# Complications of Continuous Renal Replacement Therapy

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## ABSTRACT

Continuous renal replacement therapy (CRRT) is commonly used in critically ill patients with acute kidney injury. Many studies show that compared with intermittent hemodialysis, continuous therapy has superior hemodynamic stability, metabolic clearance, and volume control. Despite these benefits, no survival advantage can be demonstrated with its use. Although study design explains much of this paradox, it is also quite plausible that the complications associated with CRRT negate its potential benefits in the critically ill patient. We summarize the common complications associated with the use of CRRT.

Acute kidney injury (AKI) is a frequent complication in critically ill patients. In those patients who require dialysis, continuous renal replacement therapy (CRRT) is often used because of its purported superiority in hemodynamic stability, metabolic clearance, and volume control compared with intermittent hemodialysis (IHD). However, numerous randomized controlled trials comparing the two modalities have failed to prove CRRT improves morbidity and mortality. Although the lack of proven benefit of CRRT has been attributed to poor study design, it is also possible that complications arising from the use of CRRT negate its potential advantages. In this article, we review the complications of CRRT as outlined in Table 1. As arterio–venous circuits are associated with more complications and are less efficacious (1,2) than veno-venous circuits, we will focus our discussion on the complications associated with continuous veno-venous hemofiltration and hemodialysis (CVVH and CVVHD). Likewise, as peritoneal dialysis is rarely used in the setting of critical illness, it will not be included in the discussion.

## Vascular Access

### Catheter Placement

Central venous access is preferentially obtained in the internal jugular vein under direct ultrasound visualization as it is the safest method and reduces the number of line malfunctions. The use of femoral veins is convenient but has been avoided in the past because of increased risk of line associated infection. However, a recently reported trial comparing infection rates from dialysis catheters based on site of insertion found that femoral placement increased the risk of infection only in patients with a BMI greater than 28 (3). Subclavian access for hemodialysis is not recommended due to increased risk of central venous stenosis (4,5). Arterio-venous fistulas, aneurysms, thrombus formation, and hematomas are the major local complications with placement of vascular access. Other significant complications include hemothorax, pneumothorax, pericardial tamponade, arrhythmias, air embolism, and retroperitoneal hemorrhage (6). It is critical to ensure proper connections with all lines and to keep the catheter in constant view to prevent accidental disconnections which can result in severe blood loss.

### Catheter Dysfunction

Recirculation of blood through a double lumen catheter results in hemoconcentration, reduced solute clearance, and premature filter clotting. Shorter femoral catheters (15 cm) have higher recirculation rates than longer ones (24 cm) (7). Femoral catheters should extend into the inferior vena cava to reduce malfunction and recirculation. Any distortion or kinking of the catheter reduces laminar blood flow and causes fibrin deposition. Impaired catheter flow is detected by increased negative arterial pressure and positive venous pressure, reducing both the catheter and filter life and reducing the delivered dose of dialysis.

### Infection

Interventions to reduce catheter related infections include stringent sterile placement technique, appropriate local dressing and catheter care, avoidance of the femoral site, use of antibiotic-coated catheters, and use of antimicrobial locking solutions when not in use (8,9). The risk of new line placement must be weighed against

**TABLE 1. Complications associated with continuous renal replacement therapy**

Vascular access
  Bleeding
  Thrombosis
  Arteriovenous fistula formation
  Hematoma
  Aneurysm formation
  Hemothorax
  Pneumothorax
  Pericardial tamponade
  Arrthymias
  Air embolism
  Infection
Extracorporeal circuit
  Air embolism
  Reduced filter life
  Reduced dialysis dose
  Hypothermia
  Bioincompatibility
  Immunologic activation
  Anaphylaxis
Hematologic complications
  Need for anticoagulation
    Hypocalcemia
    Metabolic alkalosis
    Hypernatremia
    Citrate intoxication
    Bleeding
  Thrombocytopenia
  Bleeding
  Hemolysis
  Heparin-induced thrombocytopenia
Hemodynamic instability
Electrolyte disturbances
  Hypophosphatemia
  Hypomagnesemia
  Hypocalcemia
  Hypokalemia
  Hyponatremia
  Hypernatremia
Acid–base disturbances
  Metabolic acidosis
  Metabolic alkalosis
  Citrate-induced alkalosis and acidosis
Nutritional losses
  Amino acids and proteins
  Poor glycemic control
  Vitamin deficiencies
  Trace minerals
Volume management errors
Altered drug removal
Delayed renal recovery

the risk of infection in each individual patient. Recent NF/KDOQI guidelines recommend temporary, non-cuffed dialysis catheters should not be left in place greater than 3 weeks for internal jugular and 5 days for femoral catheters (10). A tunneled, cuffed catheter should be considered if dialysis is needed for more than 3 weeks (11). Daily documentation of the need for the hemodialysis access is required as line-associated bacteremia is a core measure of quality care in hospitals.

## Extracorporeal Circuit Considerations

### Air Embolism

System pressure monitoring is important throughout the entire extracorporeal circuit. In the venous intake, negative pressures can result in air entry that could cause air embolism. Alarms exist in current systems that stop blood flow when air is detected within the circuit. Manifestations of air embolism include chest pain, dyspnea, cyanosis, cough, hypoxia, or cardiopulmonary arrest.

### Reduced Filter Life and Dialysis Dose

Reduced filter life results in a marked decrease in effective dialysis time and delivered dialysis dose. The prescribed dialysis dose is also reduced by system malfunctions, time off for diagnostic procedures, and limited expertise of the staff in troubleshooting problems. Furthermore, the effectiveness of the filter changes with time. Solute clearance is impaired as sieving coefficients decrease over time. Subsequently, ultrafiltration is reduced by increased protein layer deposition. Measurement of effective clearance and achieved dialysis dose is more difficult and laborious with CRRT but can be estimated using urea kinetic methods (12). While the optimal target dose of dialysis for CRRT and IHD in the setting of AKI remains to be determined (13–15), international efforts emphasize the importance of reducing system downtime to achieve the prescribed dose (16).

### Hypothermia

Core body temperature depression while on CRRT secondary to extracorporeal radiant heat exchange occurs in 5–50% of patients. In one study, the mean body temperature was reduced by 2.8°C along with a 26% decrease in oxygen consumption ($VO_2$) (17). This may result in heat loss of 750 kcal/day, thereby increasing the patient's daily energy requirements and need for a warming blanket; newer dialysis systems are equipped with warming devices to help counter heat loss. Thermal loss may mask fevers, delaying the recognition of infection and the prompt administration of antibiotics. In some clinical situations, such as hyperthermia or post-cardiac arrest, the extracorporeal cooling effect may be advantageous.

### Bioincompatibility and Immunologic Activation

Prolonged exposure to the filter membrane and other surfaces of the extracorporeal circuit may activate several immune mediators of inflammation. This contact activates cytokines and proteases that increase protein breakdown and increase energy expenditure (18). Although rare, anaphylactoid reactions to dialysis membranes have been reported due to bradykinin activation, especially in patients previously treated with angiotensin converting enzyme inhibitors (19,20).

## Hematological Complications

### Anticoagulation

Critically ill patients have a higher frequency of bleeding due to multiple factors and may not require

anticoagulation for CRRT. As frequent filter clotting increases blood loss and costs, and results in inadequate dosing of dialysis, some method of anticoagulation may be necessary. Systemic anticoagulation with heparin or argatroban may be used but is associated with an increased risk of bleeding and may be contraindicated in several patient populations. Frequently regional citrate anticoagulation (RCA) is utilized with improved safety and less bleeding risks (21–25). It permits effective anticoagulation across the extracorporeal circuit without impacting the patient's systemic coagulation. RCA is associated with several potential complications including hypocalcemia, metabolic alkalosis, hypernatremia, and citrate intoxication (26–29). Other means of anticoagulation are available, such as regional anticoagulation with heparin and protamine, or administration of prostacyclin, but these are complicated, not well studied, and infrequently used (30–32). Lepirudin, a direct thrombin inhibitor, accumulates in renal failure and has been reported to induce anaphylaxis in a small number of cases (17).

In patients who receive systemic or low dose heparin, heparin-induced thrombocytopenia (HIT) may develop. Many critically ill patients develop thrombocytopenia from multiple factors; HIT accounts for < 2% of these cases (33). However, a recent prospective study found 25% of patients on CRRT with premature filter clotting were HIT antibody positive (34). HIT can have devastating complications of thrombosis formation and limb ischemia. The clinical suspicion of HIT is more likely if the degree of thrombocytopenia is moderate (20–100 K/l), exposure to heparin is 5–10 days, and there are clinical signs of thrombosis. Once suspected, all forms of heparin must be discontinued pending diagnostic tests.

## Other Hematologic Complications

CRRT reduces the number of platelets and impairs their aggregation (35). Proinflammatory platelet-activating factors are also cleared by CRRT thereby potentially balancing the effects on platelets. The coagulation cascade is not activated by CRRT (36). A degree of hemolysis occurs due to the shearing forces throughout the extracorporeal circuit or when passing through the roller pump (37). Hemolysis can also result from treatment induced electrolyte abnormalities such as hypophosphatemia, hyponatremia, and hypokalemia. If hemolysis is significant, a pigment-induced nephropathy can occur, causing a secondary renal injury.

## Hypotension

Initiation of CRRT may result in a period of hemodynamic variability that often stabilizes if blood flows are steadily increased. Another determinate of hemodynamic stability is the patient's blood volume which is directly affected by the ultrafiltration rate. Aggressive fluid removal will result in intravascular volume depletion and hemodynamic instability. Additionally, intercompartmental shifts and impaired myocardial function can decrease systemic perfusion.

Invasive blood pressure monitoring and methods to assess central venous pressure, cardiac output, and systemic perfusion are helpful in maintaining stable hemodynamics and optimizing volume status.

## Electrolyte and Acid–Base Disturbances

Electrolyte imbalances and acid–base disturbances are less frequent with commercially available dialysate solutions because pharmacy mixing errors with on-site preparation are avoided. Phosphate clearance on CRRT is significantly greater than IHD due to ongoing inter-compartmental mass transfer and larger filter pore size. Hypophosphatemia and hypomagnesemia are the two most common electrolyte disturbances associated with CRRT and requires careful monitoring and replacement (38). Commercially available replacement fluids do not typically contain phosphate or magnesium so these electrolytes need to be replaced separately. Hypocalcemia and hypokalemia are also common electrolyte abnormalities.

Hyponatremia may result if dialysate solutions do not adequately compensate for a negative sodium balance. Hypernatremia can occur with the administration of tri-sodium citrate and saline solutions when employing RCA. Current recommendations suggest monitoring electrolyte and acid–base status every 6–8 hours.

## Acid–Base Disturbances

Lactate-based dialysate solutions are less commonly utilized as bicarbonate-based solutions offer improved acid–base balance and reduced cardiovascular events (39,40). The concentration of base in replacement fluid during hemofiltration needs to be higher than the serum concentration as the sieving coefficient of bicarbonate is greater than 1. Conversely, in continuous dialysis, the correction of acidosis depends only on the buffer concentration of the dialysate. Alkalemia can occur if there is a positive buffer balance between dialysate and replacement fluids. It is also occasionally seen with the use of RCA because each citrate ion is converted to three bicarbonate ions by the liver. Impaired breakdown of citrate in the face of severe hepatic dysfunction can result in citrate intoxication manifested by hypocalcemia and an anion-gap metabolic acidosis (29).

## Nutritional Losses

### Amino Acids and Protein

Critically ill patients with AKI are hypercatabolic with increased nutritional needs. Patients receiving CRRT have additional losses of key nutrients across the dialysis membrane. Lean body mass secondary to protein breakdown is due to several factors including insulin resistance, release of inflammatory mediators, metabolic acidosis, and growth factor resistance (41). Amino acid loss in patients on CRRT is estimated to be 10–20 g/day depending on ultrafiltration volumes (42–44). In patients receiving parenteral amino acids, hemofiltration

accounts for a 10% loss of the amount infused (45). Larger proteins, such as albumin, are also lost with CRRT especially as the filter ages. Large ultrafiltration rates and the use of newer membranes with increased permeability will compound the depletion of albumin and result in significant negative nitrogen balance (46). Hypoalbuminemia and malnutrition are independent predictors of mortality in the setting of AKI (47).

## Glucose

Optimal glycemic control is crucial in critically ill patients and hyperglycemia is driven by peripheral insulin resistance and increased hepatic gluconeogenesis (48–50). Dialysate solutions contain dextrose in concentrations of 100–180 mg/dl to prevent significant diffusive losses. It can account for up to 40–80 g/day but typically does not induce hyperglycemia (51). The predominate complications with the use of glucose-free solutions is hypoglycemia and inadequate nutritional supply. The use of such solutions induces gluconeogenesis using mainly amino acids as the substrate and their use is not recommended. Close monitoring of blood glucose is necessary to achieve euglycemia.

## Vitamins and Essential Minerals

Water soluble vitamins and trace minerals are readily filtered and can rapidly become depleted. Vitamin A supplementation is not recommended due to the risk of toxic accumulation. Active vitamin D is readily depleted with CRRT and if prolonged therapy is anticipated, replacement will prevent systemic depletion. Antioxidant mediators including zinc, selenium, copper, manganese, chromium, vitamin C, and vitamin E are all freely lost across dialysis membranes (52,53). Vitamin C replacement should not exceed 100–150 mg/day due to the risk of inducing oxalosis. Replacement of selenium 100 $\mu$g and thiamine 100 mg daily is advocated to prevent severe body depletion.

## Volume Management Errors

As the ultrafiltration rates needed for CRRT can be very high, training in monitoring and maintaining the desired fluid balance is pivotal to ensure that accidental volume imbalances are avoided (54). Most systems monitor the fluids within the system but do not account for other fluids. Some patients may require significant pre or post filter replacement solutions that must be accounted for accurately. A separate CRRT flow sheet and well-trained dialysis personnel help prevent these errors.

## Drug Removal

Frequently, critically ill patients require antimicrobial therapy and adequate dosing is necessary to prevent treatment failure or toxic accumulation. The pharmacokinetics of vancomycin and aminoglycosides are well characterized in patients on CRRT but newer antibiotics are less well studied. In contrast to its clearance in IHD, vancomycin has a high removal rate on CRRT due to the higher flux of volume, ongoing mass transfer, and is greater in CVVH as compared with CVVHD (55). The sieving coefficient of vancomycin can be as high as 0.8–0.9. Close monitoring of drug levels will ensure therapeutic dosing.

Increased clearance of vasopressors may occur if administered through a central line close to the hemodialysis catheter. Some catheters have an additional port for medication administration. While no studies have shown increased clearance with these catheters, it may be advisable to use distal vascular access for administration of key antibiotics and vasoactive medications.

## Recovery of Renal Function

While CRRT is often a necessary, life-sustaining therapy, it may reduce the recovery of renal function. Transient periods of hypotension, prolonged exposure to the extracorporeal membrane, and dialysis-catheter associated infections are potential etiologies for ongoing kidney injury that delays recovery. Biopsies performed in patients with poor renal recovery after an initial insult demonstrated areas of new acute tubular necrosis suggestive of ongoing renal insult (56).

## Conclusions

Critically ill patients with AKI are often treated with CRRT. Although it is presumed that it offers patients the benefits of greater hemodynamic stability, metabolic clearance, and volume control, randomized clinical trials comparing CRRT to intermittent modalities have failed to demonstrate its superiority in terms of survival. Although study design is certainly one explanation for this finding, the complications associated with the use of CRRT could also account for this clinical paradox. Ongoing research and technologic advances continue to improve the delivery and safety of this therapy. By striving to reduce the associated complications, the survival benefit of CRRT modalities may become evident.

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