# Extracorporeal Removal of Drugs and Toxins

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**KEYWORDS**

• Drug • Toxin • Dialysis • CRRT • Dosing

This article reviews the principles of drug and toxin removal by extracorporeal circuits and the appropriate management of patients on renal replacement therapy. The principles of drug removal and therapeutic dosing in intermittent and continuous therapies as well as the use of intermittent hemodialysis for the removal of toxic substances are discussed. The considerations involved in the calculation of drug dosages and toxin removal are reviewed; however, there is a paucity of information related to veterinary patients. Therefore, much of this information is extrapolated from human data.

The type of extracorporeal therapy used can greatly affect the extent of drug and toxin removal. The available modalities include intermittent hemodialysis and three types of continuous renal replacement therapies (CRRTs). Intermittent hemodialysis is primarily a diffusive process, whereas CRRT uses a combination of diffusion, convection, and adsorption. The continuous modalities include continuous venovenous hemofiltration (CVVH), a purely convective modality; continuous venovenous hemodialysis (CVVHD), a diffusive modality; and continuous venovenous hemodiafiltration (CVVHDF), which combines the aspects of both convection and diffusion. Convection uses hydrostatic pressure to force fluids and dissolved solutes out of the blood and across the semipermeable membrane of the dialyzer, whereas diffusion uses the tendency of solutes to move from an area of high concentration to that of low concentration to remove substances from the blood. Convective modalities allow for the removal of small- and medium-sized molecules, whereas diffusive modalities are limited to smaller molecules.[1] This difference has significant implications regarding drug removal. The final mechanism of solute clearance is adsorption, which refers to the adherence of solutes to filter membranes, leading to increased removal from plasma. Adsorption is saturable and therefore plays only a minor role in clearance unless the filter is changed more frequently than every 18 to 24 hours.[2]

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In addition to the type of extracorporeal therapy chosen, there are numerous other variables that play a role in determining the extent of drug removal or clearance during treatment, including the various membrane and solute characteristics.

## MEMBRANE AND PRESCRIPTION CHARACTERISTICS

Membrane characteristics affecting drug clearance include the filter material, filter pore size, and filter surface area. In addition, the dialysis prescription, namely the ultrafiltration rate ($Q_{uf}$), dialysate rate ($Q_d$), blood flow rate ($Q_b$), and for convective modalities, the selection of pre- versus post-dialyzer replacement fluids have a considerable effect on the clearance.[3] Higher permeability filters can result in significantly higher drug clearance rates than less permeable membranes, especially for intermediate–molecular weight drugs such as vancomycin.[4] The age of the filter can also affect the clearance because its performance changes over time, particularly in continuous treatment modalities.[5]

## DRUG AND TOXIN (SOLUTE) CHARACTERISTICS

The solubility, volume of distribution ($V_d$), molecular weight, protein binding, charge, and degree of renal and nonrenal eliminations contribute to the clearance of a drug during extracorporeal renal replacement therapies.[3] Antibiotics are arguably the most important group of drugs to consider because they are commonly administered to patients with acute kidney injury undergoing dialysis and their blood levels can be significantly influenced by extracorporeal therapy. This is a critical point because underdosing of antibiotics may result in treatment failure, whereas overdosing may result in unacceptable toxic side effects for the patient.

Several antimicrobial properties influence dialytic clearance. Solubility describes whether a drug is hydrophilic or lipophilic. Hydrophilic drugs, such as β-lactams, glycopeptides, and aminoglycosides, are unable to passively cross the plasma membrane of the cells, and so their distribution is limited to the extracellular fluid. The hydrophilic drugs are usually excreted unchanged by the kidney. Lipophilic drugs, such as macrolides, fluoroquinolones, tetracyclines, and chloramphenicol, may freely cross the plasma membrane of the cells, so they are widely distributed into the intracellular compartment. Lipophilic drugs usually require metabolism through various pathways before elimination.[3]

$V_d$ is another crucial consideration. This term describes the volume in which a drug would need to be dissolved to obtain the observed blood concentration, assuming homogenous mixing in the body. $V_d$ is the primary pharmacokinetic consideration used to determine the initial (loading) dose of an antimicrobial.[6] $V_d$ determines the dose needed to achieve a desired plasma concentration ($C_p$) for intravenous medications using the following calculation[1]:

$$\text{Dose} = C_p \times V_d \times \text{body weight in kilograms}$$

A large $V_d$ indicates that a drug is highly tissue bound and that only a small proportion of the drug is within the intravascular compartment, available for clearance by extracorporeal therapy.[1] $V_d$ can be increased during critical illness and renal dysfunction but should not be affected by the selected extracorporeal therapy.[6] A large $V_d$ (>1 L/kg) decreases the likelihood of a drug being substantially removed by hemodialysis or CRRT, assuming there is enough time for the drug to distribute. Drugs with a small $V_d$ ($\leq$1 L/kg) are more likely to be cleared by extracorporeal therapies.[5] A drug with a large $V_d$ but high clearance during intermittent hemodialysis is removed

from the intravascular space very quickly, but because of its distribution in tissues, only a small amount of the total drug content is removed during any single dialysis session and the plasma concentrations increase between therapies. This phenomenon is termed rebound.[1] In contrast, CRRT has a slow, continuous effect on clearance and does not result in a rapid decline in $C_p$, with subsequent rebound for drugs with a large $V_d$ because time allows for continuous redistribution of the drug from the tissues to the blood.[1] Overall, drug elimination during CRRT is much slower for drugs with a large $V_d$ than for drugs with a small $V_d$. Unlike with intermittent hemodialysis, adjustments in drug dosing during CRRT depend more on the relative contribution of the total body clearance rather than on the drug's $V_d$.[7]

Protein binding of a solute also influences clearance during extracorporeal therapies. A drug that is highly protein bound is less likely to be removed during renal replacement therapy than one that is mostly unbound because an unbound drug can cross the filter membrane, whereas a protein-bound drug cannot.[5] The unbound fraction of the drug can be used to estimate clearance in continuous modalities by multiplying this value by the $Q_d$ or $Q_{uf}$.[5] However, some studies have shown that clearance in CRRT may be underestimated by this method.[6] In general, drugs that are highly protein bound are poorly cleared by extracorporeal therapies. Disease states such as uremia, hepatic dysfunction, hypoalbuminemia, and nephrotic syndrome have been shown to decrease the protein binding of drugs.[6]

The molecular weight of a solute has a significant effect on its clearance. Most drugs have a molecular weight less than or equal to 500 Dalton (Da), whereas very few have a molecular weight greater than 1500 Da. Low–molecular weight, water-soluble substances can pass easily across a dialysis membrane. However, large, protein-bound or lipid-bound solutes are more difficult to remove.[8] Most hemodialysis membranes favor diffusive clearance of low–molecular weight solutes (<500 Da), whereas membranes used in CRRT have larger pores that allow the removal of solutes via convection, with molecular weights as high as 20,000 to 30,000 Da.[1] Therefore, CRRT membranes generally have no significant filtration barrier to non–protein-bound drugs.

Finally, the ionization of a drug may affect its ability to be cleared by extracorporeal therapies, which is because of the Gibbs-Donnan effect,[1] in which retained anionic proteins on the blood side of the membrane decrease the filtration rate of cationic solutes because of complex formation with a negatively charged membrane.

## PATIENT CHARACTERISTICS

In addition to the membrane and solute characteristics that may affect the removal of drugs in extracorporeal therapies, there are also several patient variables that can alter drug handling. Systemic pH levels, body fluid composition, tissue perfusion, residual renal function, and contribution of non-renal routes of elimination can affect clearance.[3] An individual's residual renal function can change continuously because of the dynamic nature of kidney injury and critical illness.[5] It is important to remember that renal disease may affect not only the renal handling of drugs but also the other pharmacokinetic parameters, including bioavailability, $V_d$, and hepatic metabolism, although these alterations may be difficult to quantify.[3] Drug metabolism in patients with acute kidney injury is also likely to be different from that in patients with chronic kidney disease.

Patient characteristics such as obesity, age, gender, thyroid and renal functions, and cardiac output can affect the $V_d$ of a particular drug.[8] As discussed earlier, the $V_d$ of a drug correlates inversely with its $C_p$, thus affecting the amount of intravascular drug available for elimination by extracorporeal therapies.

## CLEARANCE

Clearance describes the theoretical volume of blood from which a solute is removed per unit time.[9] A patient's native clearance depends on the ability of that solute to pass across the glomerular basement membrane; it may be affected by tubular secretion or reabsorption and is a function of the molecular weight, charge, and urine flow rate.[8] Clearance in extracorporeal therapies is defined by the extraction ratio, which is the product of the $Q_b$ and the percentage of the substance removed from the blood as it passes over the filter membrane.[10] Extracorporeal clearance is determined by the intrinsic clearance of the dialyzer membrane, duration of treatment, $Q_b$, $Q_d$, and $Q_{uf}$.[8] If the renal clearance of a drug is less than 25% to 30% of the total body clearance under normal conditions, impaired renal function is unlikely to have a clinically significant effect on drug elimination.[11] Likewise, CRRT has little influence on the total body clearance of such drugs, so it is not necessary to adjust the dose during renal replacement therapy because the therapy has a small effect on overall clearance.[5] Patients with concurrent liver failure may be an exception to this rule because CRRT may contribute a greater extent to clearance in those patients.[1] In continuous modalities, if the therapy is a significant source of clearance as is the case for drugs that are renally cleared, a loading dose followed by maintenance doses should be given.[5] Drug doses also need to be adjusted when the CRRT dose (ie, $Q_b$ and $Q_{uf}$) is altered or when the patient's volume status changes because of the change in CRRT clearance.[6]

## SOLUTE CLEARANCE AND DOSING RECOMMENDATIONS IN INTERMITTENT HEMODIALYSIS

In general, because of the relatively short course of treatment of intermittent therapies, the authors recommend administering medications as appropriate for patients with reduced renal function after the session is completed, eliminating the role of dialysis in drug clearance.

For drugs that are dosed before the treatment session, redosing may be necessary if they are significantly cleared by extracorporeal therapies. As discussed earlier, drugs that are likely to be significantly cleared are those that normally experience more than 25% to 30% renal clearance, with small $V_d$, low molecular weight, low protein binding, and no lipid binding. Determining the clearance can be helpful in estimating the doses for administering drugs during the treatment. The gold standard for estimating dialytic clearance is the recovery method.[12]

$$Cl_{dialysis} = (C_d \times V_{dialysate})/(C_p \times T)$$

In this equation Cl is clearance, $C_d$ is the concentration of the drug in the dialysate, $V_{dialysate}$ is the volume of dialysate, $C_p$ is the concentration of the drug in the plasma entering the dialyzer, and T is the time of dialysis. Alternatively, clearance can be estimated by using the arteriovenous difference method.[13]

$$Cl_{dialysate} = Q_b\,[(C_{arterial} - C_{venous})/C_{arterial}]$$

where $C_{arterial}$ is the drug concentration in the arterial line, and $C_{venous}$ is the drug concentration in the venous line. This approach allows for estimation of dialysis clearance without collecting the dialysate for measurement of drug concentrations but may lead to overestimation of the actual clearance.[14] Estimates of clearance are not generally applicable from one dialyzer to the next because of the large differences in membrane characteristics, pore size, and surface area between dialyzers. Clearance increases as the surface area increases and as the membrane thickness decreases.[15]

These theoretical considerations are valuable but, to date, are not commonly used in clinical veterinary patients.

The concept of rebound is also an important consideration in intermittent hemodialysis solute clearance. Drugs with a large $V_d$ experience a rebound in $C_p$ because the drug is redistributed from tissues.[14] After extracorporeal removal is stopped, any drug removed from the extracellular space can have a concentration gradient that causes drugs to move from their intracellular stores to the extracellular space, leading to an increase in the plasma levels.[16]

## SOLUTE CLEARANCE IN CRRT

CRRT is thought to be better tolerated by hemodynamically unstable patients and is as effective in removing solutes during a 24- to 48-hour period as a single session of intermittent hemodialysis.[17] Therefore, CRRT is a useful modality in many patients with acute kidney injury requiring renal support. The principles of solute clearance with regard to membrane, solute, and patient variables are similar in both continuous and intermittent therapies. However, the considerations are far more complex because of the prolonged course, the lack of interdialytic period, and the greater potential variabilities in $Q_b$, $Q_d$, $Q_{uf}$, and delivery of pre- versus post-dilution replacement fluids. There are various reports in the human literature evaluating individual medications in different settings of CRRT. These evaluations cannot be uniformly applied in different modalities, diseases, species, or drugs. It is most useful to consider each of the mechanisms in CRRT and individually assess how solute clearance is affected. However, it must be remembered that these techniques are not precise and are only a starting point for the patients until further research is performed in clinical patients. In addition, it must be kept in mind that critically ill patients with renal dysfunction are at a risk for toxicities associated with standard drug dosing because of accumulation and overdosing. However, underdosing of medications may also be life threatening, as is the case with insufficient antimicrobial treatment resulting in treatment failure or bacterial resistance. Therefore, for nontoxic drugs, doses can safely be increased beyond actual estimates and a 30% increase is recommended by some to ensure adequate dosing in CRRT.[18]

### *CVVHD Clearance*

Solute clearance in CVVHD is primarily determined by the $Q_d$ and the dialysate saturation ($S_d$). $S_d$ represents the capacity of a drug to diffuse through a dialysis membrane and saturate the dialysate. This value can be calculated as follows[19]:

$$S_d = C_d/C_p$$

$S_d$ can then be used to calculate diffusive clearance with the following equation[19]:

$$Cl_{CVVHD} = Q_d \times S_d$$

The efficiency of $S_d$ and thus, solute clearance in CVVHD, a diffusion-based therapy, is determined by the concentration gradient across the membrane and the molecular weight of the solute as well as the porosity and surface area of the membrane.[19] As a solute's molecular weight increases its diffusive clearance decreases because of the limitations on size in diffusion-based therapies. This effect is greater when using conventional dialysis membranes than when using synthetic CRRT membranes. As a rule, the $Q_d$ is equivalent to the diffusive clearance of small unbound solutes when using this treatment modality.[19]

Alternatively, $S_d$ can be approximated by the unbound fraction of a drug when calculating clearance.[19] Increasing the molecular weight of a solute or the $Q_d$ reduces the $S_d$ and consequently, the clearance of the drug because of the slower rate of solute diffusion and the shortened period available for diffusion.[20]

### *CVVH Clearance*

In CVVH, the primary determinants of solute clearance are the $Q_{uf}$, which drives convection, and the sieving coefficient ($S_c$). In convective clearance modalities, $S_c$ is used to describe the capacity of a drug to pass through the membrane.[19] $S_c$ is expressed as follows:

$$S_c = C_{uf}/C_p$$

where $C_{uf}$ is the drug concentration in the ultrafiltrate.[19] For most antimicrobials, the $S_c$ can be estimated by the extent of the unbound fraction ($S_c \approx 1 -$ protein-bound portion) because protein binding is the main determinant of drug sieving.[3] However, this estimate does provide potential for error because $S_c$ is a dynamic value that can be affected by the age of the membrane and the amount of blood flow that is ultrafiltrated (filtration fraction).[19] Solutes that freely cross the membrane, such as urea, have an $S_c$ equal to or close to 1.[3]

Unlike diffusive clearance, convective solute removal, or filtration, is not affected by molecular weight up to the given maximum value of the particular membrane being used.[19] The membranes used in CVVH are highly permeable, with cutoff values as high as 50,000 Da, so the molecular weight of antimicrobials have little to no effect on drug removal or sieving.[19]

Over time, drug sieving coefficients decrease likely because of a growing protein layer that builds up on the membrane surface and/or the increasing number of clotting hollow fibers in the filter.[5] The clearance of small solutes, such as urea and creatinine, is not greatly affected by an aging filter, but those of larger molecular weight solutes are likely affected.[5]

In addition, the location of the replacement solution that is used to drive solute removal, either pre- or post-filter, can influence the efficiency of solute removal.[19] In post-filter dilution, blood is not diluted before entering the filter; therefore the clearance can be determined by the product of $Q_{uf}$ and $S_c$.[19]

$$Cl_{CVVH}\ (post) = Q_{uf} \times S_c$$

However, if ultrafiltration is performed by pre-filter dilution, the patient's blood is diluted before entering the dialyzer, which decreases the concentration of the solute passing through the filter, thus decreasing clearance. In fact, there is a 15% to 19% reduction in clearance for urea and creatinine when the solution is administered prefilter as compared with postfilter.[21] A similar effect would be expected for drug clearance. In this case, clearance should be corrected for the presence of pre-filter dilution solution using the following equation[19]:

$$Cl_{CVVH}\ (pre) = Q_{uf} \times S_c \times [Q_b/(Q_b + Q_{uf})]$$

At present, there are no data for the calculation of clearance when a combination of pre- and postfilter dilution is used at varying ratios.

### *CVVHDF Clearance*

CVVHDF provides further challenge in the determination of drug clearance, especially with varied $Q_{uf}$ and $Q_d$ rates. Initially, it might be assumed that this modality would result

in an additive effect on clearance because of the use of both diffusion and convection. However, this additive effect is not produced and in fact, the opposite is true. Convection and diffusion may interact in such a way that solute removal is reduced as compared with simply adding the effects together.[19] This reduction in solute removal is because of the presence of convection-derived solute in the dialysate, which works to decrease the concentration gradient. This concentration gradient normally serves as the driving force for diffusion and therefore it lowers the overall, $S_d$.[19] As a result, the diffusive clearance of a drug in this modality cannot be accurately predicted.

Adsorption of drugs to the filter membranes is the final mechanism of clearance resulting from extracorporeal therapy. As discussed earlier, adsorption likely plays a significant role only if the filter is changed very frequently. However, adsorption can result in increased drug removal, and the capacity for adsorption is filter dependent. Dosing adjustments do not account for adsorption effects.[19]

The rule of thumb for drug clearance estimation at a given $Q_d$ and $Q_{uf}$ is that CVVH has a clearance greater than that of CVVHDF, which is greater than that of CVVHD.[5] There is a relatively small difference for small solutes, but the difference can be marked for larger molecules, such as vancomycin which has a molecular weight of 1485 Da.[4]

## DOSING ADJUSTMENTS IN CRRT

Dosing adjustments in the various modalities of CRRT can be estimated by using available drug dosing recommendations extrapolated from human clearance studies, by measuring or estimating clearance, or by therapeutic drug monitoring. Given the countless variables that affect clearance of solutes, including the membrane, drug, and patient characteristics, it is nearly impossible to establish a complete dosing guide for every drug in each patient. Therefore, it is important to understand the different principles discussed earlier that affect the clearance and determine the likelihood and extent of drug clearance. Several references from the human literature provide dosing guidelines for specific drugs based on studies in limited patient pools.[6,17,19,22] An additional reference that reports the dialyzability of drugs is the Web site, http://www.ckdinsights.com, which publishes an annual list of numerous drugs and their likelihood of being cleared by the various extracorporeal therapies.[23]

The loading dose of a drug depends largely on the $V_d$ and need not be adjusted in CRRT.[3] However, $V_d$ may be altered by many factors in critically ill patients including total body water, perfusion, protein binding, lipid solubility, pH levels, and active transport systems and may be larger in critically ill patients.[3] Consequently, dosages may need to be increased in critically ill patients to avoid inadequate dosing.

Drugs that are significantly cleared during CRRT, including amikacin, amoxicillin, ceftazidime, fluconazole, metronidazole, sulfamethoxazole, trimethoprim, and vancomycin, may require maintenance dosage increases compared with standard renal dosing by increasing the amount of each dose or decreasing the interval between doses.[3] For the concentration-dependent antibiotics (aminoglycosides, fluoroquinolones, metronidazole), the rate of microbial kill is closely related to the peak concentration above the minimum inhibitory concentration (MIC), therefore it is better to increase the drug dose while maintaining a fixed interval for drugs that are significantly cleared by CRRT.[19] The rate of kill for time-dependent antibiotics (eg, β-lactams, macrolides, tetracyclines, lincosamides) is related to the length of time for which the concentrations exceed the MIC. Therefore the recommended method of administration during CRRT is to shorten the drug-dosing interval and to maintain a fixed dose.[19] This shortened interval can be estimated by the following equation[19]:

$$Iv_{EC} = IV_{anuria} \times [Cl_{NR}/(Cl_{EC} + Cl_{NR})]$$

where $Iv_{EC}$ is the dosing interval during CRRT, $Iv_{anuria}$ is the dosing interval in a patient with anuria, $Cl_{EC}$ is extracorporeal clearance, and $Cl_{NR}$ is the nonrenal clearance.

After establishing the clearance of a drug in a particular modality, a dose can be determined. First, the dosing recommendations in patients with anuria should be addressed, by the following equation:

$$D_{anuria} = D_{normal} \times Cl_{anuria}/Cl_{normal}$$

where D is the dose.[1] Here, dosing adjustments can be performed by reducing the dose in proportion to the reduction in total body clearance. Pharmacokinetic tables can be used to determine the established clearance values and dosing intervals in people with or without anuria. In CRRT, dose can be established using the following basic equation[1]:

$$D = D_{normal} (Cl_{anuria} + Cl_{CRRT})/Cl_{normal}$$

Similarly, this equation can be applied to intermittent hemodialysis, if needed. But making these estimates can be time consuming and expensive and requires known pharmacokinetic data which is often unavailable for veterinary species.

Li and colleagues[22] reviewed the current human literature and summarized the following available methods of estimating the antibacterial dose in patients receiving CRRT:

a. CVVH[24]

$$D = C_{ss} \times UBf \times Q_{uf} \times I$$

b. CVVH[25]

$$D = D_n [Cl_{NR} + (Q_{uf} \times S_c)/Cl_n]$$

c. CVVHDF[1]

$$D = D_n \times [P_x + (1\text{-}P_x) \times (Cl_{CRtot}/Cl_{CRn})]$$

d. All modes[25]

$$D = D_{anuria}/[1 - (Cl_{EC}/[Cl_{EC} + Cl_{NR} + Cl_R])]$$

where $C_{ss}$ is the blood concentration at steady state, $Cl_{CRn}$ is the normal creatinine clearance, $Cl_{CRtot}$ is the sum or renal and extracorporeal creatinine clearance, $Cl_n$ is the normal total drug clearance, $Cl_R$ is the renal clearance, I is the dosing interval, $P_x$ is the extrarenal clearance fraction (which is equal to $Cl_{anuria}/Cl_n$), and UBF is the unbound fraction of the drug.

## SPECIFIC THERAPY FOR TOXICITIES OR DRUG OVERDOSES

In addition to their use in acute kidney injury and chronic kidney disease, hemodialysis, CRRT, and charcoal hemoperfusion are the commonly used adjunctive treatments for the management of specific drug overdoses and toxic ingestions when activated charcoal, gastric lavage, available antidotes, and supportive care are ineffective or impossible because of the patient's condition. The principles that guide the removal of a certain toxin are similar to those for the removal of drugs and other solutes. As such, the factors that affect the dialyzability of a toxin include protein binding, $V_d$, molecular weight, solubility, and charge. These factors have been addressed in greater detail earlier.

Indications for dialysis in the case of toxin ingestion include a strong history or known exposure to a dialyzable toxin, persistence of a significant blood toxin concentration, and lack of an effective medical antidote.[26] Hemodialysis is the method of choice for most toxicities and especially for the removal of low–molecular weight water-soluble molecules, with a small $V_d$, that are not protein or lipid bound.[8] As mentioned earlier, the intravascular concentrations of drugs/toxins that are lipid soluble and have a high $V_d$ decline very quickly after the first session of hemodialysis but increase again as the serum levels reequilibrate from the extravascular space during the interdialysis period. Sessions may need to be repeated because of this rebound effect.[8] CRRT has a theoretical benefit for patients who have ingested substances that are highly lipid bound and have a large $V_d$ with consequently slow transit times from the extravascular to the intravascular space.[8] In this case, clearance is achieved through prolonged treatment sessions using slower blood flow rates. However, CRRT is uncommonly used in these cases unless the solute displays significant rebound or the patient is unable to tolerate the normally used high flow rates because of hemodynamic instability.[8] Hemoperfusion is another modality that may be used for cases of intoxication. This method uses a charcoal filter, either alone or in circuit with the dialysis filter, to adsorb toxins from the blood by binding to activated charcoal or resin rather than by diffusing out of the blood down a concentration gradient.[8] Hemoperfusion filters are saturable and therefore require an exchange every 2 to 3 hours.[8] The use of these charcoal filters is limited by availability, expense, and their large priming size. In human medicine, hemoperfusion has been largely replaced by high-flux high-efficiency hemodialysis and is limited to select cases (eg, paraquat, theophylline).[27] Peritoneal dialysis has low efficacy in removing toxins and is therefore not recommended.[8]

In general, for removal of dialyzable toxins in a nonazotemic patient that is not at a high risk of dialysis disequilibrium, it is recommended to maximize the size of the dialyzer, $Q_b$, and duration of the session to achieve maximum clearance.[26] Blood flow rates of 10 to 20 mL/kg/min and treatment times of 4 to 6 hours are selected to ensure complete toxin removal.[26] In patients that are azotemic and/or at a high risk for osmotic shifts, the intensity of the dialysis prescription should be limited and CRRT or multiple sequential treatments may be used instead.

Ethylene glycol intoxication is one of the more common toxin ingestions that benefit from hemodialysis in veterinary medicine. Dialysis is able to remove not only the parent compound but also the toxic metabolites of ethylene glycol. The $V_d$ of ethylene glycol is equal to that of total body water, and it has a low molecular weight (62 Da), therefore it is cleared by hemodialysis. The parent compound is metabolized by alcohol dehydrogenase to the more toxic glycolic acid. Glycolic acid is further metabolized to oxalate, which can then deposit in renal tubules as crystals. Dialytic removal is recommended in patients with severe metabolic acidosis (pH<7.25), acute kidney injury or electrolyte imbalances that do not respond to conventional treatment, a significant level of circulating metabolites, or an alcohol level greater than 50 mg/dL.[28] The patient should be dialyzed until the toxic alcohol level is less than 20 mg/dL or for a minimum of 8 hours, with a second session 12 hours later if levels are not available.[28] The elimination half-life in people with ethylene glycol intoxication treated with dialysis is 155 minutes as compared with 626 minutes without dialysis.[29] If dialysis is performed early, before the metabolism of ethylene glycol or renal injury, the prognosis is excellent. However, if the patient already has acute kidney injury, the prognosis is significantly worse than with other causes of acute kidney injury because of the severity of renal injury caused by this toxin.[30]

Other dialyzable toxins reported in human medicine include aminoglycosides, methanol, salicylates, theophylline, paraquat, acetaminophen, lithium, mushrooms, antiepileptics, sedative hypnotics, and metformin.[8,27] In addition, there have been 2 case reports of baclofen intoxication in dogs that were successfully dialyzed using hemodialysis alone and in combination with hemoperfusion.[31,32] Although there are reported cases of dialysis being used to treat lily intoxication and grape/raisin intoxication in cats and dogs, the toxic principle of these plants is not known and therefore dialysis is primarily used for the treatment of the associated acute kidney injury rather than for the removal of the toxin.[33,34]

## SUMMARY

Intermittent hemodialysis and CRRT are becoming increasingly more available to veterinary patients for treatment of acute kidney injury and toxin ingestion. Medications are commonly administered to these patients for comorbidities and treatment of the underlying cause of renal injury, but there are no data in veterinary patients as to the appropriate dosing strategies. At present, recommendations must be extrapolated from the human literature and applied practically based on the information available about a given drug, including its $V_d$, solubility, protein binding, charge, and molecular weight. When medications with a low therapeutic index are used, it is necessary to use therapeutic drug monitoring to avoid toxicity.

The principles of drug handling can also be applied to drug overdoses and other toxicities to predict the dialyzability of the agent. In addition, the human literature may be useful in determining the likelihood of success with various medications and poisonings.

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