

Selection of Dialysate and Replacement Fluids and Management of Electrolyte and Acid-Base Disturbances

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ABSTRACT

Often, too little consideration is given to the fluids used in all forms of continuous renal replacement therapy (CRRT). However, errors in fluid prescription, delivery, or creation can be rapidly fatal; in addition, fluid associated expenses can be the overriding cost in continuous renal replacement therapies. While a standard solution is fre-

quently acceptable in most clinical circumstances, specific electrolyte and acid-base disturbances may direct changes in fluid delivery and composition. Decisions regarding fluids, whether dialysate versus replacement, including generation and composition of therapy are discussed in this review.

Often, too little consideration is given to the fluids used in all forms of continuous renal replacement therapy (CRRT). However, errors in fluid prescription, delivery, or creation can be rapidly fatal; in addition fluid associated expenses can be the overriding cost in continuous renal replacement therapies. Errors or omissions in prescription, manufacturing and delivery can have a significant rapid onset of morbidity or even mortality for the patient in the intensive care unit (ICU). Prescriptions for CRRT must be designed to minimize error and maximize safety. How CRRT fluids are delivered impacts the quality of the CRRT program. Decisions regarding fluids include how to deliver therapy (dialysate versus replacement); how to generate therapy; and composition of therapy. These may be adjusted to meet the individual needs of the ICU patient.

Dialysate or Replacement Quality

Despite much debate on how to deliver therapy, there are no convincing clinical data to support either convective, continuous venovenous hemofiltration (CVVH), or diffusive, continuous venovenous hemodialysis (CVVHD) therapies. Likewise the decision to use a combination therapy, continuous venovenous hemodiafiltration (CVVHDF), is not supported by data. Surprisingly, how fluid is delivered has little impact on the composi-

tion of the fluid. Whether replacement fluid or dialysate is utilized, the fluid should be as pure as possible. Even in CVVHD mode, given the low dialysate flow rate and porous nature of most filters, significant convective clearance occurs from backflow, with reabsorption and ultrafiltration taking place within the CVVHD dialysis membrane.

Thus, it seems reasonable to maintain a higher standard for water (dialysate) quality than the accepted North American Association for the Advancement of Medical Instrumentation (AAMI) standards for outpatient dialysis. The patient may be exposed to any endotoxin [positive *Limulus* ameobocyte lysate (LAL) assay] or frank bacterial contamination in the CRRT fluids regardless of whether they are in the dialysate or replacement fluid. The exposure risk is even greater for CRRT circuits as compared to those for intermittent hemodialysis due to the continuous nature of the therapies. Therefore, regardless of whether CVVH, CVVHD, or CVVHDF is used, the dialysate and replacement fluids need to be ultrapure at a minimum or, even better, sterile (see Table 1) (1). This issue is a potential problem with less than ultrapure fluids as exposure to low levels of endotoxin could stimulate the inflammatory cascade (2).

The issue of sterility will be even more acute and morbid if the fluid has overt contamination with bacteria or endotoxin. While this may seem extreme, reports of fluid contamination do exist. These contaminants have led to the acute development of hypotensive episodes or frank endotoxic shock. The frequency of patient exposure to contaminated fluids is unknown and possibly under recognized in patients in the ICU on CRRT. These episodes are not reported, if known, and quite difficult to ascertain given the many etiologies of increased pressor requirements or worsening cardiovascular collapse. Hence contaminated fluid may not

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TABLE 1. Dialysate water standards

Dialysate: (US)
Bacteria < 200 cfu/cc
Endotoxin < 2 EU/cc
Ultrapure
Bacteria < 0.1 cfu/cc
Endotoxin < 0.03 EU/cc
On line substitution
Bacteria < 10 ⁻⁶ cfu/cc
Endotoxin < 0.03 EU/cc
Sterile
Validated sterilization cycle and tested before release

be suspected or investigated as the etiology of a patient's deterioration.

Preserving of the purity of fluids is maintained at the level of manufacturing or preparation of the solution for CRRT. A second source of contamination will occur if additional electrolytes or solutions are prescribed; these may be added in the pharmacy (preferred) or at the bedside (greater source of error and contamination).

Fluid can be manufactured at the level of the pharmacy individually as prescribed (created by hand) or generated with the assistance of a dedicated hyperalimentation device within the pharmacy. Fluid can also be purchased premade from a compounding company, or purchased prepackaged and supplied by a manufacturer.

Generating fluids at the pharmacy/hospital level was necessary in the early days of CRRT as compounders and vendors were not available. This method is still used to develop custom fluids at some institutions, while only a few are still generating most solutions locally. There are many potential and real problems with pharmacy mixing CRRT fluids. Customization by hand in the pharmacy is very labor intensive and hence carries significant cost. Fluid generated locally will cost up to 10 fold more than commercially available solutions. In addition, these fluids have a short shelf-life and are made as needed or ordered. The time involved may be the rate limiting factor from the decision to institute therapy to its actual initiation. In addition, pharmacy generation of custom fluid increases the risk for human error.

The errors may be prescriptive. Writing a customized fluid may be onerous and errors of omission or commission are possible. Vital electrolytes or additives may be omitted. Likewise, errors of commission or prescriptive mistakes in actual fluid composition may occur. Either of these errors could lead to poor patient outcomes. Limiting choices of customized solutions can help decrease these errors.

In addition, safety issues occur in the pharmacy. Each time an electrolyte solution or additive is injected, this is associated with a chance of human error; sterile technique may be compromised; mistakes in calculations of additive dose; or human error may occur (wrong syringe, wrong vial, drawing up incorrect dose). For example, Johnston et al. reported the inadvertent use of KCl instead of NaCl in the preparation of solution. This resulted in the delivery of fluid with a fatal concentration of potassium chloride of 53.6 mm in the dialysate (3). In addition, Barletta et al. (4) reported from a survey of three pediatric listservs that 16/31 programs reported

solution errors from generating fluids in the hospital pharmacy. Two resulted in death, one noncardiac arrest and six seizures associated with sodium errors.

Purchasing fluid from a compounder is also a venue for obtaining customized fluids for CRRT fluids. The complications of compounding include increased cost compared to commercially available fluids and a shorter shelf life (usually 30 days). The shorter half-life increases costs with increased storage needs and waste due to expired fluids. Quality of compounded fluids needs to be considered as well. There have been unpublished reports of issues with sterility and/or increased endotoxins in batches supplied by a compounder which lead to acute hemodynamic compromise in ICU and an FDA adverse event report with hemofiltration in home patients (5).

The safest approach is to use commercially available fluids for dialysate and replacement fluids. These are less expensive and have longer shelf life. They are available from multiple manufacturers, generally 3 l and 5 l bags with a discrete number of fluid compositions. This may limit some centers that prefer significant customization.

In the USA commercial CRRT fluids are FDA cleared for dialysate and recently some have been approved for replacement (6). However, many centers use off-label dialysate for replacement fluid, as was done in the VA/NIH acute kidney injury study (7). To date there are no published reports of observed adverse effects using dialysate as replacement fluid.

Fluid Composition

Sodium

Sodium in the overall fluid should be physiologic (~140 meq/l). Customization of sodium is performed in some centers which utilize hypertonic citrate for anticoagulation. These fluids should be used with caution as they must be customized in the pharmacy and are not physiologic. If accidentally infused at increased rates or discontinued, this may result in significant derangements in serum sodium. Citrate anticoagulation is discussed in detail elsewhere in this issue of the journal.

The difficult question is whether custom solutions should be prescribed for baseline sodium derangements. There is no published literature to support this method. When considering the added complications in safety and cost, this is likely unwarranted. Generally the overall changes in sodium towards normal are slow with CRRT due to the low volumes of replacement fluid and or dialysate used per hour. In general sodium will move towards normal with all modalities (8).

However for severe hyponatremia, a separate infusion of D5W could be used to decrease the overall sodium concentration (Table 2). The concentration of sodium can then be modeled by changing the fraction of overall clearance delivered by D5W. Close monitoring of both sodium and glucose is essential. This offers advantages over custom solutions in that the overall sodium could be changed quicker and easier with less overall cost and no wastage of expensive custom solutions. In addition, overall clearance can be maintained without concern for too rapid correction of sodium.

TABLE 2. Effect of adding D5W IV to total CVVH or CVVHD

Hypotonic CVVH	Na concentration	Rate	Notes
Replacement Fluid	140 meq/l	$0.9 \times$ desired clearance	Calculate as input
D5W, Peripheral	0 meq/l	$0.1 \times$ desired clearance	
Final Hypotonic CVVHD	126 meq/l		
Dialysate Fluid	140 meq/l	$0.9 \times$ desired clearance	Calculate as input
D5W	0 meq/l	$0.1 \times$ desired clearance	
Final	126 meq/l		

Continuous venovenous hemodiafiltration as above can be peripheral or substituted as replacement or dialysate if desired.

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis.

Potassium

Potassium is an essential electrolyte in most CRRT. In general potassium concentrations between 0 to 4 meq/l are acceptable and commercially available. Given the nature of acute kidney injury (AKI) and renal replacement therapy (RRT) in the ICU, most patients have a degree of hyperkalemia at initiation of RRT therapy. Using modern accepted clearance rates of 20 ml/kg/hour to 35 ml/kg/hour, most hyperkalemia can be managed with potassium concentrations of 2 meq/l with success. If 0 meq/l is used careful monitoring not to induce hypokalemia is necessary.

In cases of hypokalemia, potassium could be added to replacement fluid; however separate boluses of potassium chloride are safe and effective. Treating hypokalemia in the patient on CRRT can be managed as per routine protocols in non-CRRT patients. With periodic boluses of potassium, serum potassium can be normalized and maintained with the CRRT fluid potassium concentration of 4 meq/l. Using fluids with potassium levels greater than physiologic may be acceptable but care will need to be taken to prevent overcorrection. Potassium repletion may take longer with this approach given the slow transfer kinetics associated with CRRT.

In cases of severe life threatening hyperkalemia associated with arrhythmia and/or hemodynamic collapse felt to be secondary to potassium levels, hemodialysis should be utilized. The removal of potassium with CRRT in any mode is limited by the rate of clearance. For instance, in a patient with a serum potassium of 8.5 meq/l with a clearance of 4000 ml/hour, the maximal potassium removal is less than 34 meq/hour ($4 \text{ l} \times 8.5 \text{ meq/l}$) with CRRT. How much less will depend on blood flow and mode (CVVH pre < CVVH post < CVVHD). Clinically effective therapy for severe hyperkalemia will take hours (9) in CRRT. On the contrary, removal of potassium will occur much more rapidly with conventional intermittent hemodialysis. If indicated, CRRT could be initiated after hemodialysis.

In specific cases where intermittent hemodialysis is not utilized or felt to be safe, the addition (or

increased rate) of a calcium infusion is reasonable to stabilize the myocardium. In addition, maneuvers to move potassium intracellularly are reasonable: use of an insulin drip, albuterol nebulizers, and bicarbonate bolus(es) may temporize long enough to remove adequate potassium. Of course maximizing blood flow and clearance rates (replacement fluid or dialysate rates) will also speed potassium removal.

Magnesium

Magnesium in commercially available CRRT fluids ranges between 1 and 1.5 meq/l. This level is not well studied but has been clinically successful in use without significant hypermagnesemia or hypomagnesemia noted. To maintain normal magnesium levels a bolus of 2–4 g should be prescribed when magnesium levels fall below normal or the low normal range.

As is the case with severe hyperkalemia, severe symptomatic hypermagnesemia is most efficiently managed with conventional intermittent hemodialysis.

Phosphorus

Derangements in phosphorus are extremely common in the setting of AKI. While hyperphosphatemia is a frequent complication of AKI, it is not uncommon to see hypophosphatemia in the ICU as well. In fact hypophosphatemia is frequently the result of more intensive renal replacement strategies often employed in the intensive care setting.

Phosphorus is not a standard component of replacement or dialysate fluids in CRRT. This is appropriate as CRRT is commonly employed in the setting of hyperphosphatemia where it will usually control phosphorus even when it is significantly elevated.

It is reasonable to anticipate the development of hypophosphatemia with the prolonged use of CRRT. Management of hypophosphatemia has multiple options. The most appropriate start is to ensure proper nutrition. One of the advantages of continuous therapies is the ability to control overall patient volume. CRRT can remove the volume required for nutrition as it is delivered. Enteral feeds are generally preferred (10) and may utilize those with higher phosphorus concentrations. Phosphorus can also be added to hyperalimentation as well. (The prescription must be modified when the CRRT system is removed, especially in the setting of persistent renal failure, or a rapid return of hyperphosphatemia may result.) In addition, hypophosphatemia may be treated with intravenous supplementation. We use 20 mmol of sodium phosphate over four hours and repeat as needed (frequently scheduled 2–3 times daily while on CRRT). Troyanov et al. described the safe addition of phosphorus to the CRRT fluids (11).

Acid Base Disturbances

Control of acid base disturbances with CRRT is dependent on flux of bicarbonate either from the patient to the CRRT fluids or the fluid to the

patient. Most conditions of varying magnitude are well handled with marked improvement within 48 hours (8).

The sodium bicarbonate concentration in CRRT fluids can be variable. With customized solutions bicarbonate theoretically can vary from 0 to 150 meq/l. While such a large variety may sound attractive with CRRT, it is neither practical nor useful. With prescribed CRRT clearances of ≥ 20 ml/kg/hour, most acid base disturbances can be managed with commercially available bicarbonate compositions of 25 meq/l to 35 meq/l. This control can be obtained as long as exogenous sources of alkali or acid can be discontinued; endogenous sources of acid generation or alkalosis can generally be easily controlled.

Metabolic Acidosis

Care of acidosis in these critically ill patients should be initially managed no differently than in critically ill patients not maintained on RRT. First it is imperative to diagnose its etiology and optimize the care of the patient. If the acidosis is due to intoxication, antidote when appropriate should be administered, and RRT initiated to remove the intoxicant and control the acidemia. In most intoxications managed by RRT, removal of the poison is most rapid with intermittent hemodialysis.

More likely the etiology of the acidosis is secondary to lactic acid generation. Oxygen delivery should be optimized and RRT initiated as necessary based on the degree of acidosis, presence of oliguria, or other complication felt to warrant RRT.

Likewise the treatment of diabetic ketoacidosis should follow usual care. RRT is indicated for rare cases or ketoacidosis associated with other organ failure, most notably AKI or end stage renal disease. Similarly, nongap acidosis should be managed in the usual fashion with RRT utilized for end organ failure as well. After resuscitation and medical management of acidosis occurs, RRT or CRRT may be indicated to control the degree of acidosis, treat the etiology of the acidosis, or manage other non-acid-base complications.

Even in severe acidosis, stabilization and improvement of the patient should occur with CRRT. If there is difficulty improving pH with CVVH, CVVHD, or CVVHDF with a commercially available solution (highest available bicarbonate is 35 meq/l), therapy can be changed to accommodate the patient's needs. At this point the options would be to use pharmacy customized solutions with higher bicarbonate concentrations; use of a supplemental bicarbonate drip; or increase the clearance rate of the CRRT system. By increasing the clearance rate, acid removal is increased as is bicarbonate administration. The first two options have a risk of human error, whereas with modern CRRT devices, it is simple to increase clearances to significantly greater than 35 ml/kg/hour. However, in the setting of acidosis associated with terminal ischemic organ disease, the acidosis may be difficult or impossible to control without a definitive surgical intervention.

Alkalosis

Metabolic alkalosis is best controlled with the usual treatments utilized in non-CRRT patients. Correction of volume contraction, chloride administration, and removal of exogenous alkali are the first maneuvers. Use of a 25 meq/l bicarbonate bath is sufficient in most cases. Rarely will it be necessary to consider an IV drip with hydrochloric acid, as long as the standard corrective measures are employed.

Development of metabolic alkalosis is most frequently associated with CRRT as a complication of exogenous alkalis, such as citrate anticoagulation. Management of this complication is discussed elsewhere. This can be controlled by discontinuing the citrate therapy until the pH decreases and followed by adjustment of citrate dosing. Customized bicarbonate solutions with lower concentrations of bicarbonate or an acid drip can also be prescribed but care must be used to prevent the complications of these therapies.

Conclusion

Continuous renal replacement therapy fluids, whether dialysate or replacement, are important elements of the CRRT prescription. A successful CRRT program is dependent on the proper and timely delivery of safe fluids. Care must be undertaken to understand the safest way to deliver a consistent fluid appropriate to the needs of the very ill ICU patient.

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