Dose and efficiency of renal replacement therapy: Continuous renal replacement therapy versus intermittent hemodialysis versus slow extended daily dialysis

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Acute kidney injury represents an independent risk of death in the intensive care unit and significantly contributes to in-hospital mortality. The only accepted treatment of severe acute kidney injury so far is renal replacement therapy, which is not a causative therapy but rather a life-support treatment. Renal replacement therapy can be performed by several different techniques: intermittent hemodialysis, slow extended daily dialysis, peritoneal dialysis, or continuous renal replacement therapy. There is controversy about which technique should be used, which dosage should be selected for each therapy, and whether the technique and/or the dose of renal replacement therapy may impact survival in critically ill patients. After a careful review of the recent literature, definitive conclusions cannot be drawn: Trials are in most cases underpowered and conducted over many years, in which significant changes in the practice of acute dialytic techniques have taken place. Other studies have described therapeutic modalities requiring a high level of specific expertise in the field and generally not easily reproducible in the routine practice. While practitioners are waiting for the ultimate trial to be published, we think it is worth reporting some broad concepts and few suggestions for renal replacement therapy prescription derived from current evidence and from the available experience. (Crit Care Med 2008; 36[Suppl.]:S229–S237)

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Of critically ill patients admitted to intensive care units (ICUs), 5% to 6% develop acute kidney injury (AKI) and >70% of them require the application of renal replacement therapy (RRT) (1). The mortality rate for severe AKI has exceeded 50% over the last three decades and it represents an independent risk factor for mortality of critically ill patients (2–5). Based on the most recent RIFLE classification (a mnemonic for the progression of *r*isk of renal dysfunction, *i*njury to the kidney, *f*ailure of kidney function, *l*oss of kidney function, and *e*nd-stage kidney disease), AKI can be stratified into three classes depending on the degree of severity as assessed by the extent of glomerular filtration rate loss (6, 7). Current management depends on the level of severity and includes optimization of hemodynamics and fluid status, avoidance of further renal insults, optimization of nutrition and, when appropriate, the prescription of RRT. It also is apparent that final outcome can be very different among the groups of patients belonging to different AKI severity strata.

Indications for RRT are generally clear for some patients with a "failure" level of AKI (e.g., anuria in the setting of septic shock), while they may require careful assessment in less severe situations (e.g., 12 hrs of oliguria in an 80-yr-old patient with previous chronic renal dysfunction on the day after surgery). Among the strategies to improve patient outcome in AKI, optimization of delivered treatment dose recently has been addressed. This review will focus on the concept of RRT dose, the meaning of dose calculation, and finally the prescription and delivery of RRT in the ICU based on current knowledge and evidence.

The Dose of Treatment in Renal Replacement Therapies

As with any other therapy administered in the ICU, any kind of dialysis has its "dosage." This concept has to do with restricting the "dose" term to the function of blood purification neglecting the other functions of RRT, such as volume control and restoration of homeostasis. Thus, according to the conventional view, the dose of RRT is a measure of the quantity of blood purified of waste products and toxins achieved by means of a blood cleansing technique. Given that this broad concept is too difficult to measure and quantify, a more focused definition of RRT dose describes the measure of the elimination of a marker solute. This marker solute should be reasonably representative of all solutes that are otherwise removed from blood by the kidney. This premise has two major flaws: First, the marker solute cannot and does not represent all the solutes that accumulate during AKI, because kinetics and volume of distribution are different for each solute. Second, its removal during RRT is not necessarily representative of the removal of other solutes. This is true both for end-stage renal failure and AKI. Nevertheless, despite all of these limitations, a significant body of data (8) suggests that single-solute marker assessment of dose of dialysis appears to have a clini-

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cally meaningful relationship with patient outcome and, therefore, clinical utility. In chronic kidney disease, urea often has been used as a marker molecule. In fact, in spite of its moderate toxicity, urea is the final product of protein metabolism; its accumulation describes the need for dialysis and its removal describes treatment efficiency. It is a small molecule and its volume of distribution is similar to total body water. It is not bound to protein and it freely passes through tissues and cell membranes.

The concept of RRT dose is part of the required knowledge for a safe and effective delivery of therapy: As is the case for antibiotics, vasopressors, anti-inflammatory drugs, mechanical ventilation, etc., the administration of an extracorporeal blood purification technique requires the operators to know exactly how and how much treatment should be prescribed and delivered. The deep knowledge of the used renal replacement technique may contribute strongly to optimally tailoring the treatment to each patient in terms of schedules, effective treatment delivery, and limitation of technical and clinical complications. In spite of these considerations, according to a recent survey on practice patterns in different European centers, a large percentage of operators in the field of acute dialysis seem to be uncertain on treatment prescription (9).

The amount (dose) of delivered RRT can be described by various terms: efficiency, intensity, frequency, and clinical efficacy.

Efficiency of RRT is represented by the concept of instantaneous clearance (K); i.e., the volume of blood cleared of a given solute over a given time. It is generally expressed as volume over time: mL/min, mL/hr, L/hr, L/24 hrs, etc. K does not reflect the overall solute removal rate (mass transfer), but rather its value normalized by the serum concentration: Even when K remains stable over time, the removal rate will vary if the blood levels of the reference molecule change. During RRT, K depends on solute molecular size and diffusivity, transport modality (convection or diffusion), and circuit operational characteristics such as blood flow rate (Qb), ultrafiltration rate (Qf), dialysate flow rate (Qd), and membrane and hemodialyzer type and size. Qb prescription mainly is dependent on vascular access and characteristics of utilized machines. In diffusion, K tends to correlate with Qb for small solutes unless membrane surface area or dialysate flow rates represent limiting factors. During diffusive techniques, when Qd/Qb ratio is >0.3 it can be estimated that dialysate will not be completely saturated by diffusing solutes. In the absence of a universal marker, urea and creatinine are generally used to guide treatment dose. During convective techniques, for solutes with a sieving coefficient (SC) close to 1, efficiency is described by Qf that equals K. Qf is strictly linked to Qb because of the hemoconcentration and the growing importance of oncotic pressure displayed in conditions of high Qf or low Qb. This link is described by the term filtration fraction (the fraction of plasma water that is removed from blood by ultrafiltration); it is recommended to keep Qf $<$ (0.2 $\times$ Qb). During ultrafiltration, the driving pressure jams solutes, such as urea and creatinine, against the membrane and into the pores, depending on membrane SC for that molecule. SC expresses a dimensionless value and is estimated by the ratio of the concentration of the solutes in the filtrate divided by that in the plasma water or blood. A SC of 1 (as is the case for urea and creatinine) describes complete permeability, while a value of 0 reflects complete rejection. Solute molecular size, protein binding, and filter porosity are the major determinants of SC. The K during convection is measured by the product of Qf $\times$ SC. Thus, there is a linear relationship between K and Qf, the SC being the changing variable for different solutes. During diffusion, an analog linear relationship depends on diffusibility of a solute across the membrane. As a rough estimate, we showed that during continuous slow efficiency treatments, urea K can be considered as a direct expression of Qf and Qd (10).

K normally can be used to compare the efficiency of different treatments, but it does not reflect the overall dose nor can it be used to compare treatments with different duration and schedules. For example, K is typically higher in intermittent hemodialysis (IHD) than in continuous renal replacement therapy (CRRT) and slow extended daily dialysis (SLED). This is not surprising, because K represents only the instantaneous efficiency of the system. However, mass removal may be greater during SLED or CRRT due to a longer duration and a higher product clearance over time. For this reason, the information about the time span during which K is delivered is fundamental to describe the effective dose of dialysis (intensity).

Intensity of RRT can be defined by the product of clearance $\times$ time (Kt: mL/min $\times$ 24 hrs, L/hr $\times$ 4 hrs, etc.). Kt is more useful than K in comparing various RRTs. Nevertheless, equal Kt products may lead to different results if K is large and t is small or if K is small and t is large. In the first case, the mass transfer of the solute among different compartments of the body is important. If the mass transfer is lower than K, a disequilibrium will form among compartments and the volume cleared by the treatment will be low (sometimes confined to the blood space). Thus, at similar Kt values, the possibility that intercompartmental equilibrium occurs always is more likely in treatments with large t (e.g., in SLED compared with IHD) (Fig. 1).

Furthermore, the product Kt does not take into account the size of the patient and the pool of solute that needs to be cleared. This requires the dimension of efficacy, which includes a normalization of the volume cleared by the volume of distribution of the marker molecule in the studied patient.

Efficacy of RRT is the effective outcome resulting from the administration of a given treatment dose to a given patient. It can be described as a fractional clearance of a given solute (Kt/V), where V is the volume of distribution of the marker molecule in the body. Kt/V is a dimensionless number (e.g., 50 mL/min $\times$ 24 hrs/45 L = 3 L/hr $\times$ 24 hrs/45 L = 72 L/45 L = 1.6) and it is an established measure of dialysis dose correlating with medium term (several years) survival in chronic hemodialysis patients (11–14). Urea typically is used as a marker molecule in end-stage kidney disease to guide treatment dose; the volume of distribution of urea (V_{UREA}) is generally considered as equal to patient total body water, which is 60% of patient body weight, and a Kt/V_{UREA} of $\geq$1.2 is currently recommended for IHD treatments. However, Kt/V_{UREA} application to patients with AKI has not been validated rigorously owing to a major uncertainty about V_{UREA} estimation. Some authors have suggested expressing dose as K indexed to patient body weight as an operative measure of daily CRRT. It is now suggested to deliver at least 35 mL/hr/kg $\times$ 24 hrs (15–17). If the simplification discussed above (K = mL/hr = Qf or Qd) can be considered acceptable, this CRRT dose may be expressed in a 70-kg patient as about 2500 mL/hr or 60L/day of continuous venovenous hemofiltration (CVVH) (Qf $\times$ kg $\times$

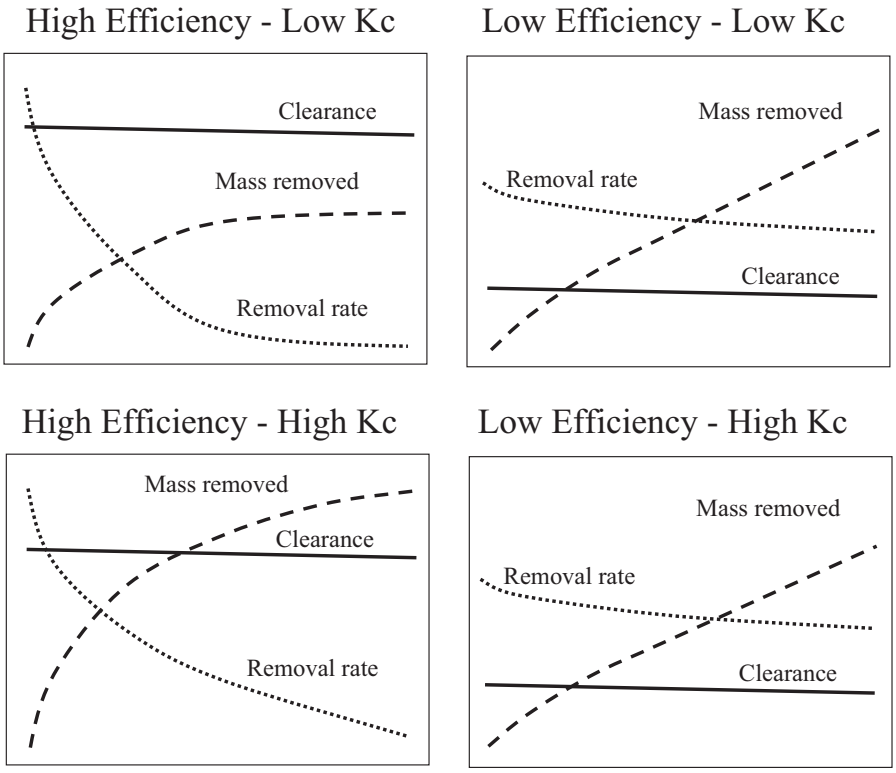

Figure 1. Schematic representation of solute kinetics with different intercompartmental transmittance (Kc) in treatments with different levels of instantaneous clearance (K). *Upper left*, with high efficiency and low Kc, though the high clearance is maintained for the entire length of the treatment, the low Kc produces a rapid decrease of the solute concentration in blood and mass removed will be limited and tending to a plateau in the second part of the session. In this case, the solution for a better efficacy will be to increase the frequency of treatments (e.g., daily rather than thrice weekly). *Upper right*, low Kc and low clearance result in low removal rates. The only solution for improving efficacy is to increase treatment time. *Bottom left*, this is the ideal condition of high Kc and high K. In this case, K can be further increased to improve efficacy until a Kc limitation is displayed. *Bottom right*, this is a typical condition of continuous renal replacement therapy (low K) and a small molecular weight solute (high Kc). The solution will be to maximize treatment length and possibly to achieve a higher clearance.

24 hrs) or CVVHD (Qd × kg × 24 hrs). Interestingly, applying Kt/V_{UREA} dose assessment methodology in such a 70-kg patient, the dosage of 35 mL/hr/kg × 24 hrs would be equivalent to a Kt/V of 1.4.

Other authors suggested a prescription based on patient body surface area (18), or on metabolic requirements based on urea generation rate and catabolic state of the single patient (19). It has been shown, however, that during continuous therapy a K <2 L/hr almost definitely will be insufficient in an adult critically ill patient (20).

Some important caveats should be considered. The major shortcoming of the traditional solute marker–based approach to dialysis dose in AKI lies well beyond the question of which methodologic application of solute kinetics is better to approach. In patients with AKI, the majority of whom are in intensive care, a solute-limited concept of dialysis dose may have grossly inappropriate results. In critically ill patients, a more holistic approach to dose of therapy should be made. This includes control of acid base, toxicity, potassium, magnesium, calcium and phosphate, intra- and extravascular volume, and temperature, and the avoidance of unwanted side effects associated with the delivery of solute control. These aspects depend on type of treatment and its dose, and they are not currently addressed by any measure of treatment delivery. Nevertheless, they should be considered when discussing the appropriate prescription of RRT and its adequacy. In fact, it is likely that patients die more often from incorrect intravascular volume control than hyperazotemia. It has been shown, for example, that restoring an adequate water content in small children is the main independent variable for outcome prediction (21, 22). This concept is much more important in small critically ill patients, in which a relatively larger amount of fluid (in percent of body weight) must be administered to deliver an adequate amount of drug infusion, parenteral/enteral nutrition, and blood derivatives. Furthermore, unlike in the field of chronic hemodialysis, in which small details may result in significant differences of delivered dose, in the setting of AKI only major changes in prescription (e.g., changing from every-other-day to daily dialysis while prescribing the same Kt/V) can really lead to "different" treatment dose delivery. Light adjustments such as prescribing a Kt/V of 1.2 vs. 1.0 can be criticized as easily falling within the delivery calculation error and not necessarily representing a reliable change in dose delivery. Accuracy therefore is another important issue in measuring effective treatment delivery.

Adequate RRT Dose: Does It Exist?

Despite all of the uncertainty surrounding its meaning and the gross shortcomings related to its accuracy in patients with AKI, the idea that there may be an optimal dose of treatment obviously has a great impact on intensivists and operators in this field. This is likely due to practical reasons ("How should I set the machine?") and to the evidence from end-stage renal disease, in which a minimum dose (Kt/V 1.2 thrice weekly) is indicated as adequate (13). The optimistic hypothesis that higher doses of dialysis may be beneficial in critically ill patients with AKI must be considered by analogy and investigated. Several reports exist in the literature dealing with this issue.

Dr. Brause and colleagues (23), using CVVH, found that higher Kt/V values (0.8 vs. 0.53) were correlated with improved uremic control and acid-base balance. No clinically important outcome was affected. Investigators from the Cleveland clinic (24, 25) retrospectively evaluated 844 patients with AKI requiring CRRT or IHD over a 7-yr period. They found that, when patients were stratified for disease severity, that dialysis dose did not affect outcome in patients with very high or very low severity scores, but did correlate with survival in patients with intermediate degrees of illness. A mean Kt/V >1.0 was associated with increased survival. This study, of course was retrospective with a clear *post hoc* selection bias. Al-

though their validity is less than ideal, these observations endure as benchmarks in the absence of more solid data.

Daily IHD was associated with improved outcome in a recent trial in which it was compared with alternate-day dialysis (26). Daily hemodialysis resulted in significantly improved survival (72% vs. 54%; $p = .01$), better control of uremia, fewer hypotensive episodes, and more rapid resolution of AKI. However, several limitations affected this study: Sicker, hemodynamically unstable patients were excluded and underwent CRRT, instead. Also, it appears that patients receiving conventional IHD were underdialyzed. Furthermore, alternate-day dialysis was associated with significant differences in fluid removal and dialysis-associated hypotension, suggesting that other aspects of dose beyond solute control (such as inadequate and episodic volume control) may have explained the findings. These observations suggest that further studies should be undertaken to assess the effect of dose of IHD on outcome.

In a randomized, controlled trial of CRRT dose, CVVH at 35 mL/hr/kg or 45 mL/hr/kg was associated with improved survival when compared with 20 mL/hr/kg in 425 critically ill patients with AKI (15). Many technical and/or clinical problems, however, can make it difficult, in routine practice, to apply such strict protocol by pure postdilution hemofiltration. A survey of several units worldwide found that very few units deliver this intensive CRRT regimen. According to Dr. Uchino and colleagues (27), median unadjusted CRRT dose was 2000 mL/hr and the corrected dose was 20.4 mL/hr/kg. Only 11.7% of patients were treated with a corrected dose of ≥35 mL/kg/hr. Finally, in the study conducted by Dr. Ronco and colleagues (15), the technique of CRRT was CVVH with postdilution, whereas current practice includes a variety of techniques in addition to CVVH, such as CVVHD and continuous venovenous hemodiafiltration (CVVHDF). Equally important is the observation that this study was conducted over 6 yrs in a single center, that uremic control was not reported, that the study was unblinded, that the frequency of sepsis was low compared with the typical populations reported to develop AKI in the world (1), and that its final outcome was 14-day mortality and not the accepted 28-day or 90-day mortality typically used in ICU trials. Nevertheless, although the external validity of this study remains untested, the 35 mL/kg/hr has been widely accepted worldwide and practice has changed to match this target in many centers.

Another prospective randomized trial conducted by Dr. Bouman and colleagues (28) assigned patients to three intensity groups: early high-volume hemofiltration (72–96 L/24 hrs), early low-volume hemofiltration (24–36 L/24 hrs), and late low-volume hemofiltration (24–36 L/24 hrs). These investigators found no difference in terms of renal recovery or 28-day mortality. Unfortunately, prescribed doses were not standardized by weight, making the potential variability in RRT dose large. Furthermore, the number of patients was small, making the study insufficiently powered and the frequency of sepsis too low compared with the typical populations reported to develop AKI in the world.

Recently, Dr. Saudan and colleagues (16) screened 371 patients with AKI treated with CRRT and enrolled 206 of them in a two-arm study: 102 to CVVH and 104 to CVVHDF. They prescribed 25 mL/hr/kg ultrafiltration in the CVVH group and 24 mL/hr/kg in the CVVHDF group; patients on CVVHDF were prescribed an adjunctive mean dialysis dose of 18 mL/hr/kg. The CVVHDF patients had significantly higher mean urea and creatinine reduction ratios 48 hrs after the initiation of continuous RRT than did the CVVH patients (50% vs. 40%, $p < .009$, and 46% vs. 38%, $p < .014$, respectively). Survival rates at 28 days and 90 days were higher with CVVHDF than with CVVH. Like previous trials, this study is underpowered; furthermore, it confounds the effects of dose and technique by adding dialysis to filtration. Nevertheless, pooled results from the last four studies (15, 16, 26, 28) seem to indicate a very large effect on survival in favor of augmented dosing (29). Although these data may still not be definitive, the best evidence to date supports the use of ≥35 mL/hr/kg for CVVH or CVVHDF, or 1.2 Kt/V daily IHD.

Another fundamental aspect of RRT, significantly affecting the meaning itself of dose, is the relation between prescribed and actually delivered therapy in patients with AKI. Delivery of prescribed dose can be limited by technical problems such as access recirculation, poor blood flows with temporary venous catheters, membrane clotting, machine malfunction, long times required for bags, and/or circuit substitution. Clinical issues such as hypotension and vasopressors requirements can be responsible for solute disequilibrium within tissues and organs. These aspects are particularly evident during IHD, less so during SLED, and even less so during CRRT. Treatment interruptions due to patient need for surgery or other diagnostic procedures also should be considered. In this case, IHD may result in a more efficient delivered/prescribed ratio.

In a prospective observational trial (30) it has been clearly showed that down-time (amount of hours spent off active treatment) adversely affects azotemic control; a significant correlation between down-time and creatinine levels was found ($p < .0001$). According to these authors, the down-time should be <8 hrs per day to maintain creatinine and urea concentrations with our operative setting (2 L/hr of ultrafiltration); for example, if one prescribed an ultrafiltration rate of 35 mL/hr/kg, only 23 mL/hr/kg would be delivered if down-time is 8 hrs/day. Dr. Evanson and colleagues (31) found that a high patient weight, male sex, and low blood flow were limiting factors affecting IHD administration, and that about 70% of dialysis delivered a Kt/V of <1.2. A retrospective study by Dr. Venkataraman and colleagues (32) also showed that, similarly, patients receive only 67% of prescribed CRRT therapy. Of note, in the CVVH dose trial (15), all patients achieved >85% of the prescribed dose. To obtain this goal, compensation for interruptions in treatment due to ICU procedures was made by increasing effluent flow rates in the subsequent hours. In a recent prospective trial, in which CRRT prescribed/delivered ratio was monitored, an average 10.7% ($p < .05$) reduction of therapy delivery was found, when compared with prescribed dose (10). This delivery reduction sometimes was caused by an estimation error resulting from the use of a dose calculator computer program, but more often was caused by the short operative treatment time compared with that prescribed.

These observations underline that RRT prescriptions for AKI patients in the ICU should be monitored closely if one wishes to ensure adequate delivery of prescribed dose and, importantly, to avoid underdialysis.

RRT Dose Delivery: Continuous, Intermittent, Hybrid

According to recent international surveys on clinical practice patterns, 80% of

centers administer CRRT, 17% use intermittent RRT (IRRT), and a very few apply peritoneal dialysis (1, 27, 33). Interestingly, in many centers intermittent techniques are utilized together with continuous ones, thus suggesting the possibility of multiple prescriptions and practices (9). Nonetheless, after years of debate, the scientific literature is not able to draw conclusions on which delivery modality is more appropriate to impact clinical outcomes. Many papers have been published on this issue and they must be analyzed critically.

From the point of view of a small solute clearance–based dose, the RRT modality that provides more dialysis seems to favorably impact the outcome. Thus, the central issue is the definition of "more dialysis" and ultimately of treatment dose. If the critical parameter is metabolic control, an acceptable mean blood urea nitrogen level of 60 mg/dL, easily obtainable in a 100-kg patient with a 2 L/hr CVVH, may be very difficult to reach even by intensive IHD regimens (34). Thus, once again we should consider that urea kinetics is just one of the parameters to be used to define treatment dose, while other solutes, water kinetics, and homeostasis control with possible immunomodulation are further elements to consider. For example, in addition to the benefits specifically pertaining to the kinetics of solute removal, increased RRT frequency results in decreased ultrafiltration requirements per treatment. The avoidance of volume swings related to rapid ultrafiltration rates also may represent another element of dose in which comparability is difficult. In such circumstances, in fact, not only are the patient results clinically stable, but less compartmentalization due to cardiopulmonary recirculation is observed, resulting in higher mean blood levels of solutes and higher solute removal at similar clearance values.

Many randomized controlled trials comparing intermittent and continuos RRT so far have provided only conflicting and puzzling results. Basing on scientific evidence, the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock (17) recently concluded that CVVH and IHD should be considered equivalent during AKI. A large comparative trial randomized 166 critically ill patients with AKI to either CRRT or IHD (35). The authors found that the CRRT population, despite randomization, had significantly greater severity of illness scores. Furthermore, despite better control of azotemia and a greater likelihood of achieving the desired fluid balance, CRRT had increased mortality. A smaller trial by the Cleveland clinic group (36) also failed to find a difference in outcome between one therapy and another. A meta-analysis of 13 studies conducted by Dr. Kellum and colleagues (37) concluded that, after stratification of 1400 patients according to disease severity, CRRT was associated with a significant decrease in the risk of death when similar patients were compared. The authors confirmed that a large, carefully controlled, randomized clinical trial should be undertaken. Another meta-analysis (38) found no difference between the two techniques.

Recently, the Program to Improve Care in Acute Renal Disease group conducted a retrospective trial and compared the outcomes of different RRT modalities in 368 patients (CRRT, n = 206 vs. IHD, n = 192) (39). Within the cohort, CRRT in comparison to IHD was associated with a significantly higher relative risk for mortality. The authors state that these data provide no evidence for a survival benefit afforded by CRRT. However, the authors admit that patients with CRRT were significantly sicker and that the results could reflect residual confounding by severity of illness. Furthermore, they state that a randomized clinical trial should be conducted "excluding patients with severe hypotension and hemodynamic instability, who may be poor candidates for traditional IHD." Probably, this sort of trial would not be of clinical relevance among critically ill patients.

Dr. Vinsonneau and colleagues (40) recently conducted a large, prospective, randomized, multicenter study in 21 ICUs over a 3.5-yr period. The primary end point was the 60-day mortality following the randomization of 360 patients with acute renal failure to either CVVHDF or IHD in centers that were familiar with both techniques. The eligibility criteria changed after 8 months because the inclusion rate was too low. No difference in 28, 60 (CVVHDF, 33% vs. IHD, 32%), and 90-day mortality between the two groups was found, and the authors concluded that all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with IHD. The study was well conducted and, at the moment, it is the best example of a randomized, controlled study effectively comparing the two techniques. Nonetheless, the study started >7 yrs ago, during which time the practices in both CVVHDF and IHD have changed considerably. As stated by Dr. Vinsonneau and colleagues, this may have led to changes in investigator practices during the study period, particularly with respect to the delivered dose of renal support. This possibility, however, is hard to verify given that the investigators, by protocol, started therapy with "initial standardized settings" then adapted these settings to meet individual patient requirements to obtain the metabolic control objectives. Interestingly, the mortality decreased in the IHD arm of the study over the time of recruitment, which reflected a change in practice toward an increase in dialysis prescription. Given the lack of control regarding the dosage in both arms of the study, definitive conclusions are hard to make regarding treatment. As mentioned in the accompanying editorial (41), the question of which treatment is better is influenced by the nature of the task. CRRT may be better in terms of total water and solute removal over 24 hrs and hemodynamic tolerance, but IHD can remove much more water and solute per hour and it does not require continuous anticoagulation nor complete patient immobilization.

However, the problem is not to achieve high efficiency in short time; we know we can (e.g., in chronic patients). It is to achieve the best blood purification and homeostasis restoration with the lowest possible rate of complications. Furthermore, the advantages of continuous therapies are largely supported when it is administered without prolonged interruptions, but that is often not the case. Again, the study by Dr. Vinsonneau and colleagues unfortunately does not provide this information. Finally, considering this as a negative trial, if it is true that all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with IHD, this means that they also can be safely treated by CVVHDF.

Other reports have drawn similar conclusions (42, 43). One of the common key points of these recent trials can be considered, however, that IHD has become safer and more efficacious with contemporary dialytic techniques. Furthermore, a liberal and extended use of CRRT may have become less safe and/or efficacious than previously considered or expected. Over the past two decades, technical ad-

vances in the delivery of IHD have dramatically decreased the propensity of IHD to cause intradialytic hypotension. These advances include the introduction of volume-controlled dialysis machines, the routine use of biocompatible synthetic dialysis membranes, the use of bicarbonate-based dialysate, and the delivery of higher doses of dialysis. Dr. Schortgen and colleagues (44) demonstrated that there was a lower rate of hemodynamic instability and better outcomes after implementation of a clinical practice algorithm designed to improve hemodynamic tolerance to IHD. Recommendations included priming the dialysis circuit with isotonic saline, setting dialysate sodium concentration at >145 mmol/L, discontinuing vasodilator therapy, and setting dialysate temperature to below 37°C. Thus, the original rationale for the widely held assumption that CRRT is a superior therapy may have dissipated over time.

On the other hand, we may speculate that similar advances have occurred in the field of CRRT. Bicarbonate-based replacement fluids are available today in conjunction with effective fluid balancing control systems. The operator interface has improved enormously and the practice of high volume hemofiltration, once the monopoly of specialized centers, is becoming routine in many nephrological and intensive care units. In our unit for example, the most recent technologies for IHD and CRRT coexist and patients are treated with both techniques depending on the specific needs and targets for prescription (Fig. 2).

In conclusion, the question of superiority of a modality for renal support may be artificial. In routine clinical practice, as designed by the Vinsonneau protocol, a change from one approach to another seems reasonable when clinical status changes (e.g., from CRRT to IHD when hemodynamics improve or patient is extubated and vice versa), even if this common sense approach has never been scientifically validated. Randomizing patients to receive one therapy or the other regardless of the conditions may yield results that are difficult to generalize to clinical practice. About 10 yrs ago, a similar passionate debate on ventilation weaning strategies (pressure support ventilation vs. T-piece spontaneous ventilation vs. continuous pressure airway pressure vs. synchronized intermittent mandatory ventilation) was ongoing. The scientific community finally agreed that it is difficult to select one method over another and that the *manner* in which the mode of weaning is applied may have a greater effect on the likelihood of weaning than the *mode* itself (45).

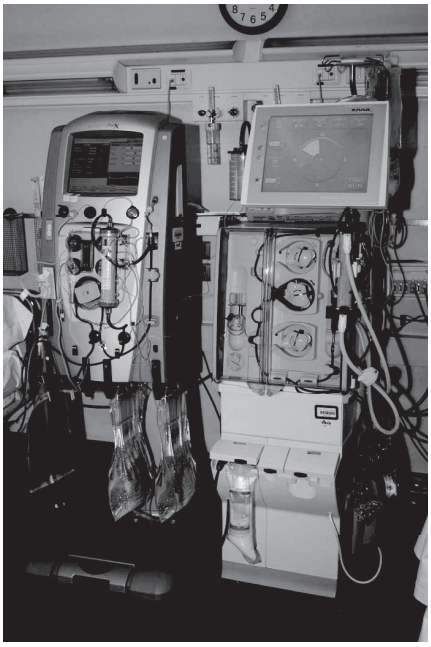

Figure 2. The latest machines for continuous renal replacement therapy *(left)* and intermittent hemodialysis *(right)* are utilized simultaneously in a critical care nephrology unit, demonstrating the need for flexible treatment and a possible rapid shift of patients from one treatment to the other.

Finally, the design of future trials should include as the primary outcome other parameters than mortality. Recently, the Beginning Ending Renal Support Therapy study group reported the results of a prospective observational study on a large worldwide cohort of 54 centers with 1,258 patients treated with RRT for AKI. CRRT was the most common initial modality used (1,002 patients, 80.0%), followed by IRRT (212 patients, 16.9%), and peritoneal dialysis/slow continuous ultrafiltration (40 patients, 3.1%) (33). Patients treated first with CRRT required vasopressor drugs and mechanical ventilation more frequently compared with those receiving IRRT. Unadjusted hospital survival was lower (35.8% vs. 51.9%; $p < .0001$). However, unadjusted dialysis independence at hospital discharge was higher after CRRT (85.5% vs. 66.2%; $p < .0001$). Multivariable logistic regression showed that choice of CRRT was not an independent predictor of hospital survival or dialysis-free hospital survival. However, the choice of CRRT was a predictor of dialysis independence at hospital discharge among survivors (odds ratio [OR], 3.333; 95% confidence interval [CI], 1.845–6.024; $p < .0001$). The choice of CRRT as initial therapy probably is not a predictor of hospital survival or dialysis-free hospital survival, but is an independent predictor of renal recovery among survivors.

Similar results were presented by other authors. In a randomized controlled trial, Dr. Mehta and colleagues (35) reported that initial CRRT was associated with a significantly higher rate of complete renal recovery than IRRT in the subgroup of surviving patients who received an adequate trial of therapy without crossover (CRRT, 92.3% vs. IRRT, 59.4%; $p < .01$). Dr. Bell and colleagues (46) showed that within 1102 patients surviving 90 days after inclusion in the cohort, 944 (85.7%) were treated with CRRT and 158 (14.3%) were treated with IHD. Seventy-eight patients (8.3%; CI, 6.6–10.2) never recovered their renal function in the CRRT group. The proportion was significantly higher among IHD patients, in which 26 subjects or 16.5% (CI, 11.0–23.2) developed need for chronic dialysis. Again, analyzing a smaller cohort, Dr. Jacka and colleagues (47) reviewed the records of 116 patients undergoing RRT and realized that renal recovery was significantly more frequent among patients initially treated with CRRT (21/24 vs. 5/14; $p = .0003$).

Hybrid techniques have arrived during the last years as a feasible compromise solution to this eternal dispute. They have been given a variety of names, such as SLED, sustained low-efficiency dialysis (48), prolonged daily intermittent RRT (49), extended daily dialysis (50), or simply extended dialysis (51), depending on variations in schedule and type of solute removal (convective or diffusive). Theoretically speaking, the purpose of such therapy would be the optimization of the advantages offered by either CRRT and IHD, including efficient solute removal with minimum solute disequilibrium, reduced ultrafiltration rate with hemodynamic stability, an optimized delivered to prescribed ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. These initial case series have shown the feasibility and high clearances potentially associated with such approaches. A single short-term, single-center trial comparing hybrid therapies to CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability (52). Recently, Dr. Baldwin and colleagues (52) randomized 16 patients to

3 consecutive days of treatment with either CVVH (8) or extended daily dialysis with filtration (8) and compared small-solute, electrolyte, and acid-base control. They did not find significant differences between the two therapies for urea or creatinine levels over 3 days. All electrolyte derangements before treatment were corrected as a result of treatment, except for one patient in the CVVH group who developed hypophosphatemia (0.54 mmol/L) at 72 hrs. After 3 days of treatment, there was a mild but persistent metabolic acidosis in the extended daily dialysis with filtration group compared with the CVVH group.

It is now possible to generate ultrapure replacement fluid and administer it in the ICU with a lower cost than CRRT, in greater amounts and for shorter periods of time. Hemofiltration may be combined with diffusion, or pure diffusion can be selected at any chosen clearance for a period of time that can encompass the day shift with its maximum staff availability or the night shift. Thus, the choices are now almost limitless: 3 or 4 hrs of IHD with standard settings or CRRT at 35 mL/kg/hr of effluent flow rate can be selected. SLED at blood and dialysate flow rates of 150 mL/min for 8 hrs during the day or SLED for 12 hrs overnight can be considered as an alternative. Otherwise, why not combine CRRT for the first 2 or 3 days when the patient is in the hyperacute phase with SLED thereafter as recovery takes place?

Going back to the lessons learned in ventilation therapy, the modes of RRT are beginning to resemble the modes of mechanical ventilation with ventilator settings seamlessly being changed to fit into the therapeutic goals and patient needs and phases of illness. Stereotyped approaches to ventilation are anachronistic and inappropriately try to fit the patient into a fixed therapy rather than tailoring the therapy to the patient. In the same vein, RRT should be adjusted to fulfill the needs of the patient.

CONCLUSIONS

As concluded by the Acute Dialysis Quality Initiative workgroup in 2001 (53, 54), delivered clearance should be monitored during all renal supportive therapies. No recommendations can be made for specific dialysis dosing for patients with specific diseases at this time. A minimum dose of RRT, however, needs to be delivered for AKI: the best evidence to date supports the use of ≥35 mL/hr/kg for CVVH, CVVHD, or CVVHDF, or 1.2 Kt/V daily IHD. It also should be recommended that the prescription should exceed the calculated "adequate" dose because of the known gap between prescription and delivery. Given that the spectrum of RRT has expanded from peritoneal dialysis and IHD alone approximately 25 yrs ago to the full spectrum of therapy from standard IRRT to high-volume CRRT, physicians ultimately may choose to take a much more flexible approach to RRT and RRT dose. Beyond such observations, a solute-based approach to the concept of dose seems too restrictive, although operatively relatively simple and, by analogy with end-stage renal failure, potentially linked to outcome. The dose/outcome domain map definitely is governed by several factors, including the type of therapy and the severity of the patient. As described in Figure 3, we may speculate that, as in any biological phenomenon in which two variables are correlated, there is an initial area of steep correlation between dose of RRT and patient outcome. Starting at the point at which zero dose or no therapy has 100% negative outcome, an area defined as "dose dependent," any small increase in dose will result in improved outcomes. This will be true until further increases in dose will not result in better outcomes and the curve will present a plateau. This region will be defined as "dose independent" or "practice dependent" or "severity dependent." In fact, beyond the breaking point of the curve, survival will not be affected by an increase in treatment dose but rather by the level of severity of the patient's medical conditions or by the number of combined measures put in place. Today, the breaking point for CRRT is at 35 mL/kg/hr in the normal population; however, if a septic population is analyzed, the breaking point may move up and the level of plateau may rise to 45 mL/kg/hr or even more.

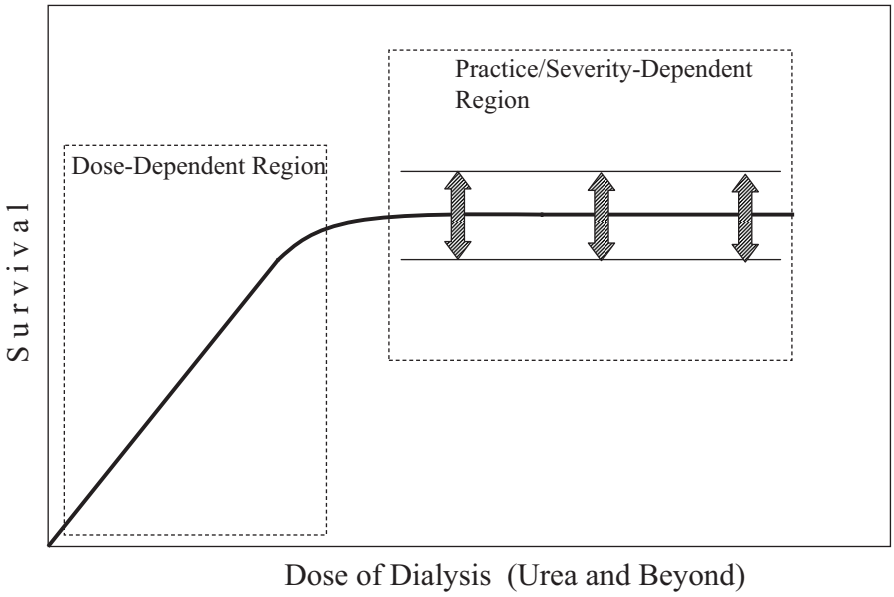

Figure 3. The dose/outcome domain map. *Left*, small improvements in treatment dose result in significant improvement in outcome. This is defined as the "dose dependent" region. *Right*, the curve reaches a plateau at which increased doses do not result in outcome improvements; the level of plateau can be influenced by the severity of illness or the treatment techniques utilized.

The level of the plateau will then be defined by other elements beyond treatment dose. In critically ill patients with AKI, these other dimensions of adequacy of RRT remain largely unexplored, but they are likely to be important for the final outcome. Future studies should focus on other aspects of dose (control of volume, acid base, toxicity, etc.) and assess their potential link with outcome.

Some of these questions already are being tested and the results likely will soon influence the field of RRT. The Dose Response Multicentre International collaboration (55) currently is seeking to address the issue of how practice patterns are currently chosen and performed. This is an observational, multicenter study conducted in ICUs. The primary aim is to study the delivered dose of dialysis, which will then be compared with ICU mortality, 28-day mortality, hospital mortality, ICU length of stay, and number of days of mechanical ventilation. It is hoped that

this international collaboration will provide a clearer picture of how RRT is chosen, prescribed, and delivered, and how such delivery may affect outcome. In November 2003, the Acute Renal Failure Trial Network initiated a multicenter, prospective, randomized, parallel-group trial of an intensive dose strategy vs. a conventional dose strategy of renal replacement therapy for the treatment of AKI caused by acute tubular necrosis in critically ill patients (56). The planned total enrollment is 1164 patients at 27 institutions during 3 yrs to achieve a power of 0.90 to detect a reduction in mortality from 55% to 45% based on renal replacement therapy dose. Patients will be randomized according to a 2×2 design to either receive IHD or CRRT. The patients randomized to intermittent therapy will then be randomized to either conventional every-other-day IHD or SLED. Patients randomized to CRRT also will be randomized to one of two different doses: 20 or 35 mL/kg/hr of effluent. This design is intended to deliver data on both a comparison between intermittent therapy and CRRT as well as one between "low" and "high" dose of RRT, regardless of treatment modality. The Australian and New Zealand Intensive Care Group also has recently been funded to conduct a multicenter, randomized, controlled trial of CRRT dose in critically ill patients with acute renal failure (56). The study will randomize 1,500 patients in 35 Australian and New Zealand ICUs to receive either postdilution CVVHDF at 25 mL/kg/hr or at 40 mL/kg/hr of effluent. This study will assume a conservative 90-day mortality rate of 60% in the control group and it is projected to have 90% power of detecting an 8.5% absolute reduction from a 90-day mortality of 60% to 51.5%. Thus, given that these studies are under way, it is likely that in the near future two large, randomized, controlled trials assessing the impact of RRT dose in AKI will be available to better inform clinical practice.

REFERENCES

1. Uchino S, Kellum JA, Bellomo R, et al: Acute renal failure in critically ill patients. A multinational, multicenter study. *JAMA* 2005; 294:813–818
2. Lameire N, van Biesen W, Van Holder R, et al: The place of intermittent hemodialysis in the treatment of acute renal failure in the ICU patient. *Kidney Int* 1998; 53(Suppl 66): S110–S119
3. Levy EM, Ascoli CM, Horowitz RJ: The effect of acute renal failure on mortality. *JAMA* 1996; 275:1489–1494
4. DuBose T, Warnock DG, Mehta RL, et al: Acute renal failure in the 21st century: Recommendation for management and outcomes assessment. *Am J Kidney Dis* 1997; 29:793–799
5. Chertow GM, Levy EM, Hammermeister KE, et al: Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 1998; 104:343–348
6. Bellomo R, Ronco C, Kellum JA, et al: Acute renal failure—definition, outcome measures, animal models, fluid therapy, and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8:R204–R212
7. Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31
8. Ricci Z, Bellomo R, Ronco C: Dose of dialysis in acute renal failure. *Clin J Am Soc Nephrol* 2006; 1:380–388
9. Ricci Z, Ronco C, D'amico G, et al: Practice patterns in the management of acute renal failure in the critically ill patient: An international survey. *Nephrol Dial Transplant* 2006; 21:690–696
10. Ricci Z, Salvatori G, Bonello M, et al: *In vivo* validation of the adequacy calculator for continuous renal replacement therapies. *Crit Care* 2005; 9:R266–R273
11. Gotch F, Sargent J: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28:526–534
12. Parker T, Hushni L, Huang W, et al: Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. *Am J Kidney Dis* 1994; 23:670–680
13. Eknoyan G, Levin N: NKF-K/DOQI clinical practice guidelines: Update 2000. *Am J Kidney Dis* 2001; 38:917
14. Eknoyan G, Beck GJ, Cheung AK, et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347:2010–2019
15. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 2000; 356:26–30
16. Saudan P, Niederberger M, De Seigneux S, et al: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006; 70:1312–1317
17. Dellinger PR, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
18. Brophy PD, Bunchman TE: References and overview for hemofiltration in pediatrics and adolescents. http://www.pcrrt.com/Protocols%20PCRRT%20Zurich.pdf. Accessed August 23, 2007
19. Sigler MH, Teehan BP, Daugirdas JT, et al: Slow continuous therapies. *In:* Handbook of Dialysis. Third Edition. Daugirdas JT, Blake PG, Todd SI (Eds). Philadelphia, PA, Lippincott Williams and Wilkins, 2001
20. Garred L, Leblanc M, Canaud B: Urea kinetic modeling for CRRT. *Am J Kidney Dis* 1997; 30(Suppl 4):S2–S9
21. Goldstein SL, Currier H, Graf C, et al: Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 2001; 107: 1309–1312
22. Foland JA, Fortenberry JD, Warshaw BL, et al: Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. *Crit Care Med* 2004; 32:1771–1776
23. Brause M, Nuemann A, Schumacher T, et al: Effect of filtration volume of continuous venovenous hemofiltration in the treatment of patients with acute renal failure in intensive care units. *Crit Care Med* 2003; 31: 841–846
24. Paganini EP, Tapolyai M, Goormastic M, et al: Establishing a dialysis therapy/patient outcome link in intensive care unit acute dialysis for patients with acute renal failure. *Am J Kidney Dis* 1996; 28(Suppl 3):S81–S89
25. Paganini EP, Kanagasundaram NS, Larive B, et al: Prescription of adequate renal replacement in critically ill patients. *Blood Purif* 2001; 19:238–244
26. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; 346:305–310
27. Uchino S, Bellomo R, Morimatsu H, et al: Continuous renal replacement therapy: A worldwide practice survey: The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators. *Intensive Care Med* 2007; 33:1563–1570
28. Bouman C, Oudemans-van Straaten H, Tijssen J, et al: Effects of early high-volume continuous veno-venous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective randomized trial. *Crit Care Med* 2002; 30: 2205–2211
29. Kellum JA: Renal replacement therapy in critically ill patients with acute renal failure: Does a greater dose improve survival? *Nat Clin Pract Nephrol* 2007; 3:128–129
30. Uchino S, Fealy N, Baldwin I, et al: Continuous is not continuous: The incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. *Intensive Care Med* 2003; 29: 575–578
31. Evanson JA, Himmelfarb J, Wingard R, et al: Prescribed versus delivered dialysis in acute renal failure patients. *Am J Kidney Dis* 1998; 32:731–738
32. Venkataraman R, Kellum JA, Palevsky P: Dosing patterns for CRRT at a large academic medical center in the United States. *J Crit Care* 2002; 17:246–250
33. Uchino S, Bellomo R, Kellum JA, et al: Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators

Writing Committee. Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. *Int J Artif Organs* 2007; 30:281–292
34. Clark WR, Mueller BA, Kraus MA, et al: Renal replacement quantification in acute renal failure. *Nephrol Dial Transplant* 1998; 13(Suppl 6):86–90
35. Mehta RL, McDonald B, Gabbai FB, et al: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163
36. Augustine JJ, Sandy D, Seifert TH, et al: A randomized controlled trial comparing intermittent with continuous dialysis in patients with AKI. *Am J Kidney Dis* 2004; 44: 1000–1007
37. Kellum J, Angus DC, Johnson JP, et al: Continuous versus intermittent renal replacement therapy: A meta-analysis. *Intensive Care Med* 2002; 28:29–37
38. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the intensive care unit: A systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; 40:875–885
39. Cho KC, Himmelfarb J, Paganini E, et al: Survival by dialysis modality in critically ill patients with acute kidney injury. *J Am Soc Nephrol* 2006; 17:3132–3138
40. Vinsonneau C, Camus C, Combes A, et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 2006; 29:379–385
41. Kellum J, Palevsky PM: Renal support in acute kidney injury. *Lancet* 2006; 29: 344–345
42. Guerin C, Girard R, Selli JM, et al: Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: Results from a multicenter prospective epidemiological survey. *Intensive Care Med* 2002; 28:1411–1418
43. Uehlinger DE, Jakob SM, Ferrari P, et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20: 1630–1637
44. Schortgen F, Soubrier N, Delclaux C, et al: Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: Usefulness of practice guidelines. *Am J Respir Crit Care Med* 2000; 162:197–202
45. Butler R, Keenan SP, Inman KJ, et al: Is there a preferred technique for weaning the difficult-to-wean patient? A systematic review of the literature. *Crit Care Med* 1999; 27:2331–2336
46. Bell M, Swedish Intensive Care Nephrology Group, Granath F, et al: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. *Intensive Care Med* 2007; 33:773–780
47. Jacka MJ, Ivancinova X, Gibney RT: Continuous renal replacement therapy improves renal recovery from acute renal failure. *Can J Anaesth* 2005; 52:327–332
48. Marshall MR, Golper TA, Shaver MJ, et al: Urea kinetics during sustained low efficiency dialysis in critically ill patients requiring renal replacement therapy. *Am J Kidney Dis* 2002; 39:556–570
49. Naka T, Baldwin I, Bellomo R, et al: Prolonged daily intermittent renal replacement therapy in ICU patients by ICU nurses and ICU physicians. *Int J Artif Organs* 2004; 27: 380–387
50. Kumar VA, Craig M, Depner T, et al: Extended daily dialysis: A new approach to renal replacement for acute renal failure in the intensive care unit. *Am J Kidney Dis* 2000; 36:294–300
51. Kielstein JT, Kretschmer U, Ernst T, et al: Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: A randomized controlled study. *Am J Kidney Dis* 2004; 43:342–349
52. Baldwin I, Naka T, Koch B, et al: A pilot randomised controlled comparison of continuous veno-venous haemofiltration and extended daily dialysis with filtration: Effect on small solutes and acid-base balance. *Intensive Care Med* 2007; 33:830–835
53. Kellum JA, Mehta R, Angus DC, et al: The First International Consensus Conference on Continuous Renal Replacement Therapy. *Kidney Int* 2002; 62:1855–1863
54. Acute Dialysis Quality Initiative Web site. www.adqi.net. Accessed January 2008
55. Kindgen-Milles D, Journois D, Fumagalli R, et al: Study protocol: The DOse REsponse Multicentre International collaborative initiative (DO-RE-MI). *Crit Care* 2005; 9:R396–R406
56. Bellomo R: Do we know the optimal dose for renal replacement therapy in the intensive care unit? *Kidney Int* 2006; 70:1202–1204