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International renal interest society best practice consensus guidelines for intermittent hemodialysis in dogs and cats

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ABSTRACT

Intermittent hemodialysis (IHD) is an advanced adjunctive standard of care for severe acute kidney injury (AKI) and other indications. Most animals with AKI are managed medically, however, when the disease is severe, medical management may not control the consequences of the disease, and animals with a potential for renal recovery may die from the consequences of uremia before recovery has occurred. Extracorporeal therapies aid the management of AKI by expanding the window of opportunity for recovery of sufficient kidney function to become dialysis independent. Intermittent hemodialysis (IHD) was introduced into veterinary medicine over 50 years ago, however, updated guidelines for the delivery of IHD have not been published for several decades. To that end, the International Renal Interest Society (IRIS) constituted a Working Group to establish best practice guidelines for the safe and effective delivery of IHD to animals with indications for dialytic intervention. The IRIS Working Group generated 60 consensus statements and supporting rational for a spectrum of prescription and management categories required for delivery of IHD on designated intermittent dialysis platforms (i.e., AKI, chronic hemodialysis and intoxications). A formal consensus method was used to validate the recommendations by a blinded jury of 12 veterinarians considered experts in extracorporeal therapies and actively performing IHD. Each vote provided a level of agreement for each recommendation proposed by the Working Group. To achieve a consensus, a minimum of 75% of the voting participants had to "strongly agree" or "agree" with the recommendation.

Introduction

Intermittent hemodialysis (IHD) is an advanced adjunctive standard of care for severe acute kidney injury (AKI) and other indications in which medical therapy fails to correct life-threatening azotemia, fluid overload, or dysregulated body fluid composition or intoxications. Severe acute kidney injury (AKI) is associated with high morbidity and mortality with reported mortality of 35%-60% in animals managed medically or with hemodialysis (Vaden et al., 1997; Worwag and Langston, 2008; Eatroff et al., 2012; Rimer et al., 2022). Medical management alone often is ineffective to control the clinical signs and metabolic abnormalities of uremia when the AKI is severe. Consequently, animals are at risk of dying within a short therapeutic window, despite potential reversibility of AKI. Adjunctive hemodialysis should be introduced in a timely manner to the medical management, when medical treatment alone is not expected to control the clinical signs and morbid clinicopathologic abnormalities associated with the AKI. Hemodialysis also is indicated for elimination of selected toxins in cases of intoxications independent of kidney function. In these circumstances a careful assessment should be performed to determine whether dialytic intervention is indicated (e.g., level of toxicity, toxin half-life, availability of antidote), and whether hemodialysis is expected to effectively remove the toxin (Foster, 2020).

Modalities for the delivery of renal replacement therapy include peritoneal dialysis, IHD, and continuous renal replacement therapy (CRRT). Over the last few decades, extracorporeal renal replacement

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therapies have become more widely available in veterinary medicine. IHD was the first extracorporeal renal replacement therapy introduced to veterinary therapeutics and remains an effective advanced treatment option for AKI with growing acceptance. Despite its established integration into veterinary therapeutics, updated veterinary guidelines for the indications, prescription, and delivery of IHD based on high grade evidence from veterinary or human literature, or considered expert opinion, are needed.

The International Renal Interest Society (IRIS) has recognized this need and commissioned a Working Group to establish best-practice guidelines for animals managed with IHD. The resulting guidelines have been tailored for intermittent treatments using IHD platforms unless specifically indicated otherwise. Guidelines reflect the consensus opinion based on current human or veterinary literature, review of case material, and the clinical experience of the members of the IRIS Working Group.

Methodology

These clinical guidelines were developed by an IRIS Working Group including six board-certified internists with formal training and extensive expertise in IHD. The Working Group generated comprehensive recommendations for the prescription and delivery of IHD to dogs and cats. Once this process was completed, a formal consensus method was used to validate the recommendations in two steps: 1) The statements were circulated to the entire IRIS Board who reviewed the consensus statements and made comments and suggestions. These were discussed further by the Working Group and the statements were revised as appropriate. 2) Twelve veterinarians with extensive extracorporeal expertise and actively performing IHD were asked to review the statements, send comments, and finally vote based on their level of support using the following scale: "strongly agree," "agree," "neutral," "disagree," or "strongly disagree." Anonymity was maintained by submitting all ballots to an independent party who forwarded the results once the voting process was completed. For a guideline to achieve consensus approval, a minimum of 75% of the voting participants had to choose either "strongly agree" or "agree." These results are reported alongside each guideline recommendation as an assessment of the strength of consensus for the guideline. The consensus guidelines are highlighted in bolded text. Text that is not bolded is provided as heading, context, or rational, but is not *per se* a consensus guideline recommendation.

Results

Timing of dialytic initiation in dogs and cats with acute kidney injury

Intermittent hemodialysis is an effective modality for the removal of retained uremic toxins, excessive fluid burdens, and correction of metabolic derangements in animals with IRIS Grade IV and V AKI. However, when it is applied late in the disease course, or when multiorgan complications are present, hemodialysis is less likely to alter the outcome of AKI (Segev et al., 2008b). Uremic toxins are distributed throughout body fluids and affect essentially all body organs. Subsequently, animals are at risk of dying from multiple organ dysfunction if dialysis treatment is delayed. It has been shown the number of organs secondarily affected by an AKI is associated with progressively increased mortality (Segev et al., 2008b). Dialytic intervention should be applied proactively prior to multiorgan failure and not as a response to it.

Statement: Dialytic intervention is indicated in animals with AKI or acute-on-chronic kidney disease, when the uremia and retained uremia toxins are expected to cause severe metabolic or organ dysfunction or damage leading to multiorgan dysfunction. Dialytic intervention should be directed to prevent (preferentially) rather than to resolve or ameliorate established morbidity or systemic organ dysfunction secondary to the kidney injury. The main indications for dialytic intervention in AKI are:

- **Serum creatinine exceeding 5 mg/dL (442 µmol/L) and trending higher in a hydrated animal.**
- **Persistent (>6 h) anuria or oliguria (<0.3 mL/kg/h) unresponsive to appropriate fluid therapy and medical management.**
- **Severe and life-threatening overhydration unresponsive to diuretic therapy and promoting target organ damage.**
- **Presence of electrolyte disturbances which cannot be controlled with medical or surgical management (e.g., hyperkalemia severe enough to compromise cardiac function).**

(100% agreement)

Dialytic intervention for intoxication

Hemodialysis is an effective option for extracorporeal removal of endogenous and exogenous toxins when their pharmacokinetic properties are compatible with clearance by the dialyzer membrane. Hemodialysis may prevent organ dysfunction or death when initiated promptly after intoxications by clearance of toxins before they fully distribute throughout the body or by shortening their exposure time (Groover et al., 2022). Extensive review of the timing of therapy, prescription for effective toxin removal, and limitation of hemodialysis in toxin removal has been published elsewhere and exceeds the scope of this manuscript (Bouchard et al., 2014; Foster, 2020).

Statement: Hemodialysis is indicated for toxin removal when there is no effective antidote or a potentially more effective therapeutic modality (e.g. hemoperfusion or therapeutic plasma exchange), and the toxin(s) concentration(s) or suspected concentration(s) is sufficient to cause morbidity, life-threatening risk, or tissue damage. The efficacy of hemodialysis is contingent upon specific characteristics of the toxin that would allow effective removal, specifically its molecular weight, protein binding, and volume of distribution. High-efficiency IHD is most effective if the molecular weight of the toxicant is less than 15,000 Da, the degree of protein binding is <80%, and the volume of distribution (Vd) is <2 L/kg. Additional considerations impacting removal include the toxin half-life and rebound potential (100% agreement)

Timing of dialytic initiation in animals with chronic kidney disease

Statement: Chronic hemodialysis is performed uncommonly in animals, but may be considered in animals with IRIS Stage 4 chronic kidney disease (CKD) when clinical signs (e.g., weight loss, inappetence, vomiting) and clinicopathologic abnormalities (e.g., acid-base, electrolyte disorders, hyperphosphatemia) cannot be controlled effectively, despite comprehensive and adequate medical management (including the use of a feeding tube). Intervention should be considered when all other means are not sufficient, however, before animals have decompensated substantially (e.g., became emaciated) and are less likely to benefit from the intervention (92% agreement).

Platform selection

The most common modalities for hemodialysis in animals with AKI are CRRT or IHD. CRRT is delivered on a CRRT treatment platform (machine) and designed for a gradual continuous delivery of treatment over days. It typically is less efficient and potentially more costly compared to IHD. Intermittent hemodialysis is delivered on an IHD treatment platform (machine), designed for relatively short discontinuous (4–5 hours) yet intense treatments. Although each of these platforms was designed to deliver a specific but seemingly opposite type of treatment, a prolonged hemodialysis simulating a continuous treatment

can be delivered using an intermittent platform, and an intermittent treatment and relatively intense treatment can be performed on animals using a CRRT platform. The goals of the treatment and the treatment prescription define the type of treatment rather than the platform used to deliver the treatment. When either platform is used for its unintended treatment purpose, each may have specific treatment limitations. For example, treatments delivered on a CRRT platform generally cannot provide a highly efficient maintenance treatment compared to intermittent platforms. Maintenance treatments delivered on CRRT platforms may be cost prohibitive, especially in large animals. IHD platforms characteristically are limited in delivering low intensity prescriptions required for initial treatments in severely uremic or small animals, due to inherent limitations to deliver appropriate blood and dialysate flow rates and limited accuracy of ultrafiltration controllers.

Statement: It is advantageous to have flexibility in dialysis platforms that will allow both continuous, low-intensity, bedside treatments (e.g., CRRT) for animals with critical disease as well as high-efficiency treatment for animals requiring intermediate to extended periods (weeks to months) of renal replacement therapy (e.g., IHD) (100% agreement)

Statement: Either platform can be used for initial management, however, in larger animals (i.e., >20 kg), maintenance hemodialysis is most effectively, practically, and economically performed with an IHD platform (100% agreement)

Statement: IHD should be regarded as having superior efficiency for toxin removal compared to continuous therapy (92% agreement)

Priming volume and priming fluids

The priming volume of the extracorporeal circuit is determined by the collective blood volumes of the hemodialyzer, the inlet and return tubing, and occasionally by additional components incorporated into the extracorporeal circuit (e.g., in-line volume monitoring chamber, hemoperfusion devices). The volume of the extracorporeal circuit in relation to the animal's blood volume is an important consideration for the prescription and delivery of hemodialysis, especially in very small animals (Cowgill and Langston, 1996; Fischer et al., 2004). It is thus important to evaluate the animal's perfusion parameters before the treatment as well as to calculate the percentage of the extracorporeal circuit volume in relation to the animal's blood volume.

Initiation of hemodialysis promotes no immediate change in intravascular volume, as the volume of blood aspirated from the animal equals the volume of priming fluid returned to the animal from the extracorporeal circuit. However, depending on the composition of the fluid used to prime the extracorporeal circuit, the intravascular volume and composition can be substantially and clinically significantly altered (Dasselaar et al., 2012). Crystalloid priming fluids have no oncotic pressure, therefore intravascular volume decreases following initiation of hemodialysis. These fluid shifts increase the risk of impaired intravascular volume, systemic perfusion, and promote hypotension. The consequent hemodilution and decreased oxygen-carrying capacity may compromise peripheral oxygen delivery if the priming volume is large compared to blood volume. The decrease in blood volume following a crystalloid prime is aggravated further when ultrafiltration is prescribed. In small, anemic, and animals considered high risk for hypotension, the priming solution should contain additional components to increase the colloid oncotic pressure (e.g., plasma, synthetic colloids) and oxygen carrying capacity (e.g., red blood cells). The decision to use synthetic colloids should consider their potential risk for further tubular injury in patients with AKI compared to the need to prevent hypovolemia and hypotension. In some animals, priming the extracorporeal circuit with whole blood or packed red blood cells should also be considered.

Statement: The extracorporeal circuit ideally should be <10% of the animal's blood volume (BV), but realistically, this circuit goal may not be achieved in all veterinary applications. For small dogs (<10 kg) and cats, the smallest available extracorporeal circuit should be used. If the circuit exceeds 15% of the animal's blood volume, consideration should be given to the composition of the priming solution to prevent hypovolemia, hypotension and hypoxemia. If the extracorporeal circuit exceeds 20% of BV, there is a predictable risk for hypovolemia, hypotension, and hypoxemia; therefore, the priming solution should provide effective colloidal and hemodynamic support and oxygen carrying capacity (e.g., synthetic colloid, plasma, whole blood prime) (83% agreement).

Statement: The expected hematocrit should be ≥20% after dilution of the blood with the priming solution. When hematocrit is <20%, blood transfusion prior to the treatment or blood priming is indicated (100% agreement).

Dose/URR/intensity/treatment duration/schedule for AKI veterinary patients

Hemodialysis is an effective modality for the removal of small and middle molecular weight uremic solutes. These solutes are removed directly from the intravascular compartment during the treatment; consequently, a concentration and osmotic gradient of uremic solutes is created between the vasculature and other body compartments (Arieff et al., 1973). This osmotic disequilibrium between body fluid compartments becomes more disparate with increased intensity of the treatment and as dialysis proceeds. The induced osmotic gradients (disequilibrium) promote the shift of fluid from the intravascular to the interstitial compartment, and comparably from the interstitial to the intracellular compartment. Fluid shifts from the intravascular compartment predispose to hypovolemia and hypotension, but equally important, fluid shifts into cells promotes expansion of the intracellular compartment (Shi and Wang, 2008). Excessive intracellular fluid shifts into the central nervous system predisposes brain edema and increased intracranial pressure. leading to a variety of neurological signs collectively termed dialysis disequilibrium syndrome (DDS). The risk for DDS increases with the intensity of the dialysis treatment and primarily determined by animal size, the degree of azotemia, the urea clearance rate, and presence of comorbid factors such as electrolyte abnormalities, acid-base status, bleeding tendency, hypertension, and preexisting neurologic abnormalities (Rosen et al., 1964). Dialysis disequilibrium syndrome may be fatal and should be prevented by prescribing a treatment intensity inversely proportional to the severity of the azotemia and directly proportional to the size of the patient. Severely azotemic animals and small animal size, especially cats, are at a highest risk for disequilibrium complications. For high risk animals, a low hourly clearance (K) or urea reduction rate (URR/h) should be prescribed, and treatment time should be extended to achieve an effective treatment goal despite the low hourly URR. The risk for DDS is considered higher during the first treatments compared to subsequent treatments, therefore more intensive treatments are allowed for similar degrees of azotemia for the 2nd and 3rd treatments compared to the first treatment. As concurrent complications are controlled in time, the risk for neurological complications decreases, and a higher URR/h is less likely to result in neurological complication.

Statement: Azotemia, electrolyte disorders, and volume control should be normalized within 24–72 h. For effective and safe IHD treatments, the urea reduction ratio (URR) outcome for the treatment should be >35%, and treatment time should not be less than 180 minutes and of sufficient duration to achieve the recommended URR treatment goals (below). If the animal is <10 kg or the BUN is at the upper end of the pre-dialysis BUN range, consider using the lower range of URR/h recommendation for each treatment category. For prescribing treatment intensity, the term URR/

h represents the linear projected hourly change in BUN over the URR outcome interval prescribed for the treatment session (total URR [%] ÷ treatment time [h]). Actual urea reduction per hour will variably exceed the prescribed URR/h due to the exponential change in BUN characteristic of IHD treatments (83% agreement).

Statement: 1st treatment: A treatment URR goal of at least 35% is recommended.

- **If pre-treatment BUN is <100 mg/dL (35.7 mmol/L), deliver the treatment at 10–15% URR/h**
- **If pre-treatment BUN is 100–200 mg/dL (35.7–71.4 mmol/L), deliver the treatment at 7.5–10% URR/h**
- **If pre-treatment BUN is 200–300 mg/dL (71.4–107.1 mmol/L), provide no greater than 5–7.5% URR/h**
- **If pre-treatment BUN is >300 mg/dL (>107.1 mmol/L), provide no greater than 5% URR/h**

(100% agreement)

Statement: 2nd treatment: A treatment URR goal of at least 40% is recommended.

- **If pre-treatment BUN is <100 mg/dL (<35.7 mmol/L), the treatment goal should establish a post treatment BUN approaching or within the reference range. A treatment providing a 10–20% URR/h intensity generally is tolerated.**
- **If pre-treatment BUN is 100–200 mg/dL (35.7–71.4 mmol/), deliver the treatment at 10%-12% URR/h**
- **If pre-treatment BUN is 200–300 mg/dL dL (71.4–107.1 mmol/), deliver the treatment at 5%-10% URR/h**
- **If pre-treatment BUN is >300 mg/dL (>107.1 mmol/), provide no greater than 5% URR/h (consider a prolonged treatment to compensate for excessive rebound or an inefficient treatment)**

(100% agreement)

Statement: 3rd and Subsequent Treatments: The treatment goal should establish a post treatment BUN approaching or within the reference range. A treatment providing a 20–25% URR/h generally is tolerated if pre-treatment BUN is <100 mg/dL (35.7 mmol/L).

- **If pre-treatment BUN is ≥100 mg/dL (35.7 mmol/L) but ≤150 mg/dL (≤53.6 mmol/L), and/or the animal is <10 kg, consider only a 10–15% URR/h to achieve a post treatment BUN < 40 mg/dL (≤14.3 mmol/L)**

(92% agreement)

Adequacy assessment

There are no veterinary outcome data evaluating treatment adequacy in animals with AKI managed by hemodialysis. Treatment adequacy can be evaluated by the overall URR, however, this measurement incompletely assesses treatment adequacy, and might be misleading, as it does not provide an assessment of the global clearance of uremic solutes from all body compartments. The most commonly used measure of dialysis adequacy in human patients is the fractional patient urea clearance, Kt/V_{urea} (Locatelli et al., 2005). This term describes the delivered urea clearance provided to the patient normalized to the patient's urea distribution volume. The Kt/V_{urea} can be calculated by measuring dialyzer clearance and estimating the patient's volume of distribution. Many modern IHD machines are equipped with ionic dialysance to estimate Kt/V (Aslam et al., 2018). This technology is based on changes in dialysate conductivity at the inlet and outlet of the hemodialyzer. When calculating Kt/V, the hydration status should be taken into consideration and the volume of distribution should be estimated appropriately.

Statement: Guidelines for maintenance treatment: URR outcomes for maintenance treatments should be at least 80%, and a minimum duration of 240 min and a minimum Kt/Vurea of ≥1.6. (92% agreement)

Statement: Urea distribution volume (V) should be calculated based on clinical estimate of hydration according to the following: BW*(hydration factor). Volume of distributions should be corrected based on hydration as follows:
-5% → 0.58
Euhydrated → 0.6
+5% → 0.62
+10 → 0.64
+15 → 0.65
+20 → 0.67
(83% agreement)

Statement: Once the derangements in body fluid volume and composition have been normalized, the treatment schedule should be maintained optimally on a thrice weekly schedule until dialysis is no longer required. Uncommonly, more than thrice weekly treatments are needed (highly catabolic state, severe overhydration, severe hyperkalemia). In animals with sufficient residual kidney function, a twice weekly schedule might be adequate. A twice weekly schedule might be dictated in some circumstances by logistic considerations.

Statement: There is no kinetic rationale for less than a twice weekly schedule (92% agreement).

Hemodialyzers

Properties such as surface area, average pore size, and membrane thickness contribute to the performance of a hemodialyzer membrane. *In vitro* performance of hemodialyzers can be classified, quantified, and compared by the mass transfer area coefficient (KoA) and the ultrafiltration coefficient (Kuf) (Fischer et al., 2004; Haroon and Davenport, 2018). As these coefficients increase, the dialyzer is capable of higher solute clearance and convective removal of water, respectively. These properties along with the membrane material and priming volume are used to select the hemodialyzer to most appropriately and safely achieve the treatment goals. Low-efficiency hemodialyzers have the smallest surface area (e.g., 0.3 m^2) and priming volume and generally have a low KoA. However, for small animals, their efficiency often exceeds that required to deliver an effective albeit less intensive initial treatment to uremic animals. High-efficiency dialyzers are used commonly in medium and large breed dogs to deliver very efficient treatments, typically yielding URR outcomes >90% and Kt/V_{urea} >2.5 during a 4–5-hour treatment. Selection of hemodialyzers with small surface areas are used to create smaller extracorporeal circuit volumes. The smaller extracorporeal volume reduces the requirements for systemic anticoagulation due to reduced transit time through the hemodialyzer at low blood flow rates (Bloom and Labato, 2011). This approach helps to prevent over heparinization, excessive cooling of blood, and improves hemodynamic stability throughout treatment. Hemodialyzers with higher Kuf ratings should be selected when high ultrafiltration requirements are prescribed (Pstras et al., 2022).

Statement: Hemodialyzers should be considered single-use and disposable. Reprocessing of hemodialyzers is not recommended due to increased risk of clotting, bacterial colonization, sterilant toxicity, and the safety for dialysis personnel (100% agreement).

Statement: Hemodialyzers made with synthetic polymer membranes (e.g., polysulfone, polyestersulfone) are hemocompatible and biocompatible (100% agreement).

Statement: A dialyzer should be chosen to fit the specific needs of the hemodialysis prescription including clearance goal, need for ultrafiltration, circuit volume relative to the animal's blood volume, and risk of clotting. Hemodialyzer requirements might be different for each patient and each treatment and should be selected to meet individual treatment goals. (100% agreement)

Statement: High-efficiency and high-flux dialyzers are preferred to maximize clearance of uremic toxins and to facilitate removal of middle molecular-weight solutes, respectively, but these devices might exceed the volume considerations of small animals and increase the transfer of dialysate impurities (e.g., endotoxins) due to back filtration unless ultrapure dialysate is used (100% agreement).

Ultrafiltration

Animals with AKI referred for hemodialysis often are overhydrated at presentation. Excess fluids are detrimental, especially in animals with concurrent anuria or oliguria. Overhydration negatively impacts most body organs and becomes life-threatening when resulting in pulmonary edema, congestive heart failure, and oliguria. Overhydration frequently promotes congestive nephropathy. The increase in intrarenal pressure decreases kidney function further and may result in oliguria or anuria (Husain-Syed et al., 2021; D' Marco, 2022). Initiation of ultrafiltration to offload the excessive fluid burden commonly is associated with increased urine as intrarenal edema and pressure are improved. A priority goal of hemodialysis is to remove excess fluids from the animal and to restore a normal hydration status.

Statement: Any life-threatening component of the overhydration (pulmonary edema, refractory hypertension) requires immediate correction with ultrafiltration applied during the first treatment. Non-life-threatening overhydration (peripheral edema, congestive nephropathy, ascites, gut edema, pancreatic edema) should be corrected during the initial two to three treatments (100% agreement).

Statement: Pleural effusion is not effectively corrected by ultrafiltration and requires thoracocentesis. Thoracocentesis should be performed at least 2 h prior to dialysis heparinization to help prevent bleeding complications (92% agreement).

It is important to recognize excessive fluid may be present in both the extra- and intracellular fluid compartments, whereas fluids are removed by ultrafiltration only from the intravascular compartment. If the vascular refill rate from other body compartments is slower than the prescribed ultrafiltration rate, blood volume will decrease. This results in decreased tissue perfusion and hypotension when ultrafiltration is excessive. The prescribed ultrafiltration rate has to be individualized for each animal, recognizing some animals tolerate a higher ultrafiltration rate than others for the same degree of overhydration.

Statement: Tolerance to ultrafiltration varies among animals and the degree of overhydration, vascular integrity (endothelial function), cardiac function, oncotic pressure, and the intensity of prescribed ultrafiltration. Most overhydrated dogs tolerate UF rates up to 8–10 mL/kg/h, and most overhydrated cats tolerate UF rates up to 5 mL/kg/h. These guidelines should be used as the maximal initial targets during the first treatment and should be adjusted during the treatment according to individual tolerance (100% agreement).

Statement: Small animals (especially cats) may have a lower tolerance to ultrafiltration due to the relatively high extracorporeal volume in relation to their intravascular volume. Similarly, caution should be exercised in normotensive and hypotensive animals; the volume and hemodynamic status should be monitored closely, and the ultrafiltration prescription adjusted based on the animal's intolerance (100% agreement).

Statement: High ultrafiltration rates on subsequent treatments (up to 15–20 mL/kg/h) might be tolerated in individual animals with persistent or ongoing fluid burdens with close supervision and monitoring. Fluid intake (oral and parenteral) should be evaluated critically in animals with persistently high ultrafiltration requirements (92% agreement).

Close monitoring is necessary in all animals undergoing ultrafiltration. Small animals, and especially cats, are more prone to hypotension during hemodialysis. A variety of tools are available to assess and monitor the tolerance of animals to ultrafiltration. Clinical assessment, in-line blood volume monitoring, blood pressure, and various laboratory tests can provide guidance on the animal's ultrafiltration tolerance. Continuous in-line blood volume monitoring assesses relative changes in blood volume and mixed venous oxygen saturation throughout the treatment and is the most sensitive method to evaluate the performance and tolerance to ultrafiltration. The rate of change and magnitude of change in in-line blood volume assessments predict if the ultrafiltration prescription is appropriate, insufficient, or exceeds the ultrafiltration goal, and if the vascular refill rate is appropriate for the delivered ultrafiltration rate. A sharp decrease in blood volume suggests that the ultrafiltration rate is excessive and not likely to be tolerated unless the ultrafiltration rate is decreased (Kopecny et al., 2023). Venous oxygen saturation also is measured continuously by in-line monitoring and reflects cardiac output and tissue perfusion. This is one of the most sensitive methods to identify intolerance to the prescribed ultrafiltration rates. With careful monitoring of changes in blood volume and venous oxygen saturation coupled to appropriate adjustments to the ultrafiltration rate, hypotension can be prevented in most patients (Kopecny et al., 2023). Care should be exercised in the interpretation of spontaneous and rapid negative changes in in-line blood volume assessments, as these observations often are the result of excitement, nausea, vomiting, or diarrhea. These abrupt changes appear over a few minutes and generally return to the previous baseline within 10–15 minutes in contrast to hypovolemia which is slower to progress and unlikely to spontaneously resolve.

Statement: Animals undergoing UF need close monitoring due to the risk of hypovolemia and hypotension. Physical examination parameters, including combinations of tachycardia, weak pulse quality, and cool extremities, support the presence of decreased effective circulating volume, but those signs represent late manifestations of hypovolemia. A moderate decrease in blood pressure is expected but should prompt reassessment of the tolerance of the ultrafiltration rate. Hypotension represents a late manifestation of hypovolemia and blood pressure should not be used as the sole parameter to monitor ultrafiltration tolerance. Real-time changes in blood volume and central venous oxygen saturation are the most timely and sensitive markers of effective circulating volume. In-line monitoring of blood volume (such as hematocrit-based estimation) and venous oxygen saturation are the standards of care in veterinary IHD (100% agreement).

Dialysate composition

The composition of the dialysate is responsible for alterations of the blood composition during the treatment, and therefore is an important component of the dialysis prescription. On most IHD platforms, the prescribed concentration of some solutes (e.g., bicarbonate, sodium) can be configured directly by the machine, whereas the composition of other solutes requires selection of acid concentrates with specific solute formulations.

When prescribing the dialysate composition, the abnormalities present in the animal's blood prior to dialysis initiation and the plasma composition goals for the treatment must be taken into consideration to

predict the appropriate dialysate composition. For example, in severely uremic and hypernatremic animals, the decrease in sodium concentration might further contribute to the decrease in extracellular osmolality, predisposing the risk for DDS. This concern also is a consideration for hyperglycemic animals. In severely uremic animals with a high risk for DDS, the dialysate sodium concentration can be profiled or modeled to change from lower to higher during the treatment to buffer the decrease in extracellular osmolality resulting from the decrease in urea concentration during the treatment, thereby decreasing the risk for DDS (Coli et al., 1998).

Sodium

Changes in disordered solute concentrations associated with uremia may not be dissociated easily from changes in urea concentration during the dialysis treatment. For example, animals with severe azotemia and hyperkalemia may require prescription of a clearance rate for urea to decrease urea concentration gradually and safely; yet, the low urea clearance rate also will apply to potassium clearance resulting in a slower correction in potassium concentration than desired. In these cases, dialysate potassium concentration should be lowered to increase the gradient between the blood and dialysate potassium concentrations, increasing the driving force for diffusion of potassium, and a longer treatment should be prescribed to achieve both therapeutic goals.

Statement: The dialysate sodium concentration is prescribed based on consideration of the animal's pre-treatment sodium concentration and the end-target sodium concentration. For most animals, end-treatment sodium concentration should be targeted to the reference range. To increase an animal's pre-treatment sodium concentration to a higher target, dialysate sodium concentration should be prescribed to approximately 8 mmol/L above the end dialysis target. In general, the dialysate sodium concentration should not promote overloading the animal with sodium (75% agreement).

Potassium

Statement: In normokalemic or hypokalemic animals, the dialysate potassium concentration should be prescribed to be close to physiologic (i.e., 3–4 mEq/L) (3–4 mmol/L) to avoid depleting the animal of potassium. In animals with severe hyperkalemia, a lower dialysate potassium concentration (0–2 mEq/L) (0–2 mmol/L) will maximize potassium clearance (92% agreement).

Bicarbonate

Most animals with severe AKI present with metabolic acidosis that can be corrected with hemodialysis by prescribing a higher dialysate bicarbonate concentration compared to blood bicarbonate concentration. This will facilitate diffusion of bicarbonate from the dialysate into the blood promoting net loading of bicarbonate to the animal to correct metabolic acidosis.

Statement: In animals with metabolic acidosis, bicarbonate concentration in the dialysate generally is set to a higher than normal concentration to promote bicarbonate loading of the animal. Normalization of serum bicarbonate is slow due to ongoing acid generation, bicarbonate distribution volume, and buffering existing acid loads during the treatment. For the first treatment (usually of low intensity) of an acidemic animal, bicarbonate concentration is typically set at 30–35 mEq/L (30–35 mmol/L). On subsequent treatments bicarbonate concentration is prescribed based on the degree of metabolic acidosis, typically in a range between 26 and 32 mEq/L (26–32 mmol/L). High bicarbonate concentration may lead to relentless panting and paradoxical CNS acidosis. Panting in the absence of obvious other causes (e.g., pain, hyperthermia) may predict the need to reduce dialysate bicarbonate concentration by 3–5 mEq/L (3–5 mmol/L). Presence of other acid-base disorders (respiratory acidosis or alkalosis) should be taken into consideration when prescribing bicarbonate concentration (92% agreement).

Calcium

The concentration of all solutes small enough to cross the semipermeable dialysis membrane should be considered in formulating the dialysate. Calcium is typically included in most acid concentrates to prevent hypocalcemia. One exception would be when regional citrate anticoagulation is used (Francey and Schweighauser, 2018).

Statement: Ionized calcium is readily removed by dialysis, and a physiologic concentration of calcium should be present in the dialysate (typically 2–3 mEq/L) (1–1.5 mmol/L) to avoid creating symptomatic hypocalcemia. If regional citrate anticoagulation (RCA) is being used, the dialysate should be calcium-free, and the animal will need an intravenous calcium infusion to prevent hypocalcemia (92% agreement).

Phosphate

Hyperphosphatemia is common in animals with AKI, thus most acid concentrates do not contain phosphorous. When dialysis is continued for more than few treatments, or a high dose of dialysis is prescribed in the attempt to facilitate the removal of uremic toxins or exogenous toxins, consideration should be given to preventing hypophosphatemia towards the end of the treatment. This is especially relevant for the dialytic decontamination of non azotemic animals following ethylene glycol intoxication, when an intense hemodialysis treatment is indicated, but serum phosphate is likely normal (see below).

Statement: Standard dialysate formulations contain no phosphate which is appropriate for the initial 1–3 treatments in animals with AKI when hyperphosphatemia is present. During subsequent dialysis treatments, dialysate phosphate concentration is set between 0 - 2 mg/dL (0–0.65 mmol/L), depending on the degree of hyperphosphatemia prior to treatment initiation. Dialysate phosphate concentration can be increased to 2 mg/dL (0.65 mmol/L) at the beginning or during the treatment contingent upon the pre-treatment phosphate concentration and the intensity of the treatment to prevent decreases in serum phosphate concentration to <2 mg/dL (0.65 mmol/L) (92% agreement).

Additives

In selected circumstances, substances are added to the dialysate to facilitate specific considerations of the treatment. One of the most common examples is the addition of ethanol and phosphorus in the dialytic management of ethylene glycol intoxication. Animals presented with ethylene glycol intoxication prior to development of AKI are appropriately treated with hemodialysis to decontaminate the animal of the ethylene glycol and its metabolites in an attempt to prevent the deleterious effects of this toxin (Schweighauser and Francey, 2016). Since these animals are typically normophosphatemic and acid concentrates do not contain phosphorus, the required high intensity dialysis treatment (to remove the ethylene glycol and its metabolites) will result in hypophosphatemia. Adding phosphorus to the dialysis concentrate prevents this potential complication. Ethanol also is added to the acid concentrate to achieve a therapeutic blood concentration to compete with ethylene glycol for conversion to its toxic metabolites via alcohol dehydrogenase.

Addition of solutes to the dialysate requires careful calculation of the amount of additive mixed with the acid component taking into consideration the dilution of the acid concentrate by the machine. The

proportioning of the acid concentrate differs among machine manufacturers and caution should be exercised before using preexisting protocols that might be formulated for one machine but inappropriate for other machines.

Statement: One should determine carefully the amount of additive to be added to dialysate concentrates or bulk dialysate based on a calculation of the dilution factor for systems with online dialysate generation or the volume of preformed dialysate fluid on a CRRT platform or IHD platforms with centralized dialysate generation. (100% agreement)

Statement: Dialysate phosphate supplementation is indicated in high intensity treatments when serum phosphate is normal at the beginning of treatment (e.g., intoxications, maintenance dialysis) to achieve a final dialysate concentration of approximately 4 mg/dL (1.29 mmol/L). (100% agreement).

Statement: When treating acute ethylene glycol intoxication, ethanol (competitive inhibitor of ethylene glycol metabolism) should be added to the dialysate to achieve a final concentration of 0.1%. This provides an efficient and effective mechanism to deliver ethanol to maintain a relatively constant blood concentration during the treatment (100% agreement).

Dialysate temperature

The dialysate temperature alters the animal blood temperature, depending on the difference between the dialysate and blood temperatures and blood and dialysate flow rates. In most cases the dialysate temperature is set to normalize or maintain body temperature. However, dialysis machines designed for human use may not provide a dialysate temperature setting appropriate for animals. Occasionally, dialysate temperature is lowered to promote vasoconstriction to treat refractory hypotension (Mustafa et al., 2016).

Statement: Dialysate temperature is set to normalize or maintain body temperature. In a routine treatment, temperature is set at 37.5°C-38.5°C (99.5–101.3 °F). Higher temperatures can be used for hypothermic animals up to a maximum dialysate temperature of 39.5°C (103.1 °F). Any ancillary devices used to modify dialysate or blood temperature should be calibrated to ensure operation within these safe temperature ranges. Higher dialysate temperature predisposes hemolysis and discomfort. Lowering dialysate temperature to 1–1.5°C below the standard temperature might promote peripheral vasoconstriction to improve blood pressure in hypotensive animals (83% agreement).

Water purification and ultrapure dialysate

Water is the largest component of the dialysate and the most abundant substance exposed to the animal treated with dialysis. With a dialysate flow rate of 500 mL/min for an animal receiving thrice weekly dialysis with each session lasting 5 h, the animal is exposed to 450 L of water per week. This provides ample opportunity for impurities within water to be delivered to the animal. Potable water contains safe concentrations of metal ions and other solutes for oral consumption. The gastrointestinal tract creates a barrier that further prevents excessive absorption of these solutes. The hemodialyzer facilitates bidirectional flux of solutes within the dialysate, including these contaminants, which may pass across the membrane and diffuse into the animal's blood, creating an opportunity for comorbid or fatal complications. To decrease the risk of back filtration, a minimum ultra-filtration rate can be set, and any undesired fluid removal can be offset with fluid administration intravenously or into the extracorporeal system. Because the magnitude of exposure is much greater with dialysis, metal ions and harmful solutes must be removed to make water safe for dialysis.

The components required to produce purified water (known as product water) is depended on the quality of the municipal water source. Devices such as sediment water filters, carbon exchange tanks, and water softeners may be needed to prepare water for further purification. Reverse osmosis and deionization are the most common methods of water purification. Reverse osmosis utilizes a semipermeable membrane through which water is pushed. This removes solutes and bacteria, yielding a pure product water. Deionization may remove dissolved solutes, but does not remove bacteria, thus it can provide pure product water but has a higher risk of bacterial colonization and biofilm formation. Reverse osmosis is recommended due to the improved safety in removing bacteria (Ahmad, 2005; Poeppel et al., 2011).

Statement: Reverse osmosis (RO) is the preferred method of water purification for use in dialysate generation (92% agreement).

All components used for the creation of product water may fail unexpectedly and without notice, therefore routine monitoring of product water is required. Local or national governmental health agencies create safe tolerances for metal ions and other contaminating solutes in product water. Product water should be sampled as close to the reverse osmosis machine as possible, before connection to the dialysis machine. Similarly, dialysate should be sampled as close to the hemodialyzer as possible. The product water and dialysate should be cultured using special culture media and tested for endotoxin quarterly to monitor for bacterial colonization (Coulliette and Arduino, 2013). It is not acceptable to use culture media or procedures applicable for clinical indications as these materials will not identify typical water contaminants. Water should be analyzed for water quality twice yearly. Water and dialysate testing should be performed by a laboratory with analytic methods specific to water quality and safety. Water quality and culture reports should be tracked in a log to monitor trends in bacterial growth and metal contamination. If bacterial counts or solute concentrations exceed recommended safe limit, dialysis using unpure water or contaminated water or equipment should not be performed until the source of these contaminations are identified and rectified (Upadhyay and Jaber, 2016). Product water and dialysate testing may need to be performed more frequently when troubleshooting identified contamination and dialysis cannot be performed until all testing conforms to recommended safe limits.

Statement: Product water testing should be performed according to the local industry or regulatory standards. Use of carbon filters, particulate filters, and water softener devices are often used to create safe product water. Water culture should be performed at least quarterly, or in accordance with the regional regulatory standards, whichever is more frequent. Metal and solute analysis should be performed at least twice yearly or as recommended by regional standards for water quality (92% agreement).

Statement: The Association for the Advancement of Medical Instrumentation (AAMI) guidelines recommends product water and dialysate should contain <100 CFU/mL of bacteria and <0.25 EU/mL of endotoxin to be considered safe for dialysate generation and treatment, respectively. However, cleaning actions should be performed to the water purification system when the product water contains >50 CFU/mL of bacteria and >0.125 EU/mL of endotoxin. Use of an ultrafilter on the dialysis machine generates ultrapure dialysate, which contains <0.1 CFU/mL of bacteria and <0.03 EU/mL of endotoxin. When testing results fall outside these limits disinfection, troubleshooting should be performed to return water, product dialysate, and ultrapure dialysate to recommended limits. When dialysate exceeds these recommendations, it is not safe to deliver to animals until problems have been rectified (100% agreement).

Anticoagulation

Clotting of the extracorporeal circuit is one of the most common complications of hemodialysis (Elliott, 2000; Fischer et al., 2004; Francey and Schweighauser, 2018). Therefore, the vast majority of the animals undergoing hemodialysis must be anticoagulated during the treatment. Systemic heparinization is the most common anticoagulation method used for intermittent hemodialysis, however, when the risk of bleeding is considered high, other alternatives including regional anticoagulation (Francey and Schweighauser, 2018) and minimal or no heparin treatments should be considered. Prior to hemodialysis initiation, a comprehensive assessment of the coagulation status of the animal is performed to select the appropriate and safest method of anticoagulation.

Statement: The minimal considerations for the anticoagulation prescription of an animal to be dialyzed for the first time should include historical evidence of bleeding (hemoptysis, epistaxis, melena, hematochezia, recently performed procedures), a complete physical exam evaluating evidence of bruising, petechiation, gingival bleeding, hyphema, evidence of pulmonary hemorrhage, and assessment of hematocrit, and platelet count. Prior to any dialysis treatment, an abbreviated coagulation profile [e.g. activated clotting time (ACT)] must be performed to guide the prescription of systemic unfractionated heparin. An ionized calcium must be measured to guide prescription of regional citrate anticoagulation. Depending on the suspected etiology and comorbidities, the hemorrhagic or thrombotic risk should be assessed further with additional testing. For subsequent treatments, an updated history (including response to previous anticoagulation, bleeding, circuit clotting) and hematocrit typically are sufficient (100% agreement).

Selection of the method of anticoagulation should consider the current coagulation status of the animal and the risk for bleeding associated with prior or future procedures that may predispose to bleeding. Some procedures considered benign (e.g., cystocentesis) might result in severe bleeding following systemic anticoagulation immediately after the procedure or performed following a dialysis treatment when the animal is still anticoagulated.

Statement: Systemic heparinization is the standard anticoagulation prescribed for intermittent hemodialysis in animals without identified risk of hemorrhagic complications. In animals at high risk of hemorrhagic complications, alternative anticoagulation protocols should be considered; the best-established protocol is regional citrate anticoagulation (RCA). When not available, minimal heparin or anticoagulation-free treatments should be considered (100% agreement).

Statement: Animals with a high risk for hemorrhagic complications (animals with hemostatic disorders or animals requiring pending invasive diagnostic or therapeutic procedures) should not be anticoagulated systemically. Hypercoagulable animals are at increased risk of clotting the extracorporeal circuit or of developing systemic thromboses and may require more intensive anticoagulation and monitoring during and between the treatments (100% agreement).

Statement: Invasive procedures should be avoided during the peridialysis period when using systemic heparinization. These include minor interventions such as venipuncture, fine needle aspiration, or cystocentesis as they may cause fatal hemorrhages. The peridialysis period is minimally >1 h before the treatment and 6 h after treatment, but these times vary with the invasiveness of the procedure and the ability to observe if bleeding occurs (100% agreement).

Statement: The standard protocol for systemic heparinization includes an initial bolus followed by a constant-rate infusion to prolong the baseline clotting time by 160–200% (e.g. 160–200 sec for ACT). The recommended initial bolus is 50 U/kg IV of unfractionated heparin for dogs and 25 U/kg IV for cats. The clotting time should be evaluated before heparin administration and re-evaluated within 5–10 minutes after, to determine if the anticoagulation target has been achieved prior to the initiating the treatment. If the initial anticoagulation target is not achieved, an additional bolus should be administered until the target is achieved. A constant-rate infusion of 50 U/kg/h (dogs) and 25 U/kg/h (cats) is started immediately with initiation of the treatment. Further assessment of the coagulation time should be performed every 30–60 min throughout the treatment. The initial dose and ongoing rate of heparin administration is adjusted based on the results of coagulation time measurements, the extracorporeal transit time, filtration fraction, visual evidence of clotting in the extracorporeal circuit, changes in treatment efficiency, and the overall risk of clotting or bleeding. (92% agreement)

The anticoagulation responses to recommended heparin dosing vary considerably between animals and between treatments in the same animal. The initial heparin bolus and constant-rate administration of heparin throughout the treatment should be adjusted based on the assessed risks of bleeding, clotting in the extracorporeal circuit, and the baseline and subsequent ACT measurement before delivering the priming dose and adjusting the constant-rate delivery, respectively. An excessive high baseline ACT measurement may result from inadvertent administration of heparin from the catheter locking solution during processing of the catheter. Unexpected or spurious baseline or in-treatment coagulation results should prompt reevaluation of the measurement prior to heparin administration or adjustment.

For subsequent treatments, the responses to previous heparin administrations should be considered. The risk of bleeding is highest in initial treatments when coexisting coagulation disorders are most likely and yet to be addressed. These include platelet dysfunction due to uremia and intrinsic coagulation disorders (e.g., disseminated intravascular coagulation) associated with the predisposing disease or its comorbidities and complications (Francey and Schweighauser, 2018).

Statement: Clinical evidence of hemorrhage during treatment should be assessed by repeated anticoagulation testing to direct adjustment of the prescription. Occult hemorrhage occurring throughout the IHD treatment may include a decreasing trend in hematocrit, an apparent increase in blood volume assessment with in-line hematocrit monitoring, hypotension, decreasing central venous oxygenation, tachycardia, pale mucous membranes, and tachypnea. If these are observed, the animal's apparent blood volume and hematocrit should be assessed. If anticoagulation parameters are above target (e.g., ACT>200 sec), anticoagulation should be discontinued or at least rapidly decreased, until coagulation parameters return to target values. Supportive administration of blood products should be considered as indicated (100% agreement).

Monitoring

All hemodialysis treatments require close monitored by trained personnel. Complete physical examination, baseline clinical parameters (e.g., blood pressure, heart rate and rhythm, hydration, pallor, temperature, mental status, body condition, urine production, stool character), and laboratory parameters need to be reviewed and recorded prior to hemodialysis initiation. These baseline clinical and laboratory parameters facilitate the interpretation of clinical findings during the treatment, including the identification of subtle clinical signs (e.g., nystagmus, vocalization, restlessness, tachycardia) and need for adjustments to ongoing medical management.

Statement: Baseline physiologic parameters should be assessed and recorded in all animals prior to initiating intermittent hemodialysis including hydration status, heart rate, capillary refill time, systemic blood pressure, respiratory rate and effort, and body temperature. Correction of hypotension and hypovolemia should be addressed prior to treatment initiation (100% agreement).

Monitoring should be performed throughout IHD by trained clinicians or technicians who are familiar with hemodialysis and its potential complications. In the hands of well-trained clinicians and technicians, most hemodialysis complications (e.g., bleeding, clotting, hemodialysis disequilibrium) can be identified in a timely manner and addressed appropriately to prevent worsening or more severe complications. Continuous ECG monitoring is recommended during the initial 2–3 dialysis sessions or in sessions in which there is suspicion the animal may have life-threatening treatable arrythmias that need continuous monitoring. Animals with identified or heightened risk for hyperkalemia should have ECG monitoring to assess the cardiovascular risk associated with the increased potassium. Bradyarrhythmias before or during the dialysis treatment may suggest increased vagal tone that should be proactively managed with anticholinergic drugs to increase heart rate to prevent a sudden vagal-induced cardiac arrest. Ventricular tachyarrhythmias are commonly observed in severely uremic animals and may not require intervention; however, some may be life-threatening and should be identified and treated.

Statement: Monitoring should be performed by trained personnel and recorded before and after treatment and every 30 minutes throughout the treatment. More frequent monitoring is justified in unstable animals. Minimally, heart rate, respiratory rate, body temperature, and blood pressure should be measured and recorded for review and trending. Monitoring central venous oxygen saturation, changes in blood volume, and hematocrit are essential to ensure safety during dialysis, particularly when ultrafiltration is performed. Ideally, these parameters are performed in real-time using an in-line blood volume and oxygen saturation monitor (92% agreement).

Statement: Blood pressure monitoring should be more frequent throughout the first treatment, as the risk for hypotension is higher due to consequences of uremia, severe electrolytes and acid-base derangements, rapid removal of solutes resulting in fluid shift out of the vascular compartment, intensity of ultrafiltration, medications with potential vasoactive effects (antihypertensives, diuretics, anesthetics), and comorbidities (GI fluid losses, hemorrhage, sepsis, pancreatitis) (100% agreement).

Statement: Continuous electrocardiogram monitoring is recommended to identify arrhythmias during the first two to three treatments. Arrhythmias are common in uremic animal during the initial treatments (ventricular premature contractions), but intervention usually is not indicated unless associated with hemodynamic compromise. Arrhythmias caused by the catheter may warrant decreasing blood flow (100% agreement).

Animals with severe AKI are often hypertensive, however, hypotension is a potential and serious complications of IHD. Hypotension may result from an excessively large volume of the extracorporeal circuit, aggressive ultrafiltration, hemorrhage, and complications associated with AKI or comorbidities (e.g., concurrent cardiac disease, sepsis, pancreatitis). Blood pressure is therefore monitored frequently throughout the treatment.

Statement: Blood pressure should be measured immediately before starting the treatment, immediately after initiation of treatment, and within 10 minutes of treatment initiation. Blood pressure should be measured at least every 10–15 minutes during the first 30 minutes of treatment, as animals may develop hypotension and cardiovascular compromise after their blood has filled the extracorporeal circuit. During the remainder of treatment, measurements should be performed at least every 30 minutes (100% agreement).

Statement: Target blood pressure: administration of antihypertensive drugs should be carefully considered prior to the dialysis treatment to prevent refractory intradialytic hypotension. Systolic blood pressure should be maintained between 120 – 160 mmHg during the treatment. Blood pressure measurements should be interpreted in light of the animal's blood pressure history, evidence of target organ damage, heart rate, central venous oxygen saturation, and stress level. If blood pressure measurements are persistently above the target range, animals should be evaluated for derangements in anti-hypertensive therapy, volume status, vasodilation, anxiety, and pain (100% agreement).

Statement: Interventions in animals with hypertension should be initiated to address the underlying cause of the abnormal blood pressure (e.g. inadequate ultrafiltration for hypervolemia, sedation/anxiolytic for stress, etc.). If systolic blood pressure is persistently (three measurements within 30–60 minutes) above 180 mm Hg during the treatment, ultrafiltration targets should be reassessed, and antihypertensive treatment is indicated. In the face of antihypertensive medications, animals are susceptible to hypovolemia during ultrafiltration requiring closer monitoring (100% agreement).

Statement: Overhydration is a major contributor to hypertension, and efforts should be directed to achieve and maintain ideal dry body weight during and after the treatment to aid in blood pressure control (100% agreement).

Statement: For animals developing intradialytic hypotension, ultrafiltration should be stopped temporarily, or minimally the ultrafiltration rate should be reduced. Efforts to ameliorate hypotension in hypovolemic animals include initial judicious volume expansion with crystalloid fluids, followed by synthetic colloid solutions, osmotically active substances (i.e. mannitol), or blood products as indicated. For persistent intradialytic hypotension refractory to volume expansion, vasopressors may be required. Alternative strategies include cooling the dialysate and/or increasing the dialysate sodium concentration. In persistently hypotensive animal, termination of the dialysis session and immediate rinse back may be necessary (92% agreement).

Statement: Blood pressure measurements should be obtained after rinseback at the termination of the treatment but should be interpreted in light of the expansion of blood volume during rinseback, which may cause transient increases in blood pressure until the rinseback volume is distributed. An additional blood pressure measurement should be obtained 30–60 minutes after the end of the treatment to determine the need for therapeutic intervention or closer monitoring if there is concern following the immediate post rinseback blood pressure assessment (92% agreement).

Timing of discontinuation

Sufficient recovery of kidney function may occur in animals dialyzed for support of AKI to become dialysis independent and maintain an acceptable quality-of-life (Bar-Nathan et al., 2022; Rimer et al., 2022). Serial monitoring of serum creatinine helps to predict recovery of kidney function, but each animal may have a different tolerance to persisting uremia. If azotemia has resolved or improved to near normal levels, most animals will no longer require need for ongoing hemodialysis and can be managed medically (Kelly et al., 2019; Bar-Nathan et al., 2022). When there is moderate return of residual kidney function, animals may be given a holiday from dialysis to allow their owners to evaluate appetite,

energy level, and reoccurrence of uremic signs in the absence of dialysis. If these are acceptable, the catheter can be removed, and the animal continued on management appropriate for its current stage of kidney function. If the uremic signs are excessive, hemodialysis can be continued indefinitely to support kidney function and the quality of life. Approximately 5 days are required after the last dialysis treatment to see stabilization of azotemia and to reveal the animal's residual excretory function. Several additional days may be needed to identify progressing complications or signs before decisions can be made to discontinue dialysis (Kelly et al., 2019). The dialysis catheter typically is left in place during this time to allow easier reintroduction of dialysis if needed. However, the catheter is a risk for thromboembolism and infection, and it may be removed earlier in animals with high risks of these complications.

Statement: The dialysis schedule should be maintained until the animal regains sufficient kidney function to become dialysis independent, namely, when clinical signs and laboratory abnormalities can be controlled with medical management alone. Animals that do not regain sufficient function can be treated indefinitely (100% agreement).

Statement: Markers of kidney function (e.g., serum creatinine, urea) should be performed pre- and post-dialysis. Sequential predialysis decreases in urea and creatinine or decreases in interdialytic slope of urea and/or creatinine suggest improvement in residual kidney function. Markers of recovery also include an increase in urine production (100% agreement).

Statement: Most animals successfully transition off dialysis therapy when pre-dialysis serum creatinine concentration is < 5 mg/dL (≤442 mmol/L) 3–5 days after the dialysis treatment. Some animals, however, remain symptomatic for uremia and benefit from continued dialysis therapy at serum creatinine concentration below this cutoff. Conversely, animals may have an acceptable quality-of-life without dialysis at higher creatinine concentrations. A minimum of 5 days should be allowed for equilibrium of creatinine following treatment when assessing residual kidney function. (92% agreement)

Statement: When considering discontinuation of dialysis in animals with partial recovery, the dialysis catheter should be maintained for 7 days following the last proposed treatment. This permits opportunity to resume dialysis treatments if residual kidney function is insufficient to transition to medical management (83% agreement).

Complications

Hemodialysis is generally a safe advanced standard of care for both dogs and cats who have life-threatening kidney dysfunction that cannot be managed medically. Nevertheless, there are numerous potential complications associated with extracorporeal procedures that are often mitigated by experienced providers and appropriate equipment and standardized procedures. Clinicians and technicians must be appropriately trained, and facilities must be adequately equipped prior to treating animals with any extracorporeal therapy including IHD. One of the most serious but infrequent concerns is DDS, which results from overly aggressive and unsafe rate of urea reduction. This potentially lethal complication should be prevented by identifying animals at risk, following the guidelines for safe URR/h prescriptions, and acting proactively when clinical signs are suspected during the treatment. In dogs, clinical signs are often insidious and provide opportunity for intervention, however, in cats, acute death may be the first and only sign of DDS; thus, extreme caution needs to be exercised during dialytic treatment of severe azotemia in this species.

Statement: When the risks of DDS are considered high, prophylactic intravenous administration of mannitol (0.5–1.0 g/kg) should be considered during or after termination of the treatment. Risk factors include small size (<6 kg), severe azotemia (BUN >300 mg/dl) (107.1 mmol/L), pre-existing neurological signs, and treatment intensity greater than guidelines (92% agreement).

Statement: Clinical signs of DDS during an IHD treatment require immediate action. Dialysis delivery should be paused using bypass, and intravenous mannitol (1.0 g/kg) should be administered. In case of seizures attributed to DDS, diazepam should be given to effect, and the treatment should be discontinued. If the neurologic signs are unresponsive to these interventions, additional diagnostic workup is indicated to rule out intracranial hemorrhage and brain stem herniation (92% agreement).

Animals with severe AKI are at risk for bleeding for multiple reasons, including platelet dysfunction and coagulation disorders (e.g., DIC). The risk is further increased once hemodialysis is initiated using systemic heparinization. Invasive procedures might be performed just prior to dialysis initiation or after termination, including placement of a dialysis catheter or feeding tube. The risk for bleeding has to be assessed individually. When bleeding risk is considered very high, or when there is evidence of active bleeding, a non-heparin, minimal heparin, or regional (e.g., citrate) anticoagulation strategy should be considered (Francey and Schweighauser, 2018).

Statement: Animals treated with hemodialysis are at a risk for bleeding. Bleeding may occur due to uremia (decreased platelet function, gastrointestinal ulceration), the underlying disease (e.g. leptospirosis-associated pulmonary hemorrhage), concurrent coagulation disorders (e.g., DIC), or due to intradialytic systemic heparinization. Attention must be given to the dialysis catheter insertion site or to any other invasive interventions, as bleeding may ensue during or after the initial treatments using systemic heparin anticoagulation. Hypotension or hypovolemia during or following dialysis treatment should prompt evaluation of internal bleeding (body cavities, gastrointestinal tract, lungs) (100% agreement).

Summary

Intermittent hemodialysis is an exceptionally effective extracorporeal therapy used in veterinary medicine primarily to manage animals with severe AKI when medical management is insufficient or is expected to be insufficient in controlling the clinical consequences of the disease. Extracorporeal therapies in general, and IHD specifically, can expand the window of opportunity for recovery of uremic animals and animals exposed to selected life-threatening intoxications. Most surviving animals with severe AKI or acute-on-chronic kidney disease managed by IHD recover within the first few weeks of treatment; however, treatment duration may extend to months before recovery occurs, and some animals never regain enough kidney function to become dialysis independent (Segev et al., 2008b; Segev et al., 2013; Segev et al., 2016). The likelihood of recovery depends on the etiology, the extent of kidney injury, and the window of opportunity provided by the dialytic intervention for kidney recovery. It is very important to have a conversation regarding realistic expectations with pet owners prior to initiating these advanced treatments.

Animals managed by hemodialysis require medical management similar to requirement for comparable grades or stages of acute or chronic kidney disease in addition to hemodialysis. However, there are some unique requirements of animals maintained with hemodialysis that need consideration. Some of these animals persist on hemodialysis for weeks or months with minimal or no fluid, electrolyte, or drug excretory capacity (Segev et al., 2008b; Segev et al., 2013; Segev et al., 2016). Most animals maintained on hemodialysis are fed using feeding tubes to meet their caloric requirements and to negate their catabolic state. This combination might create chronic overhydration, potentially

severe electrolyte and acid-base imbalances, and drug accumulations unfamiliar to most clinicians (Segev et al., 2008a). Therefore, frequent monitoring and dialytic and medical treatment adjustments need to be made and applied in the dialytic and interdialytic periods, respectively.

Clinicians performing hemodialysis need to be extremely familiar with the theoretical and technical aspects of this treatment modality, including understanding the operation of the hemodialysis equipment, appropriate and individualized treatment prescription, and monitoring and handling complications during and between dialysis treatments. In the hands of the well-trained clinicians and technicians, this therapy is very safe and effective with a low complication rate. In a few relatively large-scale retrospective studies evaluating the outcome of AKI in animals managed by hemodialysis, the mortality rate was approximately 50% (including euthanasia) (Segev et al., 2008b; Segev et al., 2013) with a favorable long-term outcome for survivors who otherwise would have had essentially no expectation for survival. (Eatroff et al., 2012).

CRediT authorship contribution statement

Ariane Schweighauser: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Catherine Langston:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Larry D Cowgill:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jonathan D Foster:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Gilad Segev:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing, Project administration. **Thierry Francey:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Conflict of Interest Statement

Gilad Segev, Larry Cowgill, and JD Foster are board members of the International Renal Interest Society but did not form part of the voting community validating this document. None of the other authors of this paper had a financial or personal relationship with people or organisations that could influence or bias the content of the paper.

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