate or worsen existing AKI. This section will explore fluid prescription benefits and risks with regard to AKI, including those derived from crystalloids, colloids, and hemoglobin-based oxygen carriers.
Do different \textit{crystalloid} solutions pose a risk of AKI?

\textbf{i. Anion composition}

\textit{Hyperchloremic vs. Balanced lactated solutions.} Large volume crystalloid resuscitation can result in significant alterations in electrolyte and acid-base balance in patients. While perhaps of limited concern in healthy subjects, these effects may create life-threatening abnormalities in the critically ill and injured. An intra-operative comparison of 0.9\% saline (NS) and lactated ringer’s solution (LR) for abdominal aortic reconstruction demonstrated hyperchloremic metabolic acidosis (HCMA) occurred with NS much more often than with LR, and NS resuscitated patients required greater amounts of blood component therapy.\cite{1} However, no differences in renal function were identified. In another small, related study, patients undergoing renal transplantation were randomized to receive either NS (n=26) or LR solution (n=25) in a double-blind fashion with a primary outcome measure of creatinine at day 3 post-transplant.\cite{2} Unexpectedly, the authors found a markedly increased incidence of hyperkalemia (> 6 meq/L) in 5 of the NS group but none of the LR group. Significant metabolic acidosis was noted only in the NS treated patients, 8 of whom received some form of therapy to raise the pH. Due to these significant differences between the groups, the trial was halted early for safety reasons.

Although hyperchloremia has been associated with impaired organ perfusion and function, including diminished renal blood flow and longer time to diuresis in comparison to lactated Ringer’s solution \cite{3, 4}, no significant differences in clinical outcomes have been reported. Acidosis has also been demonstrated to impair coagulation. Importantly, the effect of acidosis on coagulation parallels that of hypothermia.\cite{5} Of note, both LR and NS have been identified as potent triggers of immune cell activation, although the significance of these observations remains uncertain.\cite{6}

\textit{Hyperchloremic vs. Balanced solutions with non-lactate buffer.} Despite the availability of bicarbonate and acetate buffered crystalloid solutions for renal replacement therapy. These agents have not been used for maintenance fluids or resuscitation in any controlled trials.

\textbf{Summary:} There is no evidence that anion composition of currently available crystalloids increase the risk of AKI in humans. Large volume administration of saline leads to HCMA. Some animal data suggesting that HCMA can alter renal blood flow (RBF) but no data are available in humans. Compared to LR, delayed diuresis has been observed with NS. \textbf{Recommendations for clinical practice:} Other than the need to be aware of potential side effects seen with large volume crystalloid resuscitation, no recommendations can be given concerning choice of crystalloids at this time. \textbf{Recommendations for future research:} Adequately powered randomized trials will be needed to assess differences in risk for AKI form various fluids. Given that these trials will need to be very large, the likelihood that they will be conducted seems low. As an alternative to randomized trials, large observational studies might provide important information on the risks, if any, of various crystalloids. These studies should include assessment of clinical consequences related to volume requirements, metabolic acidosis, electrolyte abnormalities, and infectious complications in addition to risk of AKI.
ii. Tonicity (Saline, Mannitol)

Hypertonic Saline. Hypertonic saline (HTS) has been evaluated as a possible fluid for resuscitation in injury and sepsis, because of its purported hemodynamic, endothelial and immunomodulatory effects.\[7, 8\] Data are available that support potential benefits of hypertonic saline infusion in various aspects of the pathophysiology of sepsis, including tissue hypoperfusion, decreased oxygen consumption, endothelial dysfunction, cardiac depression, and the presence of a broad array of proinflammatory cytokines and various oxidant species as well as in the pathophysiology of traumatic brain injury associated increases in cerebral parenchymal volume.\[8\] Despite the purported advantages of HTS in ex-vivo studies, no durable outcome benefit has been identified with HTS use as a plasma volume expander even in a large multi-institutional prehospital trial specifically addressing traumatic brain injury.\[9\] HTS solutions are commonly utilized to correct abnormalities of water balance. However, due to the hypertonic nature of these solutions, they may also serve as plasma volume expanders with the added benefit of drawing fluid into the vascular compartment on the basis of water movement along a concentration gradient. HTS is also commonly coupled with dextran to support plasma volume expansion. Accordingly, HTS-dextran has been utilized for plasma volume expansion during surgery. One such study compared a single 250 cc intra-operative dose of 7.5% NS/6% dextran-70 versus 250 cc of a hydroxyethylstarch (HES) in NS in patients undergoing aortic aneurysm surgery.\[10\] Both groups were resuscitated with NS as the concomitant crystalloid solution. The authors identified no difference in acid-base balance between the two groups due to the large amounts of NS and relative small volumes of test agents given. Importantly, no differences in renal function were noted with either regimen for 24 hours post-operatively. A small study in burn patients compared those resuscitated with HTS (1991-1993) to patients resuscitated with LR in an earlier time frame (1986-1988 versus a later time frame (1993-1994). The authors found a four-fold increase in renal failure and a doubling of mortality with HTS compared to LR resuscitated patients.\[11\]

A recent meta analysis (Cochrane review) from 2002 comparing isotonic crystalloids with hypertonic solutions included 5 studies in trauma patients and demonstrated no benefit of HTS on outcome.\[12\] A 2004 Cochrane review of the issue\[13\] did not generate enough data to establish whether hypertonic crystalloid is better than isotonic and near-isotonic crystalloid for the resuscitation of patients with trauma, burns, or those undergoing surgery. However, the confidence intervals were wide and did not exclude clinically significant differences. Further trials which clearly state the type and amount of fluid used and that are large enough to detect a clinically important difference are needed. Small volumes of HTS do not appear to cause, or increase the risk, of AKI with isolated or sporadic use, but detailed studies and reporting are lacking. By contrast, HTS as a primary resuscitation fluid for burns appears to result in increased risk of AKI.

Hypertonic mannitol solutions. HT-mannitol may be harmful because of the potential to induce rapid intravascular volume expansion, leading to pulmonary edema and resulting in hyperoncotic kidney injury in those without a severe plasma volume deficit.\[14-16\] Moreover, mannitol-based volume expansion may induce AKI due to excessive osmotic diuresis in patients with hypovolemia.
**Summary:** HTS as sole resuscitation fluid is associated with ARF and excess mortality in burns. Small volume HTS appears safe with isolated or sporadic use and was not associated with AKI in available studies—detailed studies and reporting are lacking. HT-mannitol may induce AKI with excessive osmotic diuresis and untoward hyperoncotic. **Recommendations for clinical practice:** HTS should be used with caution in patients at risk for AKI and should be avoided in patients with burns. HTS is indicated for treatment of severe hyponatremia in appropriate clinical settings. Use of HTS for plasma volume expansion is not recommended. HT-mannitol is not recommended for fluid resuscitation. **Recommendations for future research:** Given the immunomodulatory properties of HTS this agent should be specifically studied to define a patient population who may benefit from HTS administration. Specifically, timing and dose should be clearly defined and explored to clarify appropriate use. Pairing HTS with other fluids such as dextran, starches, or HBOC’s should be explored as a means of maximizing potential benefits of both fluids in specific circumstances.

**Do different crystalloid solutions have different effects on mitigating the risk of AKI?**

### i. Anion composition (Chloride vs Bicarbonate)

**Radiocontrast nephropathy (RCN).** Reducing the concentration of chloride (e.g. use of bicarbonate) in solutions for the prevention of RCN has been recently tried in a small (n=119 patients), single-centered, randomized trial, in which plasma volume expansion with sodium bicarbonate based solutions was shown to be superior to NS for prevention of RCN.[17] It is unclear if the putative benefit from bicarbonate-based plasma volume expansion derives from amelioration or prevention of HCMA at the same time as contrast administration, or an undescribed interaction of contrast material with the anion. A larger trial (n=326 consecutive patients) of medium to high risk patients compared three different fluid regimens for the prevention of radiocontrast nephropathy: 1) saline + n-acetyl cysteine (NAC) (n=111), 2) sodium bicarbonate + NAC (n=108), and 3) saline + NAC + ascorbic acid (n=107).[18] In this study, 1.9% of bicarbonate + NAC treated patients sustained RCN (25% or greater creatinine increase at 48 hours post-contrast exposure), while RCN was identified in 9.9% of those receiving NS + NAC and 10.3% of those receiving NSS/+ NAC+ ascorbic acid. While the results of these two studies suggest that isotonic bicarbonate may provide greater benefit than isotonic saline, either with or without NAC, neither study can be considered to be conclusive. Thus, confirmation of these results in a large, multicenter RCT is needed.

**Rhabdomyolysis.** There is good evidence that rhabdomyolysis leads to AKI although the exact mechanisms are still in dispute. In addition to hypovolemia that is present to some degree in all patients with rhabdomyolysis (based on the antecedent cause), the myoglobin that is released into the circulation as a result of muscle damage may also cause renal cellular damage via direct renal cytotoxicity, renal vasoconstriction and renal tubular obstruction.[19, 20] Therefore, prevention of AKI in this setting involves vigorous plasma volume expansion to maintain renal perfusion pressure and dilute myoglobin and other toxins. Although there is limited evidence, clinical practice also commonly involves urinary alkalinization with bicarbonate aimed at preventing tubular precipitation of myoglobin. Correction of hypovolemia is
essential to prevent AKI.[21] Plasma volume should be aggressively expanded to restore and maintain effective circulating volume and to maintain a urine flow rate of 100 to 150 cc/hr.[22] While the administration of sodium bicarbonate together with crystalloid plasma volume expansion is widely recommended, the extent to which this interventions provides additional benefit to volume expansion with crystalloid solution alone remains uncertain. If used, bicarbonate containing solutions should be isotonic and care should be exercised to avoid metabolic alkalosis or electrolyte abnormalities (e.g. hypokalemia). While randomized controlled trials are lacking, the available evidence suggests that bicarbonate have no benefit over and above aggressive fluid resuscitation.[23-25] Knottenbelt has demonstrated that large-volume infusion of crystalloid alone creates a solute diuresis sufficient to alkalinize the urine.[21]

Summary: The value of reducing chloride (i.e. using bicarbonate) in solutions for the prevention of RCN is presently uncertain although risks are small in most patients. Bicarbonate solutions may be of value in rhabdomyolysis but more evidence is necessary. Recommendations for clinical practice: The primary recommendation for fluids to prevent AKI in the setting of radio-contrast exposure and rhabdomyolysis is to ensure that they are given. Exact volumes or anion composition cannot be determined based on available evidence, although bicarbonate appears safe in high risk groups. Consider isotonic bicarbonate in preference to NS in patients without metabolic alkalosis. Recommendations for future research: Randomized clinical trials to separate the effects of bicarbonate versus saline and other interventions (NAC, tonicity of contrast) in preventing RCN in high risk patients with and without underlying kidney disease. Randomized controlled trials are needed, to ascertain the value of bicarbonate vs. NS in the setting of rhabdomyolysis, possibly with and without mannitol.

ii. Tonicity (Hypotonic vs isotonic, saline, mannitol)

Isotonic vs. hypotonic saline. A large, prospective, randomized, controlled trial in patients undergoing cardiac catheterization found plasma volume expansion with NS to be superior to 0.45% saline.[26] However, the incidence of RCN was lower than previously reported in comparable patient cohorts (0.7% in NS and 2% in the 0.45% saline group).

Mannitol. Although studies in animals have shown mannitol to help protect the kidney against ischemic injury, human studies fail to demonstrate the efficacy of mannitol in preventing AKI. Although prophylactic mannitol has also been promoted in patients considered to be at high risk for AKI, such as those undergoing vascular (aortic aneurysm) surgery, cardiac surgery, or patients developing obstructive jaundice, several small RCTs have found no reduction in the incidence of AKI with mannitol administration or over-hydration.[27-30] In small studies of patients undergoing kidney transplantation, mannitol administration appears to have salutary effects with regard to AKI. In these studies, 250 ml of 20% mannitol given immediately before vessel unclamping reduced the incidence of AKI, as determined by a decrease need for post-transplant dialysis.[31-38] However, no durable outcome difference at 3 months was found in comparison to patients who did not receive mannitol.[38]
Mannitol results in a higher incidence of radiocontrast-induced nephrotoxicity as compared with saline plasma volume expansion alone in either diabetic or non-diabetic patients.[39, 40] Solomon et al found that 25 g of mannitol prior to contrast administration plus plasma volume expansion with saline was not associated with any reduction in risk compared with saline alone; instead, there was a trend toward harm.[39] A forced diuresis regimen which included intravenous crystalloid, mannitol, furosemide and low-dose dopamine similarly exerted no effect on the overall incidence of contrast-induced nephropathy.[40] The trial design allowed independent evaluation of the effects of mannitol and the results demonstrated no additive benefit. In patients with both diabetes and chronic kidney disease receiving radiocontrast agent, mannitol increased the incidence of nephrotoxicity.[41, 42] Conversely, the use of mannitol has been advocated in the setting of rhabdomyolysis to create an osmotic diuresis [43, 44], vasodilatation of renal vasculature[45] and free-radical scavenging.[46, 47] However, available evidence suggests that mannitol offers no benefit over and above aggressive fluid resuscitation.[23-25] Furthermore, mannitol can be harmful if urine output cannot be maintained.

Summary: Isotonic fluids are superior to hypotonic fluids for plasma volume expansion prior to contrast material with regard to AKI risk mitigation. Mannitol is of unproven benefit with rhabdomyolysis or renal transplant to decrease AKI incidence, and should not be routinely utilized in clinical practice. Mannitol may increase the risk of RCN associated AKI in diabetic patients, and should not be used in this patient population. **Recommendations for clinical practice:** Use isotonic IV fluids to reduce the risk of AKI from radiocontrast and rhabdomyolysis. Mannitol should be avoided in patients with AKI; its role in preventing AKI in the setting of rhabdomyolysis is currently uncertain and it should be avoided in the setting of RCN. **Recommendations for future research:** Further clarification regarding the duration and volume of isotonic IV fluids before and after radiocontrast agent administration to guide clinical practice.

**Do different colloid solutions pose a risk of AKI?**

*Albumin.* Human albumin has been widely used as the colloid for the treatment of hypovolemia in critically ill patients. The SAFE study which was a large multicenter RCT (n=6997) demonstrated no difference in renal outcomes (including incidence of AKI, need for RRT or duration of RRT), mortality, LOS in the ICU, or duration of mechanical ventilation between patients managed with 4% albumin or normal saline for fluid resuscitation.[48] The authors concluded that albumin is a safe as NS for resuscitation of the critically ill. Importantly the study used a preparation of albumin in NS and few patients in the SAFE trial received large volumes fluid resuscitation. Whether specific subgroups of critically ill patients, including those with AKI, fare better with albumin is unknown.

*Starches.* Some studies have shown that patients treated with certain HES solutions (High molecular weight (HMW)-HES and HES with a high C2-C6 molar substitution ratio) may suffer from renal dysfunction.[49, 50] Histological studies have shown reversible tubular cell edema causing obstruction and medullary ischemia.[51] Boldt recently reviewed the renal complications of HES use. Study limitations included a lack of fixed endpoints for intravascular volume therapy, crude measures of kidney function, and lack of
control groups in those receiving crystalloid infusions.[52] Additionally, HES has been noted to accumulate in renal tubular cells and is believed to be a cause of AKI.[52] However, appropriately controlled studies are lacking. Use of HES has been associated with AKI in post-cadaveric renal transplant patients.[50, 53] In an observational cohort study, Legendre reported an 80% rate of osmotic nephrosis-like lesions (vacuolization of proximal tubular cells) in transplanted kidneys after administration of HES with a mid-range MW (200kD) and high molar substitution ratio (0.62) to brain dead organ donors.[54] The lesions had no negative effect on graft function or serum creatinine at 3 and 6 months post transplantation. Similar lesions have been described with other substances including mannitol and dextran. Infusion of hyperoncotic colloids likely induces hyperviscosity and stasis of tubular fluid, especially when HES concentration is high (>10%). Large amounts (>2000 ml or > 20 cc/kg bw/day) of HES preparations with LMW or MMW (e.g. HES 130/0.4 or HES 200/0.5) and a low MS (0.4, 0.5) have been used safely in humans as have HWM-HES with high molar substitution (670/0.75).[55, 56]

Younes studied HES in NS compared to NS in trauma patients with hemorrhagic shock and documented that less HES volume was required to achieve an identical blood pressure compared to the NS resuscitated patients.[57] These data are consistent with that from Boldt who resuscitated 30 trauma and 30 septic patients with a more concentrated starch (10%) of lower molecular weight (100kDa) and lower molar substitution ratio (0.3) that that used in the US (6%, 670 kDa/0.75) versus albumin and found that the HES group evidenced better splanchic (septic patients only) and systemic hemodynamic indices (septic and trauma patients).[58] Finally, intra-op evidence of improved microcirculation as judged by improved tissue oxygenation was seen when comparing HES (130/0.4) to LR resuscitation during major surgery.[59] Thus, starch resuscitation may have some benefits in restoring effective circulating volume and supporting microcirculatory flow, but the data are difficult to interpret because of multiple different molecular weights and molar substitution ratios, as well as different resuscitation targets and patient populations.

Worse serum creatinine was noted in septic patients resuscitated with HES compared to gelatin.[49] This study used a low molecular weight starch with high molar substitution ratio (200 kDa/0.6-0.66) in NS, and found that serum creatinine was higher on days 6 and 7 compared to gelatin. However, baseline serum creatinine was also slightly higher in the HES group (NS) and differences between groups may not have been clinically significant nor did they persist (values were identical at 14 days). Also, survival was identical for both groups. By contrast, intra-operative infusion of 500 cc of 6% HES in a balanced electrolyte solution containing lactate (Hextend) has been associated with improved urine output, systemic perfusion, gut mucosal perfusion, and the absence of acidosis or hypocalcemia requiring correction in elderly patients undergoing major surgery with an anticipated blood loss exceeding 500ml; no differences in post-op renal function (or dysfunction) was identified.[60] This study compared Hextend to HES in NS (Hespan). Similarly, the prospective (Hextend vs Hespan) Phase III US FDA registration trial for Hextend utilized quite large volumes of Hextend (up to 5L) without identifying diminution in renal function.[61] Interestingly, patients receiving Hextend demonstrated better clotting ability as interrogated by thromboelastography that correlated with reduced intra-operative blood loss and component therapy.
Additionally, a retrospective comparison of cardiac surgery patients treated with a low molecular weight (200 kDa) and degree of molar substitution (0.5) starch vs. gelatin, or both[62] found no differences in post-operative serum creatinine. Thus, it may be that sepsis induces a sensitivity to starch resuscitation that is not evident in other conditions like trauma, surgery, and cardiopulmonary bypass that are also accompanied by a substantial inflammatory and cytokine response. In contrast, a rodent model of sepsis demonstrated improved survival with Hextend resuscitation compared to 0.9% NS or LR despite identical resuscitation endpoints.[63]

**Gelatins.** In contrast to the controversies that surround HES use, there is little negative data regarding gelatin infusions. The Cochrane analysis did not identify a significant benefit for gelatin resuscitation but neither did it identify a detrimental effect.[64] Gelatin resuscitation has been utilized to great effect in trauma, surgery and burns. However, its utility is limited by its relatively short half-life and relative low affect on colloid oncotic pressure. There is no data that gelatin infusion causes renal injury, or that its use with AKI should be restricted. Although gelatin is widely used in the UK, Australia and parts of Europe, it has never been approved for use in the US. Limited data are available comparing it to other colloids. Colloids do contain “unmeasured anions” and thus will increase the anion (or strong ion) gap, although this effect is of unknown significance.

**Summary:** Albumin in saline appears to be equivalent to 0.9% saline in terms of risk of AKI. The risks of AKI associated with HES, if any, appear to vary depending on the size, concentration, molar substitution and possibly the diluents’ composition used in these preparations. Current evidence is inconclusive to judge the risk of AKI attributable to HES. Gelatin does not appear to result in a measurable risk of AKI; however studies evaluating this endpoint have been limited. **Recommendations for clinical practice:** HES should be used with caution in patients with sepsis and renal transplantation due to limited evidence suggesting risk of AKI in these groups. However, current data do not preclude their use in these settings. HES appears safe for trauma, burns, and large blood loss emergency and elective surgery. Neither albumin nor gelatin appears to increase the risk of AKI. Insufficient evidence exists to recommend one colloid preparation over another in terms of risk for AKI. **Recommendations for future research:** HES of different concentrations, molecular weights, and degrees of molar substitution ratios in different diluents (based on chloride concentration) should be studied; possibly in sepsis and non-septic models prior to conducting a prospective randomized trial in humans in a multi-center fashion. Gelatin should be studied in a fashion similar to starch, but with additional comparators to include different crystalloid solutions of different chloride concentrations. Compound agents like hypertonic HES should have their investigation deferred until the optimal HES construction has been defined with regard to concentration, molecular weight, and degree of molar substitution ratio, and diluents’ electrolyte composition. HES administration with different concentrations, molecular weights, and degrees of molar substitution ratios, in different diluents should be specifically administered in an animal model to determine the incidence and prevalence of renal tubular incorporation of starch with both hypovolemia and hypervolemia, hemorrhagic shock, and sepsis as well as the incidence and prevalence of AKI in each of those settings.
Do different colloid solutions have different effects on mitigating the risk of AKI?

i. Cirrhosis

Albumin. Daily administration of albumin has been shown to be beneficial in reducing the risk of AKI in patients with cirrhosis and spontaneous bacterial peritonitis, although the exact mechanism underlying this effect remains opaque.[65] In a multicenter, randomized trial by Sort et al.[66] the addition of an intravenous infusion of human serum albumin to standard antibiotic treatment in patients with spontaneous bacterial peritonitis reduced the rates of renal impairment and mortality; whether the effect occurs exclusively on the basis of expanded effective circulating volume alone is not known. Although large-volume paracentesis (LVP) has been used in the treatment of ascites, the need for plasma volume expansion after therapeutic paracentesis remains controversial. While hemodynamic studies in patients with ascites have shown that a significant reduction in intravascular volume and renal impairment occurs more commonly when ascitic fluid is totally mobilized without prior or concomitant plasma volume expansion, [65, 67-69] other studies of LVP without the administration of any plasma volume expanders document no increase in renal complications. [70-72] Based on the International Ascites Club guidelines, 6-8 grams of albumin is recommended to be infused per liter of ascites fluid removed for paracentesis volumes greater than 5-6 liters.[17]

Starch. In a pilot study comparing the use of albumin and HES (in normal saline) in patients with cirrhosis and spontaneous bacterial peritonitis, renal outcome was similar between the two groups.[73] Although albumin is the most frequently used plasma volume expander for LVP, other plasma volume expanders including Dextran 70,[74] 5% synthetic polymerized gelatin (hemaccel),[75] HES (in NS),[76] have also been shown to be as effective as albumin in the prevention of complications related to large-volume paracentesis. In one study, Cabrera et al. removed a mean of 8 L of ascitic fluid from 14 patients, with replacement only by intravenous normal saline solution.[70] None of the patients had any clinical complications or alterations in kidney function tests.

ii. Renal Transplant

Albumin. Several observational studies in kidney transplant recipients suggest that volume expansion with albumin reduces the onset and the extent of post-transplant oliguria, and AKI while improving 1-year graft and patient survival. Unfortunately controlled clinical studies are still lacking.[77-79] In one study, although higher intra-operative albumin dose (1.2-1.6 g/kg bodyweight) was associated with better outcomes in comparison to those receiving lower albumin dose (0-0.4 g/kg), the possible effects of concomitantly administered mannitol, furosemide and crystalloid plasma volume expansion on outcomes cannot be ignored.[77]

Starch. Comparison of intra-operative albumin and dextran-40 in 17 renal transplant recipients from a living related donor failed to show any difference between the two plasma volume expanding agents with regard to renal function.[80]
Summary: Volume expansion appears to be useful in avoiding renal dysfunction following LVP and possibly in the setting of bacterial peritonitis even with small volume removal. It is unknown whether different colloid preparations are more or less effective for volume expansion in patients with cirrhosis. Data are inconclusive comparing different colloids in renal transplant. Recommendations for clinical practice: No recommendations can be made for selecting between colloid preparations for mitigating risk of AKI following LVP or renal transplant. Recommendations for future research: Randomized controlled trials comparing HES and albumin for LVP and most renal transplant are needed.

How potassium containing fluids should be used in patients with AKI?

Blood Products. Packed red blood cell (PRBC) transfusion will deliver a measurable amount of potassium to the blood volume of a recipient. The amount of potassium transfused increases with the age of banked blood, and is least with fresh whole blood transfusion, as sporadically occurs in military scenarios with type specific “buddy” transfusion. As banked blood ages, the integrity of the red blood cell plasma membrane is compromised leading to extracellular translocation of normally intracellular potassium. While the amount of potassium infused is measurable, hyperkalemia requiring therapy is rare with normal plasma potassium, and is virtually nonexistent with hypokalemic states. Patients at greatest risk for transfusion associated hyperkalemia are those receiving component transfusion on a massive transfusion protocol for exsanguinating hemorrhage from a variety of clinical conditions.[81] Despite this theoretic risk, the major risk with massive transfusion is hyperkalemia and hypocalcemia, is readily identified with transfusion of frozen PRBC.[82] A recent study of 131 penetrating trauma victims found that, by multivariable logistic regression analysis, independent risk factors for hyperkalemia were an emergency-room plasma potassium level of 4.0 mmol/L or higher (RR 3.40, 95% CI 1.17-9.84, p=0.024), and transfusion of 20 or more units of cell- or plasma-based transfusion products (RR 14.66, 95% CI 4.68-45.97 p < 0.001).[83] Hyperkalemia risk may also be ameliorated by preinfusion washing methods.[84] Some risk may be potentially ameliorated by incorporating activated factor VII into massive transfusion protocols as a means of reducing total transfused units of PRBC; there is no data at present to support this speculation. Since the potassium load with components other than PRBC is minimal, transfusion associated hyperkalemia is not a clinically relevant issue when transfusing fresh frozen plasma, platelets, or cryoprecipitate.

Lactated Ringer’s solution. Lactated Ringer’s solution is formulated with a small amount of potassium, and, according to conventional wisdom, has been commonly avoided as a resuscitation fluid in patients with AKI or CKD. Certainly, in patients with a normal of low plasma potassium, LR is safe with regard to hyperkalemia induction. This condition is exceedingly rare in the trauma patient population for whom LR is the predominant resuscitation fluid in the US. However, in the renal transplant patient population, large quantity plasma volume expansion with NSS was compared to expansion using lactated Ringer’s.[2] In this study, only NSS was associated with hyperkalemia (K⁺ > 6 mEq/L) and metabolic acidosis that required therapy. Moreover, this study was terminated early due to safety concerns in the NSS arm. One may
speculate that this observation reflects diminutions in RBF and GFR that accompany hyperchloremic metabolic acidosis, but the mechanism underpinning these observations has not been fully elucidated.

**Summary:** Transfusion associated hyperkalemia is rare, but should be assessed when treating a patient using a massive transfusion protocol. Lactated Ringer’s is safe for plasma volume expansion in those at risk for AKI. NSS should be used with caution in the renal transplant patient due to the risk of hyperkalemia.

**Recommendations for clinical practice:** No change in transfusion practice is recommended as transfusion associated hyperkalemia is rare. LR does not carry a risk of hyperkalemia.

**What is the risk of AKI associated with blood substitutes?**

*Hemoglobin-based oxygen carriers (HBOC).* Over the last two decades animal and human trials have explored the use of HBOC for both plasma volume expansion and restoration of oxygen carrying capacity in malaria, orthopedic surgery, cardiac surgery, and hemorrhagic shock from injury. Since the HBOCs that are currently under clinical investigation are formulated in a normal to low potassium concentration diluent, there is little to no risk of infusion associated hyperkalemia. Due to the colloidal nature of the products, and the known vasoactivity of the products, resuscitation with an HBOC utilizes less total volume compared to crystalloids and therefore, delivers less potassium. HBOC vasoactivity appears to be related to the tetrameric composition of the product, and is reduced with current products (< 3% tetrameric Hgb) compared to the 1st generation progenitor product, Baxter’s ill-fated DCLHB (> 30% tetrameric Hgb). Vasoactivity is principally related to nitric oxide scavenging, although not exclusively so and has been chiefly explored in the systemic circulation (systolic and mean arterial pressures) as well as the cardiopulmonary circuit (pulmonary artery pressures and cardiac output).[85]

There are two main US competitor products, neither of which has currently garnered FDA approval for licensing: Nothfield’s Polyheme and Biopure’s Hemopure (HBOC-201). Both products have undergone extensive preclinical testing in predominantly porcine models of hemorrhagic shock, a condition associated with AKI.[86] HBOC-201 does not demonstrate increased rates of AKI compared to standard crystalloid plasma volume expansion even in prolonged low-volume resuscitation conditions.[87] HBOC-201 controlled and uncontrolled hemorrhagic shock preclinical data also includes histopathologic and electron microscopic analysis of renal parenchyma and tubules documenting the absence of renal injury in treated pigs.[88] Similarly, both products have undergone clinical trials without an increased incidence of AKI compared to crystalloid plasma volume expansion.[89-93] These trials included patients with sickle cell disease, patients undergoing elective vascular surgery, and trauma patients. Each of these (except the sickle cell disease trial) trials include patients in RIFLE classification R as well as many in the I category. There is no evidence of increased AKI occurrence in these trials supporting the potential use of HBOC in plasma deficit conditions from which patients are at risk of AKI. The reader should note that Northfield has recently completed a pre-hospital and in-hospital hemorrhagic shock trial, the results of which are not yet publicly available, but will shed additional information on the use of HBOC in at-risk patients for AKI.
Biopure also manufactures a veterinary product, Oxypure, whose use is unassociated with renal injury in a variety of mammalian species.

**Summary:** No definitive data exists on the use of HBOCs and abrogation or induction of AKI at present.

**Recommendations for clinical practice:** No recommendation can be made with regard to HBOCs at present.

**Recommendations for future research:** Randomized controlled trials comparing HBOC plasma volume expansion and oxygen carrying capacity to crystalloid and colloid plasma volume expansion in RIFLE “R”, “I” and “F” patients in the pre-hospital and in-hospital setting.

### Fluids for Renal Replacement Therapy (RRT)

This section will review and make recommendations on the use of fluids for RRT.

**What should be the composition of replacement fluid and dialysate?**

**General considerations.** Although Peritoneal Dialysis is still used in different areas of the world, it is not the preferred modality of renal replacement therapy (RRT) in AKI. Therefore, the composition of PD solutions will not be further discussed in this review. Given the technical differences between intermittent Hemodialysis (IHD) and continuous renal replacement therapies (CRRT), different considerations apply to fluid composition in each modality. Finally, although other extracorporeal techniques (MARS, Plasma exchange) are used in AKI, given that they are generally not used as RRT, they will not be discussed in this document.

**Fluids for IHD and IHDF.** Higher dialysate sodium concentrations are associated with increased hemodynamic stability in IHD.[94-96] In IHDF, whether the replacement fluid is infused pre- or post-filter has an impact on the relationship between sodium concentration and sodium balance. During dialysis, the majority of sodium movement is due to ultrafiltration, Sodium can also potentially move by diffusion. As a result of a variety of physicochemical factors, including the difference between plasma sodium concentration and the true concentration of sodium in plasma water and the Gibbs-Donnan effect, plasma sodium concentration generally must be at least 4 mMol/L greater than dialysate sodium in order to diffuse down a concentration gradient.[97] During hemofiltration, sodium moves with plasma water across the hemofilter membrane, but due to protein coating of the membrane retarding sodium movement, the amount of sodium sieved is < 1.0. Thus, when the same sodium concentration is used in dialysate and replacement solutions, convective therapies tend to result in a greater positive sodium balance than pure dialysis.[98, 99] possibly accounting for the greater cardiovascular stability with convective techniques are compared with pure dialytic techniques for the same net rate of ultrafiltration.[100] Commercially available hemofiltration replacement fluids vary in sodium concentration from 138-155 mMol/L.[101] Studies have suggested that a positive sodium balance occurs when plasma sodium is less than 8 mMol/l higher than the replacement fluid.[98] During hemofiltration the overall sodium balance is also affected by the site of infusion of replacement fluid, as post-dilution results in greater sodium retention than mid-dilution, and mid-dilution
greater sodium retention than predilution, due to changes in protein polarization and hematocrit as blood flows through the hemofilter.

Requirements for chloride, potassium, magnesium are variable in different clinical situations. Maintenance of normoglycemia in the critically ill patient has been associated with improved outcomes.[102-104] Removal of glucose from the dialysate has been shown to create risk of severe hypoglycemia. Trace elements, including water soluble metals, micronutrients, aminoacids and folate are lost during dialysis.[105, 106]

Summary and Recommendations for clinical practice: In hemodynamically unstable patients, consider using increased sodium (up to 150-155 mMol/L) dialysate concentration. When the same sodium concentration is used in dialysate and replacement solutions, convective therapies tend to result in a greater positive sodium balance than pure dialysis,[98, 99] possibly accounting for the greater cardiovascular stability with convective techniques are compared with pure dialytic techniques for the same net rate of ultrafiltration.[100] Chloride, Potassium, Magnesium and other anion needs must be adjusted to each individual situation. Glucose. Utilize physiological glucose concentration in dialysis fluids. Replace trace elements, aminoacids, micronutrients and vitamins as necessary.

Fluids for CRRT. Existing clinical practice based on available evidence and opinion demonstrates that sodium is generally kept at an isonatric (physiologic) concentration except when special prescriptions are used in combination with some citrate anticoagulation protocols. Chloride, potassium, magnesium and anion needs are variable in different clinical situations. Hypophosphoremia due to increased clearance and intracellular shifts due to “refeeding” are common in CRRT, and may place patients at risk of complications including rhabdomyolysis.[107] Maintenance of normoglycemia has been shown to be associated with lesser mortality in the critically ill patient.[102-104] Trace elements, including water soluble metals, micronutrients, aminoacids and folate are lost during CRRT.[105, 106]

Summary and Recommendations for clinical practice: Physiologic concentrations of sodium should be used except when using citrate anticoagulation. In the latter circumstances, adjustments may be necessary given the variable contents of sodium in different citrate solutions. Chloride, potassium, magnesium anions should be present in replacement fluid and or dialysate in concentrations tailored to patient need and anticoagulation procedures. Calcium should be absent from the replacement fluid and dialysate when citrate is used as an anticoagulant. To avoid hypophosphoremia, phosphate should be provided either as a supplement in the CRRT fluids (replacement fluid or dialysate) or as a nutritional supplement.[107] To avoid hyperglycemia, Glucose can be either absent or present at physiological concentration in dialysis fluid. Loss of trace elements (water soluble metals, micronutrients, aminoacids, and folate) must be appropriately replaced.
What metabolizable anion should be used and under what circumstances?

Both lactate and bicarbonate ions have been used in replacement fluid and dialysate for CRRT. Historically, lactate has been preferentially used as a buffer due to the instability of bicarbonate-based solutions when stored over prolonged periods of time. This problem has recently been overcome, allowing commercial availability of bicarbonate-based fluids. Controlled (though not all randomized) trials have suggested that lactate and bicarbonate buffered solutions have a similar efficacy for correction of metabolic acidosis during CRRT.[96, 108-112] However, recent studies [113, 114] showed better control of metabolic acidosis with bicarbonate as compared to lactate. Barenbrock [114] also showed better hemodynamic tolerance of therapy with bicarbonate. Neither study showed a difference in mortality, but neither was adequately powered. Blood levels of lactate are generally higher when lactate is used as a buffer and may confuse the clinical interpretation of these measurements. Whether this hyperlactatemia is associated with morbidity is not clear. Depending on tissue redox status and substrate availability, lactate is either metabolized back to pyruvate and into the citric acid cycle, resulting in proton buffering, or into glucose by gluconeogenesis. Potential concerns with excessive lactate accumulation are hemodynamic compromise [111], increased urea generation [109, 115] and cerebral dysfunction.[115] Hyperlactatemia may develop in situations of impaired lactate clearance including liver failure and tissue hypoperfusion. This hyperlactatemia can be expected to be more pronounced if lactate-buffered solutions are used during high-volume hemofiltration. Accumulation of the D-isomer of lactate may also be a concern as the D-isomer constitutes 50% of the total lactate contents of racemic mixes. As D-lactate is non metabolizable by humans, it may accumulate, contributing to severely elevated lactatemia and associated with neurologic impairment.

In the IHD literature, acetate has been shown to be associated with impaired myocardial contractility and decreased cardiac function. This anion has been rarely used as a buffer in CRRT. Citrate, used primarily for its anticoagulant properties, serves as an effective buffer. Scant evidence is available on the use of citrate exclusively as a buffer in CRRT. Importantly, citrate metabolism is often impaired in liver failure or muscle hypoperfusion, both situations posing risk of hypercitratemia when citrate is utilized. Hypercitratremia carries the risk of decreased ionized extracellular calcium concentration. Importantly, blood products contain citrate as an anticoagulant; massive blood or plasma product transfusions are associated with high citrate loads, which accumulate when citrate is simultaneously used as an anticoagulant and/or a buffer. Low concentrations of citrate are present in some commercial dialysate solutions for IHD. Complications of citrate toxicity have not been associated with these agents.

Summary: Both lactate and bicarbonate are able to correct metabolic acidosis in most CRRT patients; however, correction of acidosis may not be as efficient with lactate as with equimolar bicarbonate. Worsening hyperlactatemia has been noted when lactate was used in patients with lactic acidosis or liver failure. The clinical relevance of this finding is unknown. Citrate used as an anticoagulant has also been effectively used as a buffer in CRRT. Recommendations for clinical practice: There is consensus that bicarbonate is the preferred dialysis buffer in IHD. For CRRT, bicarbonate is an effective buffer and is
currently the preferred organic buffer in commercially manufactured solutions. Lactate-buffered solutions are safe and efficacious in the majority of patients, but these solutions may be hazardous whenever lactate clearance is impaired, such as in liver failure patients or patients with severe tissue hypoperfusion. D-lactate should be removed from lactate-containing solutions, which should consists almost exclusively of L-Lactate. There is insufficient data to evaluate the use of acetate-buffered solutions in CRRT. The metabolism of sodium citrate used for regional anticoagulation during CRRT, generates three moles of bicarbonate per mole of citrate and functions as an efficacious organic buffer. Use of citrate in the setting of decreased citrate clearance or when patients receive large doses of citrate during massive transfusions should be done with individualized adjustment of citrate dose and with close monitoring of plasma ionized calcium levels. Recommendations for future research: Further studies comparing lactate and bicarbonate in high volume hemofiltration are required. Optimal acid-base management of patients with permissive hypercapnia requires further investigation.

**Should the buffer concentration be higher in patients with permissive hypercapnia?**

In patients with ARDS/ALI on lung protecting ventilator strategies, the resulting respiratory acidosis can be partially or completely compensated by elevation of plasma bicarbonate with CRRT. The discussion of to what level should acidemia be corrected is beyond the scope of this discussion.

**How should fluids be compounded?**

Assuring correct electrolyte formulation by repeat testing as needed, given that serious errors have been reported when local pharmacies compound without regular monitoring of composition.[116-118]

Recommendations for clinical practice: When dialysis fluids are compounded locally, appropriate monitoring of RRT fluid composition must be assured.

**References**


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