# Extracorporeal Therapies in the Emergency Room and Intensive Care Unit

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**KEYWORDS**

• Intermittent hemodialysis • Plasmapheresis • Continuous renal replacement
• Hemoperfusion • Plasma exchange • Extracorporeal toxin removal

**KEY POINTS**

- Extracorporeal removal of toxins can prevent complications of organ dysfunction and death.
- Knowledge of the toxin's pharmacokinetic profile can help to guide the selection of the optimal modality of extracorporeal drug removal.
- Severe uremia is refractory to medical management; however, extracorporeal renal replacement therapy can normalize electrolytes, acid–base imbalance, volume status, and remove uremic toxins.
- Immune-mediated diseases may benefit from plasma exchange as an adjunctive treatment to standard immunosuppressive therapy.

## EXTRACORPOREAL BLOOD PURIFICATION

Extracorporeal therapies have been performed in experimental animal models for more than 100 years and to treat naturally occurring disease in veterinary patients for more than 50 years. Through manipulation of blood outside of the body, extracorporeal therapies provide opportunities to treat disease and remove toxic substances that cannot be done from within the body. There are a variety of extracorporeal treatments; however, all share the common attributes of removing and returning blood to the patient, need for anticoagulation, and manipulation of the cellular and/or plasma contents of blood. The most commonly performed extracorporeal therapies are intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), hemoperfusion (HP), and therapeutic plasma exchange (TPE). Each has their own limitations and characteristics that allow for the development of very targeted therapies. The most common veterinary applications of extracorporeal therapies are used in the treatment

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of renal failure, acute toxicities, and immune-mediated diseases. An updated list of worldwide hospitals providing extracorporeal therapies can be found at www.asvnu.org.

## SOLUTE KINETICS AND OPPORTUNITIES FOR EXTRACORPOREAL MANIPULATION

Nearly all extracorporeal treatments are performed to remove some offending solute(s) from blood. In renal failure, these targets are uremic toxins that accumulate owing to decreased glomerular filtration and renal elimination. Hepatotoxins similarly accumulate in patients with synthetic liver failure. Patients with immune-mediated disease may benefit from the removal of the antigen that triggers disease as well as the offending antibody that is produced in response. Although this concept is easy to comprehend, the significance of such metabolites, toxins, inflammatory mediators, cytokines, and hormones often remains poorly understood.[1–3] Despite this situation, extracorporeal therapies improve the clinical status of patients that are suffering from such conditions. As the role and kinetics of the offending toxic molecules are better understood, extracorporeal therapies can be designed to better improve their removal.

For patients with acute toxicities, the disease-causing substance is often well-known. In dogs with ibuprofen ingestion, it is the ibuprofen itself that is responsible for the adverse effects. Other toxins, such as acetaminophen, are not highly toxic; however, their metabolites are the molecules that cause cell damage. Both the identification of the offending solutes as well as an understanding of its kinetics is crucial to determining which extracorporeal therapy may be used for effective removal. Although not routinely applied to endogenously produced molecules, pharmacokinetics (PK) is the study of exogenous solute absorption, distribution, metabolism, and elimination; a basic understanding of PK is necessary for appropriately prescribing extracorporeal treatment.

Volume of distribution ($V_d$) is a description of the theoretic distribution of a solute throughout the body. The unit of measure (L/kg) does not reflect an actual volume, but rather provides a relationship of the drug's extravascular and intravascular distribution. Water comprises approximately 60% of total body weight. Solutes with a $V_d$ of 0.6 L/kg typically distribute equally throughout total body water. When the $V_d$ is lower, it indicates restriction of the drug within the intravascular space. A large $V_d$ indicates significant accumulation of the solute in extravascular compartments, such as within the intracellular space or an affinity to accumulate within fat. Lipophilic drugs usually have a large $V_d$. Extracorporeal techniques are most effective for solutes with a low $V_d$ and are less effective for molecules with a large $V_d$, because only a small proportion of the drug exists within the intravascular space. A $V_d$ of more than 1 L/kg indicates that less than 5% to 10% of the solute is within the plasma.[4] Prolonged treatment and the processing of numerous blood volumes may be necessary for these treatments to significantly decrease the total body drug concentration. Most drugs exist within the plasma in both a free and protein-bound state. This state is commonly reported as percent protein bound. Drugs with high protein binding are commonly bound to albumin or other plasma proteins, which yields a small $V_d$.

Clearance is a concept used to describe the rate at which a solute is removed from systemic circulation and reflects the cumulative contribution of all organs participating in the metabolism and excretion of the solute.[5] However, clearance is measured in milliliters per minute per kilogram and reflects the volume of fluid (such as blood or plasma water) that has undergone complete removal of the solute. Hepatic and renal elimination are the 2 main routes of clearance for most drugs. The terminal half-life ($t_{½}$)

is the time required for the plasma drug concentration to fall by 50%.[6] Both the $V_d$ and clearance are important contributors to the $t_{½}$. Drugs with a large $V_d$ and/or small clearance rate are more likely to have a longer $t_{½}$.

Molecular weight is the sum of the weight of all atoms within a given molecule. This value, expressed in Daltons (Da) or grams per mole (typically interchangeable), is helpful to determine if a solute may be too large to pass through the pores within a dialysis membrane. It is important to recognize that protein-bound drugs will have a large molecular weight owing to the size of the bound protein molecule.

## PLATFORMS FOR EXTRACORPOREAL BLOOD PURIFICATION

The $V_d$, molecular weight, and percent protein binding of a solute will help to determine the best method of extracorporeal removal and which platform may most effectively perform this treatment.[7] There are 4 mechanisms of extracorporeal solute removal: diffusion, convection, adsorption, and separation. Both IHD and CRRT rely mostly on diffusion and convection for solute removal. Diffusion occurs when a concentration gradient is created across a permeable membrane such as blood and dialysate across fibers within a hemodialyzer or hemofilter. Molecules move from areas of higher to lower concentration. The permeability of these membranes is mainly determined by the size of pores, thickness of membrane, and surface area.[8] The molecular size of a solute is the main determinant of its ability to be removed via dialysis. Low efficiency (also known as conventional) dialyzers can remove solutes up to 1000 Da, but have higher clearance for solutes less than 500 Da. High efficiency (high-flux) dialyzers can remove solutes up to 11,000 Da.[9]

Convective removal of solutes is performed as a pressure gradient physically moves plasma water and its solutes from one side of the membrane to another. Water is a very small molecule (18 Da) and moves easily across membranes. Solutes are removed via solvent drag as the water crosses the membrane; however, their passage can be restricted by the pore diameter. Because of the physical pressure applied during convection, larger solutes may be removed via convection rather than diffusion for the same dialyzer. Solutes of up to 40,000 Da are easily removed via convection using a high-efficiency dialyzer.

Adsorption is best achieved in HP, where blood or plasma is passed through a sorbent substance that binds and removes solutes from the circulation. Activated charcoal is the most commonly used sorbent molecule in extracorporeal therapies; however, other carbon-, resin-, or polymer-based sorbent columns are also available. Charcoal can irreversibly bind protein- and lipid-bound drugs with great affinity via the van der Waals interaction between the solute and the charcoal.[10] This binding is nonspecific and nontarget solutes may also be bound and removed, including glucose, platelets, coagulation factors, and hormones.[11] To prevent this charcoal is coated to make it more biocompatible, however this decreases its adsorption capability.[12] Charcoal HP can remove solutes well up to 40,000 Da with protein binding of up to 90% to 95%.[13]

Solute separation is performed during plasmapheresis and TPE, where a fraction of whole blood, such as plasma water, is removed along with the molecules that reside within that fraction. This therapy is best for solutes with extensive (>80%) protein binding and a small $V_d$ (ideally <0.5 L/kg).

Although there are several companies that have recently developed veterinary-specific extracorporeal machines, most veterinary practitioners use machines created for adult and pediatric humans. Both IHD and CRRT use hollow fiber semipermeable membranes to remove toxic substances from blood. The main difference between

these 2 modalities is the intensity at which this removal is performed. IHD was developed earlier and was the mainstay of treating uremic people. This method can quickly decrease the circulating concentration of most small uremic toxins by more than 80% within 3 hours. However, such rapid shifts in solute and fluid removal may lead to cardiovascular instability. Because most IHD machines do not allow for treatments to extend beyond 8 hours, performing a slow and less intensive treatment was challenging. Thus, CRRT was created as a treatment that could be performed continuously throughout the entire day to be safer for people with hemodynamic instability. By design, it is less efficient to help reduce complications associated with rapid solute removal. However, meta-analyses have shown survival of people with acute kidney injury (AKI) to be similar if they were treated with IHD or CRRT,[13] even those with hemodynamic instability.[14] Such a study has not been performed in veterinary patients. The small size of some veterinary patients creates an opportunity where CRRT machines may be operated to achieve solute clearances similar to IHD treatments. CRRT machines also allow for greater flexibility because most have programmed operational modes to perform purely convective or combination diffusion/convection treatments, whereas IHD clears solutes primarily via diffusion. There are pros and cons to each of these types of machines, which have been discussed elsewhere.[15]

Both IHD and CRRT machines can perform HP with the addition of a sorbent cartridge within the extracorporeal circuit. Some cartridges have been designed to remove specific molecules, such as cytokines, endotoxin, immune complexes, and other mediators of immune response. One sorbent cartridge, CytoSorb, has been used in for the management of critically ill septic people and has shown improvement in inflammatory cytokine concentration and survival rates.[16–18]

Plasmapheresis is the act of separating and removing plasma with return of the cellular component of blood. This term is often incorrectly used to describe TPE, which involves replacing the volume of removed plasma to prevent hypovolemia, decreased colloidal oncotic pressure, or deficiencies in albumin, coagulation factors, and fibrinogen. TPE can be accomplished by filtration and centrifugation methods. Filtration or membrane based TPE can be performed on many CRRT and some IHD machines. It uses a plasma separator—a hemofilter with pores large enough to allow some plasma proteins to cross. Most of these filters have a molecular weight cut-off around 70,000 Da, which is slightly larger than albumin (66,000 Da). Systemic anticoagulation is performed using unfractionated heparin therapy to prevent clotting throughout the extracorporeal circuit. Centrifugal TPE separates whole blood according to density and allows for the removal of any component—namely, plasma, red blood cells, platelets, granulocytes, or mononuclear cells. A major advantage of centrifugal platforms is the ability to use the same machine to perform cytapheresis and cell collection in addition to TPE, something membrane-based systems cannot perform. Most of these treatments are performed using regional citrate anticoagulation; however, systemic heparin therapy can also be administered.

## EXTRACORPOREAL TOXIN REMOVAL

A common use of extracorporeal therapies in the emergency setting is an adjunctive therapy for intoxications. Any toxicity that could lead to significant organ dysfunction, serious complications, or death of the patient should be considered for extracorporeal toxin removal (ECTR). An understanding of the toxin's PK is essential for selecting the best type of extracorporeal platform. Many human drugs have undergone preclinical testing in dogs and other species, which may serve as an estimate for PK when species specific data are unavailable. Such information can be obtained via PubMed,

PubChem, and some critical care textbooks. Veterinary drugs that have been approved by the US Food and Drug Administration have undergone some PK evaluation in their target species; this information should be available in the product insert as well as published in drug formularies. It is important to recognize that normal PK parameters may not apply in overdose scenarios. Common drug doses rarely saturate all available enzymes and drug transporters involved in metabolism and elimination. However, saturation may be possible when the amount of drug ingested or administered is markedly increased; in these scenarios it is difficult to anticipate the PK parameters, but the $t_{½}$ may be prolonged and total drug exposure may be increased.[4] Unfortunately, most poison control helplines are unfamiliar with ECTR and do not typically recommend it as an effective therapy to remove the offending toxin. These centers may also provide improper recommendations for the timing of extracorporeal therapies, such as recommending hemodialysis only for uremia after ethylene glycol ingestion but not for ECTR. Therefore, emergency clinicians must have a robust understanding of PK and toxicology, as well as having a collegial relationship with the closest providers of ECTR to best identify patients that may benefit from these treatments.

There are several necessary considerations in the decision to use extracorporeal treatment.

### *The Toxin Is Likely to Cause Significant Organ Dysfunction, Injury, or Death*

Drug exposure that results in mild clinical signs or reversible organ injury (eg, a short-term increase in liver enzymes) does not typically benefit from ECTR. In the majority of poisonings occurring within the home, the exact dose of exposure is unknown. People do not commonly have a reliable estimate of the number of pills that were within a bottle before their pet ingesting its contents. Drug exposure must be estimated from the theoretic maximal exposure. The fact that the actual ingestion dose is unknown along with the unavailability of bedside testing for various poisons, ECTR may be considered to be beneficial from the worst case toxin exposure. This amount may be quite higher than actual drug exposure, which can also be decreased by the induction of emesis. In general, the more catastrophic the potential outcome, the stronger the indication for ECTR. For example, the near guarantee of AKI and significant morbidity and mortality after ethylene glycol exposure warrants aggressive treatment with ECTR.

### *Extracorporeal Clearance Is Likely to Exceed Endogenous Clearance*

When evaluating the possible benefit of ECTR for a given toxicity, the $t_{½}$ and/or drug clearance should be reviewed. Toxins with a short $t_{½}$ are unlikely to be significantly cleared by ECTR, because the time from emergency room presentation to initiation of therapy is rarely immediate. Recommendations for ECTR in people suggest that a poison is dialyzable when more than 30% of the ingested dose can be removed within a 6-hour treatment.[19] Drugs are nondialyzable when less than 3% of the ingested dose is removed during this time. Drugs should have low endogenous clearance rate (<4 mL/kg/min) to be a good candidate for ECTR.[20] After a drug has reached steady-state equilibrium, 97% of the drug is expected to be endogenously eliminated after 5 $t_{½}$ intervals. Acetaminophen has been reported to have a $t_{½}$ of 23 to 56 minutes in dogs.[21,22] Unless transporter saturation occurs, within 5 hours after acetaminophen exposure, very little of the drug remains. This timing creates a very small window of opportunity for ECTR. In humans, ECTR is indicated for acetaminophen toxicity in people only when they have neurologic complications, a markedly elevated serum acetaminophen concentration, or a marked lactic acidosis.[23] Human guidelines

have suggested that, when a poison's $V_d$ exceeds 1 to 2 L/kg, ECTR is unlikely to be effective and should not be pursued.[9,20,24]

### *Another Antidote or Life-Saving Treatment Is Not Available*

Toxicities that may be reversed pharmacologically should have the appropriate antidote administered as quickly as possible. There are few toxicities that provide this therapeutic opportunity. Systemic effects from some organophosphates may be reversed by the administration of atropine, thus decreasing the necessity to increase drug elimination with ECTR.[25] It is important to recognize that as the time from exposure until when an antidote is administered is prolonged, there may already be enough drug exposure to result in significant adverse effects. For example, the conversion of ethylene glycol to glycolic acid may be inhibited by the administration of 4-methylpyrazole (4-MP) or ethanol; however, this conversion begins minutes after ethylene glycol ingestion. At the time of 4-MP or ethanol administration, there may already be a lethal quantity of glycolic acid metabolized. Prevention of death in cats owing to a lethal quantity of ethylene glycol was only prevented by 4-MP when administered within 3 hours after exposure.[26] Studies in dogs shows that 4-MP or ethanol treatment may be effective if administered only within 6 to 8 hours of ingestion.[27–29] If enough time has passed for ethylene glycol to be metabolized to glycolic acid, 4-MP is no longer indicated.[30] Hemodialysis very efficiently removes both ethylene glycol and glycolic acid, suggesting that it is the most effective treatment for ethylene glycol toxicity.[31] Clinicians must be aware of potential antidotes for poisonings, their timeframe of efficacy, and their limitations.

### *The Benefits of Extracorporeal Toxin Removal Exceed the Risks to Patient Safety*

During extracorporeal treatments, a portion of the patient's blood is maintained outside of their body. It is recommended to design an extracorporeal circuit that will contain less than 20% of the patient's blood volume.[32] The red blood cells contained within this volume are unavailable for oxygen delivery; as the percentage of the patient's blood volume within the extracorporeal circuit increases, so does the risk of hypoxia, cardiovascular compromise, and substantial adverse effects. Historically, small patients (<5 kg) may not have been considered candidates for extracorporeal treatments owing to this risk. The increased availability of training opportunities in extracorporeal therapies has provided practitioners with tools to delivery safe and effective extracorporeal treatments. Strategies such as priming the extracorporeal circuit with synthetic colloids or blood have allowed for the delivery of safe ECTR for patients of any size.[33,34] Animals with anemia, cardiac or pulmonary disease, hypovolemia, and hypotension may be at increased risk for complications during ECTR. Astute patient monitoring, preemptive planning, and a well-trained and experienced staff can help to provide safe treatments for nearly all patients. As the risk or magnitude of adverse effect of the toxicity increases, so does the tolerability of potential complications during ECTR. For example, a cat was inadvertently administered a golden retriever's dose of vincristine intravenously, resulting in an exposure of 0.15 mg/kg, exceeding the lethal dose of 0.1 mg/kg. Medical treatment has been ineffective in preventing death in feline vincristine toxicity.[35] For this patient, ECTR is strongly indicated and the risks of this treatment are far overshadowed by the strong likelihood of a fatal outcome. TPE has successfully treated human vincristine toxicity[36] and was safely used to successfully manage feline vincristine toxicity in the author's hospital.

## SELECTING THE IDEAL EXTRACORPOREAL TOXIN REMOVAL PLATFORM

Ideally, hospitals providing ECTR will have capabilities to perform IHD, HP, and TPE. Because of the intentional slow rate of solute clearance occurring with CRRT, some have proposed that it is not an appropriate modality to treat toxicities.[20,37,38] For many veterinary patients, their small size may allow for CRRT to deliver more efficient treatments than what can be obtained in humans. In these small patients, CRRT may be an effective means of toxin removal; however, for most toxins, removal will be best with IHD, HP, or TPE. One situation where CRRT may be the ideal treatment is when a toxin has a very large $V_d$, prolonged clearance, slow intercompartmental transfer rate, and is a molecule with a high sieving coefficient across the hemofilter. CRRT may be able to maintain the plasma drug concentration below toxic a threshold, and prolonged treatment (potentially >24 hours) may be required to enhance total body elimination. By design, many machines performing IHD, HP, and TPE are not capable of treatments beyond 8 hours without starting a new session.

**Fig. 1** shows an algorithm to help select the most appropriate method of ECTR based on the limitations as described elsewhere in this article.

### *Intermittent Hemodialysis*

Conventional (low-flux) dialyzers have a small molecular weight cut-off and best remove solutes less than 500 Da, whereas high-efficiency (high-flux) dialyzers may remove solutes easily up to 15,000 Da.[24,39] Solutes from 1000 to 10,000 Da have more efficient clearance with convection compared with diffusion.[40] Purely convective treatment (intermittent hemodiafiltration or HDF) may remove solutes up to 40,000 Da with high-efficiency dialyzers.[9] The removal of toxins via IHD decreases as protein binding increases; however, solutes that are less than 80% protein bound are considered amenable to removal via IHD and HDF.[9,39,40] Increasing treatment time and volume of blood processed during the ECTR treatment allows for more effective removal of solutes with higher degrees of protein binding.[41] Uremia is typically treated with a 4- to 8-hour duration of IHD with variable blood flow rates,[32] where toxicities are treated for 6 to 8 hours using the highest blood flow rate achievable.

### *Hemoperfusion*

Activated charcoal is the most commonly used sorbent substance for ECTR. HP is most effective for solutes with a low to moderate $V_d$ (<1 L/kg).[10] Toxins with a large $V_d$ are less amenable to efficient removal via HP; however, prolonged treatment may allow for a sufficient decrease in total body drug accumulation. Charcoal HP is effective in binding solutes that are less than 95% protein bound.[42] Charcoal HP can remove both lipid- and water-soluble drugs.[43] Solutes up to 40,000 Da can easily bind to charcoal, resulting in effective removal.[44] Saturation of HP columns frequently occurs after 2 to 6 hours of use.[10] Exchanging a second charcoal cartridge may allow for increased solute removal.[45] A typical HP treatment will last 5 to 8 hours and use a blood flow rate of 150 mL/min or less.

### *Therapeutic Plasma Exchange*

Drugs with high (>80%) protein binding and a low $V_d$ (<0.2 L/kg) are ideal for removal with TPE.[46,47] Many of the nonsteroidal anti-inflammatory drugs fit this profile. For a substance that only exists within blood plasma, the exchange of 1 plasma volume would remove 37% of the original concentration. Exchanging 2 plasma volumes produces an 85% decrease, and 3 plasma volumes exchange results in a 95% decrease.[48] Most TPE prescriptions plan to exchange 1.3 to 2.0 plasma volumes;

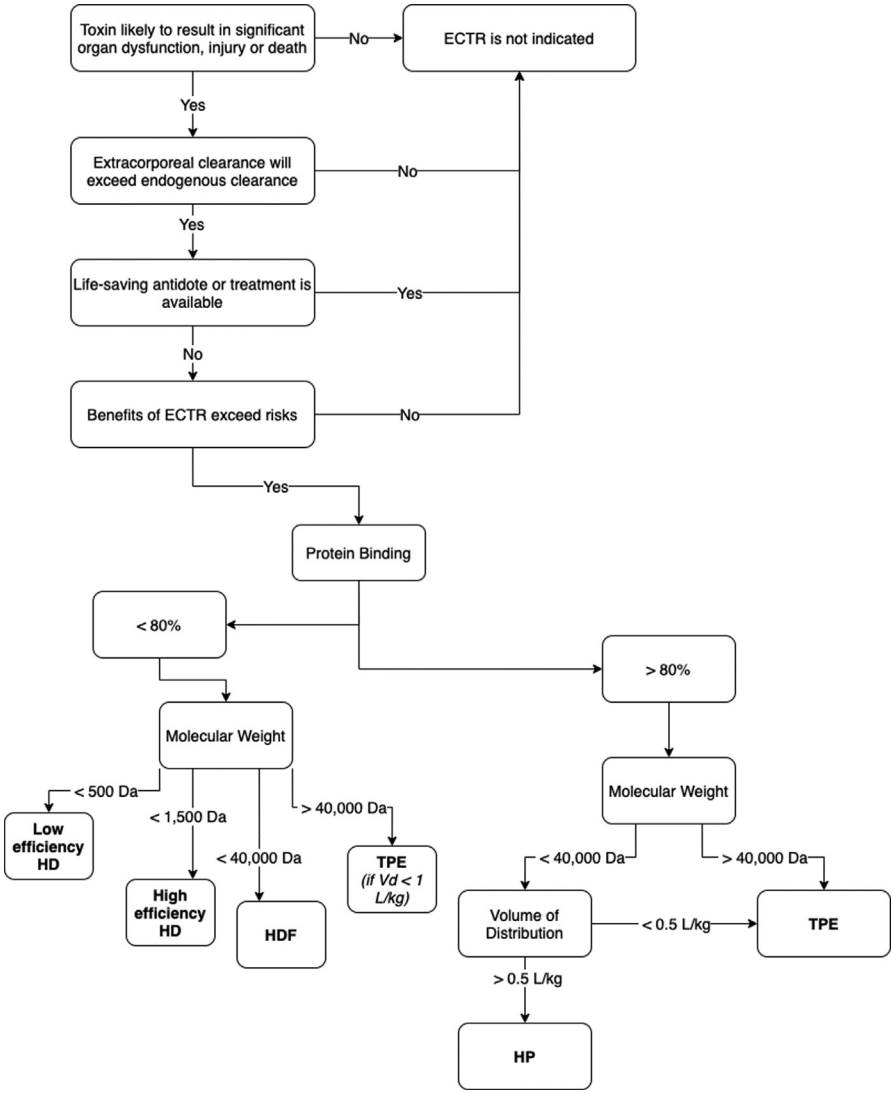


**Fig. 1.** Algorithm of when to use different methods for ECTR.

however, some have reported success with less volume exchanged.[49,50] Solutes with a larger $V_d$ are less efficiently removed because the drug existing outside of the intravascular space is not immediately available for removal. Molecular weight does not affect the clearance during TPE; solutes of greater than 1,000,000 Da can be removed via TPE.[9]

### *Other Modalities*

Although these platforms are effective in treating most toxicities, other methods may be used where indicated. The following treatments have increasing use in veterinary medicine; however, their exact role in managing disease and intoxications has not

been vetted. Anecdotal experience and published case reports exist for several of them.[51] Various resins have been used for HP and may bind targeted solutes differently than activated charcoal. Polymer resins such as CytoSorb and DrugSorb have been designed to remove inflammatory cytokines and aromatic compounds, respectively. Activated carbon sorbents, such as AimaLojic V100s, may have greater affinity and binding capabilities than activated charcoal for some solutes. Albumin and lipid dialysis use sterile dialysate containing albumin or lipid. These techniques can be used for protein- or lipid-bound toxins, allowing the free solute to cross the dialyzer membrane to be entrapped within the dialysate. It is unclear what benefit these have over HP or TPE for veterinary intoxications.

## COMMON VETERINARY INTOXICATIONS

Most intoxications require only 1 ECTR session to effectively decrease the serum drug concentration below a toxic threshold. With high drug exposure, the serum concentration may be several folds above a safe threshold. A single ECTR session may result in significant decrease (often >80%) in serum drug concentration; however, the final concentration may still exceed a toxic threshold. For example, AKI has been reported in dogs at a serum ibuprofen concentration of 138 μg/mL.[52] If a dog ingested enough ibuprofen to reach a serum concentration of 800 μg/mL, significant adverse effects would be anticipated and ECTR would be indicated if able to be performed timely. Both TPE and combined HP/HD have been used to treat ibuprofen toxicity in dogs, typically resulting in an 80% to 85% decrease in the serum concentration after treatment.[45,50,53] An 80% decrease in the starting serum concentration of 800 μg/mL would yield a serum ibuprofen concentration of 160 μg/mL, which may still result in AKI and other complications. In this scenario, increasing the dose of ECTR by increasing the amount of blood processed for HP/HD or volumes exchanged for TPE may lead to a greater decrease in the serum concentration. For drugs with a large $V_d$ and slow intercompartmental transfer rates, a second treatment on the following day may be indicated.[47]

**Table 1** lists drugs that pose toxic risks for animals as well as which ECTR modalities may be effective. Resources to help determine the best ERCT modality include evaluating published case reports and various chapters in human critical care and nephrology textbooks.

## EXTRACORPOREAL MANAGEMENT OF ACUTE KIDNEY INJURY

Both IHD and CRRT used for the treatment of uremia are considered extracorporeal renal replacement therapy (ERRT). The justification for intensive treatment of AKI lies in the possibility of recovery of renal function after an insult. However, a retrospective study of dogs with AKI demonstrated that, of the surviving dogs, only 19% had serum creatinine concentrations return to within the normal reference range.[54] In a study of feline AKI, 25% of cats were discharged with a plasma creatinine concentration within the reference range.[55] Similar to what is observed in humans, AKI in animals is associated with a high mortality rate. Mortality has been reported in several small case series and retrospective studies; however, a meta-analysis of AKI survival was recently published.[56] This article showed a pooled mortality rate of 45% in dogs and 53% in cats. Animals with infectious etiologies of AKI had superior survival to noninfectious causes.

Indications for ERRT in veterinary AKI include anuria or severe oliguria, refractory life-threatening hyperkalemia and academia, hypervolemia, and symptomatic uremia that has failed to respond to conservative management.[15,32,57] Veterinary patients

**Table 1**
**List of common veterinary intoxications grouped by effective ECTR modality**

| Hemodialysis or Hemofiltration | Charcoal HP (Often Performed in Combination with HD) | TPE |
|---|---|---|
| Acetaminophen | Amanita toxins | Amanita toxins |
| Aspirin | Baclofen[56] | Carprofen[63] |
| Aluminum[67] | Cannabinoids[57] | Deracoxib[54] |
| Baclofen | Cyclosporine[58] | Hyperbilirubinemia[64,65] |
| Bromides | Ibuprofen[43] | Ibuprofen[7,54] |
| Caffeine | Metaldehyde[59] | Meloxicam[49] |
| Diethylene glycol | Methotrexate[60] | Naproxen[54,66] |
| Ethanol[55] | Paraquat[61] | Vincristine |
| Ethylene glycol[34] | Pentobarbital | |
| Isopropyl alcohol | Phenobarbital[62] | |
| Lithium | | |
| Mannitol | | |
| Metaldehyde[49] | | |
| Methanol | | |
| Metformin | | |
| Methyl alcohol | | |
| Theophylline | | |

Published case reports of effective treatments are noted in citations.
*Data from* Refs.[7,34,43,49,54-67].

who receive ERRT for AKI typically have more severe disease, more frequent comorbidities, and higher illness scores, which likely give them a poorer prognosis than those with less severe disease who can be managed adequately with conservative therapy. A meta-analysis has shown that dogs and cats treated with hemodialysis as a part of their AKI management had higher mortality rates (53%) compared with those who received conservative care (37%).[56] This finding has also been observed in people with AKI.[58] However, in dogs and cats who survived AKI with the assistance of IHD, the 1-year mortality rates were not markedly different than the 30-day survival rates, suggesting that those patients who survive AKI can do well for some time.[59]

Determining the most appropriate time to initiate ERRT for uric AKI patients who lack life-threatening electrolyte, acid–base, or volume disturbances is not well-established in either human or veterinary medicine.[60–62] There is conflicting evidence in humans; however, some studies have shown that earlier initiation of ERRT is associated with improved mortality rates and a trend toward improved renal recovery in people with AKI.[63–65] Some authors have proposed dialysis should be considered in animals who have a blood urea nitrogen of greater than 80 mg/dL or a serum creatinine concentration of greater than 8 mg/dL.[15] This recommendation suggests starting at a lesser magnitude of uremia than an older recommendation (blood urea nitrogen >100 mg/dL, creatinine >8 mg/dL).[57] In this author's opinion, most dogs and cats with a blood urea nitrogen of less than 120 mg/dL and a creatinine of less than 5 mg/dL can typically be managed well with conservative therapy and the use of enteral feeding tubes. However, this rule is not firm; some patients tolerate uremia better than others. In human medicine, there has been a failure to determine appropriate criteria for the initiation of dialysis for AKI; the heterogeneity of reported studies precludes meta-analyses from determining the optimal time for intervention.[64] Blood urea nitrogen and serum creatinine concentrations may be altered independent of the glomerular filtration rate in critically ill patients, suggesting that functional and structural biomarkers may prove superior in the identification of patients who can benefit

from ERRT; however, studies evaluating this claim are needed in both humans and animals. Therefore, the potential benefits and risks of treatment need to be considered, including patient size, associated comorbidities, severity of disease, the local availability of dialysis, and cost. Uremic patients with oligoanuria, hypervolemia, hyperkalemia, and metabolic acidosis may benefit from ERRT.

Both IHD and CRRT can be used for the management of AKI in cats and dogs.[59,66–69] There have been no studies in veterinary patients comparing outcomes between these 2 modalities. There is no obvious advantage of one of these modalities. Because of the small size of veterinary patients, IHD machines can be manipulated to perform treatments with similar clearance rates of what is obtained during CRRT.[15] The blood volume held within the extracorporeal circuit is smaller on some IHD machines (64 mL for Baxter Phoenix neonatal circuit with a Fresenius F3 dialyzer) compared with CRRT (93 mL for Baxter Prismaflex M60 circuit with hemofilter). Most CRRT machines have automated configurations to perform diffusive, convective, or combination therapies.[70] There is no obvious advantage to any of these modalities (continuous hemodialysis, hemofiltration, or hemodiafiltration) in terms of improving morbidity and mortality in AKI. Prolonged IHD involves using either an HD or CRRT platform to deliver a conservative but extended (often 8–12 hours) treatment. Ultimately, the most effective ERRT for AKI is the platform for which the staff (veterinarian and nurses) are most trained, experienced, and comfortable performing. Reviews of the methodology of IHD and CRRT as well as some comparisons has been performed.[15,57,70–72] Because they use prepackaged sterile dialysate and replacement fluid, CRRT machines are quite mobile and may be brought to the patient's cage during treatment. This factor may allow for a critical patient to remain within the intensive care unit, where they can be monitored more closely. However, a downside to performing ERRT within the intensive care unit is the increased foot traffic, distractions, and noise, which can potentially lead to patient restlessness and decreased monitoring acuity. Through the use of prepackaged sterilized fluids, CRRT treatment are generally more expensive than IHD, where dialysate is generated in real time from the hospital's water source. This process requires purification of the water before it can be used for the creation of dialysate; the equipment used for this may hinder the mobility of the IHD machine, depending on the design of the hospital.[73]

## ROLE OF THERAPEUTIC PLASMA EXCHANGE IN TREATING IMMUNE-MEDIATED DISEASE

In addition to its role in removing protein-bound toxins, TPE allows for the removal of plasma proteins and other substances involved in the pathophysiology of disease, including antibodies, antigens, paraproteins, and antigen–antibody complexes. TPE has been used as an adjunctive therapy for veterinary immune-mediated disease for decades.[74–76] The most common veterinary diseases treated with TPE are immune-mediated hemolytic anemia and myasthenia gravis.[49,76–80] Many other disorders including immune complex glomerulonephritis, polyradiculoneuritis, hyperviscosity syndrome, and immune-mediated thrombocytopenia have also been treated, although published case reports are sparse.[49,75,76,81–86] Although traditional management of these diseases relies on pharmacologic immunosuppression, the patient is still burdened by the quantity of antibodies that have already been produced before the medical intervention taking effect. This factor may account for the persistent disease that is observed for several days or more after the introduction of immunosuppressive therapy.

As an adjunctive therapy in combination with standard immunosuppressive therapy, TPE has been observed to result in more immediate control of immune-mediated disease. Patients with immune-mediated hemolytic anemia will typically cease autoagglutinating after the first TPE treatment. Myasthenic dogs often improve strength in breathing and walking after TPE. Because immunoglobulins can redistribute from tissue stores the effect is not long lasting; therefore, 3 to 5 TPE treatments may be required before the disease is in remission.

Because of the cost and relative unavailability of apheresis, TPE was often approached as a final effort in refractory cases before euthanasia. This paradigm has been challenged owing to the marked improvement observed in most patients. Some practitioners have advocated for TPE to be considered a first-line therapy for moderate and severe cases of immune-mediated disease. Although randomized prospective studies have not been performed in veterinary medicine, case series have shown improved survival compared with historical controls (unpublished data courtesy of LD Cowgill, 2020). The use of TPE in people has undergone randomized studies, although the strength of evidence is still variable, and has helped to establish consensus guidelines regarding the usefulness of TPE for various diseases.[47] As TPE has gained traction in veterinary medicine, prospective studies are now feasible to better understand which patients can most benefit from treatment and when is the most appropriate time to initiate therapy. Providers of TPE agree that patients should not be referred as a final chance when the patient is moribund; earlier referral allows for the initiation of therapy before a marked decrease in patient stability and tolerance of treatment occurs. Certainly, some patients respond very well to standard treatment and will not show a clear benefit from TPE. TPE should be initiated for patients with more significant disease, who are anticipated to have a prolonged or protracted recovery, preferably as early in the course of the disease as reasonably possible (eg, a patient with immune-mediated hemolytic anemia who has received multiple blood transfusions).

Timing for the initiation of TPE for immune-mediated disease is not well-established. In this author's opinion, TPE could be strongly considered in the following situations.

- In the patient with immune-mediated hemolytic anemia with persistent evidence of ongoing erythrocyte destruction (auto-agglutination, spherocytosis or ghost cells visible on cytology, etc) and requiring 3 or more blood transfusions.
- Patients with severe hyperbilirubinemia with a risk of acute bilirubin encephalopathy and kernicterus.[87,88] The threshold of hyperbilirubinemia associated with adverse neurologic effects has not been well established in dogs in cats, however neurologic decompensation and kernicterus have been reported when the serum total bilirubin concentration was 35.6 to 62.6 mg/dL in dogs[86,89,90] and 17.5 mg/dL in a cat.[91]
- Before adding a third immunosuppressant drug to the patient's current drug regimen.
- Before the administration of human intravenous immunoglobulin, which is associated with risks of hypersensitivity.[92,93]
- In patients with myasthenia gravis or polyradiculoneuritis with progressive respiratory depression, before the requirement of mechanical ventilation.
- Patients with hyperviscosity, resulting in neurologic dysfunction, vascular occlusion, systemic hypertension, or other complications.
- Patients with cutaneous and renal glomerular vasculopathy.[94]
- Patients with confirmed or presumptive immune complex glomerulonephritis, particularly when renal function is rapidly declining.[95]

Based on human recommendations[47] and some shared pathophysiology, the following conditions may benefit from TPE therapy; however, clinical experience may be sparse.

- Meningitis of unknown etiology
- Immune-mediated thrombocytopenia
- Evan's syndrome
- Stabilization before thymectomy in myasthenic patients
- Refractory cases of pemphigus

## PRACTICAL CONSIDERATIONS IN PERFORMING EXTRACORPOREAL THERAPIES

### *Vascular Access*

In nearly all circumstances, extracorporeal therapies are best performed through a dedicated dual lumen jugular catheter.[96] Although the author has performed TPE using an arterial catheter placed in the dorsal pedal artery for inlet access and returned blood through a peripheral venous catheter in the cephalic vein, this practice should only be considered in patients who already have an arterial catheter and cannot tolerate sedation or the risks associated with jugular catheter placement (such as hypoxemia owing to pulmonary thromboembolism). People often have TPE performed using 2 peripheral venous catheters (typically 16G); however, this practice is challenging in dogs owing to inability to place such large catheters in many small and medium dogs, an increased tendency for positional occlusion of the vessels, and inadequate blood flow to support the rate of extracorporeal access. Even in large canine patients where it may be possible to use 2 peripheral catheters, it is still preferable to place a jugular catheter because this device provides superior blood flow rates, less occlusion, is unlikely to be removed by the patient, and can be maintained safely over many months.

Catheters should be placed using strict aseptic preparation of the access site and complete barrier protection (cap, mask, sterile gown, gloves, etc) of the operator and assistant. The right jugular vein is the preferred site of vascular access owing to its relatively straight pathway to the cranial vena cava, right atrium, and caudal vena cava. The left jugular vein can be used if the right is inaccessible owing to thrombosis from prior venipuncture, trauma, or other factors that may prevent successful cannulation. A dual lumen catheter should be selected that will be most likely to deliver the blood flow rates needed for therapy. Resistance to blood flow through the catheter is determined through Poiseuille's law, which depends on the catheter width and length. The highest flow rates are obtained by selecting the widest and shortest catheter appropriate for the size of the patient. Hospitals should stock a variety of dialysis and apheresis catheters to fit the diverse sizes and shapes of canine patients, typically ranging from 7Fr $\times$ 12 cm through 14Fr $\times$ 30 cm. Catheters should be placed using a modified Seldinger technique. Successful placement of the initial peripheral catheter into the jugular vein was found to be successful in only 64% and 77% of cats and dogs, respectively.[97] Ultrasound guidance may be used to aid in the initial cannulation of the jugular vein,[98] which can be challenging in patients with hypervolemia and subcutaneous edema, thrombosis or hematoma from prior venipuncture, or hypovolemic states. A surgical cut-down approach may also be needed in some patients. Fluoroscopy should be used to monitor and guide catheter placement. Blind placement of jugular catheters in critically ill dogs and cats had a 51% complication rate.[97] Fluoroscopy allows the operator to visualize guidewire and catheter placement, helping to prevent incorrect placement and endocardial irritation, and can confirm the final location of the catheter. Catheters used for extracorporeal treatments provide optimal

blood flow when the tip is residing within the right atrium. The caudal vena cava is an acceptable option in most patients; however, the distal lumen should be used for inlet (arterial) access to prevent access recirculation.[96]

Blood flow rate necessary to perform aggressive IHD treatment is often greater than 40 mL/min for a cat and greater than 200 mL/min for a dog. Charcoal HP typically uses blood flow rates of less than 150 mL/min to increase the contact time between the blood and the charcoal. Both TPE and CRRT have lower blood flow rates, occasionally less than 10 mL/min. Patients who are to receive only TPE may have a smaller diameter catheter placed than if the patient were to require IHD. For uremic patients, even if the initial few treatments will be performed as CRRT, placing the widest catheter possible is recommended to be able to achieve high blood flow rates needed for IHD or prolonged IHD in the latter sessions.

Patients should not have both jugular veins catheterized; otherwise, cranial venous occlusion and precaval syndrome may occur. In patients who already have a central venous catheter placed in a jugular vein, this catheter should be exchanged over a guidewire for a new catheter dedicated to extracorporeal treatment. A sampling line may be placed in the saphenous or femoral vein. If 1 jugular vein has thrombosed owing to prior venipuncture or catheterization, the placement of a catheter in the contralateral vein may restrict venous drainage and cause precaval syndrome. Subcutaneous edema accumulates within the face and neck and may extend into the thoracic limbs. This phenomenon may resolve after several days, once collateral vessels establish sufficient drainage. Laryngeal edema may create a life-threatening upper airway obstruction, which may require intubation. Removal of the jugular catheter is necessary in this event. Thrombolytics and other intravascular techniques may also be considered to reestablish venous flow. If extracorporeal treatment is still required, access can be obtained through the femoral vein; insertion of the catheter at the most proximal accessible site can accommodate a wide catheter and sufficient blood flow rates. Femoral catheters are more challenging to maintain owing to complications of bandage contamination with urine and feces as well as an increased risk of the patient chewing or dislodging the catheter. An Elizabethan collar should be worn at all times.

### *Anticoagulation*

Most platforms have integrated methods of anticoagulation incorporated into the extracorporeal circuit and operating software. The 2 most often used methods of anticoagulation are systemic heparinization and regional citrate anticoagulation.[99,100] Systemic heparinization is achieved through the delivery of unfractionated heparin into the extracorporeal circuit via an incorporated syringe pump. Enough heparin needs to be administered to prevent coagulation as the blood travels through the extracorporeal circuit. The extracorporeal transit time is one factor that can guide the dose of heparin; transit time (min) = extracorporeal circuit volume (mL) ÷ blood flow rate (mL/min). The effect of heparin is monitored through serial testing of activated clotting time or activated partial thromboplastin time. Generally, the results of these tests should be longer than the extracorporeal transit time; however, individual patient factors need to be considered. Hypocoagulable patients, those with recent trauma or surgery, and those with active bleeding should receive conservative heparinization, but may be more safely managed with regional citrate anticoagulation or a no-heparin treatment.

Regional citrate anticoagulation prevents clotting through induction of hypocalcemia within the extracorporeal circuit. To achieve this state, sodium citrate is added to the extracorporeal circuit as blood is exiting the catheter to decrease the ionized calcium concentration to less than 0.4 mmol. To prevent hypocalcemia in the patient,

calcium (either calcium citrate or gluconate) is administered at the return (venous) lumen of the catheter. Serial measurement of the ionized calcium concentration of both the extracorporeal circuit and the patient are required to ensure safety and success. This technique may be safer in hypocoagulable patients, those with active bleeding, and has been used to safely and successfully perform IHD intraoperatively (T Francey, personal communication, 2020).

No-heparin treatments do not result in significant anticoagulation to the patient or the extracorporeal circuit. This technique can be considered in hypocoagulable patients or those with active bleeding when regional citrate anticoagulation is unavailable. This technique uses intermittent saline flushes (30–50 mL every 15–30 minutes) of the extracorporeal circuit to disrupt any forming blood clots.[99] This fluid must be accounted for and removed during treatment via ultrafiltration to prevent a positive fluid balance. The blood flow rate should be maximized to shorten the extracorporeal transit time. Clotting is more likely to occur with this technique, necessitating early discontinuation of therapy; it may not be possible to deliver the entire prescribed dose of ERRT. Administration of a low dose (10–50 U/h) of heparin into the arterial side of the circuit may help to prevent clotting with minimal effects on patient coagulation. In general, no-heparin treatment can be avoided if the staff is trained and experienced with regional citrate anticoagulation, even when the machine does not have this mode incorporated into its operational software.

### *Patient Monitoring*

Patients require continuous monitoring throughout the entire extracorporeal treatment. The treatment should be performed in a location where individualized attention can be given to the patient and all supportive care can be successfully administered. A dedicated room where extracorporeal therapies are performed allows for better control over the environment and prevents the many distractions that can interfere with monitoring. Some critically ill patients, including those who may require mechanical ventilation, vasopressors, and so on, may have optimal monitoring when the treatment is performed within the intensive care unit. The best location depends on both patient status and hospital design. Regardless of location, comfortable bedding, heat support, and supplemental oxygenation should be provided. Only fractious animals require sedation, although patients with status epilepticus or hypoxemia may benefit from injectable anesthesia and/or mechanical ventilation. Patients should wear a harness that can be secured to the treatment table (**Fig. 2**) and also allows the blood lines to be secured to the harness, preventing the patient from pulling out their catheter.

Vital parameters should be assessed before, throughout, and at the completion of treatment. The patient's blood pressure, temperature, heart rate, and respiratory

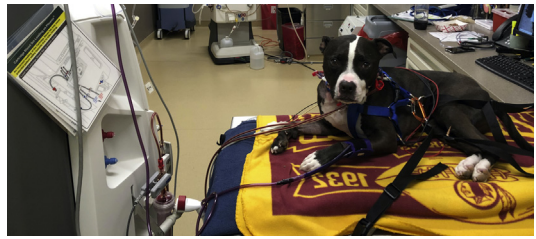

**Fig. 2.** Patient undergoing hemodialysis. Note the placement of the harness to prevent the patient from dislodging the lines and dialysis catheter.

rate should be measured and recorded. Hypotensive patients should have their blood pressure corrected before the initiation of extracorporeal treatment. Patients with low-normal systolic blood pressure and those where the extracorporeal circuit contains 20% or more of their blood are at risk of intraprocedural hypotension. This condition may be treated with the administration of an intravenous bolus of crystalloid or synthetic colloid or via administration of a vasopressor. The patient's hematocrit should be measured before treatment; priming the circuit with blood may be necessary for anemic patients. Pretreatment coagulation testing should be performed, either activated clotting time or activated partial thromboplastin time when systemic heparinization is used, or serum ionized calcium concentration when performing regional citrate anticoagulation. These tests should be performed every 30 minutes or whenever problems in coagulation are suspected.

Throughout treatment, the patient will have serial monitoring of its vital status and other metrics. Particular attention should be given to the patient at the initiation of treatment and for the first 15 minutes. This time is often when the patient may decompensate and develop hypotension, arrhythmias, hypoxemia, or other life-threatening complications. Vitals should be measured after the patient's blood has completed the initial traverse through the circuit. Any action steps to troubleshoot decompensation should be anticipated and prepared for. Vasopressors should be drawn up and be ready to be administered for patients where hypotension is anticipated. Some patients, particularly cats and small dogs, may benefit from prophylactic administration of vasopressors 5 to 10 minutes before the initiation of extracorporeal therapy. If the patient's cardiovascular status remains stable, these agents may be weaned off during treatment. Blood pressure should be regularly measured at intervals throughout treatment. Cats and small dogs should have a Doppler probe and sphygmomanometer cuff taped in an appropriate place before beginning treatment. This provides an audible pulse signal and allows for immediate measurement in the event of patient instability. Medium and large dogs may have oscillometric blood pressure measurement performed in a similar fashion. Automated measurements can be performed every 5 to 15 minutes according to patient status. Some extracorporeal platforms have an oscillometric blood pressure cuff incorporated into their system; these devices have been validated for correct measurement in humans and may not be accurate in dogs and cats. They should be validated with concurrent blood pressure measurement via dedicated veterinary devices before they are trusted, particularly during hypotensive states when they may be less accurate. A continuous electrocardiogram is monitored throughout treatment for the presence of arrhythmias. Patient heart rate, temperature, respiratory rate, and blood pressure should be recorded every 15 to 30 minutes throughout treatment. Peripheral pulse oxygenation or central venous oxygenation should be measured when possible. Dedicated ancillary devices can measure central venous oxygenation via the extracorporeal circuit and should be used in all treatments.[73] Supplemental oxygenation should be administered to all patients until their cardiopulmonary stability can be assessed during treatment.

### *Discontinuing Therapy*

For most toxicities, a single ECTR session will adequately reduce their serum concentration below a toxic threshold. However, toxins with large $V_d$, low clearance, or those with particularly high exposure may benefit from 2 or more treatments. Consultation with veterinary toxicologists and clinical pharmacologists is recommended in this scenario because point-of-care testing for most toxicities is unavailable. The length of each ECTR session and volume of blood to be processed should be maximized to achieve the highest extracorporeal treatment. As the $V_d$ of a toxin increases, the

volume of blood to be processed should similarly increase. It is common to treat a blood volume of 2 times or less to 10 times in a single session. If troublesome vascular access results in lower than prescribed blood flow rates, the treatment duration should be extended to process an appropriate volume of blood.

The prescription for ERRT in uremic patients is beyond the scope of this article, but thoroughly described elsewhere.[32,70,71] Generally, the initial treatments are more conservative and deliver a smaller dose of dialysis over a longer timeframe. This can help prevent dialysis disequilibrium syndrome and intradialytic hypotension.[101] Performing ERRT too quickly can result in increased complication rate; one study showed 37% of dogs developed neurologic signs when dialyzed for only 60 minutes per session.[102]

After ECTR, the access catheter is typically left in place until it can be determined if the patient will suffer from any adverse complication of the drug exposure. For most nonsteroidal anti-inflammatory drug toxicities, the patient will show azotemia within 48 hours of exposure. If this should occur, the access can then be used for ERRT if warranted by the severity of azotemia. Patients with AKI who are recovering renal function may have ERRT discontinued when their predialysis creatinine is less than 5 mg/dL or their uremia is mild and no longer significantly mitigated with ERRT. The catheter is left in place for 5 to 7 days after the last ERRT treatment to monitor for rebound and to confidently determine if the patient has graduated from requiring ERRT. When not in use, the catheter lumens are locked with an anticoagulant (unfractionated heparin 250–2500 U/mL or 4% citrate) to help prevent thrombosis.

When removing the jugular catheter, direct pressure should be applied for 10 minutes to encourage hemostasis. A temporary bandage should be placed around the neck for 24 hours to protect against contamination. No sutures are typically required, and the skin incision closes by second intention healing.

## DISCLOSURE

The authors have nothing to disclose.

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