CLINICAL THERAPEUTICS

Continuous Renal-Replacement Therapy for Acute Kidney Injury

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Acute limb ischemia due to a perioperative type B (distal) thoracic aortic dissection develops in a 90-kg, 20-year-old man with Marfan's syndrome who is admitted to the hospital for elective aortic-valve replacement. On postoperative day 1, he undergoes endovascular repair of the thoracic aorta. On postoperative day 4, his urine output decreases to 420 ml over a 24-hour period. He requires mechanical ventilation with a fraction of inspired oxygen (F_IO_2) of 0.70; his mean arterial pressure is 74 mm Hg with vasopressor support. He has had a positive fluid balance of 9.8 liters since admission. The serum creatinine level has increased from a baseline of 0.6 mg per deciliter (53.0 μmol per liter) to 4.4 mg per deciliter (389.0 μmol per liter). The bicarbonate level is 19 mmol per liter despite bicarbonate infusion, and the potassium level is 6.1 mmol per liter. The creatine kinase level has increased to 129,040 U per liter. An intensive care specialist evaluates the patient and recommends initiation of continuous renal-replacement therapy.

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THE CLINICAL PROBLEM

Acute kidney injury is characterized by a sudden decrease in kidney function over a period of hours to days, resulting in accumulation of creatinine, urea, and other waste products. It may be associated with retention of sodium and water and the development of metabolic disturbances such as metabolic acidosis and hyperkalemia.

The incidence of acute kidney injury depends on the population studied and the definition used. According to the Kidney Disease: Improving Global Outcomes (KDIGO) consensus guidelines, acute kidney injury is defined by an increase in the serum creatinine level of 0.3 mg per deciliter (26.5 μmol per liter) or more within 48 hours; a serum creatinine level that has increased by at least 1.5 times the baseline value within the previous 7 days; or a urine volume of less than 0.5 ml per kilogram of body weight per hour for 6 hours.[1]

Acute kidney injury has been estimated to account for 1% of hospital admissions in the United States and to develop in 5 to 7% of hospitalized patients. In the intensive care unit (ICU), acute kidney injury develops in 5 to 25% of patients; of these, approximately 6% require renal-replacement therapy during their ICU stay.[2-4] Mortality among ICU patients with acute kidney injury and multiorgan failure has been reported to be more than 50%.[4,5] If renal-replacement therapy is required, mortality may be as high as 80%.[5-7]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Acute tubular necrosis is the most common cause of hospital-acquired acute kidney injury and usually results from ischemic or nephrotoxic injury to the tubules. In the

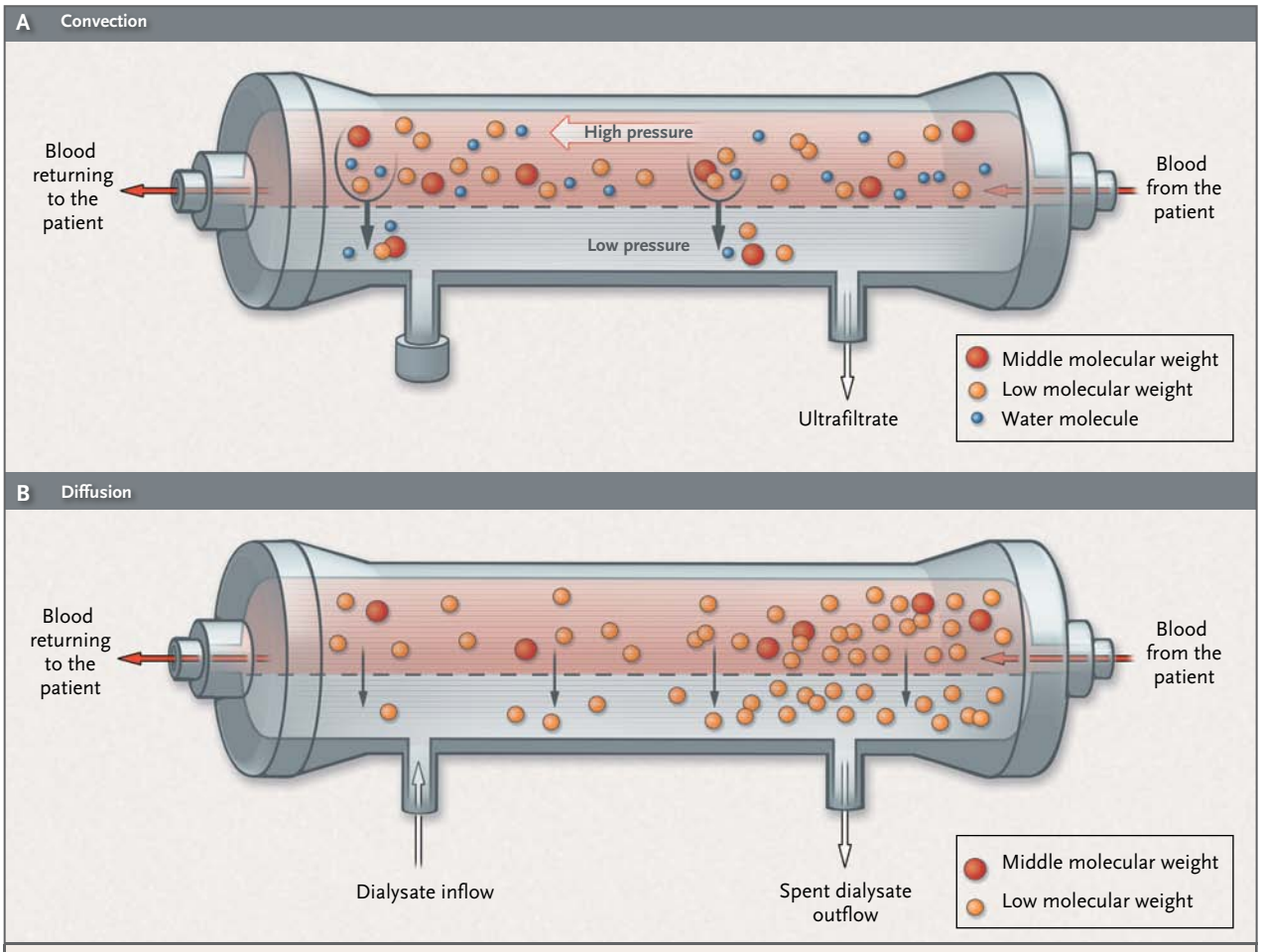

Figure 1. Transport of Solutes across a Semipermeable Membrane.

As shown in Panel A, convection occurs when solutes are transported across a semipermeable membrane with plasma water in response to a hydrostatic pressure gradient that is created on the blood side of the hemofilter. Convection enhances the removal of low- and middle-molecular-weight molecules. As shown in Panel B, in diffusion, movement of solute across a semipermeable membrane is driven by a concentration gradient between the blood and the dialysate. Solutes move from the side with the higher concentration of particles to the side with the lower concentration. Diffusion is best for clearing low-molecular-weight solutes such as urea and creatinine.

ICU, acute tubular necrosis is usually multifactorial and may develop from a combination of sepsis, impaired renal perfusion, and nephrotoxic medications.[8] The course of ischemic acute tubular necrosis can be divided into four phases: initiation, extension, maintenance, and recovery. Prolonged renal ischemia or a prolonged prerenal state leads to an initiation phase (lasting hours to days) characterized by direct injury to both tubular epithelial cells and endothelial cells.[8-10] During this phase, the glomerular filtration rate (GFR) decreases because of intrarenal vasoconstriction, tubular obstruction from epithelial-cell casts and necrotic debris, and back-leak of glomerular filtrate through the damaged tubular epithelium. Ongoing endothelial and tubular injuries lead to activation of inflammatory mediators that amplify the cellular injury and result in extension of the injury. This extension phase is followed by a maintenance phase that typically lasts 1 to 2 weeks. During the maintenance phase, the GFR stabilizes at a very low level, and uremic complications may arise. The recovery phase is characterized by tubular epithelial-cell repair and regeneration as well as a gradual improvement in the GFR.

Table 1. Solute Clearance in Continuous Renal-Replacement Therapy.*

Type of Therapy	Solute Transport	Replacement Fluid	Blood Flow	Ultrafiltrate Flow	Dialysate Flow
			ml/min	*ml/hr*	
Continuous venovenous hemofiltration	Convection	Yes	50–300	500–4000	0
Continuous venovenous hemodialysis	Diffusion	No	50–300	0–350†	500–4000
Continuous venovenous hemodiafiltration	Convection and diffusion	Yes	50–300	500–4000	500–4000

* Rates of blood flow, ultrafiltrate flow, and dialysate flow are representative of typical rates used in clinical practice.
† Ultrafiltration in continuous venovenous hemodialysis is used for regulation of the patient's fluid volume and not for convective purposes.

No specific pharmacologic therapy is effective in patients with established acute kidney injury, and the care of such patients is limited to supportive treatment, including renal-replacement therapy. In renal-replacement therapy, water and solutes pass through a semipermeable membrane and the waste products are discarded. The processes involved are ultrafiltration, convection, and diffusion.

Ultrafiltration is the process by which plasma water is forced across a semipermeable membrane by hydrostatic pressure. Convection and diffusion are processes by which solutes are transported across a semipermeable membrane (Fig. 1). Convection occurs when the transmembrane pressure gradient drives plasma water across a semipermeable membrane (as in ultrafiltration) but drags solutes with the plasma. In diffusion, solute removal across the membrane is driven by a gradient in the concentration of the solute between the blood on one side of the membrane and an electrolyte solution (the dialysate) on the other side of the membrane. The concentration gradient is maximized and maintained throughout the length of the membrane by running the dialysate in a flow that is countercurrent to the blood flow.

Traditionally, nephrologists have managed acute kidney injury with intermittent hemodialysis. Solute clearance with intermittent hemodialysis occurs mainly by diffusion, whereas volume is removed by ultrafiltration. Advantages of intermittent hemodialysis include rapid removal of solute and volume. The main disadvantage is the risk of systemic hypotension, which occurs in approximately 20 to 30% of hemodialysis treatments.[11] Approximately 10% of patients with acute kidney injury cannot be treated with intermittent hemodialysis because of hemodynamic instability.[11-15]

Continuous renal-replacement therapy includes a spectrum of dialysis methods developed in the 1980s specifically for the treatment of critically ill patients with acute kidney injury who could not undergo traditional intermittent hemodialysis because of hemodynamic instability or in whom intermittent hemodialysis could not control volume or metabolic derangements.[16-18] The slower solute clearance and removal of fluid per unit of time with continuous renal-replacement therapy, as compared with intermittent hemodialysis, is thought to allow for better hemodynamic tolerance.

In current practice, the blood circuit for continuous renal-replacement therapy is usually a venovenous circuit. Venous blood is removed from the circulation through one lumen of a double-lumen, large-bore catheter and passes through a peristaltic blood pump, which generates the perfusion pressure that drives ultrafiltration of plasma water across a biosynthetic hemofiltration membrane, thus removing volume. Solute is removed by convection (continuous venovenous hemofiltration), diffusion (continuous venovenous hemodialysis), or both (continuous venovenous hemodiafiltration) (Table 1 and Fig. 2).[16-18] In each case, the blood is then returned to the venous circulation through the second lumen of the catheter. In the two methods that use convection for removal of solute (continuous venovenous hemofiltration and continuous veno-

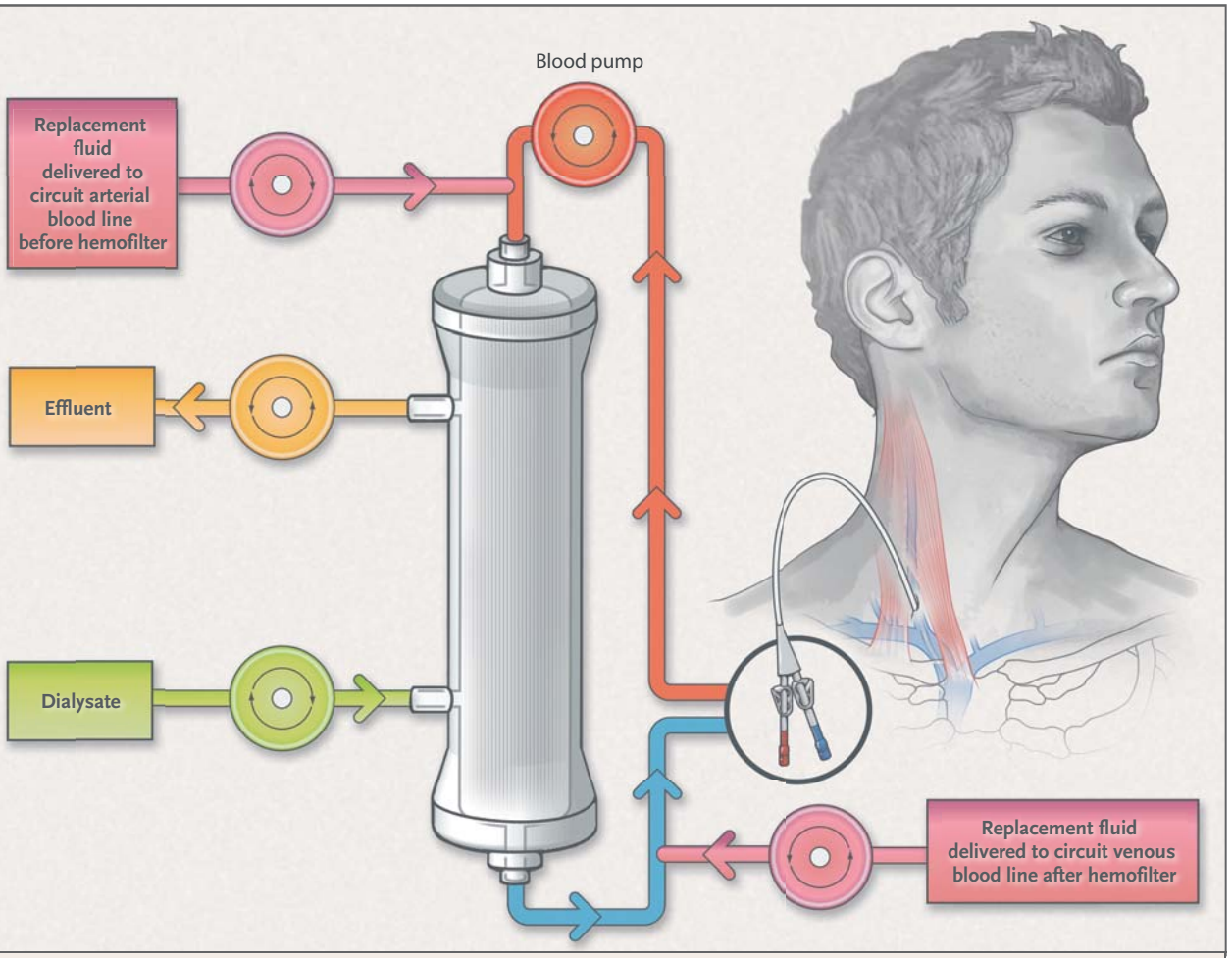

Figure 2. Circuit Components in Continuous Renal-Replacement Therapy.

Continuous renal-replacement therapy requires a central double-lumen venovenous catheter, an extracorporeal circuit and hemofilter, a blood pump, and an effluent pump. Depending on the type of continuous renal-replacement therapy, dialysate, replacement fluid pumps, or both are required. In continuous venovenous hemofiltration, solutes and plasma water are forced across the semipermeable membrane by high ultrafiltration rates (convection). Simultaneously, replacement fluid is infused into the blood with the use of a replacement pump. The replacement fluid replenishes both the volume and electrolytes removed. Replacement fluid can be infused before or after the hemofilter. In continuous venovenous hemodialysis, solutes and plasma move across the semipermeable membrane into the dialysate compartment of the hemofilter by means of diffusion and ultrafiltration. The flow of dialysate is in the opposite direction from the flow of blood. In continuous venovenous hemodiafiltration, solutes and plasma water are removed by diffusion, convection, and ultrafiltration.

venous hemodiafiltration), a high ultrafiltration rate is required to achieve convective clearance; as a result, replacement fluid must be added before or after the hemofilter in the extracorporeal circuit to restore fluid volume and electrolytes.

CLINICAL EVIDENCE

No randomized, controlled trials have shown that continuous renal-replacement therapy is superior to intermittent hemodialysis with respect to survival. In one of the larger trials, 316 patients with acute kidney injury were randomly assigned to either intermittent hemodialysis or continuous venovenous hemofiltration.[19] In-hospital mortality was 62.5% and 58.1% in the two groups, respectively ($P=0.43$). In another trial, 360 patients with acute kidney injury were randomly assigned to either intermittent hemodialysis or continuous venovenous hemodiafiltra-

tion.[20] At 60 days, mortality was 31.5% and 32.6%, respectively (P=0.98). The Cochrane Collaboration performed a meta-analysis of 15 randomized, controlled trials involving 1550 critically ill patients with acute kidney injury and concluded that continuous renal-replacement therapy did not differ significantly from intermittent hemodialysis with respect to hospital mortality (relative risk, 1.01; 95% confidence interval [CI], 0.92 to 1.12), ICU mortality (relative risk, 1.06; 95% CI, 0.90 to 1.26), or the number of surviving patients who did not require renal-replacement therapy (relative risk, 0.99; 95% CI, 0.92 to 1.07).[21]

Continuous renal-replacement therapy has advantages that may influence its use despite the lack of a demonstrated survival benefit. In the Cochrane meta-analysis, patients who received continuous renal-replacement therapy had significantly higher mean arterial pressures than patients who received intermittent renal-replacement therapy.[21] Removal of fluid with short sessions of intermittent hemodialysis can induce intradialytic hypotension, potentially increasing the risk of recurrent kidney injury. Perhaps as a result, intermittent hemodialysis has been associated with positive fluid balance, whereas continuous renal-replacement therapy may permit better management of fluid volume, allowing for adequate nutrition without compromising fluid balance.[22]

Table 2. Indications and Contraindications for Continuous Renal-Replacement Therapy in Critically Ill Patients with Acute Kidney Injury.

Indications
Classic indications
Hyperkalemia
Severe metabolic acidosis
Diuretic-resistant volume overload
Oliguria or anuria
Uremic complications
Some drug intoxications
Potential indications
Hemodynamic instability
Disrupted fluid balance (due to cardiac failure or multiorgan failure)
Increased catabolic states (e.g., rhabdomyolysis)
Sepsis
Increased intracranial pressure
Electrolyte abnormalities
Contraindications
Advance directives indicating that the patient does not want dialysis
The patient or his or her health care proxy declines continuous renal-replacement therapy
Inability to establish vascular access
Lack of appropriate infrastructure and trained personnel for continuous renal-replacement therapy

CLINICAL USE

At present, there is no consensus regarding when to initiate renal-replacement therapy; this lack of consensus has resulted in a wide variation in clinical practice. There is little debate that hyperkalemia, severe metabolic acidosis, volume overload, overt uremic manifestations, and drug intoxications are clear indications for the initiation of therapy (Table 2). Although observational studies suggest that early initiation of renal-replacement therapy in patients with acute kidney injury is associated with improved survival, these studies have considerable limitations and remain to be confirmed by adequately powered, prospective, randomized trials.[23,24] Nevertheless, clinicians often initiate renal-replacement therapy in patients before the development of overt complications of acute kidney injury, taking into account the overall clinical state of the patient and various factors, including the patient's age, the severity of illness, other organ dysfunction, and the degree of renal dysfunction (e.g., progressive azotemia and persistent oliguria).

The specific role of continuous renal-replacement therapy as compared with intermittent hemodialysis is also not precisely defined. However, most opinion leaders consider continuous renal-replacement therapy to be appropriate for patients with hemodynamic instability, fluid overload, catabolism, or sepsis with acute kidney injury (Table 2). Continuous renal-replacement therapy is also indicated in any patient who meets the criteria for intermittent hemodialysis but cannot undergo this procedure because of hemodynamic instability.[25,26]

As noted above, a large-bore, double-lumen catheter is typically used for continuous renal-replacement therapy. The preferred site of catheter insertion is the right internal jugular vein. The catheter should be inserted with the use of ultrasonographic guidance[27-29] and with adherence to infection-control policies.[30] The use of

tunneled catheters is warranted in patients who require prolonged renal-replacement therapy (>1 to 3 weeks) and is associated with a lower rate of infection and thrombosis than the rate associated with nontunneled catheters.[31,32]

There are currently insufficient data to recommend one form of continuous renal-replacement therapy over another. In continuous venovenous hemodialysis, the rate of removal of solutes (by diffusion) is inversely proportional to their molecular weight, so that larger molecules are cleared relatively inefficiently (Fig. 1). In contrast, in continuous venovenous hemofiltration, the rate of removal of solutes (by convection) is dependent only on the size of the pores in the membrane. As a result, many clinicians prefer to use continuous venovenous hemofiltration (or continuous venovenous hemodiafiltration) in the belief that convection can more effectively reduce the effects of the systemic inflammatory response syndrome by removing cytokines, most of which are in the middle-molecular-weight range. However, most controlled studies have not shown a clinically significant and sustained effect on cytokine plasma concentrations or an improvement in outcome.[33-38] Therefore, the selection of a specific method is primarily based on institutional experience and preference.

Solutions used in continuous renal-replacement therapy should be chosen to restore the acid–base balance and maintain physiologic electrolyte concentrations. There is little difference in the composition of dialysate and replacement fluids, and many commercially available dialysates are used off-label as replacement fluids. In general, replacement and dialysate solutions should contain glucose and electrolytes (generally including sodium, potassium, calcium, and magnesium) in concentrations that are in physiologic ranges. Adjustments of electrolytes may be needed depending on specific clinical circumstances (e.g., patients with severe hyperkalemia may initially require a solution with a potassium concentration of 0 to 2 mmol per liter until the hyperkalemia resolves). In addition, continuous renal-replacement solutions require a buffer anion because of loss of bicarbonate through the hemofilter. Although acetate, lactate, citrate, and bicarbonate have all been used for this purpose, bicarbonate is currently the preferred buffer.

The clearance of small solutes with continuous renal-replacement therapy is a function of effluent flow (the effluent comprising the ultrafiltrate in continuous venovenous hemofiltration, spent dialysate in continuous venovenous hemodialysis, and both in continuous venovenous hemodiafiltration). Therefore, effluent flow is commonly used as a measure of the "dose" of renal-replacement therapy administered and is reported as the effluent flow rate in milliliters per kilogram of body weight per hour.[39] Studies suggest that an effluent flow rate of at least 20 to 25 ml per kilogram per hour is necessary for adequate solute clearance.[40,41] However, clotting and protein deposition on the hemofilter membrane over time may decrease actual solute clearance.[42,43]

A retrospective study in the United States showed that because of circuit downtime only 68% of patients received their prescribed dose of continuous renal-replacement therapy.[44] The most common cause of circuit downtime is clotting of the circuit.[45] Continuous renal-replacement therapy can be administered without anticoagulation, especially in patients with an increased risk of bleeding[46]; however, this approach is generally associated with low success rates. Unfractionated heparin is the most commonly used anticoagulant. Because of the risk of bleeding associated with heparin and concern about the development of heparin-induced thrombocytopenia, the use of regional citrate anticoagulation has been increasing.[45,47-50]

Clotting can also be promoted or prevented by the technical aspects of therapy. For instance, in continuous venovenous hemofiltration, the administration of replacement fluid before the hemofilter dilutes the blood in the filter, which reduces clotting, whereas administration of the replacement fluid after the hemofilter concentrates the blood in the filter and enhances clotting (Fig. 2). Another option is to use higher blood flows. Although blood-flow rates of 100 to 150 ml per minute were common in the past, many clinicians are now using blood-flow rates of 200 to 250 ml per minute to reduce the risk of thrombosis.[51]

Prescription orders for initiating continuous renal-replacement therapy must include the form of therapy, blood-flow rate, type and rate of replacement fluid (for continuous venovenous hemofiltration and continuous venovenous hemodiafiltration), type and rate of dialysis fluid (for continuous venovenous hemodialysis and con-

tinuous venovenous hemodiafiltration), type and dose of anticoagulation (if used), and net fluid goal based on the patient's fluid status. Once the orders have been written and vascular access has been established, the circuit is set up and prepared by either the dialysis nurse or the ICU nurse. Most practitioners monitor electrolytes and acid–base status every 6 to 8 hours. If the patient's condition remains stable with minimal changes in electrolytes, measurements of electrolytes can be decreased to every 12 hours, depending on the form of treatment, solutions, and anticoagulation.

Continuous renal-replacement therapy can be discontinued once renal recovery has been confirmed or the decision is made to switch to another form of renal replacement because of the patient's clinical condition. For example, a switch to intermittent hemodialysis may be appropriate if the patient is weaned off pressors, needs mobility, or is transferred out of the ICU. Discontinuation of therapy to assess renal recovery is based on improvement in the patient's clinical condition and increasing urine output.[52,53]

Major costs of continuous renal-replacement therapy include the costs of the renal-replacement device, hemofilter, and tubing; replacement and dialysate fluids; anticoagulation; and staff time. In a study in Canada, the daily cost ranged from $498 to $731 (Canadian dollars), depending on the form of treatment and the anticoagulant used.[54] In an analysis from the Mayo Clinic, the average cost of continuous renal-replacement therapy per patient was calculated to be $8,052 (in U.S. dollars) over a mean length of stay of 17 days.[55]

ADVERSE EFFECTS

Complications of vascular access, including infection and vascular injury, are a common concern with continuous renal-replacement therapy. These complications are reported to occur in 5 to 19% of patients, depending on the access site selected.[56-58] Arterial puncture, hematoma, hemothorax, and pneumothorax are the most common complications reported. Arteriovenous fistulas, aneurysms, thrombus formation, pericardial tamponade, and retroperitoneal hemorrhage have also been described.[59]

During therapy, meticulous monitoring of machine performance and of the patient's electrolytes and hemodynamics are required to prevent complications. Common problems include hypotension, arrhythmias, fluid-balance and electrolyte disturbances, nutrient losses, hypothermia, and bleeding complications from anticoagulation.[60-62] Continuous renal-replacement therapy can result in clinically significant hypokalemia and hypophosphatemia, which may lead to severe complications if uncorrected. Hypothermia can be mitigated with the use of a blood or fluid warmer.

Another serious concern is potential underdosing of drugs. There are no clear data on the appropriate dosing of many drugs during continuous renal-replacement therapy; this is of particular concern with the use of antibiotics. Doses of antibiotics that are too low can result in inadequate treatment of sepsis; doses that are too high can lead to systemic exposure and toxicity. To ensure efficacy and prevent toxicity, drug monitoring is highly recommended.

AREAS OF UNCERTAINTY

Areas of uncertainty regarding continuous renal-replacement therapy include the appropriate indications and timing of therapy, the ideal method of treatment, the benefits of convection over diffusion, the safest and most effective anticoagulant, and the most appropriate dose. The potential effect of continuous renal-replacement therapy on renal recovery and the long-term need for long-term dialysis are unknown. Finally, as already mentioned, data are lacking on the appropriate dosing of many drugs, particularly antibiotics.

GUIDELINES

Comprehensive guidelines on the indications, timing, and technical aspects of continuous renal-replacement therapy have recently been published by the KDIGO Acute Kidney Injury Work Group.[63] The KDIGO document is based on systematic reviews of relevant trials and the best information available as of February 2011. Some of the principal recommendations for renal-replacement therapy in patients with acute kidney injury are listed in Table 3. Clinical-practice guidelines have also been developed by the American Thoracic Society.[64] These guidelines discuss the general care of patients requiring renal-replacement therapy. They recommend that continuous renal-replacement therapy be considered in patients with "severe hemodynamic

Table 3. Summary of Selected Recommendations for Renal-Replacement Therapy in Patients with Acute Kidney Injury.*

Initiation of renal-replacement therapy: Renal-replacement therapy should be initiated in patients with life-threatening changes in fluid, electrolyte, and acid–base balance. The broader clinical context and the presence of conditions that can be modified with renal-replacement therapy, along with trends of laboratory tests, should be considered in making decisions about initiation of therapy.
Type of renal-replacement therapy: Continuous renal-replacement therapy, rather than intermittent hemodialysis, should be used in patients with hemodynamic instability.
Vascular access: An uncuffed, nontunneled dialysis catheter, rather than a tunneled catheter, should be used at the initiation of continuous renal-replacement therapy. The right jugular vein is the preferred choice for insertion of a catheter. The second choice is the femoral vein, and the last choice is the subclavian vein. Ultrasonographic guidance is recommended.
Anticoagulation: In patients undergoing continuous renal-replacement therapy who do not have an increased risk of bleeding or impaired coagulation and who are not already receiving effective systemic anticoagulation, regional citrate anticoagulation, rather than heparin, should be used. In patients in whom citrate is contraindicated, unfractionated or low-molecular-weight heparin is preferred.
Dose: An effluent flow rate of 20 to 25 ml/kg/hr is recommended for continuous renal-replacement therapy in patients with acute kidney injury. Frequent assessment of the actual delivered dose is needed to adjust the prescription.

* Recommendations are from the clinical-practice guidelines of Kidney Disease: Improving Global Outcomes described in Khwaja.[1]

instability, persistent ongoing metabolic acidosis, and large fluid removal requirements."

RECOMMENDATIONS

The patient described in the vignette is an appropriate candidate for continuous renal-replacement therapy. He is receiving mechanical ventilation with a high F_IO_2 requirement. He has decreasing urine output, metabolic acidosis despite bicarbonate therapy, and hyperkalemia. He has volume overload and requires vasopressor support for hemodynamic instability. His severe ongoing rhabdomyolysis will cause persistent electrolyte abnormalities such as hyperkalemia and hyperphosphatemia, which can be better controlled with continuous treatment than with intermittent therapy. Furthermore, continuous renal-replacement therapy will provide steady acid–base, solute, and volume control without compromising his hemodynamic status.

After insertion of a double-lumen 12-French venous catheter in the right internal jugular vein, I would initiate continuous venovenous hemodiafiltration at a blood flow of 200 ml per minute, with the use of physiologic solutions and regional citrate anticoagulation if there is no evidence of shock liver. I would prescribe an effluent flow rate of 2700 ml per hour (30 ml per kilogram per hour) to ensure a delivered dose of 20 to 25 ml per kilogram per hour. I would measure the patient's electrolytes, ionized calcium levels, and acid–base status every 6 hours to monitor citrate anticoagulation and his response to therapy. Finally, I would adjust doses of medications that are removed by continuous renal-replacement therapy. Once the patient is no longer receiving pressors, has been extubated with resolving rhabdomyolysis, or both, I would make a transition to intermittent hemodialysis if there is still no sign of renal recovery.

Dr. Tolwani reports receiving consulting and lecture fees from and having licensed a patent regarding citrate to Gambro. No other potential conflict of interest relevant to this article was reported.

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

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