

# Renal replacement therapy in the intensive care unit

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**Abstract:** Acute renal failure is a common complication in the intensive care unit (ICU). Over the last 25 years, there have been significant technological advances in the delivery of renal replacement therapy, particularly as it pertains to the critically ill patient population. Despite these advances, acute renal failure in critically ill patients continues to carry a poor prognosis. In this article, we review the current literature about timing and initiation of renal replacement therapy in the ICU as well as practical considerations regarding the prescription and delivery of dialysis.

**Keywords:** acute renal failure, dialysis, continuous renal replacement therapies (CRRT)

## Introduction

Acute dialysis-dependent renal failure is a common problem in the intensive care unit (ICU) and, despite significant improvements in the care of critically ill patients, the mortality from this complication remains over 50%. The development of renal failure is an independent predictor of mortality in this patient population (Levy et al 1996; Metnitz et al 2002).

Over the last two decades there has been an evolution in the field of hemodialysis and consequently our approach to the treatment of acute renal failure (ARF). The use of new devices and techniques has allowed us to achieve better-tolerated and more efficient renal replacement therapy.

In this article, we review the current literature about renal replacement therapies, with a focus on continuous therapies and how they may be used in the ICU.

## What are the indications for renal replacement therapy in patients with acute renal failure?

A patient with ARF requires renal replacement therapy (RRT) when he or she has an acute fall in glomerular filtration rate and has developed, or is at risk of developing clinically significant solute imbalance/toxicity or volume overload. The precise timing of RRT initiation is usually a matter of clinical judgment. The classic indications for dialysis include:

1. diuretic resistant pulmonary edema
2. hyperkalemia (refractory to medical therapy)
3. metabolic acidosis (refractory to medical therapy)
4. uremic complications (pericarditis, encephalopathy, bleeding)
5. dialyzable intoxications (eg, lithium, toxic alcohols, and salicylates).

While many of these indications are typically used in the setting of chronic renal failure, the consequences of these complications are likely to be more severe in critically ill patients; therefore, there has been a growing trend to start dialysis prior to the development of these indications. Delays in the initiation of treatment have

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often been based on a concern that dialysis itself may delay recovery of renal function. These fears have been largely dispelled by a recent study by Schiffl et al (2002), which compared outcomes in patients with ARF treated with daily vs alternate day dialysis for patients with ARF. Daily dialysis was not associated with a delay in renal recovery or an adverse effect on patient outcome.

## What types of renal replacement therapy are available for use in the intensive care unit?

The available modalities of renal replacement therapy include:

- peritoneal dialysis (PD)
- intermittent hemodialysis (IHD)
- continuous renal replacement therapies (CRRT).

### Peritoneal dialysis

Peritoneal dialysis uses the peritoneum as a natural semi-permeable membrane for diffusive removal of solutes. It is a very effective treatment modality in patients with chronic renal failure, and patient outcomes are at least equivalent to those treated with hemodialysis (Held et al 1994; Murphy et al 2000). Peritoneal dialysis is also valuable in pediatric critical care where vascular access is challenging and peritoneal surface area is relatively larger than in adults (Williams et al 2002).

In adult patients, acute peritoneal dialysis is not widely used. The use of peritoneal dialysis is limited by both logistical and practical considerations. Acute peritoneal dialysis requires surgical insertion of a peritoneal dialysis catheter, requiring the additional involvement of a surgical team. Acute PD is frequently complicated by catheter leakage and malfunction. In addition, the use of PD is limited by low solute clearance in hypercatabolic patients, potential pulmonary restriction due to expansion of the peritoneal cavity, and its contraindication in postoperative patients who require abdominal surgery or surgical drains (Phu et al 2002). A study comparing PD with CRRT in critically ill septic patients with ARF showed more rapid correction of acidosis, solute clearance, and significantly improved survival with CRRT (Phu 2002).

### Intermittent hemodialysis

Hemodialysis is a process of solute clearance based on diffusion across the membrane driven by a concentration

gradient between the blood and dialysate. The total amount of solute transported per unit of time (clearance), depends on the molecular weight of the molecule, membrane characteristics (dialysance), dialysate flow, and blood flow. In general, intermittent dialysis is prescribed for 3–6 h per treatment. Chronic hemodialysis patients are treated three times per week, the adequate dose for IHD in patients with ARF has not yet been determined.

Slow efficiency daily dialysis (SLEDD) or EDD (extended daily dialysis) is a variant of IHD where the duration of dialysis is extended to between 8 and 12 h, the blood flow is lowered, fluid removal is more gradual, and solute clearance slower. SLEDD is associated with less hemodynamic instability than IHD and provides excellent solute control (Kihara et al 1994). This modality may have several advantages over continuous renal replacement therapies with respect to cost and improved patient mobility, however the two therapies have never been compared directly in a clinical trial.

Continuous renal replacement therapy (CRRT) has become increasingly popular for the management of ARF in the critically ill, and is now used to the exclusion of IHD in Australia (Mehta and Letteri 1999; Silvester et al 2001; Mendelssohn and Hyman 2002).

## Continuous renal replacement therapies (CRRT)

CRRT is any renal replacement therapy that is intended to be applied for 24 h per day in an ICU. The term CRRT describes a variety of blood purification techniques, which may differ significantly according to the mechanism of solute transport, the type of membrane, the presence or absence of dialysate solution, and the type of vascular access. CRRT provides slower solute clearance per unit time as compared with intermittent therapies but over 24 h may even exceed clearances with IHD.

Solute removal with CRRT is achieved either by convection (hemofiltration), diffusion (hemodialysis), or a combination of both these methods (hemodiafiltration). Hemodialysis most efficiently removes small molecular weight substances such as urea, creatinine, and potassium. Middle and larger molecular weight substances are more efficiently removed using hemofiltration as compared with dialysis. During hemofiltration, hydrostatic pressure causes the filtration of plasma across a semi-permeable membrane. Solutes are dragged across the membrane along with the plasma resulting in convective transport of solutes in the

same direction as water. This process requires the use of replacement fluid to prevent iatrogenic acidosis and electrolyte depletion as well as excessive fluid removal. The solutes in the removed filtrate are in the same concentration as those in the plasma, and solute concentration in the remaining plasma is diluted with substitution fluid. Combining diffusive and convective clearance with hemodiafiltration allows improved clearance of both small and large molecular weight substances. Using this method, blood urea nitrogen (BUN) clearances in the range of 23–30 mL/min can be achieved, even in hypotensive patients (McDonald and Mehta 1990).

The choice of modality is dependent on several factors including availability, cost, physician expertise, hemodynamic stability, and the primary purpose of the procedure (fluid removal vs solute clearance). There is currently only limited information comparing diffusive with convective blood purification techniques; results with CRRT techniques should be compared with those obtainable with IHD, which remains the gold standard therapy.

The most commonly applied modalities are continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Arteriovenous (AV) modes of CRRT have been used in the past, whereby dialysis access was obtained through the femoral artery and the femoral vein. This type of CRRT used the patient's own cardiac output to drive blood through the dialysis circuit. AV forms of CRRT have fallen out of favor in recent years due to the high access complication rate and the development of external circuit pumps. See Table 1 for a comparison of intermittent vs continuous dialysis therapies.

## When should renal replacement therapies be started?

There is no commonly accepted definition for the timing of initiating renal replacement therapy in ARF. It has been suggested that patient outcome can be improved by early or more intensive dialysis to keep the BUN under 80–100 mg/dL (29–36 mmol/L). Recent nonrandomized studies have not been able to document significant benefit of prophylactic dialysis (Gillum et al 1986; Conger 1995). It is interesting to note that the average urea concentration at initiation of CRRT in a recent Italian study of dialysis dosage was 17 mmol/L (Ronco 2000), however there is considerable variation in practice. A recent American survey of ICU dialysis practices found that the mean BUN

**Table 1** A comparison of intermittent vs continuous dialysis therapies

|                    | CRRT                            | IHD                                     |
|--------------------|---------------------------------|---|
| Time               | 24 hours                        | 4–6 hours                               |
| Pump speed         | 100–180 mL/min                  | 200–500 mL/min                          |
| Dialysis membrane  | 0.9 m <sup>2</sup><br>High flux | 1.1–2.1 m <sup>2</sup><br>+/- High flux |
| Dialysis flow rate | 0–2 L/h                         | 500–750 mL/min                          |
| Replacement fluid  | 1–3 L/h                         | None                                    |
| Fluid removal      | +100 mL/h to<br>–500 mL/h       | 500–1000 mL/h                           |

**Abbreviations:** CRRT, continuous renal replacement therapies; IHD, intermittent hemodialysis.

and creatinine values at the initiation of dialysis were 34 mmol/L and 398 μmol/L, respectively (Lewis 1997). However, because the BUN may reflect many factors other than the timing of initiation, no absolute value for BUN or creatinine should be used to determine when to initiate dialysis.

Only one randomized controlled trial has looked at the effect of timing of initiation of renal replacement therapy on outcome. Bouman et al randomized 106 critically ill patients with ARF to early vs late initiation of dialysis. Early initiation was started within 12 h of patients meeting the following criteria; low urine output (<30 cc/h) × 6 h refractory to optimization of hemodynamics and diuretics, and creatinine clearance of <20 mL/min (Bouman et al 2002). The late initiation group was started on dialysis when the classic indications for dialysis were met (volume overload, hyperkalemia, urea greater than 40 mmol/L). There was no significant difference between the groups in terms of ICU or hospital mortality, and no difference with respect to recovery of renal function. The results of this study must be interpreted with some caution however, as the study was underpowered to detect a clinically significant difference and the mortality rate in all treatment groups was very low.

The Acute Dialysis Quality Initiative (ADQI) consensus statement on dialysis treatment (Kellum, Mehta, et al 2002), makes no recommendations on the timing of initiation of renal replacement therapy beyond those defined by the conventional criteria that apply to chronic renal failure.

## How is dialysis dose measured in acute renal failure?

In the end-stage renal failure population, dialysis dose has been quantified using a technique called urea kinetic

modeling (UKM). Absolute concentrations of urea and creatinine are difficult to interpret; however, clearance of these marker substances appears to be the best measurement of therapy dose as it considers generation rates as well as plasma clearance. While quantification of dialysis dose using UKM is intuitive with intermittent therapies, methods for measuring clearance in CRRT are variable, hampered in part by a lack of understanding of what parameters should be used to compute dialysis dosage. The total solute clearance in CRRT techniques is the sum of the convective and diffusive clearances (Siegler and Teehan 1987), which is, in practical terms, the hourly volume of effluent fluid (ultrafiltrate and dialysate). Since the molecular weight cut off for the membranes is  $>20\,000$  Daltons, most low and middle molecular weight substances have sieving coefficients (SC) of 1. Convective clearance is therefore directly proportional to the amount of filtrate produced. Small molecules are less dependent on convective clearance and are more effectively transferred by diffusion. Slow dialysate flow rates (1–2 L/h) allow for complete saturation of the dialysate fluid with solutes. CRRT clearance is commonly expressed as the L/kg/h of effluent.

At the present time, a UKM-based calculation of plasma solute clearance is the most common method measurement of dialysis dosage with both intermittent and continuous forms of dialysis, although it is not entirely clear that the calculated clearance values can be directly compared (Siegler and Teehan 1987). This calculation is called  $Kt/V$ , where  $K$  is clearance,  $t$  is duration of dialysis, and  $V$  is the volume of distribution of urea. The limitation of this method rests in the observation that critically ill patients with ARF are frequently catabolic and have highly variable fluid volumes; both conditions violate several of the assumptions implicit in urea kinetic modeling. Quantification of solute clearance using dialysate concentrations of clearance markers (calculation of a solute removal index [SRI]) avoids some of the limitations of blood-based clearance calculations. There is no consensus as to which method should be used in all clinical situations.

## What is the appropriate dose of dialysis?

The notion of dialysis dose quantification in ARF has been controversial, due in part, to the lack of convincing evidence that azotemia control affects outcome in patients with either acute or chronic renal failure. At the present time there is no consensus as to what the minimal dialysis dose should

be in patients with ARF. Extrapolating data from the end-stage renal disease (ESRD) population (Gotch and Sargent 1985), it seems reasonable to suggest a minimum  $Kt/V$  of 1.2 should be delivered at least three times a week in patients with ARF. However, several recent studies support the belief that more intensive dialysis may be beneficial in this patient group. A randomized dose-intensity study of CVVH in 425 critically ill patients demonstrated a significant decrease in patient mortality when ultrafiltration rates of 35 mL/kg/h (approximately 3 L/h in a 70 kg male) were used as compared with 20 mL/kg/h (Ronco et al 2000). A randomized trial of intermittent hemodialysis comparing daily with alternate day dialysis showed a reduction in mortality from 46% to 28% ( $p < 0.05$ ) (Schiffl et al 2002). Unfortunately the delivered dialysis dose in the alternative day group as measured by weekly  $Kt/V$  was less than 3.6, the minimally acceptable dose in chronic dialysis patients, thus the issue of minimal adequate dose remains unresolved.

## Practical issues regarding renal replacement therapy in the ICU

### Vascular access

Vascular access for acute intermittent hemodialysis must be obtained using double lumen dialysis catheters. These may be inserted in the internal jugular, subclavian, or femoral veins. If possible, subclavian vein cannulation should be avoided because of a high incidence of subsequent venous stenosis, which may significantly complicate venous access if chronic hemodialysis is required (Stalter et al 1986; Cimochoowski et al 1990; Bambauer et al 1994). Blood recirculation from the venous to the arterial port can reduce the effectiveness of dialytic therapies, particularly during IHD. Use of a short 13.5-cm catheter in the femoral vein may result in up to 23% blood flow recirculation and can be avoided by using longer catheters (19–25 cms) when using the femoral vein for vascular access (Kelber et al 1993).

Access to blood supply for the extra corporeal circuit varies with CRRT techniques. Arteriovenous techniques, which have largely fallen out of favor, generally require cannulation of the femoral artery and the femoral vein. The variable blood flow rates lead to a higher risk of thrombosis. In general, large bore, small length catheters are preferable for AV procedures to permit a high blood flow rate. In pumped (venovenous) systems double lumen venous catheters are commonly used; the size should be selected based on the site of insertion to optimize flow.

## Membranes

Membrane characteristics that should be considered when selecting membranes for hemodialysis or CRRT include solute removal, water permeability, and biocompatibility. Dialyzer efficiency (KoA) is extremely important in IHD where therapy is administered over a relatively short period of time with high blood and dialysate flow rates. Generally speaking, the efficiency of small solute clearance in CRRT is largely determined by dialysate/ultrafiltration flow rate; therefore, solute removal characteristics are not an important factor in choosing a dialysis membrane. High flux membranes, which are designed to provide high water permeability, are generally recommended for hemofiltration procedures. Finally, although there is no conclusive evidence that membrane biocompatibility affects patient outcome, there is general consensus (Kellum, Mehta, et al 2002) that the use of synthetic membranes is preferable over cellulose-based membranes for the treatment of patients with ARF.

## Replacement/Dialysate solutions

Dialysate for intermittent hemodialysis is generally produced on-line by the dialysis machine from a combination of treated water and various electrolytes. There are stringent standards for water quality in the hemodialysis unit set out by the American Association of Medical Instrumentation (AAMI). Water purification is generally achieved by treatment with reverse osmosis, deionization, and the use of charcoal filters. Dialysate water is not required to be sterile as there is no contact between blood and dialysate.

All CRRT techniques other than slow continuous ultrafiltration (SCUF) require the use of sterile dialysate/replacement fluids to compensate for the ultrafiltrate removed. Although dialysate does not come into direct contact with blood given the low blood-side pressures, back-filtration (dialysate to blood) may readily occur, particularly with high permeability membranes (Golper 1989).

Optimal dialysate/replacement solution approximates normal plasma water composition, replacing electrolytes and minerals in physiologic concentrations without replacing the metabolic solutes, which accumulate in renal failure. The composition of these solutions can be varied extensively to achieve specific metabolic goals (eg, bicarbonate-based solutions can be used to correct acidemia and the electrolyte content can be altered to correct electrolyte imbalance) (Macias and Clark 1996; Palevsky 1996). A limitation of using sterile solution for CRRT is that they are acetate or

lactate based and the capacity to convert these buffers to bicarbonate may be limited in patients with multiple organ failure (Levrant 1997). More recently, bicarbonate-based solutions, which are better tolerated than lactate- or acetate-based solutions, have become commercially available (Zimmerman et al 1999).

When citrate anticoagulation is used in CRRT, modifications are necessary in both the replacement fluid and dialysate; often necessitating the use of customized, locally prepared solutions as commercially available solutions are not widely available. Citrate is metabolized to bicarbonate by the liver; therefore buffer is not generally required in the dialysate. Similarly, dialysate used in citrate regional anticoagulation is generally hyponatremic to prevent hypernatremia, and it is recommended that fluids are calcium free. Few commercially available calcium free, bicarbonate-based CRRT fluids have been available until recently. This has led many centers to produce such fluids in-house using pharmacy total parenteral nutritional (TPN) manufacturing facilities. Manufacturing error in the pharmacy led to pharmacy technicians using concentrated potassium chloride instead of concentrated sodium chloride in the production of CRRT fluid in Calgary, Canada, in the last year and resulted in the deaths of 2 critically ill patients. Both electrolyte solutions had been provided in almost identically labeled containers. A commercially available solution is supplied as a concentrate, which is added to 3-L bags of sterile water. Failure by critical care bedside nurses to add the concentrate to the sterile water has resulted in the deaths of 2 patients in Toronto, Canada, from massive hemolysis. These tragedies underscore the importance of using commercially prepared solutions; if addition of concentrate to sterile water is required, this should be done in a pharmacy setting.

## Anticoagulation

Anticoagulation is an essential component of all blood-based renal replacement therapies, including CRRT. The passage of blood through an extracorporeal circuit causes platelet activation and induces a variety of inflammatory and prothrombotic mediators, resulting in fibrin deposition on filter membranes. This not only affects filter longevity, but may also decrease dialyzer efficacy in terms of water and solute removal. If anticoagulation is insufficient, filtration performance deteriorates and the filter may clot, contributing to blood loss and additional costs related to filter replacement. Excessive anticoagulation may result in

bleeding complications, reported to occur in 5%–26% of treatments (Webb et al 1995).

Unfractionated heparin is the mainstay of anticoagulation for IHD and CRRT (Favre et al 1996). Heparin is generally administered as a bolus, followed by a continuous infusion into the arterial limb of the dialysis circuit, to maintain a partial thromboplastin time (PTT) of 1.5–2× normal. Low molecular weight heparin is excreted renally and should not be used without careful monitoring of factor Xa levels in patients with ARF (Schrader et al 1990).

Systemic anticoagulation is relatively contraindicated in patients at high risk of bleeding, although the heparin dose can be modified in these circumstances. Its use, however, is associated with a high incidence of bleeding and in some instances heparin-induced thrombocytopenia (Mehta et al 1992). Because of the shorter duration and high blood flow used, it is often possible to perform IHD without anticoagulation, particularly when the patient is coagulopathic. In heparin-free dialysis, blood flows are kept between 250–500 mL/min and saline flushes are administered every 15–30 min into the arterial limb of the dialysis circuit to minimize hemoconcentration and to wash fibrin strands from the kidney into the bubble trap. The volume of saline administered with such frequent flushing must be removed during the dialysis to prevent hypervolemia. This technique is associated with only a 2% clotting rate (Schwab et al 1987).

In newly postoperative patients and others with a contraindication to systemic anticoagulation, regional anticoagulation of the circuit is preferred. Regional heparinization, with pre-filter administration of heparin, and a post-filter protamine infusion has been used (Swartz and Port 1979; Abramson and Niles 1999), but regional citrate anticoagulation has become increasingly popular. Citrate anticoagulation may be used with both continuous and intermittent therapies. Regional citrate anticoagulation is achieved using a continuous citrate infusion through the arterial limb of the circuit, which chelates free calcium and inhibits the coagulation cascade. The citrate-calcium complex is removed by a combination of dialysis clearance against calcium-free dialysate and endogenous processes. In patients with normal liver function, levels of citrate and ionized calcium return to normal values within 30 min of discontinuing a citrate infusion (Mehta et al 1990). Plasma calcium levels are restored with the use of a continuous calcium infusion at the site of blood return to the patient.

The infusion rate of citrate is adjusted to keep the activated clotting time (ACT) above 160 s. Regional citrate anticoagulation requires the use of a specialized dialysis solution and frequent monitoring of ionized calcium (Kutsogiannis et al 2000). Potential complications arising from this technique include metabolic alkalosis, hyponatremia, hypocalcaemia, and citrate toxicity in patients with liver dysfunction. If properly monitored, the complication rate associated with this technique is quite low (Flanigan et al 1987). When used with CRRT techniques, filter longevity in excess of 96 h is fairly common with citrate anticoagulation, while 36–48 h patency is usually the norm with heparin (Bellomo 1993).

Low molecular weight heparin (Hory et al 1985; Wynckel et al 1991), prostacyclin analogues (Davenport et al 1994), and other anticoagulants such as danaparoid (Chong and Magnani 1992) and high molecular weight dextran (Palevsky et al 1995) have been used with both continuous and intermittent renal replacement therapies (Campbell 1999). See Table 2 for a comparison of anticoagulation strategies.

At the current time none of these methods is ideal, and selection is usually influenced by patient factors. Technical factors and experience with anticoagulants are important determinants of the success of any anticoagulation regimen.

## **Does CRRT confer an advantage over IHD in the management of acute renal failure?**

CRRT has several theoretical advantages over intermittent blood purification techniques, including better hemodynamic tolerability, more efficient solute clearance, better control of intravascular volume, and better clearance of middle and large molecular weight substances.

Hypotension is one of the most common complications associated with intermittent hemodialysis, occurring in approximately 20%–30% of all treatments. Some of the causes are dialysis specific, such as excessive or rapid volume removal, changes in plasma osmolality, and autonomic dysfunction. In critically ill patients who may be hemodynamically unstable, it would be desirable to minimize this complication, as it may lead to further organ ischemia and injury. Several prospective and retrospective studies have demonstrated better hemodynamic stability associated with CRRT (Paganini et al 1984; Davenport et al 1993); however, this observation has not been validated in a randomized controlled trial.

**Table 2** Anticoagulation modalities for continuous renal replacement

| Method                    | Filter prime               | Initial dose                            | Maintenance dose   | Monitoring  | Advantages   | Disadvantages  |
|---------------------------|----------------------------|---|--|---|--|--|
| Saline solution           | 2 L saline                 | 150–250 mL pre-filter                   | 100–250 mL/h pre-filter  | Visual check  | No anticoagulant used  | Poor filter patency  |
| Heparin                   | 2 L saline<br>2500–10000 U | 5–10 U/kg                               | 3–12 /kg/h   | ACT 200–250;<br>PTT 1.5–2.0 × normal                        | Standard method;<br>easy to use;<br>inexpensive                                | Bleeding risk;<br>thrombocytopenia   |
| LMW heparin               | 2 L saline                 | 40 mg                                   | 10–40 mg/6 h   | Factor Xa levels;<br>maintained between<br>0.1–0.41 U/mL    | Decreased risk of<br>bleeding  | Special monitoring; not<br>available everywhere;<br>expensive              |
| Regional heparin          | 2500 U/2 L<br>saline       | 5–10 U/kg                               | 3–12 U/kg/h;<br>+ protamine<br>post-filter                     | PTT; post-filter<br>ACT 200–250                             | Reduced bleeding risk  | Complex; risk of<br>thrombocytopenia;<br>protamine effects;<br>hypotension |
| Regional citrate          | 2 L saline                 | 4% trisodium<br>citrate<br>150–180 mL/h | 100–180 mL/h<br>3–7% of BFR,<br>Ca replaced by<br>central line | ACT: 200–250 maintain<br>ionized calcium<br>0.96–1.2 mmol/L | No bleeding; no<br>thrombocytopenia;<br>improved filter efficacy,<br>longevity | Complex; needs Ca<br>monitoring; alkalosis                                 |
| Prostacyclin<br>+ heparin | 2 L saline<br>+ heparin    | 4–8 ng/kg/min                           | 4–8 ng/kg/min  | Usually no monitoring<br>if heparin not<br>required         | Alternative to heparin<br>and citrate. Usually in<br>liver failure             | May need low-dose<br>heparin addition;<br>hypotension                      |
| Hirudin                   | 2 L saline                 | 625 µg/kg/h                             | 6–25 µg/kg/h<br>(Monitor<br>carefully in<br>renal failure)     | PTT, Ecarin<br>clotting time                                | Alternative to heparin.<br>Usually used if HITT                                | Bleeding risk; no reversal<br>agent  |
| Danaparoid                | 2 L saline                 | 2500 U bolus                            | 400 IU/h   | PTT antifactor Xa   | Alternative to heparin.<br>Usually used if HITT                                | Bleeding; no reversal agent  |
| Argatroban                | 2 L saline                 | –                                       | 2 µg/kg/min<br>(reduce in<br>hepatic<br>dysfunction)           | PTT   | Alternative to heparin.<br>Usually used if HITT                                | Bleeding risk; no reversal<br>agent  |
| Nafomostat<br>mesilate    | 2 L saline                 | –                                       | 0.1 mg/kg/h  | ACT   | Alternative to heparin   | Bleeding   |

Source: Mehta RL. 1992. New developments in continuous arterio-venous hemofiltration/dialysis. In Andreucci VE, Fine L (eds). International Yearbook of Nephrology, 1992. Heidelberg: Springer. Copyright © Springer Verlag. Reproduced with permission from Springer Verlag. NOTE: Dashes mean no loading dose. **Abbreviations:** ACT, activated clotting time; BFR, blood flow rate; HITT, heparin induced thrombocytopenia; LMW, low molecular weight; PTT, partial thromboplastin time.

Another advantage of CRRT is the improved efficiency of solute removal. Although the clearance rate of small solutes is slower per unit time with CRRT (17 mL/min vs more than 160 mL/min with conventional hemodialysis), CRRT is continuously administered; therefore, urea clearance is more efficient after 48 h than with alternate day intermittent hemodialysis. Clark et al (1997) developed a computer model based on 20 critically ill patients to compare solute clearance in intermittent and continuous renal replacement therapies, and found that for a 50 kg male, an average of 4.4 dialysis sessions/week would be required to achieve equivalent uremic control. In patients with a weight greater than 90 kg, equivalent uremic control could not be achieved with intermittent therapies even if daily dialysis was prescribed.

Fluid management is often a difficult issue in ICU, where nutritional requirements (TPN) and the use of IV medications necessitate the administration of large amounts of fluid to critically ill patients. The inability to severely fluid restrict fluid intake in ICU patients results in excessive volume overload, which may compromise tissue perfusion and has been associated with adverse outcomes (Mehta et al 2002). Attempts to restrict fluid in this setting may additionally compromise adequate nutrition (Campbell 1999). The capacity to adjust fluid balance on an hourly basis, even in hemodynamically unstable patients, is largely responsible for the growing popularity of CRRT.

CRRT may also have an immunomodulatory effect. The rationale for the use of CRRT for the treatment of sepsis arises from the observed association between sepsis severity

mortality rate and serum concentrations of various cytokines including TNF, IL1, IL6, and IL8. Most of these middle molecular weight molecules are water-soluble and are theoretically removable by hemofiltration-based plasma water purification. At the present time the immunomodulatory effects of CRRT remain theoretical and have not been shown to affect outcome in human studies (Honore 2000; Cole 2002).

Despite its apparent advantages over intermittent therapies, superiority of CRRT with respect to mortality or recovery of renal function has not been demonstrated. In the largest randomized controlled trial to date (n=166), intermittent hemodialysis was associated with significantly lower in-hospital (48% vs 65%) and ICU mortality (42% vs 60%). However, patients with hypotension were excluded from participating in the study, and there was a significant difference in severity scores between the treatment arms despite randomization (Mehta et al 1996). Two recently published meta-analyses compared intermittent with continuous renal replacement therapies in unselected critically ill patients (Kellum, Angus, et al 2002; Tonelli et al 2002). Both concluded that there was no difference in terms of renal recovery. However, while Kellum concluded there was improved survival with CRRT, Tonelli found no survival benefit with either modality. Moreover, the sample size required to show a 20% mortality difference between IHD and CRRT would be in excess of 1200 patients (Tonelli et al 2002).

There are also significant cost implications associated with modality choice for treatment of ARF in the ICU setting. A study comparing CRRT to alternate day IHD showed CRRT to be significantly more expensive, primarily because of the cost of CRRT fluid (Mann et al 2003). Cost differences also depend on whether these procedures are performed by critical care nurses or by renal unit nurses and whether inter-unit charges are applied.

Further studies are needed to define the subset of patients with ARF who benefit from this therapy.

## Are there non-renal indications for CRRT?

While the use of CRRT in critically ill patients with ARF is widely accepted, CRRT has also been used for some non-renal indications, most notably for the treatment of septic shock. Studies of high volume hemofiltration (HVHF) in canine (Silvester 1997) and porcine models (Grootendorst et al 1992) of sepsis showed significant improvement in

CO, MAP, SV, and hepatic arterial flow. A small study found similar benefit in severe human septic shock (Honore 2000); however, a subsequent randomized clinical trial failed to confirm these findings (Bouman 2002).

There are case reports and case series of CRRT use in a variety of other conditions including liver support, elevated ICP, intoxication, cardiac failure, ARDS, rhabdomyolysis, tumor lysis syndrome, post-cardiac surgery, but few if any prospective studies for many of these conditions (Schetz 1999). At present there are no established nonrenal indications for CRRT.

## Looking to the future

As experience with these techniques grows, innovations in technology will likely keep pace. Over the last three years, most of the major manufacturers of dialysis equipment have developed new pumps dedicated for the use of these therapies. Most of these devices (Hospal/Gambro/Cobe-PRISMA, Fresenius-Acumen, Baxter-Accura, Edwards-Aquarius) offer automated fluid balancing, and sophisticated controls that are similar to those in regular dialysis machines. Membrane technology is also evolving and anti-thrombogenic membranes are on the horizon (Yang 1991). Finally, the application of these therapies is likely to expand to other arenas including the treatment of sepsis, congestive heart failure, multiorgan failure, as a form of liver support, and in cardiopulmonary bypass for cytokine manipulation. It remains to be seen how these therapies will change our current management of these patient groups.

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