Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose

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Literature review current through: Oct 2019. | **This topic last updated:** Aug 02, 2019.

INTRODUCTION

The management of patients with acute kidney injury (AKI) is supportive, with renal replacement therapy (RRT) indicated in patients with severe kidney injury. Multiple modalities of RRT are available. These include intermittent hemodialysis (IHD); continuous renal replacement therapies (CRRTs); and hybrid therapies, also known as prolonged intermittent renal replacement therapies (PIRRTs), such as sustained low-efficiency dialysis (SLED) and extended-duration dialysis (EDD). Despite these varied techniques, mortality in patients with AKI remains high, exceeding 40 to 50 percent in severely ill patients. (See "Kidney and patient outcomes after acute kidney injury in adults".)

The initiation of RRT in patients with AKI prevents uremia and immediate death from the adverse complications of renal failure. It is possible that variations in the timing of initiation, modalities, and/or dosing may affect clinical outcomes, particularly survival, although few studies have directly examined these issues.

The optimal timing, type of modality, and dosing strategy for patients with AKI who require RRT is reviewed here. The different modalities are discussed separately. (See "Continuous renal replacement therapy in acute kidney injury" and "Prolonged intermittent renal replacement therapy" and "Use of peritoneal dialysis for the treatment of acute kidney injury in adults" and "Acute hemodialysis prescription".)

URGENT INDICATIONS

Accepted urgent indications for RRT in patients with AKI generally include:

- Refractory fluid overload
- Severe hyperkalemia (plasma potassium concentration >6.5 mEq/L) or rapidly rising potassium levels
- Signs of uremia, such as pericarditis, encephalopathy, or an otherwise unexplained decline in mental status
- Severe metabolic acidosis (pH <7.1)
- Certain alcohol and drug intoxications

The likelihood of requiring RRT is increased in patients with underlying chronic kidney disease (CKD) in proportion to the degree of reduction in glomerular filtration rate (GFR) at baseline. This was illustrated in a study that compared the prehospitalization estimated GFR (eGFR; from the most recent serum creatinine) in 1746 hospitalized patients who developed dialysis-requiring AKI with that of 600,820 hospitalized patients who did not [1].

Compared with patients with an estimated baseline GFR >60 mL/min/1.73 m^2, the risk of developing AKI requiring dialysis progressively and significantly increased with the severity of underlying CKD. The adjusted odds ratios (ORs) were 1.7, 4.6, and 20.4 for patients with stage 3 (eGFR of 30 to 59 mL/min/1.73 m^2), 4 (eGFR 15 to 29 mL/min/1.73 m^2), and 5 CKD (eGFR <15 mL/min/1.73 m^2), respectively. (See "Overview of the management of chronic kidney disease in adults", section on 'Definition and classification'.)

TIMING OF ELECTIVE INITIATION

We electively initiate RRT prior to the development of severe electrolyte disturbances and volume overload. Thus, we favor electively initiating RRT in patients with K >6.0 mEq/L or severe metabolic acidosis (pH <7.2) despite optimal medical management and who show no sign that kidney function or metabolic acidosis is improving. We electively initiate RRT among patients who are repeatedly in positive fluid balance despite aggressive attempts at diuresis, particularly if they have increasing oxygen requirements. Observational studies have demonstrated an association between the severity of volume overload at the time of initiation of RRT and mortality risk [2-4].

In the absence of clinically significant uremic symptoms or specific indications such as severe electrolyte abnormalities or volume overload, the optimal timing of RRT initiation is controversial. We generally suggest not initiating RRT in the absence of these indications, particularly if the blood urea nitrogen (BUN) is <110 mg/dL.

Randomized, controlled trials that have compared strategies of early versus delayed initiation of RRT (in the absence of obvious indications) have yielded conflicting results [5-11]. A meta-analysis of 11 randomized trials showed no benefit of early initiation on mortality [12]. There was also no difference between early and late initiation on the risk of dialysis dependence, length of intensive care unit (ICU) or hospital stay, or recovery of renal function. However, the strength of this analysis is low in part because of heterogeneity due to variable definitions of early versus late initiation. In addition, most trials had an unclear or high risk of bias for allocation concealment.

Several of the largest trials in this analysis [5-9,11] demonstrated no benefit with earlier initiation of RRT; one large trial found benefit [10].

- The best data are from a multicenter, randomized trial that included 620 patients who had severe AKI but did not have an emergent indication for RRT and required either or both mechanical ventilation and catecholamine infusion [5]. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (an increase in serum creatinine to three times baseline, **or** increase in serum creatinine to ≥4.0 mg/dL [≥353.6 micromol/L], **or** reduction in urine output to <0.3 mL/kg per hour for ≥24 hours, **or** anuria for ≥12 hours). (See "Definition and staging criteria of acute kidney injury in adults".)

  Patients were excluded who had BUN >112 mg/dL (40 mmol/L), serum potassium >6 mEq/L (or >5.5 mEq/L despite medical intervention), pH <7.15 (related to metabolic or mixed acidosis), or pulmonary edema (requirement for oxygen flow rate >5 L/min to maintain oxygen saturation >95 percent or, among intubated patients, requirement for fraction of inspired oxygen >50 percent). These patients were excluded because they were considered to have an urgent need for RRT and thus could not ethically be assigned to delayed RRT.

  Patients were assigned to a strategy of early RRT (within six hours after documentation of severe AKI) or to a strategy of delayed RRT initiation. The delayed strategy required RRT initiation after the onset of severe hyperkalemia, metabolic acidosis, or pulmonary edema, all defined by parameters included in the exclusion criteria listed above, or after an increase in BUN >112 mg/dL (40 mmol/L) or development of oliguria for more than 72 hours after allocation.

  Overall, there was no benefit associated with the early RRT strategy. Mortality at 60 days did not differ between the early- and late-strategy groups (48.5 versus 49.7 percent, respectively). Forty-nine percent of the patients in the delayed-strategy group never received RRT, and diuresis, possibly suggesting recovery of renal function, occurred earlier in the delayed-strategy group. Patients in the delayed-strategy group required more medical interventions for the treatment of complications of AKI, including more diuretics for volume management (36.5 versus 1.3 percent) and medical treatment for hyperkalemia (22.9 versus 5.5 percent) and metabolic acidosis (16.7 versus 6.8 percent). Compared with the delayed-strategy group, catheter-related infections and hypophosphatemia were more common in the early-strategy group (5 versus 10 percent and 15 versus 22 percent, respectively).

- Similar findings were reported in a second randomized trial of 488 patients that compared strategies of earlier versus delayed initiation of RRT in patients with early septic shock and severe AKI who did not have an emergent indication for RRT [11]. AKI was defined by meeting at least one of the criteria for the failure stage of the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification (an increase in serum creatinine to three times baseline, **or** increase in serum creatinine by ≥0.5 mg/dL [≥44.2 micromol/L] to ≥4.0 mg/dL [≥353.6 micromol/L], **or** urine output <0.3 mL/kg per hour for ≥24 hours, **or** anuria for ≥12 hours), which corresponds to the Acute Kidney Injury Network (AKIN) and KDIGO stage 3 definitions of AKI. Patients were randomly assigned to immediate RRT initiation (within 12 hours of AKI diagnosis) or to delayed RRT initiation. Patients in the delayed-initiation group received RRT if they developed an indication for emergent RRT (such as serum potassium >6.5 mEq/L, pH <7.15, or diuretic-resistant fluid overload) or at 48 hours after AKI diagnosis if spontaneous renal recovery had not yet occurred.

  The trial was stopped early for futility after a planned interim analysis by an independent data and safety monitoring board. There was no difference in mortality at 90 days between the early- and delayed-initiation groups (58 versus 54 percent, respectively). In the delayed-initiation group, 93 patients (38 percent) did not receive RRT; of these, 21 died before RRT was initiated, 70 had spontaneous renal recovery, and two did not receive RRT for other reasons. While the results of this trial clearly showed no survival benefit to earlier initiation of RRT, the choice of delaying RRT by only 48 hours may have limited the study's ability to detect a difference between the strategies for initiation of RRT.

- By contrast, one single-center, randomized trial showed a survival benefit conferred by early initiation of RRT (continuous hemodiafiltration) [10]. This trial included 231 critically ill patients with moderate AKI, as defined by KDIGO criteria for stage 2 (including creatinine ≥2 times baseline or urinary output <0.5 mL/kg/hour). All patients also had severe sepsis, required vasopressors or catecholamines, or had refractory volume overload; there was no exclusion for patients with emergent indications for RRT. Patients were assigned to prompt RRT initiation (within eight hours of study eligibility) or to a delayed strategy in which patients received RRT within 12 hours after progressing to KDIGO stage 3 criteria (urine output <0.3 mL/kg/hour for ≥24 hours and/or threefold increase in serum creatinine or increase ≥4 mg/dL with an acute increase of ≥0.5 mg/dL) or developed an indication for RRT (such as serum urea level >100 mg/dL [comparable to BUN >47 mg/dL], potassium >6 mEq/L, serum magnesium >8 mEq/L, urine output 200 mL over 12 hours, or diuretic-resistant edema). In the delayed-initiation group, 11 patients ended up not receiving RRT; of these, only six patients did not progress to stage 3, three patients had recovery of renal function, and three patients died.

  Compared with delayed or no initiation, earlier RRT initiation reduced 90-day mortality (hazard ratio [HR], 0.66, 95% CI 0.45-0.97). Moreover, more patients recovered renal function in the early versus delayed group by 90 days (odds ratio [OR] 0.55, 95% CI 0.32-0.93), and both the duration of RRT and the hospital stay were shorter in the early-initiation group.

  However, although this was a carefully performed trial, the effect size of the observed benefits to earlier RRT seems disproportionate to the relatively small differences in the timing of RRT initiation. Since almost all patients ended up receiving RRT, the only difference between groups was the time to RRT initiation, which was less than 24 hours. It is possible that the relatively small size of the trial or subtle bias associated with an unblinded single-center study resulted in an overestimate of the treatment benefit [13]. A shift of three events between the treatment groups would have resulted in a loss of statistically significant differences between groups.

One additional randomized trial, the Standard versus Accelerated Initiation of RRT in AKI (STARRT-AKI; NCT02568722), is underway. This multinational trial plans on enrolling 2866 patients with KDIGO stage 2 or 3 AKI who do not have an emergent indication for RRT and will randomly assign them to strategies of either early (within 12 hours) or delayed RRT initiation.

The KDIGO guidelines state that RRT should be initiated emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist but also suggest that, among patients who do not have life-threatening indications, the clinician consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests, rather than using any specific BUN or creatinine threshold, when making the decision to initiate RRT [14].

OPTIMAL MODALITY

A large number of modalities are available for RRT. These include intermittent hemodialysis (IHD), peritoneal dialysis, continuous renal replacement therapy (CRRT), and hybrid therapies such as sustained low-efficiency hemodialysis (SLED).

Data do not support the superiority of any particular mode of RRT in patients with AKI. In the majority of patients, selection of modality should therefore be based upon local expertise and availability of staff and equipment. However, in selected patients, other factors may prevail. As an example, in patients with acute brain injury or fulminant hepatic failure, continuous therapy may be associated with better preservation of cerebral perfusion. However, the costs associated with CRRT may be greater than with other modalities of RRT.

Continuous renal replacement therapies versus intermittent hemodialysis — CRRT represents a family of modalities that provides continuous support for severely ill patients with AKI. These include continuous hemofiltration, hemodialysis, and hemodiafiltration, which involve both convective and diffusive therapies. Although superior clearance of middle- and larger-molecular-weight molecules is associated with convective therapies (hemofiltration) compared with diffusive therapies (hemodialysis), there are no studies clearly showing improved clinical outcomes compared with the type of solute transport.

Studies suggest that survival and recovery of renal function are similar with both CRRT and IHD, and the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI suggest using intermittent and continuous RRT as complementary therapies in patients with AKI [14].

The majority of studies comparing CRRT and IHD have been observational or retrospective case series [15-19]. After adjustment for severity of illness, there appears to be no survival benefit associated with CRRT [20,21]. One observational series has suggested an increased adjusted mortality risk associated with CRRT, although incomplete adjustment for severity of illness may have confounded this finding [22].

Of greater importance, multiple prospective, randomized studies have also compared outcomes of AKI supported using either IHD or CRRT [23-27]. As examples:

- In a multicenter study, 166 patients with AKI were randomly assigned to IHD or CRRT [24]. CRRT was associated with significantly higher all-cause mortality at 28 days (59.5 versus 41.5 percent) and in-hospital mortality (65.5 versus 47.6 percent). However, despite randomization, patients randomly assigned to CRRT were significantly more likely to have higher Acute Physiologic and Chronic Health Evaluation (APACHE) III scores and liver failure. After adjustment for these characteristics, there was no increased risk of death with CRRT (adjusted odds of death 1.58, CI 0.7-3.3).
- In the HemoDiafe Study (a prospective, multicenter, French study), 360 patients with AKI and multi-organ dysfunction syndrome were randomly assigned to IHD or continuous venovenous hemodiafiltration (CVVHDF) [23]. The primary endpoint was survival at 60 days. Severity of illness was similar in both randomized groups, protocol adherence was good, both groups used the same dialysis membranes, and there was a low rate of crossover from intermittent to continuous therapies (3.3 percent). At 60 days, survival was the **same** in both groups (32 and 33 percent in the intermittent and continuous groups, respectively). In addition, both therapies were associated with similar rates of hypotension, including the group of hemodynamically unstable patients.

While the HemoDiafe Study was the largest and most rigorously conducted randomized, controlled trial comparing modality of RRT in AKI, definitive conclusions must be tempered by limitations of the trial design and execution. The use of heparin, rather than regional anticoagulation during continuous therapy, may have contributed to issues of systemic bleeding and clotting of the extracorporeal circuit. In addition, over the duration of the study, the mortality rate in the intermittent therapy arm declined over time, whereas it remained constant in the continuous therapy arm. The reasons for these trends are uncertain and may reflect changes in delivery of IHD over time. In addition, the mean duration of the hemodialysis treatments were longer than is typically employed in clinical practice, raising questions regarding the ability to translate these results into clinical practice. Importantly, however, this study demonstrates that is possible to successfully perform IHD in practically all patients with AKI given the findings of similar hypotensive rates with stable and unstable patients and the low crossover rate from intermittent to continuous therapy.

The Clinical Trial Comparing Continuous versus Intermittent Hemodialysis in Intensive Care Unit Patients (CONVINT) trial was a single-center, randomized, controlled trial of 252 critically ill patients in Germany who were randomly assigned to continuous venovenous hemofiltration (CVVH) at a prescribed dose of 35 mL/kg/hour or daily hemodialysis [27]. Nineteen and one-half percent of the 128 patients randomized to IHD were switched to CVVH after a mean of 4.4±12 days for severe hypotension or volume management, while 45.9 percent of patients randomized to CVVH were switched to IHD after a mean of 6.2±5.6 days because of repeated filter clotting, bleeding necessitating discontinuation of anticoagulation, metabolic control, thrombocytopenia, or improvement in overall status and need for mobilization.

Survival 14 days after discontinuation of RRT was 39.5 percent in the IHD group as compared with 43.9 percent in the CVVH group, with no difference in in-hospital mortality or mortality at 30 days of follow-up. Similarly, there was no difference in recovery of kidney function.

Meta-analyses that compared outcomes with CRRT and IHD have also been performed [28-33]. Overall, no survival benefit can be attributed to either modality.

- Recovery of renal function – Recovery of kidney function appears to be the same with CRRT and IHD. Although some studies report better recovery with CRRT [34-37], these reports only evaluated renal recovery in patients who survived, thereby failing to account for mortality differences between groups. When the analysis combined mortality and nonrecovery of renal function, both groups showed similar recovery of function [38,39]. Randomized studies have also found no such benefit with CRRT [23,25,26]. These observations were confirmed in a meta-analysis that included 3971 survivors of RRT-requiring AKI. A pooled analysis of 16 observational studies (n = 3499) showed a higher rate of dialysis dependence associated with IHD, but analysis of seven randomized trials (n = 472) showed no difference in recovery of kidney function between groups [33].
- Other differences – CRRT may be associated with the following advantages compared with IHD:
  - Enhanced hemodynamic stability, which may be particularly beneficial in hemodynamically unstable patients [25]. Hemodynamic stability is thought to be related to slower solute and volume removal and the effects of modest hypothermia often associated with CRRT.
  - More consistent net salt and water removal, particularly in hemodynamically unstable patients, thereby permitting superior management of volume overload and nutritional requirements [4,25].
  - Enhanced clearance of inflammatory mediators, which may provide benefit in septic patients, particularly using convective modes of continuous therapy [40-42]. However, a meta-analysis of convection versus diffusion demonstrated no benefit to convection [43]. Open-label, randomized, controlled trials have also shown no benefit of high-volume hemofiltration in sepsis [44] or cardiogenic shock following cardiac surgery [9].
  - Among patients with acute brain injury or fulminant hepatic failure, continuous therapy may be associated with better preservation of cerebral perfusion [45].

The actual importance of these benefits is uncertain, given the absence of a difference in survival between these modalities. As an example, although convective therapy may provide enhanced clearance of proinflammatory mediators, it may also result in removal of beneficial antiinflammatory mediators. In addition, the maximal achieved extracorporeal clearance of these mediators is low relative to the rates of generation and endogenous clearance.

Prolonged intermittent renal replacement therapy — Although prolonged intermittent renal replacement therapy (PIRRT) has been shown to have similar hemodynamic effects and provides similar metabolic control as CRRT, there are few data comparing outcomes with either IHD or CRRT [46]. In a single-center study of 60 patients treated with either PIRRT or CRRT, PIRRT was associated with comparable or better clinical outcomes [47]. Similar results were observed in a second single-center study comparing PIRRT to CVVH in 232 critically ill patients [48]. There was no difference in 90-day all-cause mortality between the PIRRT group and the CVVH group. Patients treated with PIRRT required fewer days of mechanical ventilation, required fewer days in the intensive care unit (ICU), and received fewer blood transfusions, resulting in an overall lower cost of therapy. A subsequent meta-analysis of 7 randomized, controlled trials and 10 observational studies comparing PIRRT with CRRT found no difference in mortality or recovery of kidney function associated with modality of therapy [49]. (See "Prolonged intermittent renal replacement therapy", section on 'Definition and indications for PIRRT'.)

Peritoneal dialysis — Peritoneal dialysis has a long history of use in the treatment of AKI; however, there have been few rigorous comparisons between peritoneal dialysis and other modalities of RRT in AKI.

- A prospective study was performed in Vietnam in which 70 patients with AKI due to either malaria or sepsis (48 and 22 individuals, respectively) were randomly assigned to either peritoneal dialysis or CVVH [50]. A markedly increased risk of death was observed among the group administered peritoneal dialysis (47 versus 15 percent, odds ratio [OR] 5.1, 95% CI 1.6-16). Possible reasons for the poorer survival in the peritoneal dialysis group include lower overall creatinine clearance, use of acetate (not bicarbonate) in the peritoneal dialysis dialysate, and other peritoneal dialysis-specific factors that are not yet defined [17]. In addition, the peritoneal dialysate was made in the study hospital pharmacy, while commercial peritoneal dialysate used in most countries contains lactate instead of acetate, and was performed using rigid catheters. The use of heparin in the hemofiltration arm may also have had therapeutic benefit in patients with malaria. Extrapolation from this study is limited as the study population was very different from that encountered in most developed countries.

- A randomized, controlled trial compared high-volume peritoneal dialysis to daily IHD in 120 patients with acute tubular necrosis [51]. There were no differences in mortality rate (58 and 53 percent) and recovery of kidney function (28 and 26 percent) in the two treatment arms, although peritoneal dialysis was associated with a shorter duration of need for dialysis.

- A meta-analysis of eight observational cohorts and four randomized, controlled trials found no difference in mortality comparing peritoneal dialysis to extracorporeal modalities of RRT [52].

OPTIMAL DOSING

Intermittent hemodialysis — Dosing in intermittent hemodialysis (IHD) is based upon the dose delivered per session, as well as the frequency of sessions. Thus, outcomes may vary based upon differences in dose per session, as applied to a fixed treatment schedule, or with differences in treatment schedule, as applied to a fixed dose per session. In addition, alterations in the dose per session as well as in the dialysis schedule can also be evaluated.

There have been no studies that have prospectively evaluated the impact of differences in dose per session in patients undergoing IHD on a fixed schedule, such as three times per week. Some data suggest that dosing may have an impact on patients with intermediate levels of disease severity. For example, in a retrospective study of 844 patients in intensive care units (ICUs) with AKI that used Kt/V as a measure of the delivered dose of acute IHD, improved survival was observed with a higher Kt/V (>1) among patients with **intermediate levels** of illness severity [53]. By comparison, among those either extremely ill or not very ill, the intensity of the dialysis treatments was less influential on outcome.

In one study that evaluated the impact of frequency of IHD on outcomes, 160 patients with AKI were assigned in an alternating fashion to either daily or every-other-day hemodialysis [34]. Enrolled patients were likely to have intermediate levels of illness severity, which was supported by both Acute Physiologic and Chronic Health Evaluation (APACHE) scores and the concurrent offering of continuous renal replacement therapy (CRRT) at the study center. Compared with every-other-day dialysis, daily therapy was associated with a significant reduction in mortality (28 versus 46 percent), fewer hypotensive episodes during hemodialysis, and more rapid resolution of AKI (mean 9 versus 16 days). The delivered dialysis dose in the every other day group, as assessed by single-pool Kt/V, was **low** (0.94 per dialysis). By comparison, the daily dialysis group received the same per treatment delivered dose, but it was delivered twice as frequently. Thus, this study may have best concluded that inadequate therapy is associated with increased mortality.

In contrast, the Veterans Affairs (VA)/National Institutes of Health (NIH) Acute Renal Failure Trial Network (ATN) study did **not** find a difference in mortality associated with a more intensive dosing strategy for RRT [54]. The details of this study are discussed in the next section.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for AKI recommend delivering a Kt/V of 3.9 per week for patients undergoing intermittent therapy [14]. While these results are loosely based on the results of the ATN study, several caveats need to be considered. In the ATN study, the targeted dose of IHD in both treatment arms was a Kt/V of 1.2 to 1.4 per treatment, with a median delivered Kt/V of 1.3 per treatment [54]. The weekly dose of dialysis recommended in the KDIGO guidelines is the arithmetic sum of the median dose in the less intensive arm, summed over the course of a week. Since a median delivered Kt/V of 1.3 implies that half of treatments had a delivered Kt/V of less than this value, it is not clear that a per-treatment dose of 1.3 represents the appropriate target. In addition, the approach of taking the arithmetic sum of the individual treatment dose to calculate a weekly dose is not consistent with urea kinetic modeling; the weekly dose provided by six treatments with a Kt/V of 0.65 is not equivalent to three treatments with a Kt/V of 1.3 [55]. We therefore recommend that, if IHD is provided three times per week, the targeted dose of therapy should be a Kt/V of ≥1.2 per treatment, with monitoring of the delivered dose of therapy. If this minimum dose is achieved, there is **no** evidence that more frequent hemodialysis is associated with improved outcomes, unless necessitated for specific acute indications (eg, hyperkalemia). Conversely, if a Kt/V of ≥1.2 per treatment cannot be achieved, treatment frequency should be increased.

If more frequent IHD is provided, the targeted dose per treatment may be lower; however, the optimal dose is not defined. Surveys of practice in the United States suggest that monitoring of the delivered dose of hemodialysis is only infrequently assessed [56].

The Hanover Dialysis Outcome (HAND-OUT) study compared extended-duration dialysis (EDD), provided for approximately eight hours per day, with a more intensive regimen where additional eight-hour treatment sessions were provided to maintain the blood urea nitrogen (BUN) <42 mg/dL [57]. No difference in survival or recovery of kidney function was observed with more intensive treatment.

Continuous renal replacement therapy — For patients on CRRT, we prescribe an effluent flow rate of approximately 25 mL/kg/hour in order to achieve (despite interruptions and CRRT downtime, which are inevitable) a minimum effluent rate of 20 mL/kg/hour over a 24-hour period. This is consistent with the 2012 KDIGO guidelines [14]. (See "Prescription of continuous renal replacement therapy in acute kidney injury in adults", section on 'CRRT dose'.)

Outcomes of an increased dose of CRRT have been assessed in several randomized, controlled trials and three meta-analyses [8,58-63].

Most studies found that, compared with standard-intensity dialysis, higher-intensity dialysis did not result in improved survival or clinical benefits:

- In the United States VA/NIH ATN study, all 1124 patients were treated with IHD, CRRT, or prolonged intermittent renal replacement therapy (PIRRT) based upon hemodynamic status [54]. Patients were randomly assigned to one of two dosing arms:
  - Intensive therapy – Hemodialysis and PIRRT were given six times per week with a target Kt/V of 1.2 to 1.4 per treatment (median delivered dose of 1.3 per treatment), while CRRT was provided with an effluent flow rate of 35 mL/kg per hour.
  - Less intensive therapy – Hemodialysis and PIRRT were given three times per week with a target Kt/V of 1.2 to 1.4 per treatment (median delivered dose of 1.3 per treatment), while CRRT was provided with a flow rate of 20 mL/kg per hour.

The death rate at day 60 was the same for both groups (53.6 percent with intensive therapy and 51.5 percent with less intensive therapy). In addition, the duration of RRT and the rate of recovery of kidney function or nonrenal organ failure were similar for both treatment arms. The group that received intensive therapy had an increased number of hypotensive episodes. Thus, more intensive renal support beyond that obtained with a standard thrice-weekly regimen (with a target Kt/V of 1.2 to 1.4 per treatment) or standard CRRT (with an effluent flow rate of 20 mL/kg per hour) does not improve clinical outcomes.

- In the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) study (a trial in Australia and New Zealand), 1508 patients with AKI were randomly assigned to continuous venovenous hemodiafiltration (CVVHDF) at an effluent flow of either 25 or 40 mL/kg/hour [64]. At 90 days, mortality was the same in each group (44.7 percent, odds ratio [OR] 1.00, 95% CI 0.31-1.23). In addition, the incidence of patients who continued to receive RRT at 90 days was similar with both dialysis doses (6.8 and 4.4 percent of higher- and lower-intensity groups [OR 1.59, 95% CI 0.86-2.92]).

- Three meta-analyses (3841 patients and 8 trials, 3999 patients and 12 trials, and 2402 patients and 5 trials) found that more intensive therapy did not improve survival compared with less intensive regimens [61,62]. There was significant trial heterogeneity in all meta-analyses.

- Two additional studies evaluating even higher doses of continuous venovenous hemofiltration (CVVH; 70 to 80 mL/kg/hour) in patients with severe sepsis [44] or shock after cardiac surgery [9] found no benefit associated with further augmentation of RRT dose.

Observational studies have suggested that the actual delivered effluent volume during CRRT is substantially less than the prescribed dose. In the Dose Response Multicentre International Collaborative Initiative (DO-RE-MI) study of 338 patients treated with CRRT, for example, the median delivered dose of CRRT was 27 mL/kg/hour despite a median prescribed dose of 34.3 mL/kg/hour [65]. In addition, the actual time on therapy each day in both the ATN and RENAL studies probably exceeded the time on therapy achieved in clinical practice due to enhanced attention to minimizing interruptions in therapy. We therefore suggest that the prescribed dose exceed the desired delivered dose by a factor of approximately 20 to 25 percent to adjust for interruptions in study therapy.

In a patient-level meta-analysis of seven randomized, controlled trials comparing more intensive with less intensive RRT in AKI, more intensive RRT was associated with delayed recovery of kidney function, particularly in patients in whom the initial modality of RRT was CRRT, but was not associated with mortality [66].

DISCONTINUATION OF THERAPY

RRT is usually continued until the patient manifests evidence of recovery of kidney function. Most often, recovery is assessed based on empiric data. In oliguric patients, the primary manifestation of recovery of kidney function is an increase in urine output; however, this finding may not be apparent in patients who are nonoliguric. Recovery of kidney function may also be manifest by a progressive decline in serum creatinine concentration after initial attainment of stable values (assessed daily during continuous renal replacement therapy [CRRT] or predialysis in patients managed with intermittent hemodialysis [IHD]) despite a constant dose of renal support. More objective assessment of recovery of kidney function can be obtained by measurement of creatinine clearance. As an example, in the Acute Renal Failure Trial Network (ATN) study, creatinine clearance was assessed on six-hour timed urine collections obtained when the urine output exceeded 30 mL/hour [54]. Since the serum creatinine concentration may not be constant during the collection, the average concentration can be estimated by measuring serum creatinine at the beginning and end of the timed collection or based on the midpoint serum creatinine concentration. A precise level of kidney function needed to allow discontinuation of renal support has not been established; however, a creatinine clearance <12 mL/min is probably inadequate to allow discontinuation of therapy. In the ATN study, renal support was discontinued when the measured creatinine clearance exceeded 20 mL/min and was left to the discretion of providers when in the range of 12 to 20 mL/min [54].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute kidney injury in adults".)

SUMMARY AND RECOMMENDATIONS

- Urgent indications for renal replacement therapy (RRT) in patients with acute kidney injury (AKI) include volume overload refractory to diuretics, severe hyperkalemia, metabolic acidosis, uremia, and toxic overdose of a dialyzable drug. (See 'Urgent indications' above.)
- It is preferable to initiate RRT electively prior to the development of an urgent indication. Absolute thresholds based on azotemia or other measures are not well defined; thus, when to initiate RRT is a matter of clinical judgment as well as circumstance. We electively initiate RRT prior to the development of severe electrolyte disturbances and volume overload. We favor electively initiating RRT in patients with K >6.0 mEq/L or severe metabolic acidosis (pH <7.20) despite optimal medical management who show no sign that kidney function or metabolic acidosis is improving. We electively initiate RRT in patients who are repeatedly in positive fluid balance despite aggressive attempts at diuresis, particularly if they have increasing oxygen requirements. We generally do not initiate RRT in the absence of these indications, particularly if the blood urea nitrogen (BUN) is <110 mg/dL. (See 'Timing of elective initiation' above.)
- Data do not support the superiority of either continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD). Thus, the selection of modality of RRT should be based upon local expertise and experience in combination with the needs of the individual patient. If CRRT is administered, we recommend the use of venovenous circuits rather than arteriovenous circuits (**Grade 1B**). (See 'Optimal modality' above.)
- We suggest the following strategies for dosing of RRT:
  - We recommend that IHD be provided on a three times per week schedule (alternate days), with monitoring of the delivered dose of dialysis to ensure delivery of a Kt/V of ≥1.2 per treatment (**Grade 1B**).
  - We recommend that CRRT be provided with a delivered effluent flow rate (sum of hemofiltration rate and dialysate flow rate) of ≥20 mL/kg/hour (**Grade 1B**). In order to ensure delivery of this flow rate, we prescribe an effluent flow rate of approximately 25 mL/kg/hour.

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Topic 1927 Version 35.0

Contributor Disclosures

Paul M Palevsky, MD Grant/Research/Clinical Trial Support: BioPorto [Biomarker for AKI]; Dascena [Informatics; prediction of AKI]. Consultant/Advisory Boards: Baxter [Dialysis (Hemodialysis equipment, peritoneal dialysis equipment and supplies, continuous renal replacement therapy equipment and solutions)]. **Jeffrey S Berns, MD** Consultant/Advisory Boards: Amgen [Clinical Trial EC (Darbepoetin)]; Bayer [Clinical Trial EC (Roxadustat)]. **Shveta Motwani, MD, MMSc, FASN** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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