

Renal Replacement Therapy III: IHD, CRRT, SLED

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Acute renal failure (ARF) is a common complication in critically ill patients and is associated with a mortality rate above 50% [1–5]. As many as 70% of these patients require renal replacement therapy (RRT), making it an important component of the management of ARF in the ICU. The ideal RRT controls volume; corrects acid-base abnormalities; improves uremia through toxin clearance; promotes renal recovery; and improves survival without causing complications, such as bleeding from anticoagulation and hypotension. The available RRT options include intermittent hemodialysis (IHD), continuous RRT (CRRT), and sustained low-efficiency dialysis. Currently, there is insufficient evidence to establish which modality of RRT is best for ARF in the critically ill patient. Understanding the advantages and limitations of the various dialysis modalities is essential for appropriate RRT selection in the ICU setting. This article reviews the dialysis options for the treatment of critically ill patients with ARF.

Principles of renal replacement therapy

All forms of RRT rely on the principle of allowing water and solute transport through a semipermeable membrane and then discarding the waste products. Ultrafiltration is the process by which water is transported across a semipermeable membrane. Diffusion and convection are the two processes by which solutes are transported across the membrane. The available RRT modalities use

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ultrafiltration for fluid removal and either diffusion, convection, or a combination of diffusion and convection to achieve solute clearance.

Ultrafiltration achieves volume removal by using a pressure gradient to drive water through a semipermeable membrane. This pressure gradient is known as the "transmembrane pressure gradient" and is the difference between plasma oncotic pressure and hydrostatic pressure. Determinants of the ultrafiltration rate include the membrane surface area, water permeability of the membrane, and transmembrane pressure gradient [6].

Diffusion occurs by movement of solutes from an area of higher solute concentration to an area of lower concentration across a semipermeable membrane (Fig. 1). The concentration gradient is maximized and maintained throughout the length of the membrane by running the dialysate (an electrolyte solution usually containing sodium, bicarbonate, chloride, magnesium, and calcium) countercurrent to the blood flow. Solute with a higher concentration in the blood, such as potassium and urea, move across the membrane to the dialysate compartment. Conversely, solutes with a higher concentration in the dialysate, such as bicarbonate, diffuse into the blood. Solute concentrations that are nearly equivalent in blood and dialysate, such as sodium and chloride, move very little across the membrane. Because smaller solutes like urea and creatinine diffuse more rapidly than larger solutes, lower-molecular-weight molecules (<500 d) are cleared more efficiently than heavier molecules. The rate of solute diffusion depends on blood flow rate, dialysate flow rate, duration of dialysis, concentration gradient across the membrane, and membrane surface area and pore size [6].

Convection occurs when the transmembrane pressure gradient drives water across a semipermeable membrane as in ultrafiltration but then "drags" with the water both small-molecular-weight (blood urea nitrogen, creatinine, potassium) and large-molecular-weight (inulin, β_2 -microglobulin, tumor necrosis factor, vitamin B₁₂) solutes (Fig. 2). Membrane pore diameter limits the size of the large solutes that can pass. Increasing the transmembrane pressure difference allows more fluid and solutes to be "pulled" through the membrane. Because the efficiency of solute removal depends mainly on the ultrafiltration rate, typically at least 1 L of water needs to be pulled through the membrane each hour. The

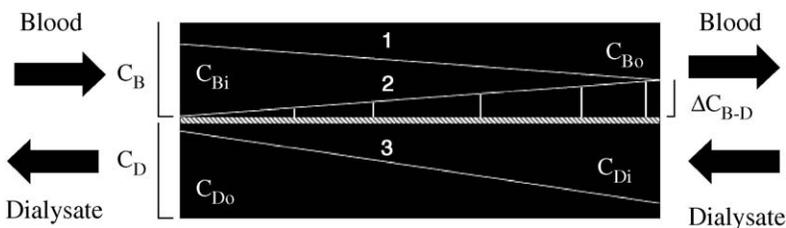


Fig. 1. Countercurrent flow of blood and dialysate solution. C_B , solute concentration in blood; C_{Bi} and C_{Bo} , inflow and outflow, respectively, of solute in blood against countercurrent dialysate flow; C_D , solute concentration in dialysate; C_{Di} and C_{Do} , inflow and outflow, respectively, of solute in dialysate against countercurrent blood flow; dashed line, membrane.

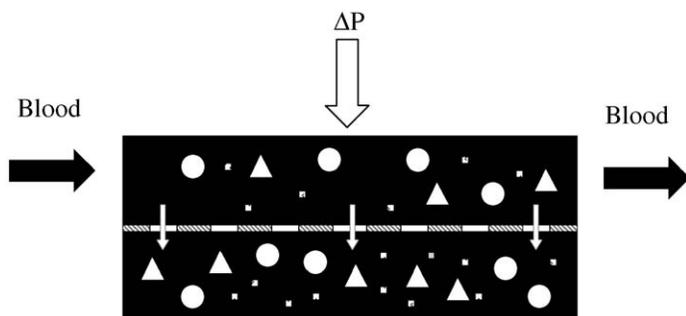


Fig. 2. Principle of convection. ΔP , pressure gradient; solid black arrow, direction of blood flow; squares, water molecules; circles and triangles, solutes; white arrows, movement of solute with water across a semipermeable membrane.

process of increasing the ultrafiltration rate to provide convective clearance of solutes is known as “hemofiltration.” Ultrafiltration rate is determined by the transmembrane pressure, water permeability of the membrane, and membrane surface area and pore size [6].

Classification of renal replacement therapies

RRTs for ARF can be classified as intermittent or continuous, based on the duration of treatment (Fig. 3). The duration of each intermittent therapy is less

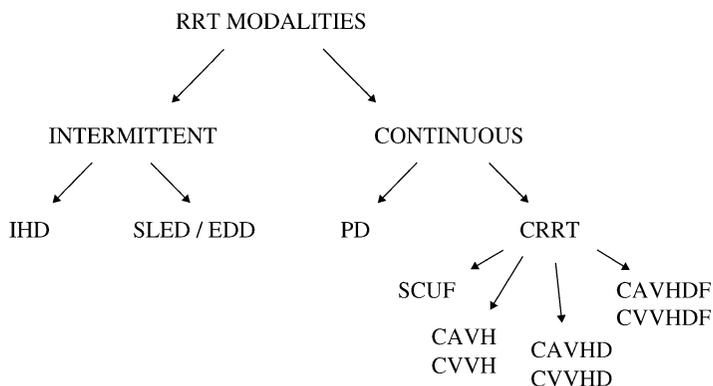


Fig. 3. Renal replacement modalities for acute renal failure. CRRT, continuous renal replacement therapy; CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis.

than 24 hours, whereas the duration of continuous therapy is at least 24 hours. The intermittent therapies include IHD and sustained low-efficiency dialysis. The continuous therapies include peritoneal dialysis and CRRT [7]. Peritoneal dialysis is rarely used in the acute setting because it provides inefficient solute clearance in critically ill catabolic patients, increases the risk of peritonitis, compromises respiratory function by impeding diaphragmatic excursion, and is contraindicated in patients with recent abdominal surgery or abdominal sepsis [8].

Intermittent hemodialysis

Traditionally, nephrologists have managed ARF with IHD, empirically delivered three to six times a week, 3 to 4 hours per session, with a blood flow rate of 200 to 300 mL/min and a dialysate flow rate of 500 to 800 mL/min. In IHD, solute clearance occurs mainly by diffusion, whereas volume is removed by ultrafiltration. The degree of solute clearance, also known as "dialysis dose," is dependent on the rate of blood flow. Increasing the blood flow increases solute clearance. Decisions regarding dialysis duration and frequency are based on patient metabolic control, volume status, and presence of any hemodynamic instability [9].

Advantages of IHD include rapid solute and volume removal. This results in rapid correction of electrolyte disturbances, such as hyperkalemia, and rapid removal of drugs or other substances in fatal intoxications in a matter of hours. IHD also has a decreased need for anticoagulation as compared with other types of RRT because of the faster blood flow rate and shorter duration of therapy.

The main disadvantage of IHD is the risk of systemic hypotension caused by rapid electrolyte and fluid removal. Hypotension occurs in approximately 20% to 30% of hemodialysis treatments. Sodium modeling, cooling the dialysate, increasing the dialysate calcium concentration, and intermittent ultrafiltration may be used to improve hemodynamic stability during IHD. Despite this, approximately 10% of ARF patients cannot be treated with IHD because of hemodynamic instability [3,4,10,11]. Systemic hypotension can limit the efficacy of IHD and result in poor solute clearance, insufficient acid-base correction, and persistent volume overload, because the rate of ultrafiltration necessary to maintain fluid balance is seldom achieved within the 4-hour dialysis session. Furthermore, hypotension can precipitate renal and intestinal ischemia, leading to delayed renal recovery and sepsis from bacterial translocation, respectively [12]. Rapid solute removal from the intravascular space can cause cerebral edema and increased intracranial pressure [13]. ARF patients with head trauma or hepatic encephalopathy are at a significant risk of brain edema and even herniation [14]. Finally, there is a lack of consensus as to how to assess solute clearance (dialysis dose) and what constitutes an adequate dose in ARF because the kinetics of urea in the chronic end-stage renal disease patient cannot be extrapolated to patients with ARF (see the article by Ricci and Ronco elsewhere in this issue).

Despite these limitations, Schiffl et al [15] performed a prospective randomized study comparing daily IHD (6 d/wk) with alternate-day IHD (3 d/wk) in 160 patients with ARF caused by severe acute tubular necrosis following a recent ischemic or nephrotoxic injury. Notably, patients who were hemodynamically unstable or required CRRT were excluded. The primary end point of this study was survival 14 days after the last session of hemodialysis. Using intention-to-treat analysis, the mortality rate was 28% for daily dialysis and 46% for alternate-day dialysis ($P = .01$), demonstrating an improved survival with more frequent dialysis. After adjustment for a variety of confounders, the odds ratio of death in conventional IHD group versus the daily group was 3.92 (95% confidence interval [CI], 1.68–9.18). Daily hemodialysis resulted in better uremic control, fewer hypotensive episodes during the hemodialysis session, and a significantly shorter time to recovery of renal function.

There are several limitations to this study. First, more severely ill patients (those requiring CRRT) were excluded from the study. Second, the delivered dose of dialysis was substantially (20%–30%) lower than the intended (prescribed) dose in both groups. The mean time-averaged blood urea nitrogen was lower in the daily hemodialysis group compared with the standard, alternate-day hemodialysis group (60 versus 104 mg/dL), indicating that the patients who received conventional IHD were underdialyzed.

Although the results of the study suggest an advantage of daily HD over conventional IHD, it is unclear whether the increased dialysis dose improved outcome by improving uremic control or by reducing the volume of fluid removed during each dialysis, and thereby resulting in less hemodynamic instability.

Continuous renal replacement therapy

Although the worldwide standard for RRT is IHD, CRRT has emerged over the past decade as a viable modality for management of hemodynamically unstable patients with ARF. Continuous therapies have evolved from systems that relied on arterial access and blood pressure to maintain blood flow through the extracorporeal circuit to pump-driven systems that use double-lumen venous catheters. The arteriovenous (AV) circuit is now rarely used in CRRT because of poor solute removal and complications from arterial cannulation. Unlike IHD, CRRT is a continuous treatment occurring 24 hours a day with a blood flow of 100 to 200 mL/min and a dialysate flow of 17 to 40 mL/min if a diffusive CRRT modality is used. The different CRRT modalities can use diffusion, convection, or a combination of both for solute clearance [16].

Types of continuous renal replacement therapy

All types of CRRT use membranes that are highly permeable to water and low-molecular-weight solutes. CRRT modalities are classified by access type



Fig. 4. Principle of slow continuous ultrafiltration. Q_B , blood flow rate; Q_{UF} , ultrafiltration rate.

and method of solute clearance. Venovenous circuits are now the standard and the various venovenous modalities of CRRT differ by their mechanism of solute removal. The four main types of CRRT in order of increasing complexity are slow continuous ultrafiltration, continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration [16].

In slow continuous ultrafiltration, low-volume ultrafiltration at a rate of 100 to 300 mL/h is performed to maintain fluid balance only and does not result in significant convective clearance of solutes (Fig. 4). No fluids are administered either as dialysate or replacement fluids, and the purpose of treatment is for volume overload with or without renal failure. Indications include volume overload in patients with congestive heart failure refractory to diuretics.

In CVVH, solute clearance occurs by convection; solutes are carried along with the bulk flow of fluid in a hydraulic-induced ultrafiltrate of blood (Fig. 5). No dialysate is used. Clearances are similar for all solutes that have a molecular weight in the range to which the membrane is readily permeable. The rate at which ultrafiltration occurs is the major determinant of convective clearance. The ultrafiltration rate is determined by the transmembrane pressure, water permeability, pore size, surface area, and membrane thickness. Typically, hourly ultrafiltration rates of 1 to 2 L/h are used to provide adequate solute removal.

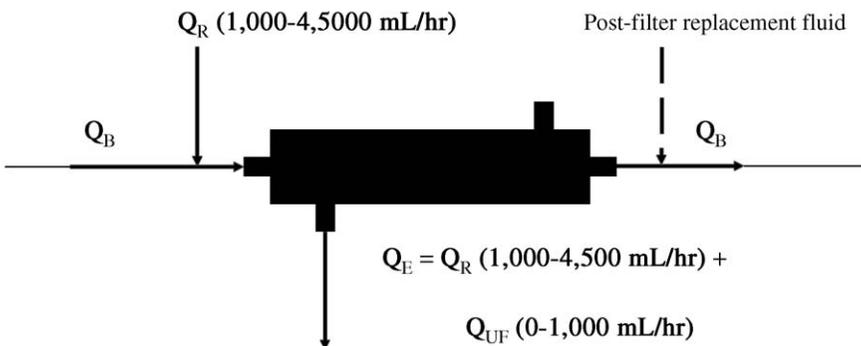


Fig. 5. Principle of continuous venovenous hemofiltration. Q_B , blood flow rate; Q_E , effluent flow rate; Q_R , replacement fluid flow rate; Q_{UF} , ultrafiltration flow rate.

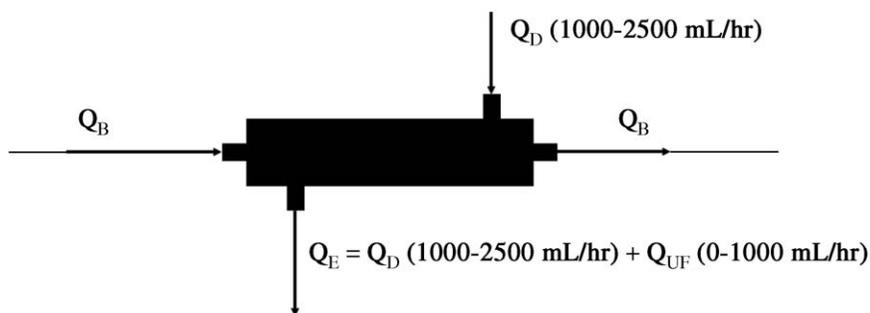


Fig. 6. Principle of continuous venovenous hemodialysis. Q_B , blood flow rate; Q_D , dialysate flow rate; Q_E , effluent rate; Q_{UF} , ultrafiltration rate.

These high ultrafiltration rates rapidly cause volume contraction, hypotension, and loss of electrolytes. Intravenous “replacement fluid” is provided to replace the excess volume that is being removed and replenish desired solutes. Replacement fluid can be administered either prefilter or postfilter.

In continuous venovenous hemodialysis, a dialysate solution runs counter-current to the flow of blood at a rate of 1 to 2.5 L/h (Fig. 6). Solute removal occurs by diffusion. Unlike IHD, the dialysate flow rate is slower than the blood flow rate, allowing small solutes to equilibrate completely between the blood and dialysate. As a result, the dialysate flow rate approximates urea and creatinine clearance. Ultrafiltration is used for volume control but can allow for some convective clearance at high rates. Continuous venovenous hemodiafiltration (Fig. 7) combines the convective solute removal of CVVH and the diffusive solute removal of continuous venovenous hemodialysis. As in CVVH, the high ultrafiltration rates used to provide convective clearance require the administration of intravenous replacement fluids.

Replacement fluids can be administered prefilter or postfilter. Postfilter replacement fluid results in hemoconcentration of the filter and increased risk of

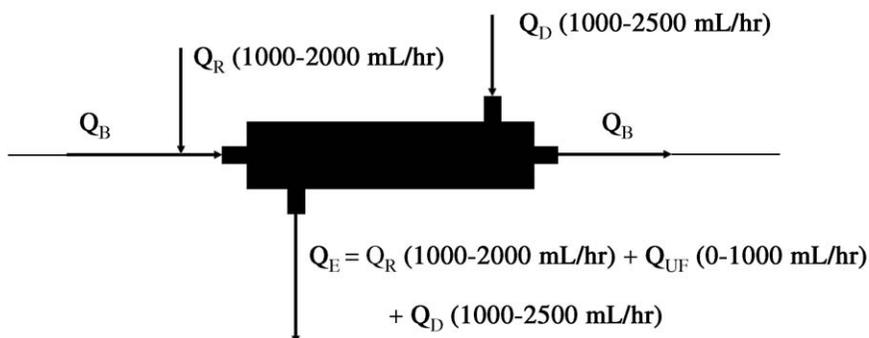


Fig. 7. Principle of continuous venovenous hemodiafiltration. Q_B , blood flow rate; Q_D , dialysate flow rate; Q_E , effluent flow rate; Q_R , replacement fluid flow rate; Q_{UF} , ultrafiltration flow rate.

clotting, especially when the filter fraction is greater than 30%. The filtration fraction is the ratio of ultrafiltration rate to plasma water flow rate and is dependent on blood flow rate and hematocrit [17]. Prefilter replacement fluid dilutes the blood before the filter, resulting in reduced filter clotting. Dilution of solutes before the filter reduces solute clearance by up to 15% by lowering the diffusion driving force and convective concentration.

Continuous renal replacement therapy: advantages and disadvantages

The advantages of CRRT include hemodynamic tolerance caused by slower ultrafiltration [18]. The gradual continuous volume removal makes control of volume status easier and allows administration of medications and nutrition with less concern for volume overload. Because it is a continuous modality, there is less fluctuation of solute concentrations over time and better control of azotemia, electrolytes, and acid-base status. The improved hemodynamic stability may be associated with fewer episodes of reduced renal blood flow, less renal ischemia, and more rapid renal recovery. Mehta et al [19] examined this issue in a prospective study in which 166 ICU patients with ARF were randomized either to IHD or CRRT. CRRT patients who survived were significantly more likely to show renal recovery than those treated with IHD. Because CRRT does not cause rapid solute shifts, it does not raise intracranial pressure like IHD.

The cumulative solute removal with CRRT is greater than that achievable with IHD. Ronco et al [20] provided convincing evidence that increasing solute clearance with CRRT can improve outcome in critically ill patients with ARF. In a prospective randomized controlled trial, 425 critically ill patients with ARF were assigned to CVVH, using ultrafiltration rates of 20 mL/h/kg (group 1), 35 mL/h/kg (group 2), or 45 mL/h/kg (group 3). The ultrafiltration rate of 20 mL/h/kg was based on the average rate used in clinical practice as reported in the literature at the time of the study. The blood flow rates ranged from 120 to 240 mL/min and the replacement fluid was administered postfilter. The primary study outcome was survival at 15 days after discontinuation of CVVH. Secondary outcomes were recovery of renal function and CRRT-related complications. Patient survival after discontinuing CVVH was 41%, 57%, and 58% in groups 1, 2, and 3, respectively. Survival in group 1 was significantly lower than group 2 ($P = .0007$) and group 3 ($P = .001$), demonstrating a survival advantage for patients treated with CVVH at a rate of at least 35 mL/kg/h. It is unclear, however, whether the reduction in mortality was solely caused by small molecule (urea) clearance or by both small molecule clearance and increased middle molecule clearance.

There are several theoretical nonrenal advantages of CRRT. CRRT can remove toxins with a large volume of distribution and slow back diffusion from tissue into the circulation. Examples of such toxins are methotrexate and procainamide. The ability of convective CRRT modalities to clear larger-molecular-weight molecules (up to 30,000 d) suggests that it may be beneficial in patients with sepsis or multiorgan failure. Experimental and clinical data show that many middle

molecules, such as tumor necrosis factor, that may be involved in the inflammatory response can be removed by CRRT [21]. The significance of this mediator removal is unclear, however, and the impact of CRRT on outcome of sepsis in the ICU has not been confirmed.

The main disadvantages of CRRT include access and filter clotting and the consequent need for anticoagulation. CRRT should ideally run with minimal interruption. Filter clotting seriously compromises solute clearance, maintenance of electrolyte and acid-base balance, and volume management [22]. Sepsis is a frequent finding in patients with multiorgan failure, and the associated inflammatory response results in platelet microthrombi and leukocyte-platelet aggregates that clot the dialyzer membrane. Unfractionated heparin has been the mainstay of anticoagulation for prevention of dialyzer filter clotting; however, it is associated with a 30% risk of life-threatening bleeding and the development of heparin-associated antibodies. Additionally, it requires adequate supplies of antithrombin III to achieve its anticoagulant effect. Altogether, these factors make it a less than optimal choice in critically ill patients. Although a variety of other anticoagulants (citrate, prostacyclin, low-molecular-weight heparin, nafamostat, saline flushes) have been used in CRRT, regional anticoagulation with citrate is gaining more acceptance [22,23]. Use of citrate anticoagulation, however, increases the complexity of CRRT by requiring customized dialysate solutions or replacement fluid and frequent monitoring of laboratory results to minimize metabolic complications. Another disadvantage of CRRT is increased cost and demands on ICU nurse time compared with IHD.

Intermittent hemodialysis versus continuous renal replacement therapy: outcome

There are few prospective studies comparing IHD with CRRT with respect to outcomes, such as mortality or recovery of renal function. Many older studies used CRRT modalities with AV access, which are no longer commonly used, or had problems with study design. More recently, Kierdorf and Sieberth [24] compared IHD with CVVH and found no difference with respect to survival (34.1% versus 39.6%). Mehta et al [19] randomized 166 patients to CRRT (CVVH or continuous venovenous hemodiafiltration) or IHD. Univariate intention-to-treat analysis revealed a higher mortality among patients receiving CRRT. Patients randomized to CRRT had higher APACHE III scores and had a higher prevalence of liver failure, however, confounding the results. Multivariate analysis revealed no impact of RRT modality on all-cause mortality or recovery of renal function. Instead, severity of illness scores, such as APACHE III scores and number of failed organs, were more important prognostic factors. Kellum et al [25] published a meta-analysis of 13 clinical trials, totaling 1400 patients. There was no mortality difference between CRRT and IHD (relative risk [RR] = 0.93; 95% CI = 0.79–1.09). After adjusting for severity of illness and study quality,

mortality was found to be lower in the CRRT group (RR = 0.72; 95% CI = 0.60–0.87). The authors concluded that insufficient data existed to draw strong conclusions, mainly because of the lack of randomized controlled trials and the influence of biases and confounding variables.

Sustained low-efficiency dialysis or extended daily dialysis

Sustained low-efficiency dialysis and extended daily dialysis are slower dialytic modalities run for prolonged periods using conventional hemodialysis machines with modification of blood and dialysate flows. Typically, sustained low-efficiency dialysis and extended daily dialysis use low blood-pump speeds of 200 mL/min and low dialysate flow rates of 300 mL/min for 6 to 12 hours daily. Sustained low-efficiency dialysis and extended daily dialysis combine the advantages of CRRT and IHD. They allow for improved hemodynamic stability through gradual solute and volume removal as in CRRT. At the same time, they are able to provide high solute clearances as in IHD and remove the need for expensive CRRT machines, costly customized solutions, and trained staff. Because sustained low-efficiency dialysis and extended daily dialysis can be done intermittently based on the needs of the patient, they also avoid the interruption of therapy for various diagnostic and therapeutic procedures that may be required in such patients. Kumar et al [26] described their prospective experience of 25 patients treated with extended daily dialysis and 17 patients treated with continuous venovenous hemodialysis at University of California Davis Medical Center. No significant differences in mean arterial pressure or inotrope requirements were observed between the two groups. Mortality was higher in the extended daily dialysis group (84% versus 65%). The APACHE II scores were higher, however, in the extended daily dialysis group at onset of treatment. The authors argued that extended daily dialysis was more cost effective by removing the need for constant monitoring of dialysis equipment and reducing nursing workload.

Summary

Advances in RRT in the last few years have resulted in multiple RRT modalities available for treating ARF in the ICU. CRRT is gaining greater acceptance with the use of venovenous access and its advantages in hemodynamically unstable patients. There are little data as to the best modality of RRT. There are few randomized controlled trials and most existing studies are retrospective and poorly controlled. Many confounders exist, such as severity of illness and etiology of renal failure, which are probably the most important factors affecting outcome in ICU patients with ARF. Some recent studies also suggest that higher doses of dialysis confer a survival advantage. Choice of modality should

probably be tailored to the needs of the individual patient. IHD is best for patients requiring rapid metabolic control (eg, in hyperkalemia), whereas volume overload is best managed with CRRT. Patients who are hemodynamically unstable or who have increased intracranial pressure are best treated with CRRT. Patients in whom anticoagulation is contraindicated might be better managed with IHD unless CRRT with citrate is used. CRRT is limited by its greater cost and demands on nursing time and the constraint it places on a patient's mobility. Theoretically, the choice of RRT might also depend on the underlying disease and etiology of ARF, but this question requires further study. The choice of modality should be based on the clinical status of the patient, the resources available in the institution, and the cost of therapy.

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