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NEPHROLOGY FORUM

Continuous renal replacement therapy in the critically ill patient

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CASE PRESENTATION

A 49-year-old African American woman known to have AIDS, a medical history of pulmonary *Mycobacterium avium* complex (MAC), and early cognitive dysfunction believed related to HIV dementia was brought to the University of California, San Diego Medical Center from her skilled nursing facility with a history of cough and shortness of breath of 2 days' duration. Because she had been non-compliant in taking her medications, she was admitted to the hospital for presumptive *Pneumocystis carinii* infection or community-acquired pneumonia superimposed on an exacerbation of asthma.

The patient had last been hospitalized one year previously for altered mental status. Following an extensive workup, her cognitive changes were thought to be secondary to heroin abuse and untreated HIV. She was provided with a legal conservator and was given antiretroviral agents. Approximately 3 weeks after starting antiretroviral medication, she developed an immune reconstitution syndrome due to occult *Mycobacterium avium* infection (MAI) with mediastinal lymphadenopathy and fever. The patient underwent a thoracoscopic lymph node biopsy and was treated with azithromycin and ethambutol with a good response. She was transferred to a skilled nursing facility and did well for quite some time, recovering cognitive function to the level of a 4- to 5-year-old. Two months prior to that hospitalization, she was released from her conservatorship and was discharged from the nursing home to live with her mother. She attempted to take all her medications but admitted to being non-adherent, because she often forgot. She had not been taking her antiretrovirals for about one month and had also missed her trimethoprim/sulfamethoxazole doses. She had sustained a fall 8 weeks prior to hospitalization and fractured her left hip. Colposcopies for abnormal Pap smears were complicated by bleeding and required transfusions. A workup for this problem revealed that she had an isolated Factor VII deficiency. She also had poor nutrition due to poor dentition and had been unable to have her teeth extracted due to her coagulopathy. Her last CD4 count, when she was taking antiretrovirals 3 months prior to this admission, was 175×10^3 μL and her viral load had been undetectable. Her AIDS-defining illness included MAI and cervical cancer.

Her medical history also was significant for a distant history of Potts disease of the spine that had been treated, and active tuberculosis had been ruled out. The history also included diabetes mellitus, a distant history of deep-vein thrombosis, gastrointestinal bleeding, asthma, hepatitis C, oral thrush, and intravenous drug use one year previously. She was hepatitis A immune, hepatitis B core antibody positive, surface antibody negative, toxoplasmosis positive, cryptococcal antigen negative, and cytomegalovirus IgG positive; her last pneumococcal vaccine was in 1998. She had no known drug allergies and on admission was supposed to have been taking azithromycin, 600 mg/day; ethambutol, 900 mg/day; fluconazole, 100 mg/day; furosemide, 20 mg/day; sulfamethoxazole, double strength once daily; lamivudine, 300 mg/day; lopinavir; ritonavir, 3 capsules twice daily; tenofovir, 300 mg/day; calcium, 600 mg/day; fluticasone, 220 μg twice daily; aspirin, once daily; trazodone, 150 mg at night; and paroxetine, 20 mg/day. She smoked one pack of cigarettes daily, denied alcohol or drug use for over a year, and was not sexually active.

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On admission she was alert. The respiratory rate was 42 breaths/min; heart rate, 115 beats/min; blood pressure, 120/60 mm Hg; and she was afebrile. Her oxygen saturation was 98% on a 96% high-flow face mask. She weighed 160 lbs and was 5 feet, 4 inches tall. The physical examination was remarkable for anicteric sclera, equal reacting pupils, no lymphadenopathy, normal heart sounds with no murmur or rub, clear lung fields with a few basilar rales, a soft, non-tender abdomen with normal bowel sounds, and edema of both legs. Laboratory studies on admission revealed normal electrolytes, with a BUN and serum creatinine of 4 mg/dL and 0.9 mg/dL, respectively; serum bicarbonate of 22 mEq/L; albumin, 1.6 g/dL; AST, 71; ALT, 17; LDH, 471; alkaline phosphatase, 153 U/L; and bilirubin, 1.6 mg/dL. The white blood cell count was 23.8×10^3 mL; hemoglobin, 9.7 mg/dL; hematocrit, 28.9%; platelet count, 148×10^3 μL; and INR 1.6. Urinalysis showed trace protein and moderate bilirubin and no cells or casts. The pH was 7.36; PCO_2, 45 mm Hg; and PO_2, 117 mm Hg. Blood and sputum cultures were negative and a chest radiograph showed bilateral air-space opacities. A CT scan of her neck and thorax showed ground-glass opacities and nodules throughout the parenchyma that were smaller than those seen on a CT 3 months prior.

Over the course of 24 hours, the patient's respiratory status deteriorated and she was intubated. Antiretroviral therapy was not started, given the risk of an immune reconstitution syndrome. She was given broad-spectrum antibiotics. She continued to have increasing oxygen requirements with increasing opacities in her lung parenchyma; the clinical diagnosis was acute respiratory distress syndrome (ARDS). She continued to be fairly stable hemodynamically and was excreting 1 to 2 liters of urine per day until day 14 of the hospitalization, when she had a sudden decrease in her blood pressure to 80/40 mm Hg, was placed on vasopressor support, and became oliguric. A nephrology consultation was requested with the possible thought of initiating continuous renal replacement therapy.

On examination, she was paralyzed and intubated on pressure support ventilation with 100% FiO_2, tidal volume of 400 mL/min, PEEP 12 cm water at a ventilation rate of 16/min, and maintaining an oxygen saturation of 92%. Her blood pressure was 109/60 mm Hg; phenylephrine was increased to 160 μg/kg/min and vasopressin to 0.04 μg/kg/min. She was edematous and had distant heart sounds with no murmur. Examination of the lungs revealed decreased air entry to both lung fields up to the mid-lung, with diffuse bilateral rhonchi. Her abdomen was soft and non-tender, and bowel sounds were present. The extremities showed 2+ edema. Laboratory tests revealed: sodium, 140 mEq/L; potassium, 4 mEq/L; chloride, 102 mEq/L; bicarbonate, 26 mEq/L; uncorrected anion gap 12 (corrected 18); BUN, 16 mg/dL; creatinine, 1.3 mg/dL (baseline at admission, 0.9 mg/dL); glucose, 358; albumin, 1.6 g/dL; calcium, 9 mg/dL; inorganic phosphate, 4.4 mg/mL; magnesium, 2.6 mEq/L; troponin, 1.8; and aspartate aminotransferase (AST), 425. The white blood cell count was 19.2, and differential counts showed 70 segmented polymorphonuclear cells and 4 bands; hemoglobin was 8.4 mg/dL; hematocrit, 25.2%; and platelets, 146,000 mm^2. Blood gases revealed a pH of 6.97; PCO_2, 110 mm Hg; PO_2, 73 mm Hg; and oxygen saturation of 93%. Urine output was <5 mL/hour, although it had been 1200 mL over the previous 24 hours. Overall net fluid status was 12 liters positive since admission, and she had received 2 liters of fluid over the previous 6 hours.

DISCUSSION

DR. RAVINDRA L. MEHTA (*Professor of Clinical Medicine, Division of Nephrology, Department of Medicine, UCSD Medical Center; and University of California, San Diego; San Diego, California*): This patient illustrates a relatively common scenario for clinicians managing critically ill patients. The development of hypotension and oliguria in the setting of multiorgan failure often prompts a request for continuous renal replacement therapy (CRRT) to be initiated. Before using CRRT, one should assess several factors: the therapeutic potential, goals for management, practicality of delivering CRRT, and the likelihood of improving survival.

Therapeutic potential for CRRT techniques

Continuous renal replacement therapy can be utilized to remove or add solutes and fluid, regulate volume and plasma composition, and prevent toxicity. The ability to achieve each of these goals depends on the operational characteristics of the specific type of CRRT utilized and how it is applied.

Continuous therapies encompass a variety of modalities that vary in their operational characteristics. Solute removal is achieved either by convection, diffusion, adsorption, or a combination of these methods. Convective techniques such as continuous venovenous hemofiltration (CVVH) generally utilize ultrafiltration rates of 1 to 3 liters per hour. However, high-volume hemofiltration with 6 liters of ultrafiltrate produced every hour has been used to remove middle- and large-molecular-weight cytokines in sepsis [1, 2]. Fluid balance is achieved by replacing the ultrafiltrate removed with a replacement solution. The composition of the replacement fluid can be varied, and the solution can be infused before or after the filter. In contrast to intermittent hemodialysis (HD) and slow low-efficiency dialysis (SLED), diffusion-based continuous techniques have dialysate flow rates that are significantly slower than the blood flow rates (17–34 mL/min versus

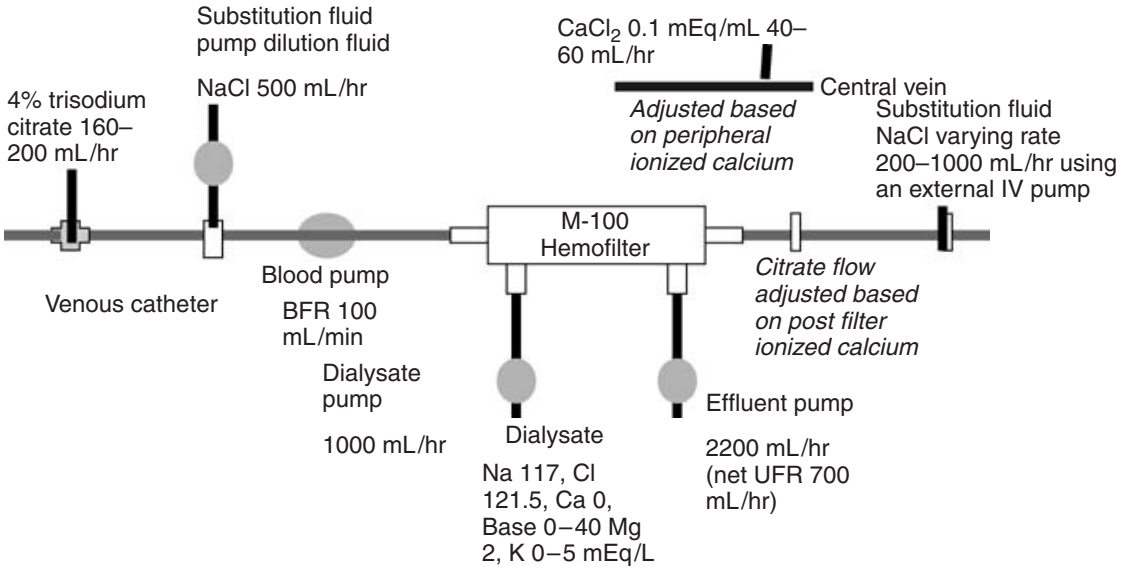

Fig. 1. CRRT circuit using regional citrate anticoagulation with the Gambro PRISMA machine and M-100 filter.

100–200 mL/min); this difference results in complete saturation of the dialysate [3]. Small molecules are preferentially removed by these methods. Hemodiafiltration (HDF) uses both diffusion and convection in the same technique [4]. Hybrid techniques are now emerging that utilize the basic principles of CRRT and combine convective and diffusive clearances with selective adsorption of solutes to the CRRT membrane. These therapies vary in what is processed (blood, plasma, or ultrafiltrate), the components (membrane sorbents or cell-based systems), and the sequence of convective, diffusive, and adsorptive clearances (in parallel, in series, or concurrently). These techniques (reviewed in [5]) are still largely experimental but will likely be increasingly utilized in the future.

Solute removal in CRRT is governed by the characteristics of the membrane, the force applied (convection, diffusion, adsorption, or a combination), and the site of infusing the replacement fluid (pre versus post filter). The sieving coefficient [SC = solute concentration in ultrafiltrate (UF)/(solute concentration in plasma at filter inlet plus plasma concentration at filter outlet/2)] describes the properties of the membrane that dictates solute removal in convective circuits. Protein-bound solutes or those that exceed the molecular weight cutoff (generally 20,000 daltons for polysulfone and polyacrylonitrile membranes) have sieving coefficients less than 1. In diffusion-based circuits, because of complete saturation of the dialysate, the computation of UF/plasma solute concentrations similarly represents the permeability of the membrane. In all forms of CRRT, the "effluent" from the filter represents the end product of the filtration process and comprises the ultrafiltrate in CVVH, the spent dialysate in CVVHD, and the combination of the ultrafiltrate and spent dialysate in CVVHDF. Consequently, filter clearance (UF × V/P) for most CRRT circuits is equal to Qef (the effluent flow rate = V) × SC (UF/P) for most small and middle molecules and is directly proportional to the amount of effluent volume. Blood-side clearances often do not match the filter clearances, as membrane adsorption modifies the amount of solute in the ultrafiltrate. Consequently, for some solutes (such as TNF-α) that are adsorbed by membranes, SC can be low but overall blood clearance can be greater than filter clearance.

Continuous renal replacement therapy techniques vary in their ability to remove small and middle molecules. For small-sized solutes (for example, urea nitrogen, creatinine, phosphates), filter clearances were directly proportional to the effluent volume and did not vary significantly with convective or diffusive removal across a spectrum of effluent volumes (0.5–4.5 L/hr) [6]. In contrast, β-2 microglobulin removal was influenced by the membrane type and the amount of convective clearance [6]. The effect of these clearances on drug dosing also should be considered. Drug removal largely depends on the sieving coefficient of the drug, the degree of protein binding, and the ultrafiltration rate. The pharmacokinetics of different drugs in CRRT and guidelines for dosing have been described [7–9].

Clearance of molecules in CRRT circuits also depends on the site of replacement solution administration either pre or post filter (Fig. 1). Removal of ultrafiltrate across the filter concentrates the cellular elements and proteins in the blood emerging from the filter and is directly proportional to the ratio of ultrafiltrate to plasma flow rate (filtration fraction = FF). Previous studies have demonstrated that FF >20% contributes to reduced filter performance and filter clotting. Consequently, if UF rates are increased, the blood flow rate should be increased

Table 1. Comparison of techniques

	IHD	SLED/EDD	SCUF	CVVH[a]	CVVHD[a]	CVVHDF[a]	PD
Access	VV	VV	AV or VV	VV	VV	VV	Peritoneal catheter
Membrane permeability	Variable	Variable	High	High	High	High	Peritoneal
Anticoagulation	Short	Long	Prolonged	Prolonged	Prolonged	Prolonged	None
Blood flow rate *mL/min*	250–400	100–200	<100	200–300	100–200	100–200	–
Dialysate flow *mL/min*	500–800	100	0	0	16.7–33.4	16.7–33.4	0.4
Filtrate *L/day*	0-4L	0-4L	0-4L	24–96	0	24–48	2.4
Replacement fluid *L/day*	0	0	0	21.6–90	4.8	23–44	0
Effluent saturation%	15–40	60–70	100	100	85–100	85–100	
Dialysate base	Acetate + bicarbonate	Acetate + bicarbonate	–	–	Lactate, bicarbonate, none (citrate)	Lactate, bicarbonate, none (citrate)	Lactate, bicarbonate
Replacement fluid base	–	–	–	Lactate, bicarbonate	–	Lactate, bicarbonate	–
Solute clearance mechanism	Diffusion	Diffusion	Convection	Convection	Diffusion	Both	Both
Urea clearance *mL/min*	180–240	75–90	1.7	16.7–67	21.7	30–60	8.5
Duration *hours*	3–4	8–12	Variable	>24	>24	>24	>24

Abbreviations are: SCUF, slow continuous ultra-filtration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration. Modified from Mehta RL [87].

[a] In the absence of pumps, arteriovenous circuits can be utilized to provide continuous therapy (CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration). A key limitation of AV methods is that the blood flow rate cannot be controlled and, consequently, the ultrafiltration rates and solute clearances are variable.

to maintain FF less than 20%. Clark et al have modeled the maximum ultrafiltration rate that can be sustained for any given blood flow rate to maintain FF <20% [10]. In convective removal, the only way to increase solute clearances is to increase the amount of ultrafiltrate generated and consequently increase the volume of replacement fluid given. When replacement fluid is infused post filter, solute clearance is equal to SC × Qef. Pre-dilution fluid replacement reduces the FF and reduces the solute concentration in the blood entering the filter. The effective small-solute clearance for pre-dilutional hemofiltration is equal to Qef × (Qb/[Qb + Qr]), where Qb and Qr represent blood and replacement fluid rates. Clearance in pre-dilution hemofiltration is less than in post-dilutional hemofiltration for the same Qef. However, because of the dilution of blood entering the filter, much higher filtration fractions (larger Qef and Qr) are feasible in pre-dilutional hemofiltration [11]. Troyanov et al have calculated the effect of pre-filter dilution on filter clearances for various solutes for a CVVH circuit of 4.5 L/hr effluent volume where all the fluid is given predilution [6]. Observed decreases in clearances ranged from 31% to 40% for urea, creatinine, and phosphates, and 40% to 45% for β_2-microglobulin. Hemofiltration circuits thus are more vulnerable to alterations in FF and pre-dilution fluid for dose delivery.

Dialysate "flow across" the membrane markedly improves clearances by diffusion and retains the simplicity of the procedure. Combining convection and diffusion allows flexibility in enhancing middle- and small-molecule clearances by increasing the volume of ultrafiltrate and dialysate, respectively [3, 4, 12, 13]. Additionally, since overall solute clearance is derived from both convective and diffusive components, it is easier to maintain FF within the optimal range at a relatively low blood flow rate. Adsorptive clearances depend upon the selective or non-selective binding of molecules to the filter membrane. In general, the adsorptive capacity varies and, depending on the membrane's surface area and binding characteristics, saturation of adsorptive sites will occur before the filtration capacity is reduced. Adsorptive clearances for middle molecules are time-dependent, with maximal values occurring in the initial few hours of therapy [6]. In septic patients treated with CRRT, filter adsorption was saturated within 6 to 8 hours [14]. Most CRRT circuits currently do not manipulate the adsorptive capacity of the membranes; however, this is likely to be utilized more commonly as hybrid technologies evolve.

While utilizing the same forces for solute and fluid removal, CRRT techniques are operationally different from intermittent techniques. The major difference is that time is no longer a limiting factor for blood purification (Table 1). As a consequence, it is possible to use slower blood and dialysate flow rates and achieve weekly clearances that are equivalent—and often superior—to intermittent techniques. The effect of time on different solute clearances is best demonstrated by comparing equivalent kidney clearances [15] (Table 2).

In intermittent techniques, hemodynamic instability, shortened dialysis times, and logistic factors often adversely affect the dose delivered [16]. In CRRT, maintaining filter performance is also key to achieving a continuous solute removal rate; however, because the time for clearance is increased, there is more of a "cushion" to compensate for increased demand and decreased efficiency.

Continuous renal replacement therapy techniques offer a significant advantage over intermittent dialysis for fluid control and management of acid-base and

Table 2. Comparison of small, middle and large solute clearances across various modalities

Solute	Parameter	Modality		
		CVVH	Daily HD	SLED
Urea Nitrogen	TAC	40.3	64.6	43.4
	EKR	33.8	21.1	31.3
Inulin	TAC	25.4	55.5	99.4
	EKR	11.8	5.4	3.0
Beta 2 Microglobulin	TAC	9.4	24.2	40.3
	EKR	18.2	7.0	4.2

Abbreviations are: TAC, time averaged concentration (mg/dL); EKR, equivalent renal clearance (mL/min) = G/TAC; CVVH, 31/hr, pre-dilution; Daily HD, BFR 350 mL/min, dialysate flow rate 600 mL/min, 4 hrs session 6 times per week; SLED, BFR 200 mL/min, dialysate flow rate 100 mL/min, 12 hrs session 7 days per week.

G = generation based on a 70 kg patient with initial volume excess of 10 liter, initial blood urea nitrogen (BUN) 90 mg/dl, initial inulin 100 mg/L, initial β2M 20 mg/L, nPCRv 1.8 g/kg/d, inulin G 0.3 mg/min, β2M G 0.17 mg/min.

Modified from Liao Z [15].

electrolyte imbalances [17–19]. Acid-base balance depends on the underlying acid-base disturbance, the operational characteristics of the procedure, the amount and type of base used, and the site of delivery of the base. A consequence of all CRRT methods is the ongoing loss of bicarbonate and electrolytes across the filter generally equivalent to the plasma concentration of these solutes times the total effluent (ultrafiltration and dialysate) flow rates [20]. Bicarbonate losses can be replaced by addition of sodium bicarbonate or other base (for example, lactate, acetate, citrate) to replacement solution administered intravenously, addition of base to the dialysate, or by a combination of these techniques [21]. One of the major advantages of CRRT is that the composition of replacement fluid and dialysate can be modified to achieve any specific change in plasma composition [22].

Several centers use standard hemofiltration solutions that have predetermined concentrations of base, usually lactate, and ions; however, in many instances customized solutions need to be made [23–28]. When base solutions other than bicarbonate are used, replacement of buffer stores depends on the metabolic rate for conversion to bicarbonate. In the absence of lactic acidosis, endogenous lactate clearance does not appear to be impaired. However, the filter clearance of lactate accounts for only 2.4% of overall lactate clearance [28].

The beneficial role of bicarbonate as buffer instead of lactate has been investigated [29]. Hilton et al [25] have shown that bicarbonate-based solutions are associated with improved hemodynamic stability, although no difference was found by Thomas et al [26], who compared lactate- and bicarbonate-based solutions. Additional clinical studies have confirmed that lactate-based substitution fluids foster hemodynamic stability [30]. Use of lactate as base has been associated with an increase in urea generation and possibly is related to increased catabolism [31]. Additionally, the ability to convert lactate to bicarbonate might be impaired in the setting of hypotension and multi-organ failure and could contribute to the deleterious effects of lactate accumulation [25].

One practical issue with the use of bicarbonate-based solutions is that it is difficult to store premixed bicarbonate solutions. LeBlanc et al [32] advocate preparing a non-sterile bicarbonate solution using a standard hemodialysis machine. This method has been used successfully at the Cleveland Clinic and other centers [33]. However, the risk for infection is unknown, particularly if the solutions are stored for several hours or days prior to use [34]. This is particularly important if there is any backfiltration as can occur in a non-integrated CRRT system using an infusion pump to control the ultrafiltrate. Another factor to consider is that premixed solutions containing calcium and bicarbonate show evidence of microprecipitation of calcium carbonate crystals, and this should be avoided [35]. Citrate-based anticoagulation offers an alternate method for acid-base management, as the citrate is converted in the liver and muscle to bicarbonate. The combination of citrate anticoagulation and bicarbonate-containing solutions has been used effectively to manage complex acid-base disorders [23, 36–39]. We utilize standard citrate orders to allow our pharmacy to make the appropriate dialysis solution. Our standard formulation uses 1 liter of 0.45% saline, to which is added 40 mL of 23% saline (yielding a sodium concentration of 117 mEq/L and a chloride concentration of 121.5 mEq/L), 1.5 mEq/L of magnesium, and 0–5 mEqL of potassium. We use a dialysate dextrose concentration of 0.1% [23]. In some circumstances, we add bicarbonate to the dialysate, substituting the 23% NaCl with $NaHCO_3$ so that the final concentration of sodium is 117 mEq/L.

Continuous renal replacement techniques have three inherent characteristics that make them highly effective and versatile methods for fluid control [18]: (*1*) the use of highly permeable membranes, (*2*) the infusion of various replacement solutions, and (*3*) the continuous nature of the techniques. These factors permit fluid removal that is limited only by the primary driving force (mean arterial pressure for non-pumped systems, pump speed for pumped systems), the efficacy of the filter over time, and the availability of sterile replacement solutions. Adjustments in the ultrafiltration and replacement fluid rates allow CRRT techniques to serve as fluid regulatory systems that can maintain fluid balance without compromising the system's ability to maintain metabolic balance. A major distinction for these methods is the ability to dissociate solute removal (for example, sodium) from fluid balance. As an example, by varying the composition of the replacement fluid or dialysate, solute balance can be altered while overall fluid balance can be kept even, negative, or positive [18].

Table 3. Techniques for fluid balance in CRRT

Variable	Common	Alternate
Intake	Variable	Variable
Non-CRRT output	Variable	Variable
Ultrafiltration rate	Variable to achieve fluid balance	Fixed to achieve target effluent volume
Substitution fluid rate	Fixed = or < UFR	Varies to achieve negative, zero, or positive fluid balance
Fluid balance	Achieved by varying UF rate	Fluid balance is achieved by adjusting amount of substitution fluid
Key difference	Output is varied to accommodate changes in intake and fluid balance goals	Output is fixed to achieve desired solute clearance and allow flexibility in accommodating varying intake
Advantages		
Patient factors	Similar to strategy for fluid removal in intermittent dialysis	Keeps solute clearance constant. Allows for variation in intake. Individualizes prescription
CRRT factors	Fluid balance calculations can be deferred to longer intervals (e.g., every 8–12 hours)	Therapy parameters dissociate clearance requirements from fluid balance. Reduces interactions with CRRT pump to adjust UF rates. Simplifies regimen for caregiver. First step to utilizing CRRT for fluid regulation
Disadvantages		
Patient factors	Assumes patient in static state. Mimics ESRD prescription. Intake may fluctuate. Fluid boluses not accounted for. Over- or undershoot common. Solute clearances fluctuate, particularly if dependent on convection	Requires hourly calculations for amount of replacement fluid to be given. Potential for fluid imbalances if a balance sheet is not used
CRRT factors	Requires frequent interactions with CRRT pump to adjust UF rates. Underutilizes CRRT for fluid removal only	May require use of an external pump to achieve fluid regulation

Fluid removal in CRRT is achieved by formation of an ultrafiltrate. The ultrafiltration rate used depends on two factors: the type of technique and the fluid balance requirements of the patient. Most modern CRRT pumped systems have a wide range of ultrafiltration rates that depend on the modality used. In convective techniques (CVVH), the ultrafiltration rate can vary from 0.5 to 12.0 L/hr, although most centers use a range of 1.0 to 3.0 L/hr. When dialysate is used (CVVHDF), almost all the current machines limit ultrafiltration rate to a maximum of 2 L/hr. These operative ranges are more than sufficient to achieve adequate fluid removal in almost all patients. Overall fluid removal is, however, limited by the patient's hemodynamic status. The ability to remove large volumes of fluid can be manipulated in several ways for fluid balance [18]. It is important to distinguish between fluid balance across the CRRT machine and the patient's overall fluid balance. The CRRT fluid balance, determined by the software in the CRRT machine, represents the difference in volume of ultrafiltrate and replacement and other fluids administered through the CRRT pumps and hung on the CRRT balancing system. All CRRT systems currently available only allow the CRRT fluid balance to be negative or zero but not positive. This feature is a legacy from intermittent hemodialysis machines that are utilized primarily for fluid removal. Patient overall fluid balance obviously is computed as the net difference in volume computed from all intakes and outputs (including the CRRT system fluids) over a given period of time.

Patient fluid balance in CRRT can be achieved in two ways, either by what I call the common strategy or the alternate strategy (Table 3). Most commonly, ultrafiltration rates are varied at set intervals to match the needs for fluid balance. A wide range of negative fluid balances can be achieved by this technique by increasing the ultrafiltration rate in excess of intakes. However, achieving a zero or positive fluid balance requires a reduction in the ultrafiltration rate coupled with an increase in the replacement fluid. Fluctuations in the ultrafiltration rate alter the effluent volume, and thus solute clearances are variable. This becomes particularly important when clearances are limited to 1 to 2 L of effluent volume. An alternative approach is to set a fixed ultrafiltration rate to achieve an effluent volume that meets the desired clearance. In this strategy, ultrafiltration rates are always greater than all intakes, and a negative, zero, or positive overall fluid balance is achieved by varying the amount of replacement fluid. This method has several advantages: it allows a fixed clearance to be delivered, accommodates fluctuations in fluid intake, individualizes the prescription for each patient, and permits CRRT to serve as a fluid regulatory device. It also simplifies the delivery of therapy for the caregiver because it dissociates fluid balance from clearance parameters and minimizes adjustments to the CRRT pumps. The effluent volume is fixed, so it is easier to manage the practical aspects of the therapy, for example, changes in the waste bags.

The fixed ultrafiltration rate strategy for fluid balance can be adapted to support the varying fluid balance need of critically ill patients. This method targets the desired net balance every hour to achieve a specific hemodynamic parameter, for example, central venous pressure, pulmonary artery wedge pressure (PAWP), or mean

Table 4. CRRT prescription using the Gambro PRISMA machine and M-100 filter

	Setting	Rationale
Machine	Gambro PRISMA	Available machine
Modality	CVVHDF	Allows combination of diffusive and convective clearance. Consequently, UF rates can be limited and do not require high blood flow rates for filtration fraction (FF).
Membrane	M-100	0.9 m^2 AN69 polyacrylonitrile membrane adequate for clearances required.
Blood flow rate	100 mL/min	Not constrained by access, adequate flow for maintaining filtration fraction <25%.
Anticoagulation	4% tri-sodium citrate	At access exit through three-way stopcock to chelate ionized calcium and prevent clotting. Rate 160-200 mL/hr adjusted to maintain post-filter ionized calcium 0.25–0.4 mmol/L. Provides base from conversion of citrate to bicarbonate.
	0.1 mEq/mL calcium chloride	Replaces calcium removed across filter, administered through separate central line at initial flow rate of 40–60 mL/hr and adjusted to maintain peripheral ionized calcium of 1.12–1.32 mmol/L.
Effluent volume	2.2 L/hr	Allows small solute clearance of approximately 37 mL/min, adequate clearance to compensate for catabolic state and for reduction due to partial pre-dilution.
Dialysate flow rate	1 L/hr	Slower than blood flow rate with complete saturation of dialysate for small solutes. Diffusive clearance = 16.7 mL/min.
Pre-dilution fluid	0.5 L/hr	Administered pre-filter, pre-pump dilutes blood entering the filter with filtration fraction of 25%.
Post-filter replacement fluid	0.7 L/hr	Administered post filter in venous circuit. Volume greater than all anticipated intake to allow fixed effluent volume and clearance. Volume adjusted hourly to achieve desired fluid balance.
Dialysate fluid composition	0.45% saline + 40 mEq of Na as $NaHCO_3$ or NaCl + Mg 2.0 mEq/L + 2–5 mEq/L KCl + 0.1% dextrose	Low sodium (117 mEq/L) allows removal of sodium load in tri-sodium citrate (Na = 420 mmol/L, citrate 140 mmol/L), varying amounts of bicarbonate added to provide extra base for correction of acidosis and compensate for bicarbonate loss across filter, no calcium allows removal of citrate-calcium chelate.
Pre-dilution fluid composition	0.9% saline	Isotonic for diluting blood.
Post-filter fluid composition	0.9% saline, 0.45% saline + 75 mEq/L of sodium bicarbonate, sterile water + 150 mEq/L of sodium bicarbonate	Normal saline adequate to maintain normal sodium levels. Additional bicarbonate added to solutions depending on acid-base status and bicarbonate requirement.
Monitoring	Serum electrolytes and blood gases	Initially every 12 hours then every 24 hours, adjust solutions composition.
	Post-filter ionized calcium	Every 12 hours: adjust citrate flow rates.
	Peripheral ionized calcium	Every 12 hours: adjust $CaCl_2$ drip.
	UF/plasma urea nitrogen	Every 12 hours: assess filter efficacy and allow pre-emptive change in filter if ratio <0.6.
	Fluid balance	Set goals q 24 hours and monitor and adjust fluid balance by varying amount of replacement solution hourly to achieve target balance desired.

arterial pressure. Once a desired value for the hemodynamic parameter is determined, fluid balance can be linked to that value. For example, if it is desirable to keep a patient's PAWP between 14 and 16, a sliding scale for hourly fluid management can be formulated so that for PAWP values of 12 to 14, net fluid balance is maintained at zero; for values greater than 14, fluid is removed; for values less than 12, fluid is replaced. In essence, this method maximally utilizes the ability of CRRT to control fluid balance. A key issue here is that by incorporating the desired hemodynamic level, CRRT techniques have tremendous flexibility and are not simply devices for fluid removal. They allow overall control of fluid management as fluid regulatory devices. This external control is a key advantage over intermittent hemodialysis. We have found that targeted intervention is easier to achieve, quantitate, and monitor, and it generally facilitates understanding among care providers. For example, it is usually easier to agree on a target hemodynamic parameter such as PAWP than it is to decide on a patient's overall volume status. It is important to emphasize that the continuous nature of CRRT allows individualization of the fluid balance prescription. During CRRT there are periods when fluid balance is required rather than fluid removal, and it can be necessary to switch the approach from a fluid removal only to a fluid regulation strategy depending on the need. The fluid management prescription is therefore somewhat dynamic and subject to frequent modifications depending on the clinical condition. It has been our experience that frequent consultations between intensivists

and nephrologists on establishing target parameters are extremely useful in this regard.

Matching the goals of therapy to the therapeutic potential of CRRT

For any individual patient, immediate and ongoing goals need to be precisely defined. These depend on a thorough understanding of the patient's condition and the CRRT technique. Definition of fluid goals is a key factor for the optimal management of critically ill patients. In practice, this is achieved by an overall assessment of the patient's volume status. Often this task is difficult, as it depends on knowledge of the hydration state (total body water), the capacity of the circulatory system (resistance and compartmental distribution), and the content of osmotically active solutes. In critically ill patients, it is difficult to assess the hydration state, particularly if large volumes of fluid have been used for resuscitation in short periods. Records of weights are often erroneous given the difficulty in weighing patients with multiple tubes on ventilators, and estimates of fluid losses can be wrong in patients with large insensible losses (for example, patients with burns and open wounds). Assessment of circulatory capacitance is helped by measurement of central filling pressures, cardiac output, and systemic vascular resistance; however these are prone to measurement error. While it is possible to assess the solute content by sequential measurement of blood chemistries, dilution of solutes by large volumes of fluid and compartment redistribution can significantly affect solute concentrations. As was apparent in today's patient, it is fairly common to find that a patient with marked edema and several liters of fluid excess has a limited intravascular volume. In this situation, although fluid removal is required, it initially might be necessary to maintain an adequate intravascular volume by altering the composition of fluids infused (colloids and blood products) and influencing the systemic resistance. If CRRT is used to remove fluid without recognition of these factors, the rate of fluid removal can greatly exceed the capacity of the patient to mobilize fluid from the interstitial and intracellular compartments into the intravascular compartment and will result in hemodynamic instability, as evidenced by a decrease in blood pressure and organ perfusion. Similarly, an underestimation of the patient's volume requirements could result in an inadequate rate of fluid removal with resultant worsened fluid overload. In the patient being discussed, the immediate goals included correcting acidemia by providing bicarbonate to correct metabolic acidosis, preventing further fluid overload, and improving hemodynamic stability. Ongoing goals included fluid removal, weaning of vasopressors, maintenance of acid-base and electrolyte balance, and support of organ function.

Whether to provide dialytic support, and if so, when, are two of the fundamental questions facing nephrologists and intensivists in patients with acute renal failure. Although these decisions are integral to the management of any critically ill patient with renal failure in the intensive care unit, limited data inform the decision to dialyze. The decision is often based on an estimation of the likelihood for, and timing of, renal functional recovery. Factors that influence the likelihood of renal functional recovery include knowledge of the nature and timing of renal insult, the severity of the underlying illness and associated co-morbidities, and the presence of other factors known to adversely influence renal function, such as prolonged hypotension. Two factors tend to dissuade nephrologists from initiating dialysis in the intensive care unit. First, there are well known risks of the dialysis procedure, including hypotension, arrhythmia, and complications of vascular access placement [40]. Second, there is a strong concern that some element of the dialysis procedure will slow the recovery of renal function and increase the risk of end-stage renal failure [41, 42]. Long-standing data have showed renal lesions consistent with fresh ischemia in experimental animals and humans dialyzed without systemic hypotension, long after their initial renal injury [43, 44]. Thus, in current practice, the decision to dialyze is most often based on clinical features of volume overload and biochemical features of solute imbalance (azotemia, hyperkalemia) [45–47].

When acute renal failure complicates the course of a critically ill patient in the intensive care unit, it is usually associated with multiple organ failure, which can influence the course of the patient in two ways. There can be a rapid decline of renal function that does not permit much of an adaptive response as occurs in ESRD; this characterized the course of today's patient. Second, therapeutic interventions designed to support other organ function, for example, volume resuscitation, sometimes exceed the renal excretory capacity and contribute to a worsening of the underlying state. In these circumstances, it is apparent that the goal for any therapeutic intervention is to provide support for various organs and compensate for the adverse effects of other therapeutic interventions, thus providing an opportunity for the patient to recover from the underlying illness. Renal functional recovery is thus largely influenced by recovery of other organ function. Dialysis in this setting has the primary goal of providing adequate renal support for other organ function. This is in contrast to the patient with ESRD, in whom the goal for dialysis is to ameliorate the effects of uremia, and the determinant for long-term outcome is primarily the delivery of dialysis.

The CRRT prescription ideally is targeted to match the therapeutic potential of the technique to specific goals for the patient. In this patient, the elements of the prescription and the circuit are shown in Table 4 and Figure 1,

respectively. CVVHDF was selected to provide diffusive and convective clearance of 37 mL/min (approximately 30 mL/kg/hr). Circuit patency was maintained with regional citrate anticoagulation and pre-dilution fluid to maintain a filtration fraction of 25%. Because the patient was acidemic, additional bicarbonate (40 mEq/L) was added as sodium bicarbonate to the dialysate to replace the 40 mEq/L of sodium chloride, thereby keeping the sodium concentration at 117 mEq/L. Fluid balance was targeted to a central venous pressure of 13 to 15 by varying the amount of replacement fluid given every hour; the dialysate and fluid compositions were adjusted to accommodate changes in the patient's acid-base and electrolyte status. Table 5 shows the patient's course for the first 96 hours after starting CRRT. Eight days after initiation of therapy, her therapy was changed to intermittent dialysis for continued renal support for oliguric renal failure. Following three dialysis sessions on consecutive days, she became hypotensive again. Continuous renal replacement therapy was restarted and continued for 48 hours. On the 16th day after admission, therapy was held. The patient was given an overall short- and long-term prognosis, and her parents decided to institute comfort care measures only. She died shortly thereafter.

This patient's course illustrates three important concepts. Early intervention with CRRT for support of organ function requires a change in the traditional thought process of waiting for specific metabolic or biochemical abnormalities prior to initiation of dialysis. The broad goals for treating acute renal failure with dialysis are to (*1*) maintain fluid and electrolyte, acid-base, and solute homeostasis, (*2*) prevent further insults to the kidney, (*3*) promote healing and renal recovery, and (*4*) permit other support measures (for example, nutrition) to proceed without limitation. As I said earlier, CRRT techniques differ in their operational characteristics and their ability to provide renal support, and these differences should be considered in the dialysis decision. For instance, CRRT techniques can be successfully utilized for fluid regulation [18], selective replacement of specific electrolytes, for example, bicarbonate, without the addition of sodium or fluid [48], or to add substances to the blood [49]. Similarly, the use of combined techniques such as combined plasma filtration and adsorption for sepsis and cell-based and hemoperfusion devices for hepatic support devices is emerging [50–55]. As a consequence, the traditional indications for renal replacement might need to be redefined. For instance, excessive volume resuscitation, a common strategy used for multi-organ failure, might be an indication for dialysis even in the absence of significant elevations in BUN. In this respect it might be more appropriate to consider dialytic intervention in the intensive care unit patient as a form of renal support rather than renal replacement. This terminology serves to distinguish between the strategy for replacing individual organ function and one to provide support for all organs. It is thus possible to widen the indications for renal intervention and provide a customized approach for the management of each patient. It is also apparent that this approach will increasingly become the norm as we move into the era of using dialysis for non-renal problems [12, 49, 56, 57].

A second lesson is that CRRT techniques offer immense flexibility for supporting the changing needs of critically ill patients. In today's patient, modifications in the dialysate and substitutions in fluid composition were made to optimize her ventilatory management with inverse ratio ventilation and permissive hypercapnia. The traditional way to treat acidosis in this setting is to give sodium bicarbonate, which contributes to a high sodium load and consequent sodium and fluid retention. In this patient, CRRT allowed independent manipulation of the sodium and bicarbonate composition, keeping the sodium levels constant and not causing fluid overload. Correction of her acidemia probably contributed to improved hemodynamic stability, and it likely provided support for overall organ function. This feature of CRRT sharply contrasts with intermittent techniques, in which time and therapy limitations (for example, choice of dialysate baths) limit the scope of therapeutic maneuvers. The varying fluid balance requirements could be achieved while maintaining hemodynamic stability, thus utilizing the patient's underlying state to dictate the extent of fluid regulation. Control of uremia and maintenance of acid-base and electrolyte balance were similarly facilitated by the continuous nature of the therapy.

Finally, the decision to intervene with CRRT demonstrates the multidisciplinary nature of this therapy. Often it is difficult to ascertain whether provision of dialysis will substantially change the patient's outcome [58–60]. The many physicians involved may differ in their assessment of the likelihood of success, and often the patient's family requests ongoing support. One approach is to offer a "trial of therapy" for a specific, pre-defined time period. Establishing a trial of therapy requires a definition of the goals, identification of the measurable end points, and a delineation of specific criteria for evidence of improvement. Agreement should be obtained from all involved parties (physicians, patients and their family, nurses) for the time point at which criteria will be evaluated and the magnitude of change in the measurable criteria accepted as evidence for improvement [61]. Depending on the patient's course, the trial of therapy can be extended for an additional time interval or a decision made to withdraw care. This approach has several advantages: it allows time to evaluate improvement and to provide evidence of benefit, gives the family time to adjust, resolves conflict, limits resource utilization, and standardizes the approach for the caregiver. Ongoing communication is a necessary step for this approach to be successful. In the patient being discussed, a trial of therapy was offered for 4 days

Table 5. Patient course on CRRT

Time	Vitals	Pertinent labs (Standard units)	Comments
At start		pH 7.18, PO_2 67, PCO_2 87, bicarbonate 24	Received 150 mEq bicarbonate IV, on norepinephrine
12 hours	Stable hemodynamics (BP 90/50 mm Hg at initiation)	pH still low at 7.15, bicarbonate increased to 28	Replacement fluid composition changed from NS to sodium bicarbonate (150 mEq/L) added to sterile water. Norepinephrine stopped, fluid removal at −50 mL/hr started
24 hours		pH 7.35, PO_2 73, PCO_2 80, bicarb 44, Na 133, K 3.8, Cl 77, bicarb 40, glu 148, BUN 35, creat 1.3	Weaned off vasopressin, Neosynephrine 80 μg/kg, fluid balance even for last 24 hours
36 hours	BP 100/50	pH 7.34, PO_2 101, PCO_2 71, bicarb 38	Off Neosynephrine. Fluid balance −500 mL. Targeted to CVP 13–15. Replacement fluid bicarbonate reduced to 75 mEq/L. FiO_2 reduced to 90%.
48 hours		pH 7.34, PO_2 79, PCO_2 65, bicarbonate 34, PO_4 2.9, AST/ALT levels reduced from high of 2405/771	Stable on therapy, replacement started for PO_4 of 2.9. Fluid balance −1200 mL.
96 hours	BP 130/60 off pressors	FiO_2 80%, pH 7.36, PO_2 65, PCO_2 52, Na 138, K 3.7, Cl 100, bicarb 29, glucose 137, Ca 10.7, PO_4 1.9, ionized Ca 1.19 mmol/L, BUN 32, creat 0.7, T Bil 5.7, WBC 19.1, hemoglobin 10.4, platelets 66; 15 bands, cultures yeast in sputum	Urine output 15 mL/hr, fluid balance targeted to CVP 12–13 cm water, negative balance 2.4 L, replacement fluid bicarbonate reduced to 50 mEq/L. Routine filter change. Chest x-ray improved.

with the goals of improved acid-base balance, hemodynamic stability, and respiratory status assessed by changes in arterial pH, mean arterial pressure and vasopressor requirements, and oxygen requirements. CRRT techniques require ongoing and periodic assessments if they are to be used optimally. It is thus imperative that a team approach be used for managing patients on CRRT, because the therapy prescription and delivery are influenced significantly by a clear delineation of the operational characteristics. Lack of communication often contributes to adverse results with these techniques. In this case, the intensivist and nephrologists met with the patient's caregiver and explained the gravity of the patient's condition and the elements of the trial of therapy prior to initiation of CRRT. Following initiation of therapy, daily evaluations and discussions by the intensivists, nephrologists, and the critical care and nephrology nursing teams were continued to assess the therapeutic response and modify the therapy. In essence this is a necessary component of the care for these patients. Often the simple facts of ongoing communication to set goals, defining the scope of the therapy, and assessing for response are omitted in the care of the critically ill. When intermittent dialysis techniques are used, the exposure of the patient and hence the involvement of the nephrology team at the bedside are limited to the duration of the therapy.

Continuous renal replacement techniques are now widely utilized across the world. However, several questions remain unanswered. Does CRRT have any outcome benefit [62–64]? Is it cost-effective [65, 66]? What dose should be utilized [10, 67, 68, 69]? When should therapy be started [70–72]? When should CRRT not be used [17, 73]? These questions require ongoing research and clinical trials to be effectively answered. While evidence is being assimilated, consensus statements from the Acute Dialysis Quality Initiative provide some guidance [73]. As experience with CRRT grows, innovations in technology will likely keep pace. Over the last decade, most of the major manufacturers of dialysis equipment have developed new pumps for these techniques. Most of these devices (Gambro/Hospal Prisma; Baxter Accura) offer automated fluid balancing and sophisticated controls similar to those in standard dialysis machines [74]. Membrane technology is also evolving, and adsorbent, highly permeable membranes are on the horizon [75, 76]. Recent work in the area of blood flow monitoring suggests that future CRRT machines will include ultrasound blood flow measurement. Such flow measurements can be computer-linked to the blood pump to ensure correct blood flow, and a screen display could represent this flow pictorially [77]. Furthermore, on-line monitoring of filtrate could be used to indicate urea clearance as a continuous display to clinicians during therapy [78].

QUESTIONS AND ANSWERS

DR. JOHN T. HARRINGTON (*Dean Emeritus, Tufts University School of Medicine, Boston, Massachusetts*): You mentioned that there is a "common" strategy of fluid management versus an "alternative" strategy of fluid management. It seems to me that the common approach, which I suspect too many of us use, is simply one group of people handling those multiple hanging plastic bottles by the patient's bedside, and the nephrologist handling the dialysis machine in isolation. The surgeon or the intensivist pours the fluid in and the nephrologist valiantly tries to keep up with it or maybe even get a liter or two ahead. How do you, in the real world, manage the potential conflict between the common approach and your alternative strategy?

DR. MEHTA: Your question is an excellent one. We've developed the alternative strategy, so I'm somewhat biased toward that approach. The common strategy is used frequently because when the nephrology team rounds,

they find the patient has been fluid overloaded four liters, when the strategy was to try to get them down to zero balance. A simple approach is to increase the ultrafiltration rate. However, changes in ultrafiltration rate can be easily altered by other care providers, such as the surgical intern who might not have the requisite knowledge of the system. In addition, you are affecting the clearance, because the ultrafiltration rates and the effluent volumes change.

We have found that by keeping the effluent rate constant and varying the replacement fluid, any specific fluid balance state required by the intensivist can be achieved with less interference. This strategy requires that the intensivist and nephrologist define a common fluid balance goal, for example, "the net negative or positive liters at the end of a particular time period." Additionally, you determine which physiologic parameter is most easily mapped to that fluid balance state, such as PAWP, mean arterial pressure, or right-ventricular volume. One can then write a sliding scale for fluid regulation around that particular parameter. Consequently, the patient characteristics start driving the therapy rather than the physician trying to second-guess it at periodic intervals.

DR. HARRINGTON: If you look at the mortality rate for acute renal failure over the last 25 years, it remains horrendously high—anywhere from 25% to 50%. I've begun to call acute renal failure a malignant disease; patients are dead within two weeks with our kind of malignant disease, especially acute renal failure complicated by multiorgan system failure. Yet trials of different treatments in ARF have been disappointing, for instance, the atrial natriuretic peptide study. How can we best study different drugs, like erythropoietin or minocycline, or different modalities, such as CRRT, in ARF patients with widely disparate clinical characteristics?

DR. MEHTA: I think that this is the crux of the problem for the nephrology community: We do not have a standard way of defining acute renal failure. We do not look at acute renal failure as a continuum of these processes; we look at it as a serum creatinine elevation from a particular point, and then it's called acute renal failure. In essence, it is a *change* in renal function over a short period of time. But how we define it has been based largely on serum creatinine levels, which is not the most effective indicator. So I believe that our first step is to develop a standardized definition. And I don't think this definition will be based on one particular criterion, but will be in more than one domain. And those domains will include the susceptibility to injury (predetermined); a second is the nature and timing of the injury; third would be the response variable, for example, serum creatinine or other marker; and finally, what else has happened as a consequence of the injury. If you look at those four domains you come up with a scoring system similar to the Ransom's criteria for pancreatitis and the Child's C classification for cirrhosis. We recently proposed a classification that incorporates these elements [79]. I think if we are able to determine where the patient is in the course of the illness, we will have an opportunity to target interventions specifically at a time point.

DR. HARRINGTON: Who is going to put together that study, and where is the funding for that study going to come from? The MDRD study of chronic renal disease cost $60 million; trials in acute renal failure would be much more expensive.

DR. MEHTA: Actually, $30 million will be spent by the Veterans Administration NIH trial on acute renal failure looking at dialysis dose. I think a partnership between industry and the NIH would be an obvious source for funding for this. But we need more observational studies, and we need more paradigm changes to get to the right model for us to use.

DR. FRANCIS B. GABBAI (*Professor of Medicine, Division of Nephrology, University of California, San Diego*): One of the findings in patients with CRRT is that urine output frequently falls to zero. This is in contrast with patients treated with intermittent hemodialysis who frequently maintain a low urine output but one seldom as low as zero. For a long time, we have associated very low urine output with a bad prognosis in terms of recovery of renal function. Would you comment on this difference between CRRT and intermittent hemodialysis, its potential cause or causes, and its implication in terms of recovery of renal function?

DR. MEHTA: I'd like to answer that with two specific viewpoints. One is that you simply could be selecting the more severely ill patients to go on CRRT who are more hemodynamically unstable and therefore have less of an opportunity to make urine. The second is that CRRT gradually lowers the solute concentrations, which constitute driving forces for osmotic diuresis.

DR. ROBERT W. STEINER (*Clinical Professor of Medicine, Division of Nephrology, University of California, San Diego*): Ravi, you discussed the flux of the small molecules across the dialyzer membrane. Could you comment on calculating the effect of changes in the dialysate composition and ultrafiltration rate on potassium balance, for example, and on how to calculate urea removal in a patient on continuous modalities vis-a-vis nutritional management?

DR. MEHTA: Since the concentration of solutes in the effluent mirrors that in the plasma, the total amount of solute (electrolytes) removed can be computed. Consequently, the composition of the dialysate or substitution fluid can be altered to maintain balance. Additionally, the urea nitrogen removed by CRRT can be computed and the protein catabolic rate calculated. Nutritional management in CRRT is an area that I did not mention in my talk, but it is clearly an important aspect of the procedure. If you use glucose-based solutions in

the dialysate or the substitution fluid, the delivered glucose contributes significantly to a caloric load and can cause hyperglycemia [80]. We have stopped using glucose in the dialysate or substitution fluid for this reason. It is still quite common for people to use a 1.5% dextrose peritoneal dialysate fluid for the dialysate or a 5% dextrose solution as a substitution fluid, particularly when you want to lower the serum sodium. In the last three years, we have started prescribing sterile water with added bicarbonate (150 mEq/L) rather than using a 5% dextrose solution as a substitution fluid.

Another factor to be considered is that there is a significant amino acid loss across the high permeable filter. The high fluid removal capacity in CRRT allows any amount of fluid required for nutritional supplementation to be administered easily while maintaining fluid balance. These features permit a high protein and caloric load to compensate for the catabolic state in acute renal failure. However, studies by Bellomo et al [81] have shown that if you go up to 2.0 g/kg or 2.5 g/kg of protein loading, a positive nitrogen balance cannot be achieved and there is no additional nutritional benefit. Thus, even though CRRT permits unlimited nutritional support, there is no advantage in "overfeeding" patients. On the other hand, burn patients are usually given very high nutritional supplementation, and in those patients it's quite a bit easier to maintain the steady-state BUN levels lower than would otherwise be possible.

DR. RODRIGO J. FERNANDEZ (*Clinical Assistant Professor, University of California, San Diego*): The present case would require an ultrafiltration rate of about 2520 mL/hr by Dr. Ronco's previous study [67]. But even in that paper only 80% or 85% of the patients were able to achieve that 35 mL/kg of ultrafiltration. And in practice, some patients weigh 90 kg or more. How do you technically achieve such a high ultrafiltration rate considering that the Gambro Prisma has a maximal blood flow rate of 180 mL/min that would allow an ultrafiltration rate of up to 1000 mL/hr at usual settings?

DR. MEHTA: In our patient, the effluent volume was 2500 mL/hr and the ultrafiltration component of that was 500 mL/hr. So we got the same amount of solute clearance but the equivalent convective clearance of 1500 mL/hr. That's one way to get around it if you are looking purely at small solute clearance. If you wanted to achieve 35 mL/kg/hr of middle molecule clearance, then certainly you would have to ratchet up the blood flow rates. And the current versions of some of the machines do make it limiting for the blood flow rate. But if you want to achieve that, you have to be conscious of increasing the blood flow rate, adding predilution, and making sure that your fluid management strategy is very consistent; otherwise you have a challenge there. Currently we are exploring the feasibility of providing higher effluent volumes in a prospective study, which should provide some answers.

DR. ROBYN CUNARD (Assistant Professor of Medicine, Division of Nephrology, Veterans Affairs San Diego Healthcare System and University of California, San Diego): There is increasing interest on the part of intensivists to perform CRRT independent of nephrologists. Is there any evidence that this is a good practice?

I also have another question. Is the reason that it is difficult in randomized controlled studies to show a survival advantage with CRRT compared with IHD related to the increased incidence of risks associated with this treatment modality, such as bleeding and infection?

DR. MEHTA: In some countries in the world and a few centers in the US, this therapy is done purely by intensivists. In the majority of US centers, nephrologists prescribe and perform CRRT. This largely relates to the fact that CRRT is a dialysis procedure that is specifically included in nephrology training. Credentialing for dialysis in this country has been related to nephrology training; most intensivists have not had formal training in dialysis procedures. I think that your question relates to the issue of closed versus open ICUs. Literature supports the notion that closed ICUs have better outcomes [82]. This means that if the intensivists handle everything, they have better outcomes than if other subspecialists come into the picture. I think, though, that from our own experience, it is probably better to consider CRRT a multidisciplinary procedure in which the physicians who do it are well informed and experienced. I hope that in the United States at least this will remain a multidisciplinary procedure under the control of nephrologists. A recent article from UK intensivists showed that only about 8% of the patients who were in the ICU with intermittent hemodialysis, and the nephrologists were generally not involved in that care [83].

Your second question, related to complications, is a very important one. Here's the difficulty: when you use a continuous therapy in a critically ill patient, who is already prone to a lot of adverse events, how do you know whether a complication was because of the therapy or because of the underlying disease process? That's the biggest question we have. We know that acute renal failure itself contributes to adverse outcomes, such as sepsis and death, and that dialyzed patients have a higher risk. No one, however, has addressed the question of why this is the case and whether complications contribute to the risk. We are exploring these issues.

DR. HARRINGTON: Early in your discussion you mentioned adsorption of substances into the membrane itself as one of the reasons for utilizing CRRT as renal replacement therapy, because time is on your side. Could you give us an example of that?

DR. MEHTA: There has been an intense interest in trying to use these therapies for treating sepsis, even in the absence of renal dysfunction. We know that cytokines are

released in this setting and that they are removable by the membranes by adsorption. So it's quite feasible that if you could apply CRRT, you might be able to lower cytokine levels. Studies have demonstrated, however, that changing the filters every 12 hours might be required to reduce cytokine levels [13, 14]. However, the difficulty is knowing when to use CRRT in that situation, knowing what level you're going to remove, and being selective about it [12, 56].

DR. CLAYTON SMILEY (*Fellow, Division of Nephrology, University of California, San Diego*): When anticoagulating the circuit on CRRT, some individuals use citrate and others use heparin; is there an advantage to one approach versus the other?

DR. MEHTA: Yes; several published studies, including our own experience, clearly demonstrate that citrate anticoagulation offers better filter life, better filter performance, and less bleeding risk in comparison to heparin [23]. This has now been shown for both CVVHDF circuits and CVVH circuits. In fact, a recent article looked at a randomized controlled trial of heparin versus citrate in CVVH and showed that citrate anticoagulation produced less filter clotting [39].

DR. MITA SHAH (*Fellow, Division of Nephrology, University of California, San Diego*): Replacement fluid is often administered in high volumes to patients who are hypoalbuminemic. Most often crystalloid, are these solutions contributing to the volume overload of these CRRT patients? Can you discuss alternative replacement fluid strategies?

DR. MEHTA: In our CRRT system, we prescribe crystalloids predominantly because of the expense of using colloids. But there is certainly room for changing some part of the volume replacement to colloids, as is done in some patients, particularly those with liver disease who are getting fresh frozen plasma (FFP) or albumin solutions. But no good data, even in the absence of CRRT, suggest that using colloids has a marked benefit over using these crystalloids. What is emerging, though, is small-volume resuscitation with hypertonic saline, because it tends to reduce endothelial swelling; these solutions have not been tried in CRRT.

DR. HARRINGTON: In the last few years, studies in intensive care unit patients have shown that rigorous control of blood sugar leads to a significant fall in mortality rates and decreases the likelihood of ARF [84]. My specific question is, does CRRT help or hurt in controlling blood sugar in these critically ill patients?

DR. MEHTA: If you use glucose solutions for substitution fluid or dialysate, you're contributing to the hyperglycemic load of these patients. To my knowledge, no single study has looked at hyperglycemia or glucose control in CRRT as a separate issue for this population. But it is certainly a very intriguing question and I think it deserves more attention. A study by Bellomo about a decade ago showed that patients on CRRT who had high insulin levels had a worse outcome, and suggested that metabolic control is a major issue in these patients [85].

DR. NICHOLAS ROWDER (*Fellow, Division of Nephrology, University of California, San Diego*): You have discussed when it is reasonable to start CVVHD, but besides a patient becoming hemodynamically stable, are there other factors that would make you stop CVVHD and switch treatment to intermittent dialysis?

DR. MEHTA: To my knowledge, only one study has addressed this specifically; I'll get to that in a moment. Clinically the issue is: Can you have adequate hemodynamic stability and an improved catabolic state, such that you can get away from using CRRT? And this is partially a response also to Dr. Steiner's question. You could do a urea nitrogen appearance rate and calculate a catabolic rate. That parameter can quite clearly tell you when CRRT will still be required because, if you are still getting a protein catabolic rate of 1.5 to 2.0 g/kg, there's no way you're going to be able to maintain the same level of steady-state solute balance without continuing CRRT. In addition, fluid management is a key determinant; so even if patients might otherwise be getting better, if they still require large amounts of fluids to be removed, that might be better accomplished with CRRT.

A study from the University of Alabama was shown at the CRRT conference last year [86]. They have 14 CRRT machines, so they're basically doing CRRT on 5 to 10 patients every day. They had looked at this question and they measured creatinine clearances. When the creatinine clearance was about 15 mL/min, that seemed to be a cutoff when you could easily stop CRRT. No one else has looked at it in that way, but I think that's a reasonable approach to utilize and further examine.

DR. HARRINGTON: Ravi, perhaps you can end providing us with the best reference regarding the terminology and definitions of renal replacement therapy.

DR. MEHTA: I would recommend the ADQI consensus statement regarding CRRT [73].

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