CHAPTER 158

Outcomes of Intermittent Hemodialysis in Critically Ill Patients With Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Compare general short- and long-term outcomes of intermittent versus continuous dialysis modalities in patients with acute kidney injury.
2. Compare impact of intermittent dialysis versus continuous renal replacement therapies on hemodynamic stability and de novo chronic kidney disease (CKD) and progression to end-stage renal diseases.
3. Discuss contraindications to intermittent dialysis and on particular clinical problems, including vascular access, anticoagulation, and dose of dialysis.

Acute kidney injury (AKI) is common in critically ill patients and associated with high morbidity and mortality.[1] Worldwide, 13.5% of patients in the intensive care unit (ICU) receive renal replacement therapy (RRT) for AKI.[2] For such patients, 90-day survival is approximately 50%, and dialysis dependence at 90 days is roughly 21%.[3]

Current modalities of RRT for AKI include conventional acute intermittent hemodialysis (IHD), multiple variations of continuous renal replacement therapy (CRRT), hybrid treatments (such as prolonged intermittent renal replacement therapy [PIRRT]), and high volume peritoneal dialysis. There are significant practice variations in the provision of PIRRT across institutions, with respect to prescription, technology, lack of standardization of the procedure, and delivery of therapy. As reviewed in a recent paper,[4] clinical trials generally have demonstrated that PIRRT is not inferior to CRRT regarding patient outcomes and offers cost-effective RRT along with other advantages usually ascribed to IHD, such as early patient mobilization and decreased nursing time. Overall, PIRRT is less common than CRRT, the latter being prescribed in the United States and Europe by 20% to 30% of clinicians and to about 10% of patients. However, PIRRT is more common in the Asia-Pacific region: up to 25% of patients are treated with PIRRT in Australasia, Malaysia, and the Philippines.

In the recent global study on the epidemiology of AKI in patients admitted in the ICU, AKI occurred in 57.3% at day 1 of ICU stay, and RRT was needed in 23.5% of these AKI patients.[2] The RRT procedures used were CRRT in 615 sessions (75.2%) and intermittent hemodialysis in 197 sessions (24.1%); peritoneal dialysis occurred in only six sessions (0.7%). In a recent multicenter randomized trial on timing of initiation of RRT in critically ill AKI patients, a total of 462 RRT modalities were applied; 47% of modalities were IHD, 32% with CRRT and in 21% both modalities were used.[5]

Although acute IHD and CRRT are thus the two most-used modalities in the ICU, practice patterns vary regionally because of cost, reimbursement policies, resources of the healthcare institution, and the technical expertise of the physician and nursing staff. Recently, IHD has undergone resurgence through variants that provide slower fluid and solute removal over longer periods of time, resulting in improved hemodynamic stability and increased solute clearance. Other advantages of intermittent therapies are early patient mobilization and decreased nursing time. In this regard, because dialysate can be prepared in the hemodialysis unit, after which the 90-L container filled with dialysate can be transported easily, the GENIUS (Fresenius Medical Care AG, Bad Homburg, Germany) batch hemodialysis system is used frequently in the treatment of dialysis requiring AKI in ICU patients.[6–8] Genius is a single-pass batch dialysis machine that combines the advantages of a simple

operation (because of the uncomplicated technical design of a batch system) with highly efficient dialysis therapy. The technical features of the Genius dialysis machine are described in detail elsewhere.[7,9]

This system can be used for conventional IHD and the PIRRT modalities.[6,10,11] An important factor in the application of a given modality is whether the management of the AKI patient in the ICU is exclusively in the hands of the intensivist or is a combined management of intensivist and nephrologist. In the United States, where therapy prescription and delivery are managed primarily by nephrologists, IHD still is applied predominantly. In contrast, in Australia, CRRT is used most commonly and managed by intensivists. A recent survey in German ICUs revealed that selection of initial RRT modality in AKI is more dependent on the size, local structures, and education of the intensivists rather than on the patient needs,[12] whereas in a more general European survey[13] most of the intensivists were responsible for prescribing RRT (92.6 %). Half of the respondents reported using both IHD and CRRT, but only 10% preferred IHD over CRRT. The reasons for preferring CRRT were the perception of better hemodynamic stability, better therapeutic effect resulting from cytokine removal, and easier fluid balance control. However, no study has ever provided proof of a better outcome with CRRT versus IHD.

In many parts of the world, ICU nursing staff members deliver all modalities of acute RRT; in other countries, support from nephrology staff is required. As machinery platforms become more universal for CRRT and IHD, it is likely that ICU expertise in all modalities will grow, provided in-service education and support are adequate to develop and maintain technical skills. The Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guideline for Acute Kidney Injury[14] suggests that for the majority of critically ill AKI patients the available modalities of RRT are complementary, with the caveats that CRRT and PIRRT be used in hemodynamically unstable patients and that CRRT is preferred for patients with acute brain injury or other causes of increased intracranial pressure of generalized brain edema.

This chapter addresses the outcomes of conventional IHD in critically ill patients with AKI. For sake of clarity, the intermittent character of hemodialysis is considered only if the dialysis session is not longer than the "classic" 4 to 5 hours; the hybrid treatments (such as PIRRT) are discussed in other chapters of this book.

VASCULAR ACCESS

Access for IHD is usually via uncuffed untunnelled (temporary), semirigid double-lumen polyurethane or silicone catheters preferably in the internal jugular or femoral veins, or less frequently subclavian catheters, because the latter are associated with a higher incidence of procedural complications, venous stenosis, and thrombosis. Overall, KDIGO guidelines recommend right-sided internal jugular catheters with bias-cut spiraled ports as the first choice for intermittent HD and PIRRT, with femoral and left-sided internal jugular catheters as the second and third choices, respectively. However, a recent randomized controlled trial (RCT) found no differences in catheter dysfunction and dialysis performance between either jugular or femoral access groups.[15] Tunneled dialysis catheters are difficult to insert and exchange and should be reserved for patients who require prolonged RRT (>3 weeks), or with nonrecovery of renal function who are transitioning to maintenance dialysis.[14,16]

Anticoagulation

Worldwide, unfractionated heparin is still the most widely used anticoagulant, but many European centers have switched from unfractionated to low-molecular-weight (LMW). The European practice guideline for prevention of dialyzer clotting suggested in 2002 using LMW rather than unfractionated heparin in HD for chronic dialysis patients,[17] and many European centers have extrapolated this incorrectly to IHD for AKI, although studies in this setting are lacking.[18] However, LMW heparins are expensive and generally have not been found superior to heparin in terms of dialysis-related bleeding or other complications.[19] There are a variety of alternatives to standard use of heparin. Low-dose heparin protocols are successful in lowering bleeding risk, although some systemic anticoagulation does still occur.[20]

A multitude of other anticoagulation regimens have been developed, including argatroban, lepirudin, danaparoid, fondaparinux, prostacyclin, and nafamostat. Most of these equally lead to systemic anticoagulation, precluding their use in patients at high bleeding risk. Options then include tight heparinization (using the minimally effective dose of heparin), regional citrate anticoagulation, or anticoagulation-free dialysis.[21] Recently, acetate-free citrate-containing dialysate concentrates were introduced into clinical practice. Besides the advantages of acetate-free dialysate, this provides a modest local anticoagulant effect inside the dialyzer. Citrate containing dialysate allows reduction of heparin dose while maintaining extracorporeal circuit patency and dialyzer clearances.[22]

For "high-risk" patients, anticoagulation can be avoided frequently and successfully during IHD using saline flushes.[14] In most patients, a 2-hour dialysis session can be performed without anticoagulation, but in patients with thrombocytopenia and coagulation disorders, even longer sessions up to CRRT can be performed without anticoagulation without clotting. The HepZero study[23] compared "standard-of-care" heparin-free dialysis, defined as regular saline flushes or predilution hemodiafiltration, against dialysis using a heparin-grafted membrane (Evodial, Gambro-Hospal). The primary end point was successful completion of the first dialysis session according to well-defined criteria. The end point was reached in 68.5% of patients randomized to the heparin-grafted membrane group as compared with 50.4% in standard of care. Use of this heparin-grafted membrane was noninferior to saline infusion, but superiority could not be demonstrated. A combination of a heparin-grafted polyacrilonitrile (AN69ST) membrane with a 0.80 mmol/L citric acid-containing dialysate without systemic anticoagulation recently was used as IHD modality in critically ill patients.[24] This combination showed circuit clotting in 17.5% and in 19% of sessions with prescribed treatment time of at least 4 hours. Clotting shortened treatment time in 15.2% of sessions by a median of 55 minutes. Complete clotting of the circuit with inability for retransfusion occurred in 4.2% of sessions. These results favorably compare as to clotting complications with the published outcomes of other anticoagulation-free IHD strategies, but the incidence of circuit clotting in this cohort appears to be higher than previously reported for regional citrate anticoagulation with a calcium-free dialysate. Results of these studies[23,24] align with a recent single-center study from France[25] and clearly position the use of heparin-grafted membranes as a valid alternative to saline infusion in patients at high risk of bleeding.

Regional citrate anticoagulation (RCA) is another technique providing sufficient anticoagulation of the

extracorporeal blood circuit, thus minimizing contact activation-associated coagulopathy, while avoiding systemic anticoagulation.[26,27]

Other than treatment complexity that necessitates close monitoring and adjustment of RRT prescription, the main potential complications of RCA are metabolic.[28,29] More simple and user-friendly RCA protocols have been described for use with the Genius closed-loop dialysis batch system,[30] but in principle, these protocols also could be used with regular dialysis machines, provided the ratio of dialysate to blood flow is maintained stable.

In a large RCT, bleeding complications were more frequent in the CRRT group and were the major reason for switching modalities from CRRT to IRRT.[31] With IRRT, anticoagulation may be omitted or minimized and does not take place all day long.

Pschowski et al.[32] recently investigated procedural (i.e., RRT-related) and nonprocedural blood loss as well as transfusion requirements in regard to the chosen mode of dialysis (i.e., IHD versus CVVH) in 250 patients with RRT requiring AKI. Major all-cause bleeding complications were observed in 23% IHD versus 26% of CVVH group patients ($p = .95$), but the rate of RRT-related blood loss events and mean total blood volume lost was increased under CVVH compared with IHD.

Overall, complete avoidance of anticoagulation is more successful with intermittent therapies, because the lower blood flow rates employed during continuous modalities increase the propensity to clotting. With heparin-free protocols, it is particularly important to address factors such as venous catheter function and the degree of extracorporeal hemoconcentration.

SELECTION OF THE MEMBRANE

The clinical importance of this issue has diminished as the cost differential between synthetic (more biocompatible) and cellulosic (less biocompatible) membranes has narrowed and the use of unsubstituted cellulosic membranes has decreased. In fact, in most parts of the world, and especially in Europe, membranes manufactured from unsubstituted cellulose are meanwhile used very rarely or have even disappeared from the market. As a consequence, the "original" biocompatibility discussion has lost most of its clinical relevance in large parts of the world.[33] Nevertheless, if for economic or other reasons, only unsubstituted cellulosic membranes are available or preferable, it is better to dialyze patients with AKI, rather than not dialyze them, because biocompatible membranes cannot be obtained.

DOSE OF DIALYSIS IN INTERMITTENT HEMODIALYSIS

Depending on catabolic demands, electrolyte disturbances, and volume status AKI patients may undergo dialysis treatments for 3 to 5 hours on a thrice-weekly, alternate-day, or daily schedule. Dialysis dose can be increased in several ways: increasing treatment time (e.g., extended daily dialysis), by increasing treatment frequency (e.g., daily dialysis), or by increasing the intensity of each individual dialysis session, usually quantified as the product of urea clearance (K) and treatment time (t) divided by body urea volume (V) (Kt/V). In an observational study, Paganini et al. demonstrated a survival benefit in patients with intermediate severity of illness scores when the delivered Kt/Vurea was more than 1.0 per treatment as compared with a delivered Kt/Vurea of less than 1.0 per treatment.[34] From a conceptual viewpoint, the concept of Kt/V is hard to defend in patients with AKI at ICU, because neither urea generation nor urea distribution volume are constant nor accurately measurable. In addition, there have been no prospective clinical trials evaluating the relationship between the delivered Kt/V when dialysis is provided on a constant treatment schedule and outcomes. Schiffl et al. reported on a prospective trial of 160 patients with AKI assigned in an alternating fashion to alternate-day or daily IHD.[35] The more frequent treatment schedule was associated with a reduction in mortality at 14 days after the last dialysis session from 46% in the alternate-day dialysis arm to 28% in the daily treatment arm ($p = .01$). Duration of renal failure declined from 16 ± 6 days to 9 ± 2 days ($p = .001$). However, this study has been criticized because the delivered dose of therapy per session was low in both treatment arms (Kt/Vurea < 0.95), resulting in a high rate of symptoms in the alternate-day dialysis arm that may have been due to overtly inadequate dialysis.[36]

The KDIGO Clinical Practice Guideline for Acute Kidney Injury recommends delivering a Kt/Vurea of 3.9 per week when using IHD in AKI, calculating the weekly Kt/Vurea as the arithmetic sum of the delivered dose of all treatments.[14] This recommendation is based loosely on the results of the impact of frequency of IHD as evaluated in the Acute Renal Failure Trial Network (ATN) study.[37] In this study, 1124 critically ill patients were randomized to an intensive or less intensive strategy for the management of RRT. When patients were hemodynamically stable, they received IHD, and when hemodynamically unstable they received CRRT or SLED, regardless of treatment arm. Patients randomized to the less intensive treatment strategy received IHD on a thrice-weekly (alternate-day except Sunday) schedule, while patients randomized to the intensive arm received six-times-per-week (daily except Sunday) IHD. Sixty-day all-cause mortality was 53.6% in the intensive treatment arm as compared with 51.5% in the less-intensive arm ($p = .47$), with no interaction by modality. Eloot et al., using different dialysis strategies resulting in equal Kt/Vurea, were able to demonstrate in chronic HD patients that total solute removal was dependent on the duration of the treatment, despite the lack of differences in Kt/Vurea.[37a] This effect was, not unexpectedly, more expressed as the molecular size of the considered solute increased. Remarkable, however, was that also for small solutes such as urea and creatinine, an increase in total solute removal with longer dialysis sessions was observed. In addition, Kt/Vurea is hampered by the lack of a variable urea distribution volume and urea generation in critically ill patients. Furthermore, this approach for calculating an equivalent weekly Kt/V is not consistent with urea kinetic principles, and rigorous data for the appropriate dose of therapy when treatments are delivered more frequently than three times per week are not available.[38] Based on these and other arguments, the European Renal Best Practice (ERBP) position statement on the KDIGO guidelines does not recommend using Kt/Vurea as a measure of dose of dialysis in AKI when using intermittent (or extended) RRT in AKI.[33] For intermittent therapies, the ERBP group suggests to adapt the duration of IHD "to allow maintenance of metabolic and volume status." This is based on the ATN trial,[37] in which intermittent treatments of approximately 4 hours with a blood flow of 350 ± 60 mL/min and a dialysate flow of 730 ± 130 mL/ min were prescribed either on alternating days (less-intensive arm)

or 6 days/week (more-intensive arm) without differences in mortality or recovery of renal function.

COMPARISON OF OUTCOMES BETWEEN INTERMITTENT VERSUS CONTINUOUS DIALYSIS MODALITIES

The choice of intermittent versus continuous therapy currently is based on the experience of the nephrology team and the availability of therapies.[39,40] When both therapies are available, the indication of CRRT or IHD is based on the patient's neurologic, hemodynamic, and catabolic status. Ideally, the therapy should be tailored to the patient's demands, which changes daily in the critically ill. It is now accepted that more than one therapy will be used for managing patients during the course of AKI. Transitions from CRRT to IHD are common and reflect the changing needs of patients during their AKI course. For instance, patients in the ICU initially may start on CRRT when they are hemodynamically unstable, transition to SLED-EDD when they improve, and leave the ICU on IHD. In the ATN trial, 57% of the patients had more than one therapy, whereas 23% and 20% had IHD and CRRT alone.[37] Whenever possible, all dialytic modalities should be used as indicated to best support patient needs through their course.

The different forms of CRRT are intended to run on a continuous basis (24 hr/day). However, frequent blood pump halting and prolonged manipulation time for the replacement of tubing systems can result in inadequate treatment doses and blood loss in these patients. Uchino et al.[41] reported that the median daily down time was 3.0 hours (1.0 to 8.3), and concluded that the term *continuous* in CRRT is somewhat inaccurate because of frequent interruptions in CRRT treatment. Frequent interruptions of CRRT resulting from extracorporeal circuit failure inevitably increase CRRT down time and also are associated with blood loss, requiring multiple blood transfusions[42] and increasing costs.[43] In this regard a recent study on CRRT[44] found down time of 3.3 (2.8 to 5.7) hours per day, even after introduction of a specialized CRRT team in their ICU. In the recent meta-analysis on extended daily dialysis versus CRRT the mean therapy duration in 12 studies where it was reported varied between 15.2 and 23.5 hours per day.[45]

Given the perceived greater hemodynamic tolerance of CRRT as compared with IHD, particularly in patients with underlying hemodynamic instability, it has been postulated that CRRT would be associated with improved clinical outcomes.

Both modalities achieve a satisfactory degree of metabolic control. Despite numerous observational studies, randomized controlled trials (RCTs),[31,46–56] and meta-analyses,[49,57–60] neither modality has been found superior in terms of mortality. The most inclusive meta-analysis by the Cochrane collaboration[60] found similar hospital mortality, ICU mortality, length of stay, and renal recovery in critically ill patients treated with CRRT or IHD. Some authors have pointed to flaws in the design of many of the above-cited RCTs.[57] However, some of these biases were logistic and in that case inherent to the very nature of the strategies implied,[61] such as the incapacity to enroll patients into continuous protocol arms because of unavailability of appropriate devices,[56] or the impossibility to reach the preset exchange volume.[31] Logistical factors thus also should be taken into account when deciding on CRRT or IRRT.[61] Other biases skewing the results in some of these RCTs are related to study design, conduct, and reporting flaws.

HEMODYNAMIC STABILITY

In critically ill patients with AKI requiring RRT, one of the most common and severe complications related to IHD is symptomatic intradialytic hypotension (IDH).[62] IDH affects an estimated 30% of dialysis treatments among critically ill patients with AKI.[63] It has been suggested that IDH impairs, and at times precludes, renal recovery,[46,64,65] and also is associated independently with greater in-hospital mortality.[46] Interventions to mitigate hemodynamic instability of IHD in end-stage renal disease (ESRD) patients, which also are applied in AKI patients, include cool dialysate,[66] albumin administration,[67] sequential ultrafiltration (UF)-HD,[68] sodium modeling,[69] biofeedback,[70] and extending dialysis time.[71]

Despite the optimization of practice guidelines, including many of the above-mentioned interventions in the ICU setting,[72,73] many patients remain affected by IDH, which is associated with increased morbidity. By prolonging the course of the AKI and inducing repeated renal damage, IDH may affect evolution to ESRD. The origin of intradialytic hypotension is multifactorial, depending on factors related to the patient and the disease and on the dialysis modalities. Continuous and/or more extended therapies are claimed to provide better hemodynamic stability, although there is little or no evidence to underpin this. For example, the European Renal Best Practice workgroup feels that hemodynamic stability also can be preserved in IHD, when correct attention is given to the connection procedure, using limited blood and dialysate flow rates, lowering dialysate temperature, and prolonging the procedure.[33] Schortgen et al.[73] showed that adherence to specific guidelines to improve hemodynamic tolerance of IHD progressively improved the tolerance also in critically ill patients. After implementation of these guidelines (Table 158.1), these researchers observed fewer

TABLE 158.1

Guidelines to Improve Hemodynamic Tolerance of IHD in Critically Ill Patients With Acute Kidney Injury

Recommendations for systemic use	• Use only modified cellulosic membranes rather than cuprophane • Connect the two lines of the circuit, which have been filled with 0.9% saline, to the catheter simultaneously • Set dialysate sodium concentration to ≥145 mmol/L • Limit the maximal blood flow to 150 mL/min with a minimal session duration of 4 hours • Set dialysate temperature to ≤37°C
Advice for the most hemodynamically unstable patients	• Start session by dialysis and continue with ultrafiltration alone • Cool dialysate at 35°C • Stop vasodilator therapy
Additional recommendations	• Start session without ultrafiltration, then adapt UF/h rate according to hemodynamic response • Strictly adapt ultrafiltration order to patient's volemia and weight loss requirement

systolic blood pressure drops at initiation and during the IHD sessions. Although the ICU mortality rates before and after implementation of the guidelines were similar, death rate and length of ICU stay after the implementation were significantly less than predicted from SAPS II scores. Other studies have demonstrated that adherence to these simple measures can decrease dramatically the incidence of hypotension during IHD sessions.[31,51] These studies demonstrated that improved hemodynamic tolerance could be achieved using IHD when teams were trained and simple prescription rules were applied.

More recently the impact on the cardiovascular stability during IHD for AKI of online monitoring devices that control blood volume (BV) and blood temperature in the ICU setting has been explored.[74] In a prospective single-center three-arm randomized controlled trial, 600 dialysis sessions in 74 consecutive AKI critically ill patients were involved to assess intradialytic hypotension. Standard dialysis therapy with constant ultrafiltration (UF) rate, cool dialysate, and high sodium conductivity (Treatment A) was compared with regimens with adjunctive interventions including BV control (Treatment B) and the combination of BV and active blood temperature control (Treatment C). Each dialysis session was assigned randomly to one of the three treatment arms and served as statistical unit; 572 dialysis sessions were analyzed (188, 190, and 194 in treatments A, B, and C, respectively). Hypotension occurred in 16.6% treatments, with similar rates among the arms. Hemodynamic parameters and dialysis-related complications did not differ between therapies. Based on generalized estimating equation adjusted to dialysate sodium conductivity, higher SOFA score the day of dialysis session, the need for vasopressors, and lower systolic blood pressure at the onset of the session were identified as independent predictors of hypotensive episodes, whereas regimens containing the new online monitors were not.

A recent study[75] concluded that sodium modeling was unable to reduce intradialytic hypotension during hemodialysis for AKI in the ICU.

IMPACT OF INTERMITTENT HEMODIALYSIS VERSUS CONTINUOUS RENAL REPLACEMENT THERAPY ON DE NOVO CHRONIC KIDNEY DISEASE AND PROGRESSION TO END-STAGE RENAL DISEASE

Whether the choice of RRT modality may affect renal recovery and if so, whether treatment with IHD, compared with CRRT, may have higher rates of dialysis dependence is subject of a never-ending debate.

Several somewhat older studies have suggested that CRRT is associated with improved rates of recovery of kidney function in surviving patients as compared with IHD;[52,65,76–78] all of these studies are notable for higher mortality rates in the CRRT group.

On the other hand, several meta-analyses on this topic[57,59,60,79] failed to demonstrate superiority of CRRT on recovery of kidney function. A more recent systematic review[80] included 23 studies, 7 RCTs, and 16 observational studies. In AKI survivors, IHD as initial treatment modality was associated with a 1.7 times greater risk for dialysis dependence when compared with initial treatment with CRRT (odds ratio 1.73; 95% CI 1.35–1.68). This finding was robust across subgroups, including those with CKD, but the differences between IHD and CRRT did not reach statistical significance when the analysis was restricted to RCTs (OR 1.73; 95% CI 0.73–1.68; n = 7). However, the included RCTs were relatively small and of moderate quality and did not all include hemodynamically unstable patients. Allocation bias was present in observational trials, with IRRT appearing to be preferentially allocated to patients with lesser illness severity, greater hemodynamic stability, and some degree of chronic kidney disease at baseline. On the other hand, although the study does not seem to contain a pooled analysis for mortality, most included studies seem to display a higher short-term mortality in CRRT, not allowing patients to survive and reach the end stage. In addition, including observational studies may decrease the power base of systematic reviews.

Recently, a large population-based Canadian study of critically ill patients surviving to 90 days after an episode of AKI treated with RRT used propensity matching for treatment allocation.[3] The exposure of interest was the initial type of RRT received. This was defined as the receipt of any form of CRRT or IHD, based on the first RRT physician claim that was recorded in the administrative database. Of the 5771 patients who started with CRRT, 40% survived to day 90, while of the 7706 who started IHD, 56% survived to day 90. CRRT survivors were more likely to have been mechanically ventilated, experienced sepsis, or undergone cardiac surgery on the index hospitalization. Individuals for whom IHD was the initial form of therapy were more likely to have a history of CKD, a prior episode of AKI, and prior consultation with a nephrologist. Out of a total of 2315 CRRT recipients, 2004 (87%) were matched successfully and extensively to 2004 IHD recipients. Participants were followed over a median duration of 3 years. The authors found that at 90 days after initiation of IHD, 20.8% of patients were on dialysis compared with 16.4% of CRRT patients ($p < .0003$). At follow-up, after a mean of approximately 3 years, the prevalence of chronic dialysis was 6.5 per 100 person-years among patients initially treated with CRRT compared with 8.2 among patients initially treated with IHD ($p < .0001$; hazard ratio 0.75%–95% CI, 0.65–0.87). This relation was more prominent among those with preexisting CKD and heart failure. Collectively, the data in the systematic review[80] and of Wald et al.[3] imply that among critically ill patients with AKI requiring RRT, initial therapy with CRRT may confer a higher likelihood of recovery to dialysis independence, but apparently at the expense of a higher acute mortality. It can be argued that despite extensive and apparently "successful" matching of the two patient groups, the retrospective analysis of administrative databases or population registries, not providing patient-level data and registered in very heterogeneous populations of critically ill patients is not without problems. It would be interesting to see confirmation of the results of Wald et al.[3] in a prospective RCT before definitely concluding that CRRT is more "protective" for long-term kidney function than IHD in patients surviving AKI.

In an accompanying editorial Bellomo and Schneider[81] based on the results of Wald et al.[3] calculated that, assuming that 50% of patients with severe AKI are alive at 90 days, for every 100 patients treated with conventional IHD, 2.7 extra patients will be on chronic dialysis for a median period of more than 3 years. Assuming a total cost of care for 1 year of dialysis in the United States of between $129,000 and $173,000 (data from before the bundling),[82] this effect on recovery would add approximately $150,000 per year for 3 years to the cost of patient care ($4500 per IHD-treated patient). This additional cost would exceed the higher cost of the CRRT therapy, neutralizing one of

the arguments frequently used by the proponents of IHD over CRRT. This cost calculation is based on a number of assumptions, reflecting US cost calculations, and thus not immediately applicable outside the United States. Furthermore the data provided in the study of Berger[82] are based on the US reimbursement policy before the "bundling" and thus less relevant in present times. Finally, as the study by Wald et al.[3] also included patients who already had CKD before their AKI episode, it is unknown how many of those patients would have reached the end-stage CKD anyway, therefore attenuating the extra cost hypothesized by Bellomo and Schneider.[81]

Supporting the hypothesis that CRRT as initial dialysis modality in critically ill patients is associated with better short-term renal recovery in surviving patients can be found in a recent study by Sun et al.[83] These authors compared continuous venovenous hemofiltration (CVVHF) (greater than 72 hours) to extended daily hemofiltration (EDHF) (8 to 12 hours daily) for the treatment of septic AKI. Patients in the CVVHF group had significantly higher recovery of renal function (50.77% of CVVHF group vs. 32.50% in the EDHF group, $p = .026$). Median time to renal recovery was 17.26 days for CVVHF patients and 25.46 days for EDHF patients ($p = .039$). Use of CRRT was associated with a (nonsignificant) trend for fewer episodes of hypotension. However, 60-day all-cause mortality was similar between CVVHF and EDHF groups (44.62%, and 46.25%, respectively; $p = .844$). Although this study is interesting, it is a retrospective analysis of a rather small study (145 patients, studied over 4 years).

Relevant to the earlier discussion is the recent investigation of Liang et al.,[84] who analyzed a retrospective cohort study of adults admitted to ICUs from 2000 to 2008 and who received RRT (continuous RRT and IHD) for AKI and survived to hospital discharge or 90 days. The selection of the dialysis strategy was based largely on the patient's hemodynamic status. Renal recovery (alive and not requiring RRT) and reasons for nonrecovery (death or ESRD) at 90 and 365 days were analyzed. Of 4738 patients with KDIGO stage 3 AKI, 1338 (28.2%) received RRT, and 638 (47.7%) survived to hospital discharge (353 IHD [55.3%] and 285 CRRT [44.7%]). Recovery from AKI was lower for IHD versus continuous CRRT at 90 days (66.6% IHD vs. 75.4% CRRT; $p = .02$) but similar at 365 days (54.1% IHD vs. 59.6% CRRT; $p = .17$). In multivariable analysis, there was no difference in odds of recovery at 90 or 365 days for patients initially treated with CRRT versus IHD. These results suggest thus that renal recovery and clinical outcomes in survivors are similar between IHD and CRRT, when initial RRT modality is chosen primarily on hemodynamic parameters.

In conclusion, all these discrepant results published in the studies already discussed show that, although some studies show a trend towards higher risk for chronic dialysis in AKI patients who have been treated with IHD, the possibility cannot be excluded that confounders such as CKD already present before AKI or mortality before the end stage has been reached may have skewed the interpretation.

CONTRAINDICATIONS TO INTERMITTENT HEMODIALYSIS

CRRT is considered the therapy of choice in patients with, or with risk for, brain edema, although this is based on a limited number of rather old and moderate quality studies. In specific conditions, for instance, in patients with cerebral edema[85] or liver failure, CRRT is an absolute preference.[86]

Ronco et al.[85] studied patients who were treated for 2 subsequent days in random sequence with IHD (one 4-hour session; Kt/V ≥ 1) and CVVH (one 24-hour session; Kt/V ≥ 1). Brain computed tomography scans were obtained before and after the IHD and CVVH sessions in each patient. Under baseline conditions, the only macroscopic morphologic alteration was a slight brain edema in some patients. Significant changes in the density of white matter and gray matter were observed after IHD in all patients, whereas no changes were observed after CVVH. The investigators concluded that in contrast to CVVH, IHD may lead to higher water content in the brain after each session, leading to a postdialytic brain edematogenic state. No other study has been performed in this area.

Davenport et al.[86] investigated the effect of various modes of RRT in 30 consecutive patients referred with fulminant hepatic failure and AKI. Cardiac output decreased during the first hour of 30 intermittent machine hemofiltration treatments, as did tissue oxygen delivery and tissue oxygen uptake. In contrast, there was no significant change during 30 continuous hemofiltration and/or dialysis treatments. Intracranial pressure remained stable during the continuous modes but increased during intermittent machine hemofiltration, with the greatest increase, 55% ± 9%, within the first hour. Mean arterial blood pressure was stable during treatment with the continuous modes, but decreased during the first hour of intermittent machine hemofiltration, resulting in a maximum reduction in cerebral perfusion pressure of 35%. In this group of critically ill patients suffering from combined liver and renal failure, continuous modes of RRT seem to result in better cardiac and intracranial stability than standard intermittent modes of treatment.

SUMMARY AND CONCLUSIONS

The major advantages of IHD are the fast removal of small solutes and toxins, allowing a more restricted treatment period, less need for anticoagulation, and more down time for diagnostic and therapeutic interventions. Therefore the different modalities (CRRT and IHD) may not be completely interchangeable in individual patients and individual clinical situations across a heterogeneous ICU population. Treatment with RRT requires balancing the pros and cons of different RRT options and modalities depending on the specific clinical situation. In fact, all ICUs performing RRT for AKI should have all modalities available. Newer hybrid therapies such as extended duration dialysis, sustained low-efficiency dialysis, or the Genius system, which are used increasingly in Europe, allow this type of flexibility and can be used in a wide range of settings from near continuous, very low efficient to intermittent high efficient and therefore may combine some of the advantages of IHD and CCRT while avoiding their disadvantages.[87]

Key Points

1. Convincing evidence that continuous replacement therapies are associated with better overall outcomes than intermittent hemodialysis is still lacking.

2. More advantages of intermittent hemodialysis are the fast removal of small solutes and toxins, allowing shorter treatment periods, less need for anticoagulation, and more down time for diagnostic and therapeutic interventions.
3. Currently there are no equivocal data demonstrating the superiority of any modality of renal replacement therapy for critically ill patients with acute kidney injury.
4. Dialysis treatment of these patients requires balancing the pros and cons of different dialysis options and modalities depending on the specific clinical situation and the availability and local experience of the intensive care unit and nephrology team.

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