REVIEW ARTICLE

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Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury

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Acute kidney injury (AKI) is defined as an abrupt decline in kidney function and is assessed on the basis of the glomerular filtration rate.[1] In the absence of a direct assessment of the glomerular filtration rate, AKI is diagnosed when there is an accumulation of creatinine (a nitrogenous waste product that is excreted by the kidney) or a reduction or cessation of urine output; the severity is staged on the basis of the magnitude or duration of these changes[1] (AKI stages are described in the Supplementary Appendix, available with the full text of this article at NEJM.org). AKI may be functional, mediated by hemodynamic factors (prerenal AKI); may result from obstructed urine excretion (postrenal AKI); or may result from intrinsic processes involving one or more renal structures (e.g., the vasculature, glomerulus, interstitium, or tubules). As a result of sepsis, shock, and exposure to nephrotoxins, critically ill patients are predisposed to the development of intrinsic AKI, which is generally attributed to acute tubular injury.

Although elevated levels of urea and creatinine define the progression and severity of AKI, their accumulation parallels that of less well-characterized metabolites that mediate the toxic effects of uremia.[2,3] Fluid and electrolyte homeostasis is impaired in AKI, leading to volume overload from the accumulation of sodium and water and to hyperkalemia and metabolic acidosis from impaired potassium and acid excretion. The severity of these abnormalities depends on the extent of kidney impairment and the rate of catabolism. The main objective of kidney-replacement therapy (also termed renal replacement therapy and, less generically, dialysis) is to mitigate these life-threatening consequences, thereby preventing death from uremia.

The indications for initiating kidney-replacement therapy have been debated almost since its initial clinical availability in the 1950s, which reflects efforts to balance the benefits of uremic control against the risks of treatment.[4] Although the technology and safety of kidney-replacement therapy have markedly improved, such therapy is still associated with severe complications, including delayed recovery of kidney function.[5-7] Kidney-replacement therapy for AKI is most commonly provided as hemodialysis or hemofiltration, although peritoneal dialysis has seen a resurgence in areas of low resource availability.[8]

A review of continuous kidney-replacement therapy for AKI, published in 2012,[9] described the technical aspects of the treatment and reviewed many of the then-unresolved issues. We provide an update of extracorporeal kidney-replacement therapy, including techniques, indications, and treatment intensity, in critically ill patients with AKI.

TECHNICAL ASPECTS

Central to all forms of extracorporeal kidney-replacement therapy are vascular access and a pump-driven extracorporeal circuit that perfuses blood over a semi-

permeable membrane, across which accumulated solutes, salt, and water are exchanged (Fig. 1). The hemodialyzers or hemofilters used as artificial kidneys during kidney-replacement therapy are generally composed of semipermeable cellulose or synthetic polymer membranes fabricated as hollow fibers through which blood is perfused, allowing for a large exchange surface (1 to 2.5 m^2) in a compact cartridge (Fig. 2). Vascular access is achieved with the use of a large-bore, double-lumen catheter inserted in an internal jugular vein (preferentially the right vein) or femoral vein. These sites are considered to be equivalent in terms of efficacy and safety, with similar risks of hemorrhage. The rates of infection associated with femoral catheters are higher than the rates with jugular catheters in patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) above 28.[10] Cannulation of the subclavian vein is avoided because of a greater risk of complications during insertion and the risk that subsequent venous stenosis or occlusion will limit arteriovenous access, should kidney function not be restored.

TREATMENT APPROACHES

Extracorporeal kidney-replacement therapy is provided as conventional or prolonged intermittent hemodialysis or as one of the forms of continuous kidney-replacement therapy (Fig. 2 and Table 1).

INTERMITTENT HEMODIALYSIS

In intermittent hemodialysis, solute is removed predominantly by diffusion. Treatment is usually provided three to seven times per week, with each session lasting from 3 to 6 hours. To achieve sufficient solute and volume removal during such relatively brief treatments, high dialysate and blood flow rates are required. Rapid solute removal facilitates treatment of life-threatening acid–base and electrolyte disturbances (e.g., hyperkalemia) and drug intoxications or poisonings due to dialyzable substances[11-14] (Table 2). Furthermore, the short duration of treatment sessions permits patients to be mobilized for nursing, rehabilitation, and medical procedures. However, the need for rapid ultrafiltration to manage volume overload during relatively short treatment sessions and the rapid lowering of urea and other solute levels in the blood predispose the patient to intradialytic hypotension, although the risk may be mitigated by strategies such as prolonging treatment time, limiting the ultrafiltration rate, and altering the composition and temperature of the dialysate.[15,17-19] Rapid lowering of urea levels that were markedly elevated before dialysis, particularly in the case of prolonged elevations, may result in neurologic symptoms ranging from headache to impaired sensorium to — infrequently — seizures, as a result of delayed equilibration of solutes, which leads to cerebral-cell swelling from osmotic shifts of fluid. The risk of disequilibrium may be mitigated by initiating dialysis with short sessions and using low blood flow to minimize osmotic stress.[20] Rapid removal of some antibiotics during intermittent hemodialysis necessitates adjustment in dosing to ensure maintenance of therapeutic levels, a particular concern in treating critically ill patients who have sepsis.[21] An approach that extends hemodialysis treatments by reducing blood and dialysate flow rates during treatment sessions of 8 to 16 hours, referred to as prolonged intermittent kidney-replacement therapy, has been used in hemodynamically unstable patients as an alternative to continuous treatment.[22]

CONTINUOUS KIDNEY-REPLACEMENT THERAPY

Continuous kidney-replacement therapy was developed to mitigate the risk of hemodynamic instability during intermittent hemodialysis. Continuous treatment may be provided as continuous hemofiltration, with convective solute clearance; continuous hemodialysis, with solute cleared predominantly through diffusion; or as continuous hemodiafiltration, which combines diffusive and convective clearance. Convective therapies are associated with greater clearance of higher-molecular-weight substances (1500 to 50,000 daltons), theoretically including proinflammatory mediators. However, cutoff points for standard hemofiltration membranes do not allow effective clearance of cytokines,[23] and continuous strategies have not reduced mortality[24-26] and have even worsened the prognosis in some instances.[24] As the name implies, continuous kidney-replacement therapy is designed to be provided continuously over a period of 24 hours (or longer); this therapy uses lower rates of solute and fluid removal than intermittent hemodialysis but achieves similar or better clearances over time. The slower rate of fluid removal is

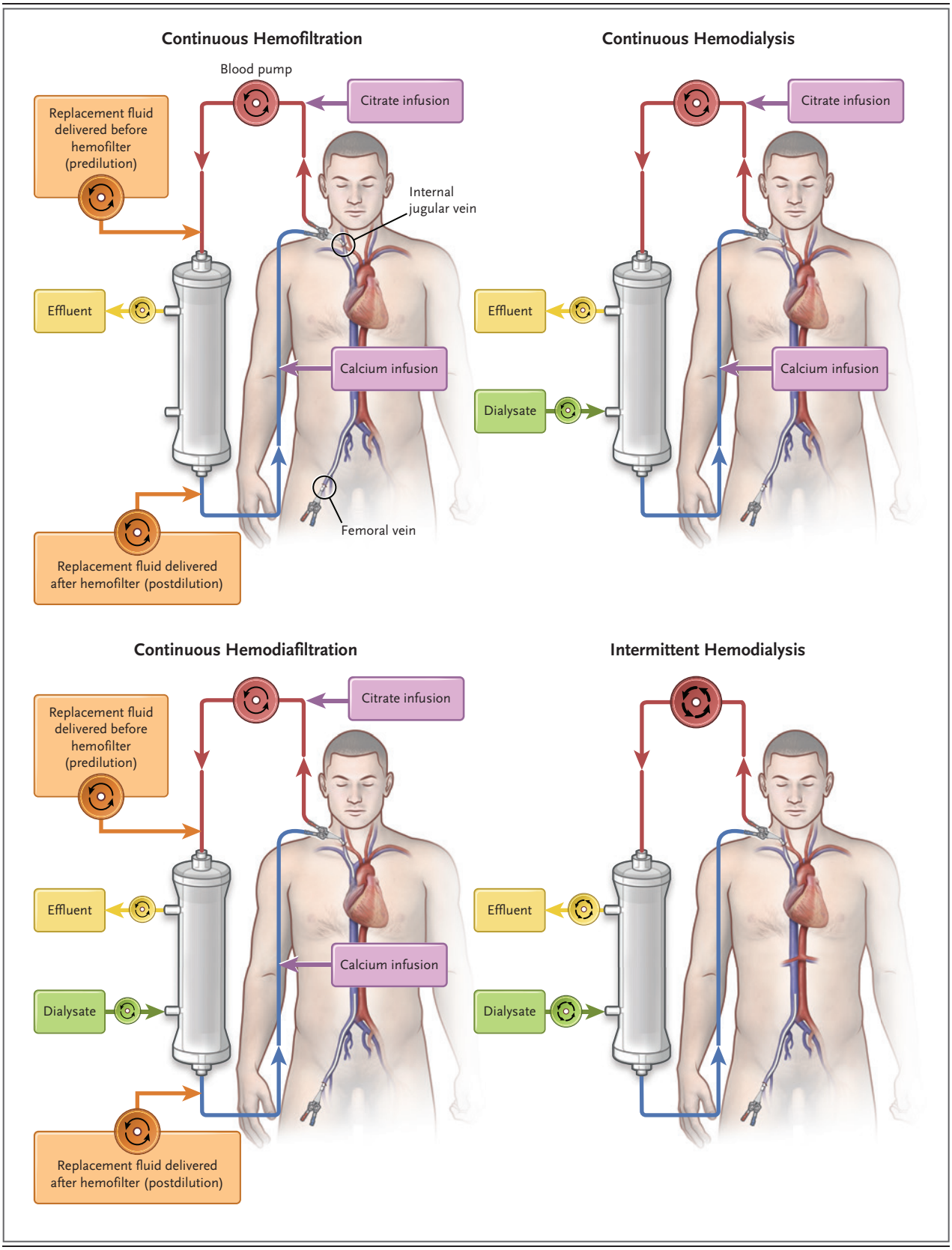

Figure 1 (facing page). Circuitry for Kidney-Replacement Therapy (KRT).

A double-lumen, large-bore catheter is placed in a central vein (avoiding the subclavian vein). Pump-driven flow allows for perfusion of blood through a cartridge containing a semipermeable membrane usually fabricated as hollow fibers (referred to as a hemofilter or hemodialyzer, depending on the treatment approach). During hemofiltration (top left), fluid (ultrafiltrate) containing high concentrations of urea and other solutes is driven across the membrane by a hydrostatic pressure gradient and drained through an effluent port. Replacement fluid (crystalloid solutions with an electrolyte composition approximating that of plasma water) is infused before the hemofilter (predilution) or after the hemofilter (postdilution) to replace the ultrafiltrate volume in excess of the desired fluid loss. During hemodialysis (top right), dialysate is perfused in the opposite direction of blood flow across the external surface of the hollow-fiber membranes to allow diffusion of solutes, with ultrafiltration provided to the extent needed to achieve the desired fluid loss. During hemodiafiltration (bottom left), higher ultrafiltration rates are combined with dialysate flow, and replacement fluid is infused either before or after the hemofilter to replace the excess ultrafiltrate, as in hemofiltration. Effluent flow comprises both spent dialysate and ultrafiltrate. During continuous KRT, regional anticoagulant therapy may be provided through infusion of citrate (to chelate calcium in the extracorporeal circuit) before the cartridge and infusion of calcium after the cartridge (or systemically) to maintain normal systemic ionized calcium levels. Alternatively, continuous KRT can be provided with the use of heparin anticoagulation or without anticoagulation. The configuration of the extracorporeal circuit for intermittent hemodialysis (bottom right) is similar to that for continuous hemodialysis; however, higher blood and dialysate flow rates are used. Intermittent hemodialysis may be performed without anticoagulation or with heparin anticoagulation.

considered to cause less hemodynamic stress, particularly among vasopressor-dependent patients, although this has never been rigorously shown.[27] Given the continuous nature of this treatment approach, clearance of affected antibiotics is more consistent over time, although augmented dosing may be needed to replace antibiotics cleared by the treatment.[28]

ANTICOAGULANT THERAPY

Clotting of the extracorporeal circuit is a common complication. Anticoagulant therapy is often provided to maintain circuit patency but can increase the risk of bleeding and can sometimes be omitted, particularly when treatment duration is shorter or higher blood flow rates are used, as is often the case with intermittent hemodialysis. The decision to use anticoagulant therapy should be based on an assessment of the risks of hemorrhage as balanced against the risk of blood loss and treatment interruption from clotting of the extracorporeal circuit. Anticoagulation is most commonly achieved with the use of unfractionated or low-molecular-weight heparin or, during continuous treatment, by regionally inhibiting the coagulation cascade with an infusion of citrate into the extracorporeal circuit to chelate calcium and a calcium infusion to maintain systemic ionized calcium levels[29] (Fig. 1).

COMPARISON OF CLINICAL OUTCOMES

There has been substantial debate about whether continuous kidney-replacement therapy provides better clinical outcomes than intermittent hemodialysis. Although observational studies suggested advantages of continuous treatment with respect to hemodynamic tolerance, patient survival, and recovery of kidney function,[30-32] these findings were not confirmed in randomized, controlled trials.[33-36] In the largest trial, the 60-day survival rate was similar with intermittent hemodialysis and continuous kidney-replacement therapy (32% and 33%, respectively; $P=0.98$), and there were no significant differences in the incidence of treatment-associated hypotension or recovery of kidney function.[33] Consistent results have been reported across other trials, and meta-analyses have not identified differences in survival or recovery of kidney function among the various approaches.[27,37-39] The outcomes have also been similar in comparisons of prolonged intermittent treatment and continuous treatment.[39] Patients with increased cerebral pressure, intracerebral edema, or both (e.g., those with acute brain injury or fulminant hepatic failure) are susceptible to impaired cerebral perfusion from osmotic disequilibrium and dialytic hypotension during intermittent hemodialysis; therefore, continuous kidney-replacement therapy is preferred for these patients.[15]

TIMING AND INTENSITY OF KIDNEY-REPLACEMENT THERAPY

The timing of initiation and the intensity of kidney-replacement therapy are related. They have been the subject of focused investigation over the past two decades that has been driven by the hypothesis that earlier and more intensive

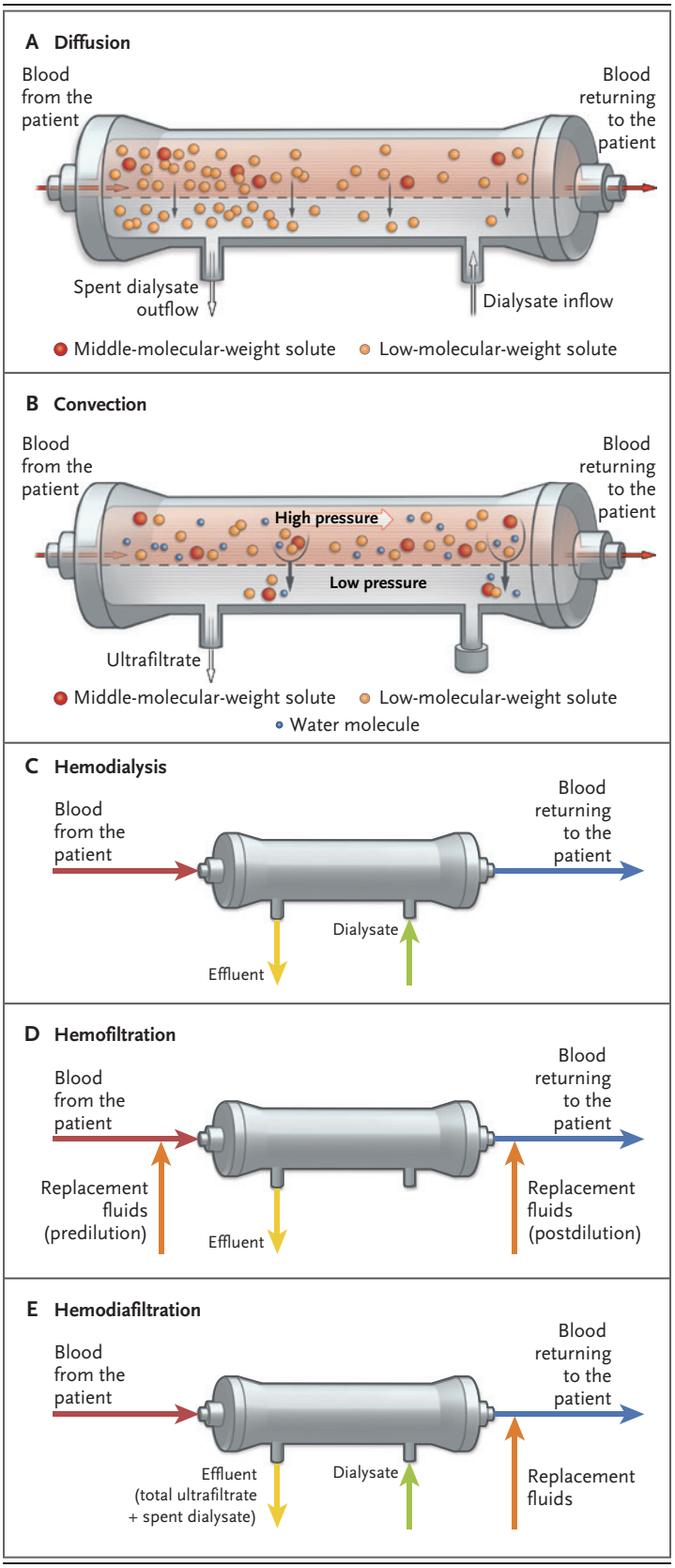

Figure 2. Mechanisms of Fluid and Solute Transport during KRT.

Solute transport during KRT occurs through two physical mechanisms: diffusion (Panel A) or convection (Panel B). During hemodialysis, low-molecular-weight solutes diffuse across the dialysis membrane (Panel A), driven by their respective concentration gradients. Perfusion of dialysate opposite to the direction of blood flow helps maintain the concentration gradient across the length of the hemodialyzer fibers. Control of fluid and sodium balance is provided by ultrafiltration, driven by a hydrostatic gradient between blood and dialysate. During hemofiltration, a large ultrafiltrate volume, in excess of the volume required for management of fluid and sodium balance, is generated by the hydrostatic gradient across the membrane, and solute is entrained in the bulk flow of plasma water across the membrane (Panel B). Although the rate of diffusion is inversely related to the molecular weight of the solute, convective flux is limited primarily by the ratio of the molecular diameter of the solute to the diameter of the membrane pores. As a result, higher-molecular-weight species will be transported across the membrane more efficiently by convection than by diffusion. The circuits used for KRT are shown in Panels C, D, and E, in which the direction of blood flow is from left to right. In hemodialysis (Panel C), dialysate is perfused through the hemodialysis filter against the direction of blood flow, and the effluent is composed of the spent dialysate plus any ultrafiltration for volume management. During hemofiltration (Panel D), no dialysate is perfused through the hemofilter, and the effluent consists only of ultrafiltrate. Given the high rates of ultrafiltration required to achieve adequate solute clearance, crystalloid solutions with physiologic concentrations of electrolytes are infused to prevent intravascular volume depletion. Fluid and sodium balance is determined by the difference in volume between the ultrafiltrate generated and reinfused replacement fluids. The replacement fluids may be infused after the hemofilter (postdilution), which is associated with hemoconcentration of blood within the hemofilter and may increase the risk of filter clotting, or before the hemofilter (predilution), which mitigates the degree of hemoconcentration but dilutes the solute concentration in the blood entering the hemofilter, thereby decreasing treatment efficiency. Hemodiafiltration (Panel E) combines diffusive and convective solute transport, with perfusion of dialysate through the hemofilter combined with generation of an ultrafiltration rate greater than that required for volume balance, necessitating reinfusion of replacement fluids (shown here infused after the hemofilter, but they could be infused before the hemofilter). During continuous therapy, dialysate and ultrafiltration rates are much lower than blood flow rates and the concentration of small solutes in the effluent (the combination of spent dialysate and total ultrafiltrate) approximates that in the plasma. The dose of continuous KRT can therefore be quantified on the basis of the total effluent flow, usually expressed as milliliters per kilogram of body weight per hour. The composition of the dialysate and the reinfusion fluid, including potassium, sodium, buffer, and other constituents, can be adjusted in response to specific metabolic perturbations.

Table 1. Comparison of Intermittent Hemodialysis and Continuous Kidney-Replacement Therapy (KRT).*

Variable	Intermittent Hemodialysis	Prolonged Intermittent KRT	Continuous KRT		
			Hemofiltration	Hemodialysis	Hemodiafiltration
Session duration (hr)	3–6	8–16	24/day	24/day	24/day
Solute transport	Predominantly diffusion	Predominantly diffusion	Convection	Predominantly diffusion	Diffusion and convection
Blood flow (ml/min)	200–500†	200–400	100–300	100–300	100–300
Dialysate flow (ml/min)	300–800	100–300	0	17–100	17–50
Replacement fluid (ml/min)	0	0	17–100	0	17–50
Urea clearance (ml/min)	>150	50–200	<100	<100	<100
Net ultrafiltration (ml/min)	0–17	0–10	0–5	0–5	0–5
Total effluent flow (ml/kg of body weight/hr)‡	NA	NA	10–80	10–80	10–80

* NA denotes not applicable.
† Very high blood flow may be difficult to achieve because of hemodynamic instability or catheter dysfunction.
‡ Total effluent flow, which is used as an index of the dose of continuous KRT, is equal to the sum of the dialysate flow, replacement fluid administered, and net ultrafiltration.

treatment to avoid volume overload and restore the composition of body fluids to nearly normal values would decrease morbidity and mortality among critically ill patients with AKI.

TIMING OF INITIATION

Several factors should be considered in the decision to initiate kidney-replacement therapy. Table 2 summarizes the indications for such treatment in critically ill patients. Avoidance or treatment of volume overload is often listed as an indication for early initiation of kidney-replacement therapy. Observational data show a strong correlation between the magnitude of fluid accumulation and mortality among patients with AKI[40,41]; however, this correlation does not establish causality, since patients with more severe hemodynamic compromise and a higher risk of death often require larger resuscitation volumes. Rigorous study is required to assess the degree to which volume overload mediates the higher mortality and whether earlier initiation of ultrafiltration mitigates the risk.

The severity of pulmonary vascular congestion and the response to diuretics must be considered in the decision to initiate kidney-replacement therapy. A single-center, randomized, controlled study showed that patients with refractory fluid overload after surgery (mainly cardiac surgery) that included worsening pulmonary edema benefited from early initiation of kidney-replacement therapy.[42] This finding is consistent with the recommendation that severe pulmonary edema be a mandatory indication for kidney-replacement therapy.[15,19,43]

Severe hyperkalemia is defined by its effects on cardiac conduction. The presence of clinically significant conduction abnormalities generally necessitates emergency initiation of kidney-replacement therapy in patients with AKI, whereas medical management is often sufficient for more moderate hyperkalemia (Table 2).[15,19]

Severe metabolic acidosis is often cited as an indication for urgent initiation of kidney-replacement therapy. However, a randomized trial showed that medical management with bicarbonate infusion was associated with both improved survival and a decreased need for kidney-replacement therapy, suggesting a role for alternative management even in patients with this indication.[44] The role of kidney-replacement therapy in most forms of lactic acidosis, with the exception of metformin toxicity, is controversial.[45] Extracorporeal lactate clearance is substantially lower than endogenous turnover, which limits the efficacy of this approach in altering clinical outcomes.[46]

Complications of advanced azotemia, including encephalopathy, bleeding, and pericarditis, are also routinely listed as formal indications to start kidney-replacement therapy.[15] However, these complications occur more frequently in patients

Table 2. Indications for KRT in Critically Ill Patients.*

Urgent indications in patients with AKI
Refractory, severe hyperkalemia†
Refractory, severe metabolic acidosis†
Refractory, severe pulmonary edema†
Uremic complications: pericarditis, bleeding, and encephalopathy‡
Urgent indications in patients without AKI
Severe intoxication due to lithium, toxic alcohol poisoning (especially from ethylene glycol or methanol), metformin, or salicylate
Nonurgent indications
Persistent, severe AKI with blood urea nitrogen level >112 mg/dl, oliguria or anuria for more than 72 hr, or both§
No indications
Severe AKI (KDIGO stage 3) in the absence of complications¶
Sepsis in the absence of complicated AKI

* AKI denotes acute kidney injury.

† "Refractory" in this context means that standard medical treatment is not sufficient to control the abnormalities. For instance, hyperkalemia may be managed with medical treatments, including ion exchange resins, intravenous insulin (with glucose infusion), β_2-agonists, and intravenous bicarbonate when there is associated metabolic acidosis and furosemide (in patients without oliguria), with correction of respiratory acidosis when possible. Another example is the management of pulmonary edema with diuretics. The severity of these abnormalities is determined not solely on the basis of any specific laboratory value but also on the basis of several other factors: the rate of onset of the abnormality, its clinical and electrocardiographic consequences (in particular, nodal block and widening of the QRS complex in patients with hyperkalemia), and the persistence of the underlying physiological problem. Although no randomized, controlled trials have examined life-threatening indications for KRT, it is widely accepted that hyperkalemia, metabolic acidosis, and pulmonary edema that are severe and refractory to medical management are urgent indications for KRT.[15]

‡ Uremic complications are seldom observed in patients with AKI. In addition, these complications may be difficult to ascertain in critically ill patients with shock sepsis, who are often intubated, sedated, and mechanically ventilated.

§ These relative indications are supported by the results of the AKIKI 2 trial.[16] To convert the value for blood urea nitrogen to millimoles per liter, multiply by 0.357.

¶ KDIGO (Kidney Disease: Improving Global Outcomes) stages range from 1 to 3, with higher stages indicating more severe kidney injury. Stage 3 is defined by a serum creatinine level that is 3 times the baseline level or 4 mg per deciliter (354 μmol per liter) or higher and urine output of less than 0.3 ml per kilogram of body weight per hour for 24 or more hours or anuria for 12 or more hours.

with advanced chronic kidney disease than in those with AKI.

It has been suggested that biomarkers such as neutrophil gelatinase–associated lipocalin and the product of tissue inhibitor of metalloproteinase 2 times insulin-like growth factor–binding protein 7 can facilitate the diagnosis of AKI. However, they have not proved useful in determining when kidney-replacement therapy should be initiated.[47]

In the absence of objective indications (e.g., severe volume overload, hyperkalemia, or metabolic acidosis, each of which is unresponsive to medical therapy) for the initiation of kidney-replacement therapy (Table 2), long-standing expert recommendations were to defer such treatment until the blood urea nitrogen level exceeded 100 mg per deciliter (35.7 mmol per liter).[48,49] Until recently, however, this dictum was not well substantiated and was challenged by advocates of early initiation of kidney-replacement therapy.

Generally, in the absence of objective indications, two strategies for the initiation of kidney-replacement therapy in patients with severe AKI are possible: early (preemptive) initiation, before the onset of severe complications, or watchful clinical and biologic surveillance (delayed initiation), with treatment deferred until an objective indication is present.[50] Observational studies suggested a survival advantage with early initiation of kidney-replacement therapy.[51-53] However, the majority of these studies involved only cases in which kidney-replacement therapy ultimately was initiated, and cases of severe AKI that were managed without kidney-replacement therapy were excluded, which introduced significant bias. The actual clinical question is not whether kidney-replacement therapy should be started earlier or later but whether at a specific point it should be started or deferred[50] (Fig. 3).

Three multicenter, randomized, controlled trials were designed to evaluate strategies of preemptive as compared with delayed initiation of kidney-replacement therapy in a total of 4034 patients who had severe AKI but without prespecified objective indications for such treatment.[5,6,54] Patients assigned to the early strategies received kidney-replacement therapy within several hours after randomization; for those assigned to the delayed strategies, kidney-replacement therapy was deferred until prespecified criteria were met (Table S1). Mortality (assessed at either day 60 or day 90, according to the study design) ranged between 44% and 54% and did not differ significantly between treatment groups in any of the trials. Notably, substantial proportions of patients assigned to delayed treatment initiation never received kidney-replacement therapy, with a pooled rate of 40% across the three trials.[5,6,54] A meta-analysis of data from individual patients in nine studies that were published between 2010 and 2020 showed consistent results.[55]

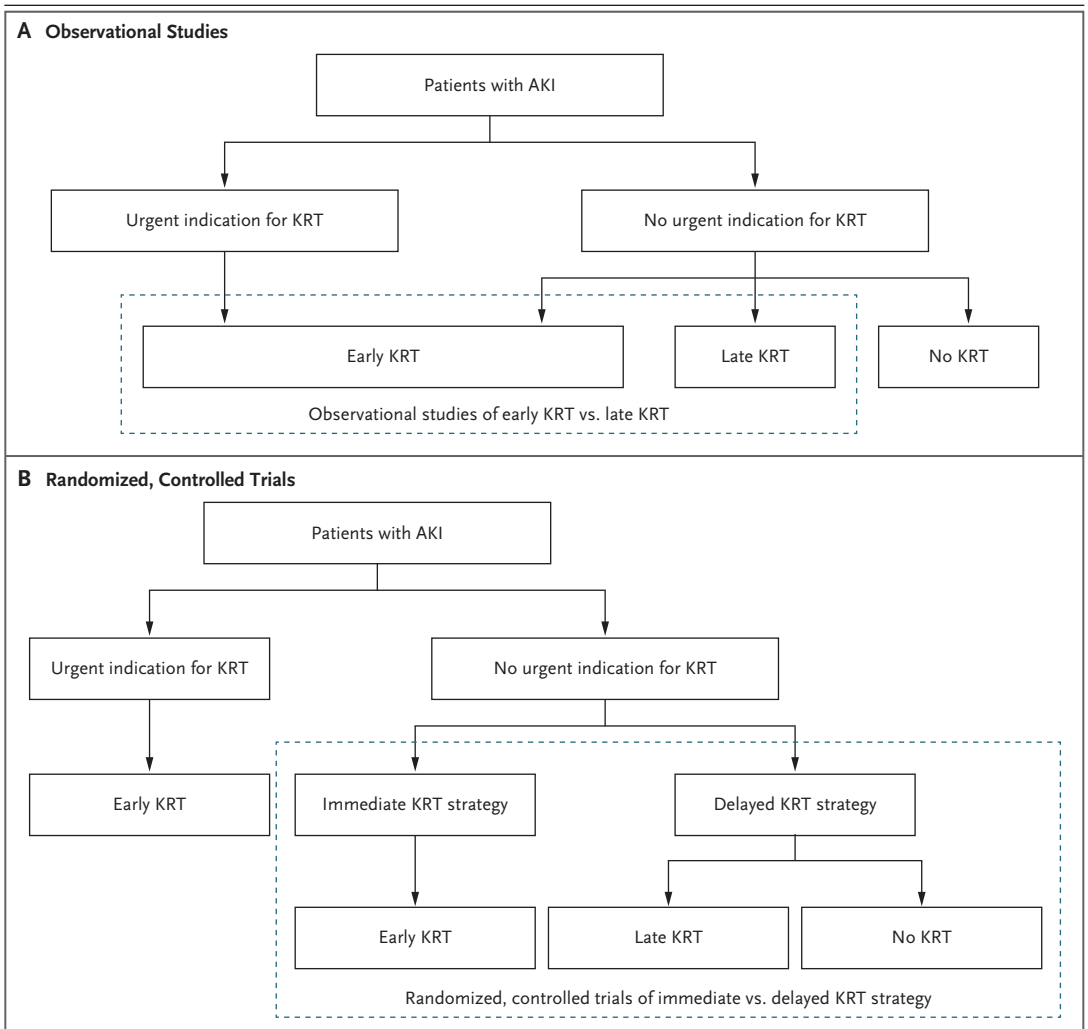

Figure 3. Differences between Study Participants in Observational and Randomized, Controlled Studies of KRT Initiation.
Persons with severe acute kidney injury (AKI) may or may not have an urgent indication for KRT. Observational studies (Panel A) have generally been limited to studies comparing early and late initiation of KRT (dashed box), including patients with an urgent indication for KRT in the early-KRT cohort and excluding patients without an urgent indication for KRT who are managed expectantly and never receive KRT. However, the controversy regarding the timing of KRT is limited to those patients who do not have an urgent indication for KRT. Randomized, controlled trials (Panel B) have been limited to persons without an urgent indication for KRT and have compared immediate initiation of KRT with strategies of delayed initiation (dashed box). In these studies, only some of the study participants assigned to delayed KRT ultimately received KRT; the others had recovery of kidney function and survived or died without having received KRT. Patients receiving early KRT on the basis of urgent indications such as refractory volume overload, hyperkalemia, or metabolic acidosis were excluded from these studies.

These data convincingly show that there is no need to initiate kidney-replacement therapy in patients with severe AKI who do not have potentially severe complications, provided watchful surveillance with active medical management is instituted. This approach was endorsed in recent recommendations.[56] Although these trials show that a strategy of delayed initiation of kidney-replacement therapy is not associated with an increase in mortality and is associated with decreased use of such treatment, the trials were not designed to determine how long kidney-replacement therapy can be safely delayed. Given differences in protocols, the difference in the median time to treatment initiation between the early and delayed strategies among participants

who ultimately received kidney-replacement therapy ranged from as little as 25 hours in one study[6] to as much as 52 hours in another[5]. The proportion of patients who did not ultimately receive kidney-replacement therapy in three trials[5,6,54] was greatest (49%) in the study with the largest difference in timing between the two strategies.[5]

Delayed initiation reduces the risk of iatrogenic complications, but at some point, the accumulation of uremic toxins may increase morbidity and mortality. This issue was recently examined in a multicenter, randomized, controlled trial comparing moderately delayed initiation of kidney-replacement therapy with even more delayed initiation in patients with severe AKI who had no objective indication for such treatment.[16] The strategy of moderately delayed treatment initiation was the same as the delayed initiation used in one of the prior trials[5] (i.e., treatment initiation triggered by a blood urea nitrogen level higher than 112 mg per deciliter [40.0 mmol per liter] or oliguria for more than 72 hours), whereas for the strategy of even more delayed treatment initiation, the trigger was a blood urea nitrogen level of 140 mg per deciliter (50.0 mmol per liter). Multivariable analysis indicated an increased mortality rate (odds ratio for death at 60 days, 2.16 [95% confidence interval, 1.17 to 4.01]; P=0.01) with the greater delay in treatment initiation.

INTENSITY

Several single-center studies suggested that more intensive delivery of kidney-replacement therapy is associated with improved clinical outcomes.[57-59] However, such results were not consistent across all studies[60,61] and were not confirmed when evaluated in larger multicenter, randomized, controlled trials.[62,63] Quantification of the intensity, or dose, of kidney-replacement therapy varies according to the treatment approach. For intermittent treatment, the dose is based on both clearance per treatment and frequency of treatment, whereas with continuous treatment, the dose is quantified according to the total effluent flow rate (Fig. 2). Two large, multicenter, randomized trials[62,63] examined the intensity of kidney-replacement therapy in critically ill patients with AKI; one study focused exclusively on continuous treatment, and the other allowed for repeated changes between intermittent and continuous therapy on the basis of hemodynamic status. Neither study showed that survival was improved when effluent flow rates with continuous treatment were increased to more than 20 to 25 ml per kilogram of body weight per hour or when intermittent hemodialysis was delivered more frequently than three times per week, with a target normalized urea clearance (Kt/V_{urea}, in which K represents the rate of urea clearance by the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea in the patient) of at least 1.2 per treatment.

These results were confirmed in a patient-level meta-analysis of seven trials, which also showed delayed recovery of kidney function with more intensive therapy.[64] Even higher effluent flow rates (up to 120 ml per kilogram per hour) have not been associated with improved outcomes.[25,26,65] More intensive kidney-replacement therapy is also associated with an increased risk of electrolyte disturbances — most notably, hypophosphatemia — and prolongation of ventilator dependence,[62,63,66] and more intensive intermittent hemodialysis is associated with an increased risk of hypotension.[62] On the basis of these data, in the absence of severely hypercatabolic states, the recommended intensity for continuous kidney-replacement therapy is an effluent flow of 20 to 25 ml per kilogram per hour, and the recommendation for intermittent hemodialysis is three sessions per week, with a Kt/V_{urea} of at least 1.2 per session. More frequent hemodialysis may be required if this threshold for solute clearance cannot be reached.

Volume management is an independent measure used to determine the required intensity of kidney-replacement therapy. Ultrafiltration rates depend on the patient's overall status and the resuscitation phase. Ultrafiltration is not appropriate during the initial phases of resuscitation. Modest ultrafiltration to maintain net fluid balance may be appropriate after the patient's condition has been stabilized, with more aggressive ultrafiltration once the patient is hemodynamically stable and no longer requires volume resuscitation or vasopressor infusion. Studies attempting to define optimal rates of ultrafiltration have yielded inconsistent results.[67,68] During continuous kidney-replacement therapy, net ultrafiltra-

tion can be managed independent of solute clearance; for patients receiving intermittent hemodialysis, treatment sessions may need to be prolonged or provided more than three times per week, or additional isolated ultrafiltration treatments may need to be provided to achieve the desired fluid removal.

RECOVERY OF KIDNEY FUNCTION AND CESSATION OF TREATMENT

Kidney-replacement therapy is usually discontinued when kidney function "recovers," although recovery is not consistently defined. In clinical practice, several simple criteria are used: resumption of diuresis or a spontaneous decline in the blood urea nitrogen level, the creatinine level, or both. No study has assessed these cessation criteria rigorously; however, they were used in the three largest trials on the timing of kidney-replacement therapy.[5,6,54]

Both early initiation of kidney-replacement therapy and intensive treatment have been associated with delayed recovery of kidney function. One study showed earlier resumption of diuresis and a spontaneous decline in the plasma creatinine level among patients assigned to the strategy of delayed treatment initiation,[5] and a second study showed greater dependence on dialysis after day 90 among patients assigned to the strategy of early initiation.[6] These findings are particularly important because persistent kidney failure at day 90 is used to define end-stage kidney disease. Pooled data from seven studies of intensity of kidney-replacement therapy also showed greater dialysis dependence at day 28 in association with more intensive kidney-replacement therapy.[64] Conceptually, kidney-replacement therapy could interfere with kidney recovery through mechanisms that are independent of the treatment approach. Dialytic hypotension is an obvious mechanism,[69] but other factors may be relevant. In particular, despite improvement in membrane biocompatibility, no membranes can be considered fully biocompatible.[70] Data suggest an interference, driven by proinflammatory processes,[71] between kidney-replacement therapy and recovery of kidney function. These findings might suggest that kidney-replacement therapy acts as a second hit in an already diseased kidney. If this hypothesis is confirmed, kidney injury induced through kidney-replacement therapy is an important concern[72] and might be analogous to ventilator-induced lung injury.[73]

AKI usually resolves after several days or weeks, although recovery may be incomplete or followed by progression to chronic kidney disease (CKD).[74,75] AKI and CKD may therefore be viewed as interconnected syndromes in which CKD confers a predisposition to the development of AKI, and maladaptive repair of the injured kidney results in the development or progression of CKD.[76]

CONCLUSIONS AND FUTURE DIRECTIONS

It took years to develop and refine approaches to kidney-replacement therapy and to identify indications for such treatment in patients with AKI. Greater knowledge of the indications for treatment and increased availability of the various treatment approaches will permit more rational use of kidney-replacement therapy and result in reduced health care costs. Recent crises in the supply of kidney-replacement therapy machines during the coronavirus disease 2019 (Covid-19) pandemic have highlighted the importance of optimizing the technique. Well-conducted randomized, controlled trials and meta-analyses have shown that in the absence of severe complications of AKI, a strategy of watchful surveillance with active medical management can be used. Such a strategy could diminish demand during surges in AKI. Similarly, continuous treatment with effluent flows greater than 20 to 25 ml per kilogram per hour or intermittent treatment provided more frequently than three times per week, with an adequate dose delivery per treatment, is not associated with improved outcomes. Finally, except in rare circumstances, there is no evidence that continuous treatment is superior to intermittent treatment or vice versa, suggesting that the particular treatment used should be based on local expertise and staffing considerations. Strategies should be developed to improve monitoring and determine which patients will ultimately need kidney-replacement therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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