Urea Kinetics and Intermittent Dialysis Prescription in Small Animals

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KEYWORDS

• Hemodialysis • Kt/V • $_{sp}$Kt/V • $_{dp}$Kt/V • $_{e}$Kt/V • $_{std}$Kt/V
• Urea clearance • Urea generation

Intermittent hemodialysis is an extracorporeal renal replacement therapy with a 40-year foundation in veterinary therapeutics, but only recently has it transitioned from a clinical curiosity to the advanced standard for the management of acute renal failure in dogs and cats.[1–7] No conventional medical therapies can reproduce the efficacy of hemodialysis for correction of the cumulative biochemical, acid-base, endocrine, and fluid disorders associated with kidney failure. Acute kidney injury (AKI) is the most common indication for intermittent hemodialysis in dogs and cats. Delay in instituting dialysis leads to greater uremic symptomology, morbidity, and recruitment of additional organ dysfunction.[5,7,8] Indefinite use of intermittent hemodialysis in animals with chronic kidney disease is equally indicated, but cost and logistic realities have limited its routine use for this indication. Hemodialysis alone or in combination with hemoperfusion is an important therapy to clear toxins and toxic metabolites from animals after accidental poisoning or drug overdosage or to relieve excessive iatrogenic or pathologic fluid loads.[5,9–11] The dog and cat equally share the demand and use of therapeutic hemodialysis, but the techniques and equipment for the delivery of intermittent hemodialysis are safe and effective for animals as small as 1.5 kg or as large as 600 kg. Diverse creatures from tortoises and rabbits to sheep and horses have been managed with creative modifications of the procedures and equipment devised for human application.[6]

THERAPEUTIC PRINCIPLES OF HEMODIALYSIS

The therapeutic role of hemodialysis is to eliminate (clear) accumulated uremia retention solutes (uremia toxins) and water from the body and alleviate the morbidity and clinical features they impart to animals with uremia. Uremia retention solutes are

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broadly and arbitrarily classified based on their physicochemical properties as small (water-soluble) solutes (molecular weight [MW] <500 Da), middle molecules (>500 Da), and protein-bound solutes, which, together with their compartmentalization, influence their propensity and accessibility for dialytic removal.[12–14] Hundreds of solutes have demonstrated intrinsic toxicity that mimics or reproduces particular aspects of the uremic syndrome, and thousands of retained solutes have now been demonstrated by mass spectroscopy in subjects with uremia.[13–15] Some retained solutes, like urea, have minimal inherent toxicity but serve as markers for retention of similar but unidentified solutes with greater clinical significance; whereas, others clearly mediate the clinical consequences of uremia.[16–19] Extensive prospective studies in human patients with kidney failure confirm significant outcome benefits associated with the extent of small-molecular-weight solute removal (ie, dialysis dose).[20–23] However, uremic toxicity is more complex than can be explained by retention of small-molecular-weight solutes and attention has refocused on retention of middle molecules and protein-bound solutes that are removed poorly by dialysis.[13–15,24,25]

Urea is a small molecular weight (60 Da) nitrogenous metabolite whose plasma concentration exceeds that of all other uremic solutes. It contributes minimally to the clinical manifestations of uremia but has remained fundamentally associated with the morbidity and outcome of the uremic syndrome because of its abundance and its link to the metabolism of dietary and endogenous nitrogen.[16,26,27] Azotemia must be viewed as a marker for the collective appearance of numerous small water soluble compounds, protein carbamylation, redirected metabolic pathways, or other small-molecular-weight solutes coupled to nitrogen metabolism or bound to body proteins.

The proven correlation of urea removal by hemodialysis with outcomes in renal failure has prompted the designation of urea as a surrogate index for all putative small-molecular-weight retention solutes that remain unidentified or unmeasured.[16,22] Reduction of urea appearance and the extrarenal removal of urea are used to prescribe the therapy for uremia and to monitor the efficiency and adequacy of these therapies.[28–31] This designation is both rational and problematic. Urea is uncharged, present at high concentration, readily detected, and readily diffuses across all body fluid compartments and the dialysis membrane. As such, it serves as an excellent solute to document dialyzer performance and whole-body clearance of low-molecular-weight solutes. However, these unique features and its minimal uremic toxicity question whether it appropriately or accurately reflects the dialytic behavior of other solutes with more profound uremic toxicity and thus may over represent removal of these solutes.[17,19,32]

Dialytic therapies alter the composition of body fluids by exposing blood to a contrived solution, the dialysate, across an interposed semipermeable membrane. The mass transfer of solute and water occurs by diffusive and convective forces across the membrane, and the magnitude of the exchange is predicated on the chemical and physical characteristics of the solute and the ultrastructure of the porous membrane. These principles directly influence the adequacy of hemodialysis and must be integrated into its prescription. Water and low-molecular-weight solutes (<500 Da) pass readily through the membrane pores, but the movement of larger solutes, plasma proteins, and the cellular components of blood are restricted by pore size and physical characteristics of the membrane. Diffusive transfer (dialysis) occurs by the thermal motion of the molecules in each solution (blood and dialysate) causing their random encounter with the membrane and subsequent transfer through porous channels of the appropriate size. These random events are proportional to the respective concentration and thermodynamic potential of the solute on each side of

the membrane and the physical properties of the dialysis membrane. The diffusive potential for every solute varies under differing physiologic conditions, but molecular weight is the main determinant of kinetic motion. When there is no concentration gradient for a solute across the membrane, the solute is at filtration equilibrium. At this point, the driving force for diffusion stops and there is no further net change in concentration of the respective solutions despite ongoing bidirectional and equal molecular exchanges between them.

Membrane permeability is determined by its thickness, its effective surface area, and the number, size, and shape of its pores or diffusion channels.[33] In addition to intrinsic solute and membrane characteristics, molecular charge, protein binding, volume of distribution, and cellular seclusion influence the bulk transfer of uremia toxins and solutes from the body independently from their predicted diffusion.

Convective transport of solutes across dialysis membranes is associated with the process of ultrafiltration, in which water is driven through the membrane by hydrostatic pressure gradients. Diffusible solutes dissolved in the water are swept through the membrane by solvent drag.[33] Unlike diffusive transport, convective transport does not require a concentration gradient across the membrane and does not alter diffusive gradients or serum concentrations. The transmembrane hydrostatic pressure gradient between the blood and dialysate compartments, the hydraulic permeability, and the surface area of the membrane determine the rate of ultrafiltration and solute transfer. During hemodialysis, a dialysate-directed transmembrane pressure gradient (dialysate pressure < blood-side pressure) is generated to initiate and control the rate of ultrafiltration. Independent changes in the dialysate and blood-side pressures can influence the rate of ultrafiltration by attendant changes to the transmembrane pressure. The hydraulic permeability of a dialyzer is determined by physical features of the membrane (eg, composition, thickness, pore size) and is rated by its ultrafiltration coefficient, K_{uf}, defined as milliliters of fluid transferred per hour per millimeter mercury of transmembrane pressure. Hemodialyzers are qualified as low flux or high flux according to their K_{uf}. A minimal transmembrane pressure of 25 mm Hg is required for ultrafiltration to offset the oncotic pressure of plasma proteins, which favors fluid reabsorption and opposes ultrafiltration. Convective transport can contribute to total solute removal, especially for large solutes with limited diffusibility. However, for standard hemodialysis, ultrafiltration primarily is targeted at fluid removal, and convective clearance contributes less than 5% to total solute removal.

PRESCRIBING INTERMITTENT HEMODIALYSIS

The hemodialysis session is defined by the dialysis prescription, which is an interactive procedure involving the patient, the attending clinician, and the dialysis delivery system. For the prescription to be effective, the clinician must understand the clinical and biochemical status of patients, the principals of dialysis, and the operational capabilities of the dialysis delivery system. It also is necessary to have a clear understanding of the therapeutic goals for the dialysis session and insure that the goals are achieved (**Box 1**). The effects of hemodialysis may be permanent in the case of intoxications or overhydration or transient if there is ongoing generation of toxic metabolites as in renal failure or accumulation of fluid as in heart failure. The dialysis prescription attempts to correct all disordered solutes, but for most it represents a blind projection to achieve a theoretically forecasted outcome. Most uremia toxins are not known with precision and not measured routinely. Urea has been designated the surrogate index for all putative small-molecular-weight uremic toxins, and

Box 1
Clinical considerations influencing the hemodialysis prescription

1. Patient characteristics (species, size, age, body condition)
2. Severity of the azotemia and retained uremic toxins
3. Degree of anemia
4. Electrolyte and mineral disorders: sodium, potassium, chloride, bicarbonate calcium, magnesium, and phosphate
5. Acid-base imbalances and depleted or deficient solutes: bicarbonate, calcium, glucose
6. Exogenous intoxications (eg, ethylene glycol)
7. Hydration status and fluid balance
8. Physiologic disturbances: blood pressure, hematocrit, body temperature, oxygenation, change in body weight, mental state
9. Coagulation status
10. Medications, surgical history, and comorbid clinical conditions
11. Dialysis treatment history

reduction of urea appearance and extra-renal removal of urea are used both to prescribe and to monitor the efficiency and adequacy of dialytic therapy.

Hemodialysis Prescription for Acute Uremia

The major application of intermittent hemodialysis is for the transient elimination of innumerable and unspecified solutes and fluid retained during AKI that otherwise would be cleared by healthy kidneys. The benefits of intermittent dialysis are transient, and with cessation of dialysis, the concentrations of urea and all retained uremia solutes with continued generation increase immediately until a new steady state is achieved or until the next dialysis session (**Fig. 1**). It is firmly established that dialytic removal of these solutes to minimize the time-average urea concentrations mitigates the associated morbidity and mortality of uremia but does not resolve all uremic symptomatology.[16,21,22,34] It is equally established that additional classes of retention solutes are poorly dialyzed by conventional high-flux diffusive and hemofiltration techniques limiting the efficacy of extracorporeal therapy.[13–15,34–36] The diffusive removal of urea and small-molecular-weight solutes is exceptionally efficient in animals, but clinical sequelae associated with abrupt excursions in the solute and fluid content of patients often limit the rate and magnitude that they can be altered. The intensity of the dialysis treatment can be adjusted by altering blood flow rate (Q_b), dialysate flow rate (Q_d), clearance of the hemodialyzer (K_d), rate of ultrafiltration, or length of the dialysis session (T_d) to accommodate the size and therapeutic needs of the animal. After dialysis, blood urea nitrogen (BUN), and other retained uremia solutes, increases in proportion to urea generation from dietary nitrogen and endogenous protein catabolism (G) and inversely with residual renal function (K_r) (see **Fig. 1**). Higher dietary protein intake, increased catabolism, and lower residual renal function will produce a steeper increase and higher steady-state concentration of urea after dialysis unless interrupted by an intervening dialysis treatment before achieving steady state. The peak predialysis urea, time-averaged urea concentrations, and the exposure to urea and other uremic toxins will be lower the more frequently and effectively patients are dialyzed.[29,30,37,38]

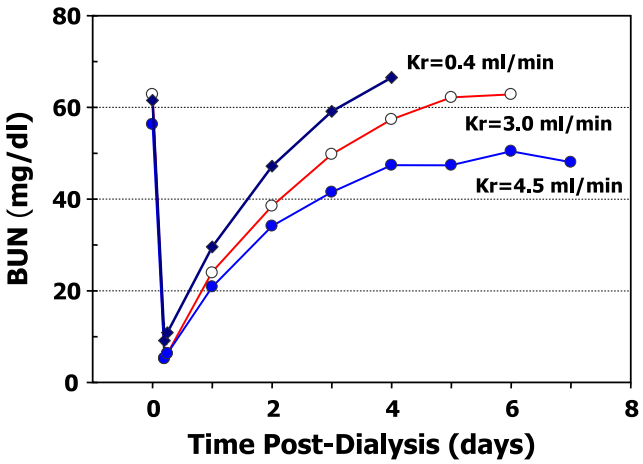

Fig. 1. Changes in BUN during and after 5-hour hemodialysis treatments in a 33-kg dog presented for AKI at varying degrees of residual urea clearance during recovery. The predialysis and immediate postdialysis BUN concentrations reflect a simple assessment of treatment intensity (dose). The $_{e}$Kt/V (~2.9 per session) for the dialysis treatments was identical for each level of urea clearance, and the BUN increases immediately following dialysis to its steady state (3–6 days). The rate of increase and the steady-state BUN concentration following dialysis is influenced by the patient's residual urea clearance (Kr). (*From* Cowgill LD, Francey T. Hemodialysis. In: DiBartola SP, editor. Fluid therapy in small animal practice. St Louis (MO): Elsevier; 2006. p. 650–77; with permission.)

The dialysis prescription must accommodate the physiologic, hematologic, and biochemical status of patients before dialysis and target the desired modifications at the end of the session (see **Box 1**). The prescription is individualized for each patient and every dialysis session by selecting dialytic options that best achieve the solute removal and ultrafiltration goals of the session without predisposing therapeutic risk (**Box 2**). Hemodialysis prescriptions for animals with acute uremia have been derived empirically as consensus-based guidelines for a diverse array of animal types and clinical conditions. There has been little validation or standardization of dialysis therapy based on outcome assessment.

The hemodialysis prescription for animals with AKI is prioritized to resolve hyperkalemia, profound azotemia, fluid imbalance, metabolic acidosis, and persisting nephrotoxins as well as to accommodate ongoing therapies (eg, parenteral feeding). The initial treatments must be prescribed judiciously to prevent overtreatment when the risks of dialysis-related complications (disequilibrium), hypovolemia and hypotension, and bleeding are high. Consequently, dialysis goals for initial treatments in animals with AKI differ considerably from the goals and prescription for later dialysis treatments.

Hemodialyzers

For small animals, the hemodialyzer is selected initially on its contribution to the extracorporeal volume and secondarily on its diffusive, convective, and biocompatibility properties. **Table 1** provides guidelines for dialyzer selection based on the size of patients and the expected compromise to vascular volume. For cats and dogs weighing less than 6 kg, a dialyzer with a surface area between 0.2 m^2 and 0.4 m^2 and a priming volume less than 30 mL is generally tolerated but may represent up to 40% of vascular volume. A synthetic dialyzer (neonatal or pediatric) with a surface area between 0.4 m^2 and 0.8 m^2 and a priming volume less than 45 mL is appropriate for use in dogs weighing between 6 and 12 kg. Dialyzers with surface areas up to

Box 2
Components of the hemodialysis prescription

1. Selection of the hemodialyzer (surface area, fiber bundle volume, solute and ultrafiltration characteristics, hemocompatibility, and biocompatibility)
2. Selection of extracorporeal circuit and priming solution
3. Blood flow rate (Qb)
4. Dialysis time (Td) and scheduled bypass time
5. Dialysate composition or modeling
6. Dialysate flow rate and direction (Qd)
7. Treatment schedule
8. Access connection (single needle reversed direction)
9. Anticoagulation (anticoagulant, target activated clotting time, protocol)
10. Ultrafiltration (volume target, rate)
11. Ancillary medications
12. Monitoring schedule
13. Rinse back (solution, volume, air)
14. Catheter locking solution
15. After treatment (medications, monitoring)

1.5 m^2 and priming volumes up to 80 mL can be used on dogs between 12 and 20 kg. Larger dialyzers with surface areas greater than 2.0 m^2 and priming volumes greater than 100 mL can be used in dogs weighing more than 30 kg.

Purposeful selection of a dialyzer with a smaller surface area and priming volume than recommended is warranted in patients who are markedly azotemic to reduce the intensity of the treatment and risk of clotting at slow blood-flow rates. Solute removal follows first-order kinetics, and animals with marked azotemia (BUN, >250 mg/dL) will experience quantitatively greater urea removal per unit of time and blood flow than those with lesser degrees of azotemia. The smaller the volume of the dialyzer, the shorter will be the resident time for blood in the dialyzer. At a blood flow rate of 20 mL/min, the resident time of blood in a 28 mL dialyzer is only 1.4 minutes; whereas, the resident time would be 9 minutes in a 1.5 m^2 dialyzer with

Table 1
Recommended extracorporeal volumes used for hemodialysis in dogs and cats

	Body Weight (kg)	Dialyzer Volume (mL)	Total Extracorporeal Volume (mL)	% Blood Volume
Cats, dogs	<6	<30	<70	13–40
Cats	>6	<30	<70	<23
Dogs	6–12	<45	<90	9–19
Dogs	12–20	<80	100–160	6–17
Dogs	20–30	<120	150–200	6–13
Dogs	>30	>80	150–250	6–10

a blood volume of 180 mL. At 20 mL/min, both dialyzers would deliver the same clearance, approximately 20 mL/min.

Treatment intensity

Initial dialysis treatments typically are less intensive (less solute removal, slower blood flow rate, smaller dialyzer surface area, and possibly shorter treatment time) than those prescribed for subsequent treatments. At slow blood flow rates, urea extraction across the dialyzer approaches 100%, and urea clearance ($K_{d\text{-}urea}$, in mL/min) is approximately equal to extracorporeal blood flow (Q_b, in mL/min) regardless of the size of the dialyzer. When large surface area, high-flux dialyzers are used, $K_{d\text{-}urea}$ increases quantitatively with Q_b until blood flow exceeds 200 mL/min.[30] At blood flow rates higher than 200 mL/min, the relationship flattens as urea clearance is influenced by membrane characteristics and dialysate flow in addition to Q_b.[30] At blood flow rates greater than 300 mL/min, dialyzer performance is influenced minimally by increased single-pass flow, and total solute removal increases in proportion to the cumulative flow through the dialyzer. The total volume of blood passed through the dialyzer during the treatment ($Q_b \cdot t$, where t is the dialysis treatment time) has been established as a reasonable predictor of the intensity of the treatment as estimated by the urea reduction ratio (URR) (**Figs. 2** and **3**).[4,5,8] This relationship can be used as an operational parameter to guide the prescription and delivery of dialysis by targeting the URR to differing severities of uremia and phases of management (**Table 2**).

Dialysis time

The treatment interval is determined in sequence once the target URR and approximate volume of blood requiring dialytic processing are defined for the treatment (see **Figs. 2** and **3**). From this volume ($Q_b \cdot t$), appropriate combinations of blood flow rate (Q_b) and dialysis time (*t*) can be derived. A long dialysis session time (slow Q_b)

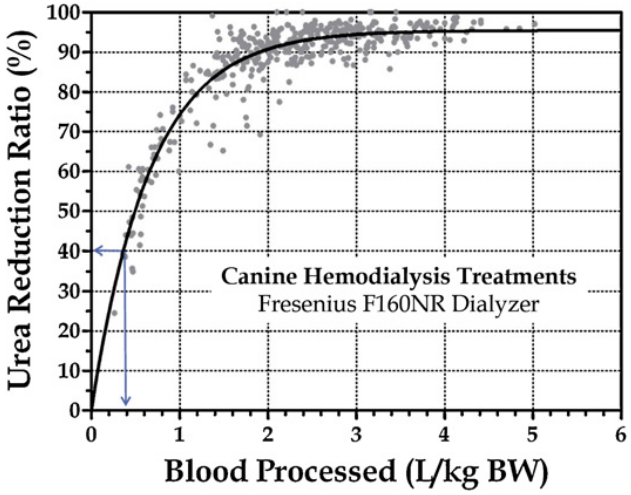

Fig. 2. Predicted urea reduction ratio as a function of the volume of blood processed in 413 hemodialysis sessions with a Fresenius F160NR hemodialyzer (Fresenius Medical Care, Waltham, MA, USA) in dogs. URR was computed from predialysis and immediate postdialysis BUN concentration (Appendix 1, Equation 1). The volume of blood processed ($Q_b \times t$) was indexed to body weight to compare dogs of different sizes. The solid line represents the exponential regression of all treatments. To achieve a low-intensity treatment with URR equal to 40%, a volume of 0.4 L of blood/kg body weight (*arrows*) must be dialyzed during the treatment. Similarly, a URR treatment goal of 90% requires approximately 1.8 L/kg of blood to be dialyzed.

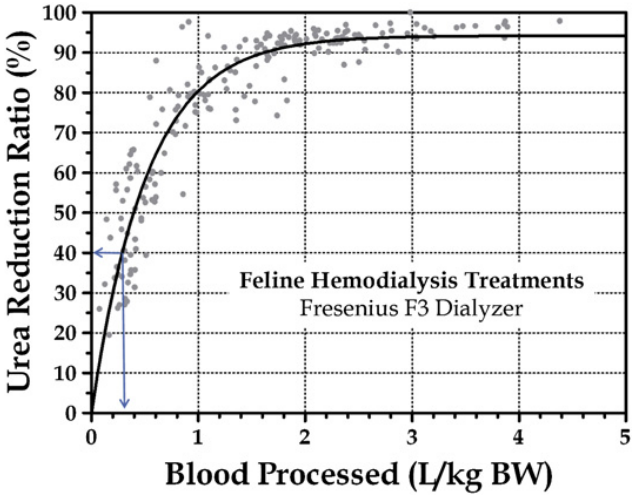

Fig. 3. Predicted urea reduction ratio as a function of the volume of blood processed in 200 hemodialysis sessions with a Fresenius F3 hemodialyzer (Fresenius Medical Care, Waltham, MA, USA) in cats. URR was computed from predialysis and immediate postdialysis BUN concentration (see Appendix 1, Equation 1). The solid line represents the exponential regression of all treatments. To achieve a low-intensity treatment with URR equal to 40%, a volume of 0.3 L of blood/kg body weight (*arrows*) must be dialyzed during the treatment. Treatment predictions are specific to each dialyzer and should be established independently in ever dialysis program.

is preferable to a short session time (fast Q_b) for patients with moderate to severe azotemia. A dialysis session time less than 180 minutes generally dictates faster and perhaps inappropriate blood flow rates that induce rapid changes in BUN and life-threatening dialysis complications. Short treatments usually cause inadequate URR outcomes that delay resolution of the azotemia.

The hourly URR can be used as an additional guide to select an appropriate treatment time. An excessive hourly URR is more likely to cause intradialytic complications than the absolute decrease in BUN over the dialysis session.[4] The risk of dialysis disequilibrium syndrome can be minimized by adherence to the hourly URR recommendations as indexed to the degree of azotemia in **Table 2**. An appropriate treatment

Table 2
Treatment intensity prescription

Initial Treatment	
BUN <200 mg/dL	URR <0.5 @ no >0.1 URR/h
200–300 mg/dL	URR 0.5–0.3 @ no >0.1 URR/h
>300 mg/dL	URR ≤0.4 @ no >0.05–0.07 URR/h
Second treatment	
BUN <200 mg/dL	URR 0.6–0.7 @ 0.12–0.15 URR/h
200–300 mg/dL	URR 0.6–0.4 @ no >0.05–0.1 URR/h
>300 mg/dL	URR ≤0.4 @ no >0.05–0.1 URR/h
Third and subsequent treatments	
BUN <150 mg/dL	URR >0.8 @ >0.15 URR/h
150–300 mg/dL	URR 0.5–0.6 @ 0.15–0.1 URR/h
>300 mg/dL	URR 0.5–0.6 @ <0.1 URR/h

time can be determined by dividing the URR goal for the treatment by the recommended hourly URR. URR is determined cumulatively over the entire dialysis treatment, but the rate and absolute change in serum urea and osmolality will be highest at the beginning of the treatment. Hourly URR recommendations could exceed safe guidelines at the beginning of the treatment in extremely azotemic animals if the URR goal is too high or the treatment time is short despite appropriate URR prescription for the entire treatment.

Use of extended, slow dialysis treatments also facilitates removal of large volumes of fluid that risk volume contraction and hypotension during shorter treatments. Treatment intensity is indexed conventionally to urea transfer, which occurs faster than other solutes (eg, potassium, phosphate, and creatinine) that are less diffusible or compartmentalized and poorly transferable. Longer treatments enhance removal of urea in addition to secluded solutes that do not behave like urea.[31,38,39]

Extracorporeal blood flow

Blood flow is the last parameter determining treatment intensity as the URR goal, required volume of processed blood, and treatment time are determined. For a 20 kg dog presenting with AKI and a BUN of 295 mg/dL, a URR of 0.4 (40%) might be prescribed. The requisite treatment volume for this target would be 0.4 L/kg or 8.0 L of total treatment (see **Fig. 2**). Appropriate combinations of dialysis time and blood flow rate are next computed to achieve the 8.0 L goal. For a 240-minute dialysis session time (0.1 URR/h), the required Q_b would be 33 mL/min (ie, 8000 mL/240 min; 1.7 mL/kg/min); whereas, for a 360-minute session time (0.06 URR/h), the required Q_b would be 22 mL/min (1.1 mL/kg/min). A higher first-treatment URR target could be selected with appropriate extension of the treatment time to maintain a safe hourly URR.

Without URR-derived estimates for Q_b, blood flow must be determined empirically. When the initial BUN concentration is greater than 300 mg/dL, the blood flow rate should be limited to 1.0 to 1.5 mL/kg/min or less to prevent overly intense or rapid treatments. If the BUN concentration is between 150 and 300 mg/dL, blood flow should be limited to 1.5 to 2.0 mL/kg/min for initial treatments. By the third and subsequent treatments, the BUN is usually less than 150 mg/dL, and blood flow can be increased cautiously to 5 mL/kg/min. For intense treatments during the maintenance phase of management, blood flow rates between 10 and 20 mL/kg/min or the maximal flow achieved by the vascular access can be used.

For severely uremic cats or small dogs with BUN concentrations greater than 250 mg/dL, it is preferable to extend the treatment time to greater than 5 hours while providing exceptionally slow blood flow and urea clearance rates to deliver URR target less than 0.1 URR/hr. In some cases, it may not be possible to adjust the pump speed sufficiently to deliver a blood flow rate slow enough to correct the azotemia safely. For example, a 4 kg cat with an initial BUN of 330 mg/dL would require approximately 1.2 L of blood processing to achieve a treatment URR of 0.4 (or 40%) (see **Fig. 3**). If the treatment were delivered safely over 360 minutes (0.07 URR/hr), the required Q_b would be 3.3 mL/min. The dilemma is that most dialysis machines cannot accurately deliver a blood flow at this low rate. A faster Q_b will intensify the treatment and shorten the time-to-treatment goal unacceptably. At a Q_b of 10 mL/min (which is still too slow for many machines), the treatment time would be only 120 minutes (0.2 URR/hr) and unsafe for the target URR. In these circumstances, it is possible to extend the treatment time and lower the effective Q_b by alternating periods of active dialysis with deliberate intervals of bypass in which blood flow continues but dialysate flow (and hence dialysis) is stopped. By alternating 5 to 10 minutes of dialysis with 5 to 20 minutes of bypass, the effective Q_b and hourly URR is decreased and the

time-to-treatment goal is extended by 2-fold to 4-fold. Ultrafiltration continues during bypass facilitating fluid removal during the extended treatment time. Blood flow can be increased during the bypass intervals to minimize clotting in the extracorporeal circuit without the risk of excessive dialysis.

Dialysate composition

Dialysate is formulated to maximize removal of uremia toxins, prevent depletion of normal blood solutes, replenish depleted solutes, and minimize physiologic and metabolic perturbations during and after the dialysis sessions. Conventional dialysate formulations for dogs and cats include sodium, approximately 145 mmol/L (dogs) and 150 mmol/L (cats); potassium, 0.0 to 3.0 mmol/L, bicarbonate, 25 to 40 mmol/L; chloride, approximately 113 mmol/L (dogs) and approximately 117 mmol/L (cats); calcium, 1.5 mmol/L; magnesium, 1.0 mmol/L; and dextrose, 200 mg/dL. The conventional dialysate flow is 500 mL/min counter current to the blood flow, and for practical purposes there is little advantage to decrease or increase dialysis flow to modify solute clearance unless Qb is greater than 300 mL/min.

Rapid solute removal exposes patients to nonphysiologic osmotic shifts that can cause osmotic disequilibrium between the vasculature, the interstitium, and cells. The accompanying shifts of fluid out of the vasculature and interstitium can cause signs of hypovolemia, hypotension, cramping, nausea, vomiting, and neurologic manifestations of dialysis disequilibrium syndrome. Patients may experience additional hypovolemia, hypotension, and poor catheter performance when ultrafiltration is superimposed on these effects. These signs are especially likely to develop early in the treatment when solute removal is greatest. To offset these trends, the sodium composition of the dialysate can be modeled (or profiled) so that dialysate sodium is adjusted systematically during the treatment to counteract solute disequilibrium, promote vascular refilling, and lessen or prevent these adverse signs.[40–43]

Dialysate sodium can be programmed to change in stepped or linear adjustments from hypernatremic (155–160 mmol/L) during the initial stages of the dialysis treatment to isonatremic or hyponatremic (150–140 mmol/L) at the termination of the treatment to offset the shifting of fluid out of the vasculature during the beginning of the treatment. During the hypernatremic phase of the profile, the sodium gradient from dialysate to plasma causes sodium loading and expansion of intravascular volume during this critical time when the extracorporeal circuit has filled, ultrafiltration has started, and solute removal and fluid shifts are greatest.[41–48] A modeled dialysate with a sodium concentration of 155 mmol/L for the initial 20% to 25% of the treatment, 150 mmol/L for the next 40% of the treatment, and 140 to 145 mmol/L for the remainder of the treatment has been is used for small dogs that are not hypertensive and predisposed to hypovolemia.[5] A respective sodium profile for cats of 160 mmol/L, 155 mmol/L, and 145 to 150 mmol/L appears to prevent hypotension in the face of the large extracorporeal volume required for hemodialysis.

Modeling dialysate sodium from isonatremic or hyponatremic to hypernatremic (dogs: 145 mmol/L for the initial 20% to 25% of the treatment, 150 mmol/L for the next 40% of the treatment, and 155 mmol/L for the remainder of the treatment; cats: 150 mmol/L, 155 mmol/L, and 160 mmol/L, respectively) has been used preventively to forestall neurologic manifestations of dialysis disequilibrium in severely azotemic animals. This sodium profile promotes osmotic (sodium) loading of the extracellular fluid at a time when urea disequilibrium can cause intracellular fluid shifts exacerbating cerebral edema and increased intracranial pressure.[5,7] Although this profile has been derived empirically and has not validated prospectively, it appears to offer protection in animals with BUN concentrations greater than 200 mg/dL. Sodium

profiling will alter patients' sodium balance if not programmed to provide a neutral balance in which sodium loads are offset by sodium removal. A transient positive sodium balance is accepted in patients at risk for dialysis disequilibrium, but a positive sodium balance, postdialysis thirst, interdialysis weight gain, hyperkalemia, and hypertension may develop with sodium modeling.[7,49,50]

The dialysate potassium concentration is generally set at 3 mmol/L. This concentration can be used for most animals with acute or chronic renal failure. The bulk of potassium is sequestered in intracellular pools accessible to dialysis only following transfer to the vascular compartment. Dialysate potassium may be set to a lower concentration or 0 mmol/L to promote potassium transference during short dialysis sessions in animals with severe hyperkalemia or during treatments using slow blood-flow rates. Life-threatening electrocardiographic abnormalities resulting from hyperkalemia can be reversed completely within minutes of initiating hemodialysis using a dialysate containing 0 mmol/L of potassium.[5,7] Consequently, for dialysis sessions in which the predialysis serum potassium is greater than 6.0 mmol/L, a dialysate containing 0 mmol/L of potassium has been recommended.[1,3,5,8] Transfer of potassium from secluded intracellular pools may lag behind its rate of removal from the extracellular compartment causing transient hypokalemia at the end of dialysis sessions.[51] A rebound hyperkalemia may occur following the delayed transfer within hours of ending dialysis that extends to the next dialysis treatment. Daily dialysis may be required until the bulk of the potassium burden is corrected.

The use of dialysate potassium concentrations less than 1.0 mmol/L can generate large gradients or rapid changes in serum potassium concentration and potentially alter the intracellular/extracellular potassium ratio, the resting cell membrane potential, and increase the risk for ventricular arrhythmias and sudden cardiovascular death.[52–54] Sudden intradialytic cardiovascular death is uncommon in animal patients undergoing acute dialysis; however, these risks should be considered in the potassium prescription. For safety, the dialysate should be changed to 2 or 3 mmol/L of potassium with the appearance of ventricular arrhythmias during treatments employing a dialysate potassium less than 1.0 mmol/L.

Buffer formulation

The acid load in patients is buffered by base equivalents supplied by bicarbonate in the dialysate. Bicarbonate is formulated to a concentration between 25 and 40 mmol/L to promote accrual of new buffer by patients and to replenish deficits caused by uremia. A low dialysate bicarbonate concentration (25 mmol/L) has been suggested for patients with severe metabolic acidosis (serum bicarbonate, <12 mmol/L) to prevent rapid correction of the bicarbonate, increased cerebrospinal fluid (CSF) P_{CO_2}, and decreased CSF pH, that could precipitate paradoxic cerebral acidosis, cerebral edema, and dialysis disequilibrium syndrome.[1,5,55,56] In practice, it is difficult to change the serum bicarbonate concentration during short treatments at low blood flow rates even with high dialysate bicarbonate concentrations.[57] Dialysate bicarbonate can be set to 30 to 32 mmol/L with little likelihood of neurologic complication but should be decreased if the animal shows signs of tachypnea, restlessness, stupor, blindness, or other clinical evidence of impending dialysis disequilibrium syndrome.

Serum bicarbonate will increase more rapidly in animals with severe metabolic acidosis undergoing intensive dialysis (as in antifreeze intoxication), and dialysate bicarbonate concentration should be set between 20 and 25 mmol/L. A low dialysate bicarbonate concentration also should be selected for treatment of animals with metabolic or respiratory alkalosis. For maintenance hemodialysis treatments of greater than 4 hours, a dialysate bicarbonate concentration of 30 mmol/L will produce

a postdialysis serum bicarbonate concentration of approximately 23 mmol/L. A dialysate concentration of 35 to 40 mmol/L yields greater accrual of buffer but often is associated with relentless panting during the treatment.

Dialysate additions

Hyperphosphatemia is a common feature of acute and chronic uremia,[58–60] and for both conditions the dialysate is formulated to contain no phosphate to facilitate phosphate removal. The dialysance of phosphate is more complex than for either urea or creatinine with 4 contributory pools possibly participating in its removal.[61] These interactive extracellular, intracellular, and reserve pools of phosphate are large, compartmentalized, poorly exchangeable with the serum pool, and subject to regulatory control. Consequently, the amount of phosphate eliminated during a dialysis treatment may be small compared with the overall phosphate load.[62,63] Hyperphosphatemia usually is not corrected during short and less intensive treatments, but it can be normalized or transient hypophosphatemia can develop with daily hemodialysis schedules or treatments longer than 4 or 5 hours.[5,61,63] Postdialysis hypophosphatemia quickly rebounds after treatment without development of clinical signs in uremic animals. In contrast, persistent hypophosphatemia and the risks of hemolysis, decreased oxygen delivery, or central nervous system and neuromuscular disturbances can develop in animals with normal predialysis serum phosphate concentrations when dialyzed with a standard (no phosphate) dialysate. For these conditions (ie, hemodialysis for toxin or fluid removal or well-managed patients with chronic kidney disease [CKD]), the dialysate phosphate concentration can be adjusted to physiologic ranges by addition of a neutral sodium phosphate solution (Fleet Enema, Fleet Brand Pharmaceuticals, C. B. Fleet Company, Inc, Lynchberg, VA, USA) to the dialysate concentrate. The required additive will vary with the proportioning ratio of the delivery system, but 67 mL (2.2 oz) or 133 mL (4.5 oz) of Fleet Enema solution per gallon of concentrate solution produces a dialysate phosphate concentration that is approximately 2 mg/dL or 4 mg/dL, respectively, when proportioned at roughly1:40.[7]

Ethyl alcohol is an important additive to bicarbonate-based dialysate for the treatment of acute ethylene glycol or methanol intoxications.[64] Alcohol is added directly to the acid concentrate in sufficient volume to produce an enriched dialysate with a proportioned concentration of approximately 0.1% ethanol. The alcohol achieves a steady-state blood concentration that competitively inhibits alcohol dehydrogenase and minimizes further metabolism of the ethylene glycol during the treatment.[65]

Dialysate temperature

Dialysate temperature is an integral and functional component of the dialysis prescription. The temperature generally is set to the upper temperature limit of 38°C to 40°C for human delivery systems. Signs of chills at these temperatures can be controlled with heated blankets or heat lamps. Dialysate temperature also can influences the hemodynamic stability of patients during routine dialysis treatments and patients predisposed to hypotension during hemodialysis.[46,52,66–71] Heat accumulation from a dialysate temperature higher than body temperature can trigger a thermal homeostatic reflex causing peripheral vasodilatation, decreased peripheral vascular resistance, and symptomatic hypotension in animals undergoing ultrafiltration.[46,52,67,68,72] Animal patients may be protected inadvertently from moderate or overt hemodynamic events by the imposed lower temperature limits of human dialysis delivery systems. Hemodynamic tolerance during hemodialysis may be improved when patients maintain isothermic balance or are slightly cooled.[67–71] If core temperature increases greater than normal during the dialysis session, the dialysate temperature should be adjusted

to maintain an isothermic core temperature throughout the treatment.[73] For animals predisposed or symptomatic for hypotension during dialysis, decreasing the dialysate temperature by 0.5°C to 1.5°C could induce peripheral vasoconstriction, central redistribution of blood, increase vascular resistance, and improve oxygenation during the treatment.[71]

Anticoagulation

The interaction of blood with the materials and irregularities of the dialysis membrane and extracorporeal circuit activates all triggers and components of the coagulation cascade and aggregation of platelets to promote thrombosis in the extracorporeal circuit. The predisposition to clotting necessitates routine anticoagulation of patients during the dialysis session.[74] Inadequate anticoagulation promotes thrombosis of the dialyzer, inefficient treatment, blood loss in the extracorporeal circuit, and potential for an abrupt cessation of the treatment. Excessive anticoagulation can cause serious bleeding, although this is infrequent. Unfractionated heparin has been used as the standard anticoagulant for intermittent hemodialysis for 40 years, but coagulation remains variable from animal to animal and treatment to treatment and requires individualized prescription.[7] See the section on heparin and anticoagulation in this edition for a detailed review of anticoagulation and its prescription in hemodialysis.

HEMODIALYSIS PRESCRIPTION FOR CHRONIC KIDNEY DISEASE

Experience with long-term intermittent hemodialysis for animals with chronic kidney disease is less than for acute uremia, yet hemodialysis is clearly indicated, effective, and affords a good quality of life for these animals. Many of the considerations used to prescribe acute hemodialysis are equally valid for chronic dialytic therapy; however, chronic malnutrition, fluid overload, hyperkalemia, hyperparathyroidism, metabolic bone disease, refractory hypertension, progressive anemia, infection, and drug interactions and toxicities replace concerns of hyperkalemia, hypothermia, hypovolemia, and dialysis disequilibrium syndrome so prevalent in animals with AKI. Adequacy standards for animals with CKD await future definition, but intensive hemodialysis provided every 2 to 3 days can augment the medical management of CKD.

The dialysis prescription for CKD is targeted to reduce the azotemia maximally during each session. Animals starting hemodialysis with severe uremia should be approached similarly to those with acute uremia until the predialysis BUN is less than 100 mg/dL. Thereafter, high-intensity dialysis schedules are well tolerated. Chronic dialysis prescriptions have been derived empirically but should promote a predialysis BUN less than 70 mg/dL, a postdialysis BUN less than 10 mg/dL, and a time-averaged BUN less than 50 mg/dL. The targeted $_{sp}$Kt/V should be greater than 2.0 per session to provide an equivalent renal clearance (EKR) at least 10% of normal renal function (see later discussion). The choice of dialyzer and dialysate composition generally are the same as for maintenance treatments in animals with AKI. Blood flow rate can be increased cautiously to 15 to 25 mL/kg/min or to the performance limits of the vascular access, and dialysis time lengthened to 300 minutes or longer. The temptation to reduce dialysis time with opportunities to use higher-efficiency dialyzers and faster blood and dialysate flow rates should be avoided. Longer treatment times facilitate the removal of many solutes, including creatinine, phosphate, potassium, and middle-molecular-weight solutes that have different kinetic profiles and are slower to dialyze or have delayed transference from cellular or sequestered compartments than urea.[29,30,38,39,66]

Three treatments per week is the traditional schedule for human patients with end-stage CKD and is used for animal patients with serum creatinine concentrations

greater than 8 mg/dL. A twice-weekly dialysis schedule has been used for animals with serum creatinine concentrations between 5 mg/dL and 8 mg/dL before starting dialysis therapy but likely represents the minimum schedule that will be beneficial.[27,30,38,39,66] The benefits of hemodialysis can only be improved with more frequent and longer dialysis schedules that impart greater efficiency to this intermittent clearance technique rather than more intensive dialysis provided less often.[27,29,38,39,63,75,76] A twice-weekly dialysis schedule will be effective only if patients have sufficient residual renal function (ie, a continuous clearance) to offset the effects of solute accumulation in the interdialysis interval to maintain predialysis azotemia and the TAC_{urea} within therapeutic guidelines (see **Fig. 1**).

HEMODIALYSIS PRESCRIPTION FOR DISORDERS OF FLUID BALANCE

Animals with oliguric or anuric AKI as well as nonoliguric animals with severe CKD are subject to fluid accumulation and life-threatening overhydration.[2,59] Once established, overhydration may not resolve with cessation of fluid delivery or diuretic administration, leaving no medical therapies to manage these disorders. Restoration of fluid balance is an important indication for hemodialysis and a consistent component of the dialysis prescription.

The volume and rate of fluid removal must be prescribed for each dialysis session based on the estimated fluid burden and deviation from the animal's ideal dry body weight. Ideal dry body weight is a progressively derived value determined as the body weight at which additional fluid removal would produce hypotension or signs of hypovolemia.[77,78] Ideal dry weight is usually predicted from recent historical weight measurements before the onset of illness, or it is estimated from the postdialysis weight when blood pressure was controlled or there was no demonstrated fluid accumulation. Ideal dry weight should not be considered a static parameter but should be redefined regularly to compensate for ongoing changes in lean body mass and body fat. The determination of dry weight can be elusive when based on clinical parameters alone and is facilitated by more objective techniques, including blood volume assessment and bioimpedance spectroscopy.

The rate and volume of ultrafiltration achieved is contingent on the hemodynamic stability of the animal. Ultrafiltration prescription may remove fluid from the vascular space faster than its rate of redistribution (refill) from the interstitium and intracellular compartments. This imbalance can promote hypovolemia, hypotension, and circulatory collapse if ultrafiltration is not prescribed and monitored carefully. Slow rates of ultrafiltration between 5 and 10 mL/kg/h are generally tolerated by dogs and cats, but faster rates must be prescribed cautiously and adjusted according to the animal's vital signs and blood pressure or by use of fluid monitoring equipment (eg, in-line blood volume monitor, venous oxygen saturation, continuous weight, bioimpedance spectroscopy).[7,77–82] In-line blood volume monitors are especially useful to assess the efficacy and the safety of ultrafiltration (**Fig. 4**).[7,83]

Animals often tolerate ultrafiltration better at the beginning of the treatment than at the end, and the rate of fluid removal can be profiled to achieve greater fluid losses at the beginning and scaled back later in the session to achieve the same treatment goal. Sodium profiling can be used to offset the hypovolemic and hypotensive effects of aggressive ultrafiltration to maximize fluid removal. Sodium loading during the hypernatremic stages of the modeling profile expands intravascular volume and facilitates redistribution of fluid from the interstitium and intracellular compartments.[5,7] The administration of small doses of 6% hydroxyethyl starch (hetastarch, at 1–2 mL/kg) helps to achieve ultrafiltration targets by maintaining intravascular volume, supporting

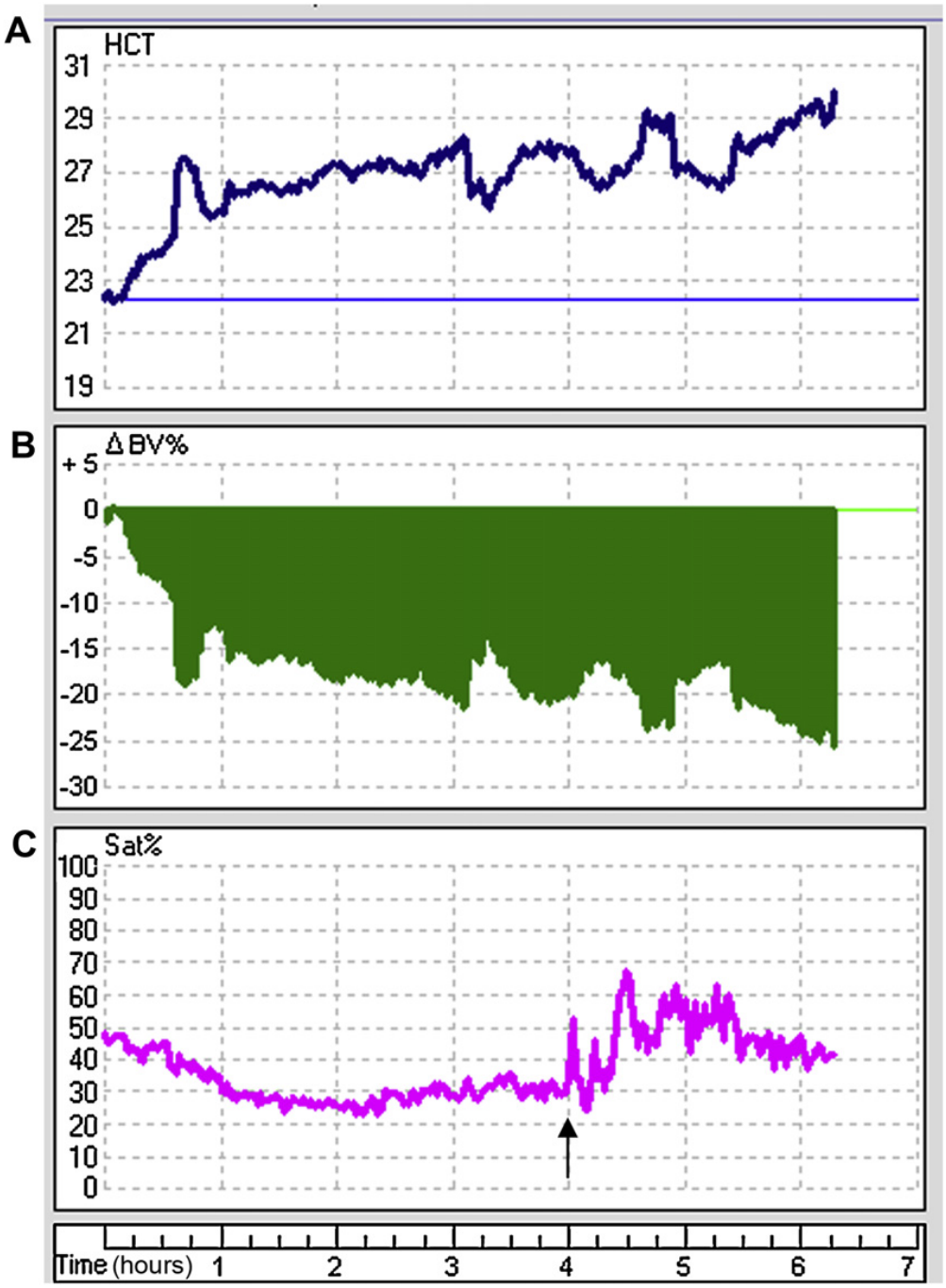

Fig. 4. Change in hematocrit (HCT, *A*), relative blood volume (⊿BV%, *B*), and venous oxygen saturation (Sat%, *C*) assessed by an in-line monitor in a dog with AKI during hemodialysis and continuous ultrafiltration. The figure illustrates the decreases in relative blood volume and venous oxygen saturation associated with hypovolemia induced by ultrafiltration. The late increase in oxygen saturation reflects the supplemental administration of oxygen (*arrow*). (*From* Cowgill LD, Francey T. Hemodialysis. In: DiBartola SP, editor. Fluid therapy in small animal practice. St Louis (MO): Elsevier; 2006. p. 650–77; with permission.)

vascular refilling, and preventing hypotension. The net volume of fluid subsequently removed will far exceed the volume administered and improve the efficiency of the ultrafiltration prescription.

Progressive hypovolemia from excessive ultrafiltration is detectable with in-line blood volume and venous oxygen saturation monitors well before development of

hemodynamic signs, permitting adjustment of the ultrafiltration targets to avert hemodynamic complications (see **Fig. 4**). Venous oxygen saturation can also be observed visibly as darkening (desaturation) of blood in the extracorporeal circuit. Any decrease in venous oxygen saturation should prompt immediate assessment of patients and possible adjustment to the ultrafiltration goals. Changes in blood pressure and heart rate are rarely sensitive or early predictors of hypovolemia under these conditions.

Ultrafiltration and diffusive solute removal are independent processes controlled by separate functions of the delivery system. Animals with life-threatening fluid overload who do not need dialysis or who would be placed at risk from intensive dialysis can be managed safely by prescribing periods of ultrafiltration without hemodialysis or by scheduling independent periods of ultrafiltration before or after the azotemia has been treated to an appropriate URR. During ultrafiltration without dialysis, the machine is placed in bypass mode to stop dialysate flow to the dialyzer (and diffusive solute removal) while blood flow and transmembrane pressure gradients are maintained to continue ultrafiltration. This technique permits slower and more complete fluid removal without producing unsafe rates of diffusive hemodialysis. Isolated ultrafiltration can be used in patients who are nonuremic to treat fluid congestion associated with heart failure and pulmonary edema refractory to diuretics.[84–90]

HEMODIALYSIS PRESCRIPTION FOR ACUTE INTOXICATIONS

Elimination of toxins and support for the consequences of intoxication are important but overshadowed applications of hemodialysis.[91–94] This use of hemodialysis is especially important if there has been a delay in medical management, there is limited endogenous clearance of the toxin or its metabolites, or there is no specific antidote for the toxicant. The dialytic removal of exogenous toxins is governed by the same molecular characteristics that define dialytic clearance of endogenous toxins. Molecular size, concentration in plasma water, distribution volume, degree of protein binding, and lipid solubility significantly influence the potential for a toxin's elimination.[9,10,95] Toxins or drugs with low molecular weights (<1500 Da), small volumes of distribution, and minimal protein binding are excellent candidates for diffusive and convective clearance. Ethylene glycol has a molecular weight of 62 Da, negligible protein binding, and a volume of distribution equivalent to total body water (0.5–0.8 L/kg) and is an excellent candidate for dialytic removal. With timely dialysis, ethylene glycol can be removed from the body before its enzymatic oxidation to more toxic metabolites, including glycoaldehyde, glycolate, glyoxylate, and oxalate.[5,10,92,95] Redistribution (rebound) of a toxin or drug from peripheral tissues or cellular compartments to plasma may limit the efficacy of dialysis to resolve the poisoning. If redistribution of the toxin from extravascular pools is much slower than its dialytic removal, the animal may become reintoxicated within hours after completing dialysis. For these sequestered toxins, the length and frequency of dialysis may need to be increased to facilitate their whole-body elimination.

Hemoperfusion is an adsorptive extracorporeal therapy used to manage endogenous and exogenous intoxications that are not cleared efficiently by hemodialysis. Adsorption is the principle of molecular attachment of a solute to a material surface. During hemoperfusion, blood is exposed directly to an adsorbent with the capacity to selectively or nonselectively bind toxins of defined chemical composition within the blood path. Hemoperfusion is more effective, eliminating high-molecular-weight, protein-bound, or lipid-soluble toxins or drugs that are cleared poorly, if at all, by hemodialysis. Toxic indications include mushroom poisoning (amanitin toxins and phalloidin), herbicides, insecticides, overmedication, hepatic failure, and

sepsis.[10,91,96] Candidate toxins include barbiturates, salicylates, antimicrobials, antidepressants, chemotherapeutics, as well as nonsteroidal antiinflammatory drugs that historically have been regarded as poorly removed by either hemodialysis or hemoperfusion. Hemoperfusion represents an important extension of the extracorporeal therapies that can be provided when there are no effective or efficient therapeutic alternatives.

Activated charcoal has been the adsorbent used most commonly to eliminate endogenous and exogenous toxins in vivo.[10,96,97] Toxic substances are cleared according to their molecular size and affinity for the charcoal, their concentration in extracellular fluid, distribution volume, degree and affinity of protein binding, and lipid solubility. Activated carbons can remove solutes with a molecular mass ranging from 60 Da to greater than 40,000 Da.[9,97]

The use and established benefits of extracorporeal therapies for known toxins are poorly defined. Extracorporeal therapy is generally indicated if the clinical signs of intoxication are progressive or deteriorating and if the toxin can be cleared faster with the intervention than by endogenous clearance. For an intoxication like ethylene glycol, experience with hemodialysis is extensive, documented, and effective; and treatment decisions are easily justified. It can be recommended and justified above all other treatments. For other toxins, documented efficacy and outcomes are limited, but the window and opportunity for possible benefit is finite and decreases hourly following exposure.

The goals for extracorporeal therapies (hemodialysis or hemoperfusion) are to eliminate the toxin and its metabolites entirely from the animal as quickly as possible and to correct the accompanying fluid, electrolyte, and acid-base disturbances, and attending uremia. For suspected poisonings amenable to extracorporeal elimination hemodialysis or hemodialysis/hemoperfusion should be initiated immediately upon diagnosis to insure rapid elimination of the toxin regardless of previous antidotal therapy or the absence of clinical signs.

Ethylene glycol (antifreeze poisoning) is a common intoxication in companion animal practice.[59,60] It is generally possible to eliminate 90% to 95% or more of the toxin with a single intensive hemodialysis treatment.[5] Guidelines for the URR can be used to predict ethylene glycol reduction and guide the dialytic prescription as urea (MW: 60 Da) is similar in molecular size and distribution volume to ethylene glycol (MW: 62 Da).[5] To achieve a 90% ethylene glycol reduction during the course of treatment, it is necessary to select treatment parameters that would promote the same URR for that patient.

For animals that are nonazotemic, 90% to 100% of the toxin should be removed during the first dialysis treatment. A second treatment is provided if delivery is incomplete during the first session or if there is rebound of ethylene glycol after treatment. The highest volume, high flux hemodialyzer compatible with the extracorporeal volume requirement of the animal should be used to maximize diffusive removal of the toxins. Blood flow rates between 15 and 25 mL/kg/min or faster are tolerated. A standard dialysate flow between 500 and 600 mL/min is used but can be increased if the blood flow rate is greater than 300 mL/min. A dialysate formulated with 3 or 4 mmol/L potassium, 30 to 35 mmol/L bicarbonate, and a physiologic sodium concentration is appropriate unless specific electrolyte, acid-base, or hemodynamic disorders are present. A neutral sodium phosphate additive should be formulated in the dialysate for animals who are nonuremic to prevent hypophosphatemia (see previous discussion of dialysate additives). Ethanol should be added to the dialysate concentrate to achieve a dialysate ethanol concentration of approximately 0.1% in an effort to inhibit ongoing metabolism of ethylene glycol to its toxic metabolites during the

extended hours of dialysis (see previous discussion of dialysate additives). Ultrafiltration can be used to correct pulmonary edema or congestive heart failure secondary to the toxin or fluid administration. However, ultrafiltration is minimally effective for pulmonary effusions arising from respiratory distress syndrome or uremic pneumonitis associated with antifreeze poisoning.

In patients who are uremic, the goals for aggressive toxin removal may be constrained by requirements to prevent dialysis disequilibrium syndrome, and dialysis must be delivered carefully to accommodate all of the patients' needs. If the BUN concentration is less than 125 mg/dL, an intensive treatment as used in patients who are nonuremic is suitable. For animals with BUN concentrations greater than 150 mg/dL, the dialysis prescription should targeted a 90% to 100% ethylene glycol reduction, but it must be delivered with a slow-extended treatment tailored to the hourly URR targets appropriate for the degree of azotemia (see **Table 2**). For patients who are severely uremic, safe urea reduction and greater toxin removal is achieved when dialysis is provided over 6 to 10 hours. The remainder of the dialysis prescription should be formulated to specific complications accompanying the uremia, fluid volume status, acid-base and electrolyte disturbances, and hemodynamic stability. Ethanol can be added to the dialysate concentrate as described for nonazotemic animals (previously discussed).

Application of extracorporeal therapies should not be limited to single modalities but should be sequenced and combined to best match the clinical course and kinetics of the toxicant. Continuous versus intermittent therapies should not be considered mutually exclusive but rather complimentary. There is little justification not to include a dialytic device with a hemoperfusion cartridge when contemplating hemoperfusion. For many toxins, hemodialysis has potential to improve toxin clearance in concert with hemoperfusion despite theoretical predictions to the contrary. The dose, blood concentration, changes in protein binding of the toxin, concurrent drugs/toxins, acid-base status, membrane type, and other variables may influence the diffusive potential of a toxin under different clinical conditions.

Hemoperfusion with activated charcoal is generally safe but poses potential disadvantages or complications not generally experienced with hemodialysis. One of the principal concerns is the innate hemocompatibility of the adsorbent. Hemoperfusion with activated charcoal (as well as other sorbent materials) can cause thrombocytopenia and leukopenia as platelets and leukocytes become adhered to the sorbent or entrapped in fibrin films or clots formed on the charcoal. Thrombocytopenia can be especially problematic if daily treatments are required that precludes adequate regeneration of platelets between treatments. If hemoperfusion is not combined with hemodialysis, patients may experience significant cooling because of the duration the extracorporeal blood is exposed to room temperature. The sorbent bed may also become saturated at unpredictable times during the treatment resulting in incomplete removal of the toxin.

HEMODIALYSIS OUTCOME/ADEQUACY AND QUANTIFICATION OF HEMODIALYSIS DELIVERY

Survival is the optimal outcome for animals managed with either acute or chronic hemodialysis. For AKI, survival is until renal function has recovered. For chronic kidney disease it is survival per se as there is no prospect for recovery of renal function. Survival is predicated on more than the adequacy of dialysis delivery and ultimately dependent on the diversity of the underlying etiology, comorbidities, age, chronicity, residual renal function, and economics that may be disassociated from recovery of

renal function or adequate delivery of dialysis.[98] Consequently, survival is a difficult outcome parameter to correlate specifically to dialytic interventions, and, in animals, dialysis adequacy may be measured more appropriately by length of survival, owner-perceived quality of life (eg, activity, social interaction, appetite), elimination of uremic symptomatology (hypertension, hyperphosphatemia, anemia), nutritional adequacy, and elimination of dialysis-associated complications.

Nonetheless, the kinetically modeled dose of dialysis (Kt/V) has been shown to correlate independently with survival as an outcome in humans undergoing maintenance hemodialysis,[20–22] and it is likely to demonstrate similar links to the success and adequacy of dialysis in animals. The empirical use of proven standards of dialysis adequacy and clinical experience in human patients are useful first approximations for the establishment of veterinary guidelines of adequacy until evidence-based standards are determined for animals.

QUANTIFICATION OF HEMODIALYSIS DELIVERY

The delivery (dose) and efficacy of hemodialysis can be expressed in a variety of ways with differing degrees of complexity and utility. Predialysis and immediate postdialysis concentrations of routine serum chemistries (eg, urea nitrogen, creatinine, phosphorus, bicarbonate, electrolytes) are the simplest expressions of efficacy and can be interpreted similarly to their use in conventional therapy (see **Fig. 1; Fig. 5**).[28,99] Although useful, these instantaneous assessments do not permit prescription of dialysis to animals of differing size or metabolic status or clarify the impact of therapy beyond the dialysis session. The predialysis and postdialysis concentrations of plasma urea (or creatinine) can be expressed further as reduction ratios (URR and CrRR, respectively), which represents the fractional or percent change in urea during the treatment. Urea reduction ratio is the most universally used predictor of adequacy for a dialysis session in animals (see **Figs. 3** and **4**, see **Table 2**; Appendix 1, Equations 1 and 2).[1,3,5,7,22,100–102] Most cats and small dogs will achieve a URR approaching 95%. This level of treatment intensity is considerably higher than achieved in humans where the URR target is 60% to 65%. In large animals (50–70 kg), this degree of treatment intensity is often difficult to obtain, and a URR of 80% to 85% is typical.

Reduction ratios are convenient for clinical assessment but do not account for all aspects of solute transfer. Uremic toxicity and patient well-being are not predicted necessarily by the highest or lowest concentration or the intermittent change of specific uremia solutes.[103] The integrated exposure to uremia toxins over time is considered by some a more realistic determinant of well-being and therapeutic adequacy.[21,38,104,105] For urea, the integrated exposure can be expressed as the time-averaged concentration (TAC_{urea}) calculated as the area under the BUN profile (curve) divided by the duration of the dialysis cycle (see **Fig. 5**, Appendix 1; Equation 3). TAC_{urea} has been highly predictive of dialysis adequacy and outcome for survival but fails to distinguish the contributions of dialysis dose, urea generation, nutritional adequacy, residual clearance, and distribution volume to urea metabolism during the dialysis cycle.[22,104,106,107]

At face value, neither predialysis BUN nor TAC_{urea} are adequate surrogates to characterize the adequacy of dialytic therapy or urea metabolism. An animal with a low-predialysis BUN or TAC_{urea} can represent effective dialysis (high dialysis delivery), recovering renal function (increased residual renal clearance), inadequate nutrition (low urea generation rate or protein catabolic rate [PCR]), or volume overload (expanded urea distribution volume). Conversely, under dialysis, worsening renal

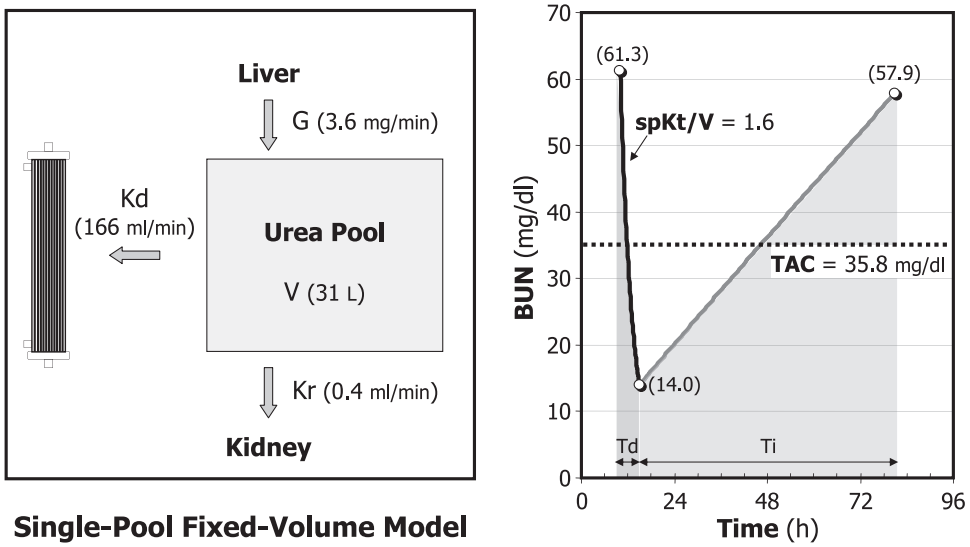

Fig. 5. (*Left panel*) Single-pool, fixed-volume kinetic model of the urea metabolism and representative modeled kinetic parameters determined in a 33-kg dog on intermittent maintenance hemodialysis consuming approximately 56 g of dietary protein. Urea is generated in the liver as the major end product of protein metabolism. The urea generation rate, G (mg urea/min), determines the appearance of urea in the urea pool with a volume, V (L). Its removal from the urea pool is determined by the continuous residual renal clearance, Kr (mL/min), and intermittently by hemodialysis via the urea clearance of the dialyzer, Kd (mL/min). (*Right panel*) Graphic illustration of a 3-point BUN profile (before and after hemodialysis values in parentheses) that can be fitted to the single-pool model in the right panel. With direct measurement of renal and dialyzer urea clearances (Kr, see Appendix 1, Equation 5 and Kd Appendix 1, Equation 4, respectively), kinetic modeling allows computation the urea generation rate (G, see Appendix 1, Equation 7), the urea distribution volume (V, see Appendix 1, Equation 8), and the time-average concentration of BUN (TAC_{urea}, see Appendix 1, Equation 3). The dose of dialysis expressed as the fractional clearance of the urea distribution volume using single-pool kinetics ($_{sp}Kt/V$, see Appendix 1, Equation 9) can also be calculated. Td is the duration of dialysis, and Ti is the duration of the interdialytic interval. Area-under-the-curve (AUC) is the area under the BUN versus time curve and can be estimated using a trapezoidal method or, ideally, calculated by fitting the changes in BUN to the kinetic model. (*From* Cowgill LD, Francey T. Hemodialysis. In: DiBartola SP, editor. Fluid therapy in small animal practice. St Louis (MO): Elsevier; 2006. p. 650–77; with permission.)

function, high catabolic rate, or volume contraction can all be reflected by a high-predialysis BUN or TAC_{urea}.

The dose of dialysis delivered to patients can be defined alternatively by the amount of clearance (solute removal) provided by the hemodialyzer during the dialysis session. Using the instantaneous clearance of the dialyzer for urea (K_d, mL/min) and the dialysis session length (t, minutes), the dose of dialysis can be defined as K_d x t, which predicts the volume of the patient cleared of urea during the treatment (mL). The value for the depurated volume can be indexed further to the total reservoir or distribution volume of urea in patients (V, mL) to compare treatment efficacy among patients of different body sizes as V is equal to the patients' total body water. This expression of dialysis dose is analogous to conventional dosing of drugs as mg/kg body weight. The value obtained with this kinetic expression, Kt/V, (see Appendix 1; Equation 9) is unitless and represents the fractional clearance of the urea distribution volume.[27–29,108] Kt/V has become the international reference for dialysis dosing and delivery.[31] This assessment of dialysis dose and intensity is founded on the instantaneous measurement of K_d (see Appendix 1; Equation 4), which may not be constant over the session as well as the

imprecise estimation of V from the patients weight and hydration status. It is limited also by simplifying assumptions regarding urea generation, fluid removal, and solute transference during the session, which requires more extensive evaluation.

A more precise understanding and integrated description of solute (ie, urea) dynamics throughout the dialysis session can be derived from kinetic modeling of the intradialytic and interdialytic changes in BUN similar to pharmacokinetic profiles used to describe drug metabolism.[27,109] Urea kinetic modeling is fundamental to understanding the prescription, monitoring, and quality assurance of hemodialysis procedures and must be familiar to all practitioners of this therapeutic modality. It dissects the mutually independent influences of dialysis, residual renal function, nutrition, catabolism, and distribution volume on the intermittent perturbations in urea concentration during and between the dialysis sessions. This kinetic approach to urea metabolism also yields the fractional clearance of urea (Kt/V) as a measure of the integrative dose in addition to G, PCR, and the distribution volume of urea (V) that are interdependent but otherwise beyond clinical assessment.

The simplest kinetic assessment of urea during intermittent hemodialysis is represented by a single-pool (sp), fixed-volume model, in which the entire distribution of urea is contained in a single pool (ie, total body water) that is presumed not to change in volume or urea input during the treatments (see **Fig. 5**).[30,33,105,109] In this simplified model, the only kinetic variable is total urea clearance (K) represented by the sum of residual renal clearance (Kr) and the clearance of the dialyzer (Kd) (see **Fig. 5**, Appendix 1; Equations 5 and 4, respectively).[30] The absolute removal of urea from this system will be reflected by the change in urea concentration at any time during dialysis such that:

$$C_t = C_0 e^{-Kt/V} \quad (1)$$

where C_t is the urea concentration at time = t; C_0 is the predialysis urea concentration at t = 0; K is the total urea clearance; and V is the volume of urea distribution. Rearrangement of Equation 1 provides Equation 2 for sp conditions,

$$_{sp}Kt/V = \ln(C_0/C_t) \quad (2)$$

Equation 2 is the fundamental kinetic expression for the fractional clearance of urea (dialysis dose) during a single dialysis session. In the simplified single-pool model, the kinetic prediction of dialysis dose can derived very simply from the measured predialysis and postdialysis BUN concentrations. It must be emphasized, that this expression represents a gross oversimplification of the events and kinetic variables during therapeutic hemodialysis and should be used only to provide a rough estimate of the integrated dialysis dose.

During a therapeutic dialysis session, the relationships between G, V, and K (illustrated in **Fig. 5**) are more complex, highly interdependent, and cannot be described mathematically by a single simple relationship. Mathematical description of each variable, however, can be defined in terms of the other two with formal urea kinetic modeling (see Appendix 1; Equations 6–9). When one of the variables (G, V, or K) is known, the others can be resolved by simultaneous iterative solution of the equations to yield a unique solution for the unknowns when residual renal clearance (K_r), instantaneous dialyzer clearance (K_d), ultrafiltration volume, and the measured changes in BUN during and after the treatment are known.[30,33,105,109] These computations are performed easily with commercially available software or can be programmed into routine spreadsheet applications.

This simplified single-pool, fixed-volume model loses accuracy if total body water changes during or between treatments, which is typical. The model also loses accuracy during high-intensity treatments of short duration, when urea distribution does not behave as a single homogenous compartment. Delayed diffusion from the intracellular compartment or variations in diffusion among discrete fluid compartments (eg, skin, muscle, gut) with different perfusion and transference characteristics creates a solute disequilibrium between compartments that promotes a postdialysis rebound of urea that is not predicted by immediate postdialysis blood sampling.[30,39,110] Deviations in the assumptions for single-pool, fixed-volume kinetics can be minimized by measurement of the postdialysis urea at 45 to 60 minutes after the end of the dialysis treatment rather than immediately postdialysis. By this time, intercompartmental shifts (or rebound) have reestablished solute equilibrium, and the plasma concentration reflects the equilibrated concentration of urea across all body compartments.[30,111]

Most dialysis treatments also require ultrafiltration, and urea generation proceeds throughout the session, which further deviate the serum urea concentration from single-pool predictions. These collective deviations from single-pool, fixed-volume assumptions can be incorporated into formal urea kinetic analyses by using more mathematically complex double-pool or noncompartmental kinetic modeling methods.[33] The double-pool variable-volume kinetic model accounts for intercompartmental solute diffusion during and after completion of hemodialysis. The $_{dp}$Kt/V is regarded as the standard for dialysis dose but is not applied routinely because of its complexity. Optionally, correction algorithms that account for these compartmental deviations have been applied to single-pool assessments using additional blood sampling and appropriate software in human patients.[112] These correction formulas minimize many of the limitations of single-pool estimates but have not been validated in animals. More accurate predictions of dialysis dose can also be obtained using single-pool kinetic calculations by incorporating an equilibrated BUN obtained 45 to 60 minutes after cessation of the treatment as the end-dialysis value. Use of the equilibrated BUN yields $_{e}$Kt/V as a measure of dialysis dose that closely approximates the $_{dp}$Kt/V and better reflects whole-patient urea clearance. Both the $_{e}$Kt/V and the $_{dp}$Kt/V assessments of dialysis dose will be lower than the dose predicted as the $_{sp}$Kt/V.

Ionic Dialysance

Online measurement of these kinetic determinants of dialyzer performance and dialysis dose can be derived for each dialysis treatment as an alternative to blood-based modeling methods with ionic dialysance techniques available on modern delivery systems.[113–116] Dialysance is a measure of solute mass transfer across the dialysis membrane when the solute is present in both the blood and dialysate. The clearance of a solute by the dialyzer is equal to its dialysance when the solute is present only in the blood and is absent in the dialysate. Ionic dialysance is a kinetic assessment of the transfer characteristics of the ionic solutes in the blood and dialysate. The collective concentration of ionic solutes in solution can be measured by the conductivity of the solution to the passage of an electric current. The conductivity of both plasma and the dialysate is influenced primarily by the concentration of sodium and chloride and will change with perturbations of these solutes.[113,115] The collective dialysance of small molecular weight ions (eg, sodium) is considered equivalent to the dialysance of urea, and, consequently, ionic dialysance can be used as a reasonable surrogate for the dialysance of urea. In conventional single-pass hemodialysis circuits in which the dialysate contains no urea, urea dialysance becomes equal to urea clearance, and ionic dialysance becomes an acceptable predictor of the urea clearance of the

dialyzer, $K_{d\text{-}urea}$. The ionic dialysance is computed from measurements of dialysate conductivity (concentration of ionic solutes) at the inlet and outlet ports of the dialyzer in response to transient changes in inlet conductivity of the dialysate and the instantaneous dialysate and blood flow rates.[115,117–121]

When ionic dialysance is programmed sequentially during the dialysis treatment, serial updates of the instantaneous clearance ($K_{d\text{-}ionic}$) of the dialyzer can be monitored, and the depurated volume for treatment ($K_{d\text{-}ionic}$ x t) is predicted at the end of the session. The $_{ionic}$Kt/V, as a surrogate for $_{sp}$Kt/V, is provided when the ionic dialysance is indexed to urea distribution volume, V. The availability and simplicity of ionic dialysance to predict dialysis delivery at every treatment should promote a better understanding of the kinetics of dialytic therapy and the efficacy of dialysis prescriptions.

It is also possible to make interim projections of the $_{ionic}$Kt/V for the session to insure the treatment targets will be met by the end of the scheduled session time. If therapeutic targets will not me met under current circumstances, adjustments to treatment time, blood flow, and dialysate flow, access repositioning, or dialyzer exchange can be initiated to modify the forecast treatment to assure adequacy.[122] Sudden or progressive decreases of $K_{d\text{-}ionic}$ during the treatment can alert to possible clotting in the dialyzer or development of access recirculation that may compromise the adequacy of the treatment (**Fig. 6**).

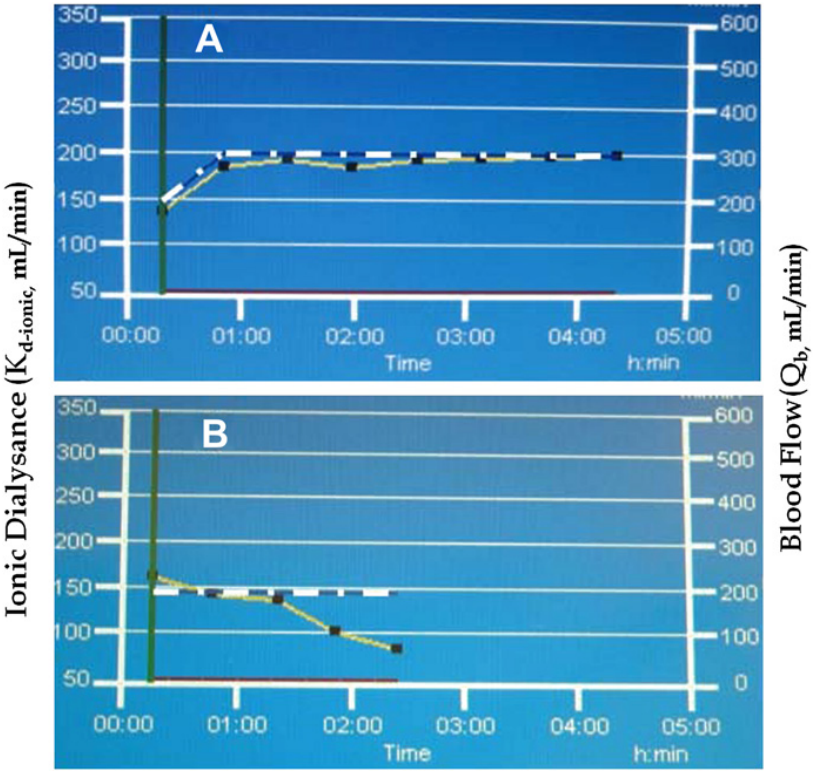

Fig. 6. Screen shots of the ionic dialysance display of the Gambro Phoenix (Gambro USA, Lakewood, CO, USA) illustrating the ionic dialysance (*solid line*, left axis) and blood flow (*dashed line*, right axis) throughout a dialysis session. Panel *A* demonstrates constant dialyzer performance and extraction ratio during the treatment with a $K_{d\text{-}ionic}$ of approximately 195 mL/min at a Q_b of 300 mL/min (extraction ratio, 0.65). Panel *B* illustrates a marked and progressive decrease in $K_{d\text{-}ionic}$ after 1.5 hours of treatment associated with extensive clotting of the dialyzer necessitating termination of the treatment. (*From* Cowgill LD, Francey T. Hemodialysis and extracorporeal therapy. In: DiBartola SP, editor. Fluid therapy in small animal practice. St Louis (MO): Elsevier; 2010, in press; with permission.)

Hemodialysis Schedule

Animal hemodialysis is provided intermittently three times weekly based on human convention. This schedule represents a compromise between clinical benefits, time constraints, and financial burden. However, there are marked theoretical efficiencies and clinical benefits to schedules with increased dialysis frequency.[38,75,76,123–126] For example, six treatments per week at a $_{sp}$Kt/V of 1.0 per treatment are more efficient and provide better clinical outcomes than three conventional treatments per week with a $_{sp}$Kt/V of 2.0 per treatment. To reconcile these differences, the concept of standard Kt/V ($_{std}$Kt/V; see Appendix 1; Equation 10) has been proposed to compensate for the differences in efficiency when comparing schedules with different intermittence.[28,103,125,127] Standard Kt/V is a hypothetical continuous urea clearance that would achieve a constant blood urea concentration identical to the average predialysis urea concentration for all intermittent treatments provided during the week. This theoretical concept allows comparisons among dialysis schedules with differing dialysis times and intervals, including the extreme case of continuous therapy.

A dialysis schedule with 3 4-hour treatments per week with a $_{sp}$Kt/V of 2.0 per treatment is equivalent to a $_{std}$Kt/V of 2.7. Increasing the schedule to 6 2-hour treatments per week ($_{sp}$Kt/V, 1.0 per treatment) with the same total 12 hours of weekly dialysis substantially increases the amount (efficiency) of dialysis delivered to an equivalent $_{std}$Kt/V of 3.9 (see Appendix 1, Equation 10). Stated differently, a thrice-weekly, 240-minute treatment schedule ($_{std}$Kt/V, 2.7) requiring 12 hours of treatment could be provided with equivalent efficacy in 70 minutes per session if provided 6 times weekly for a total weekly dialysis time of 7 hours. Although reduction of the individual treatment time is possible according to this analogy (for illustrative purposes), this recommendation would not be clinically prudent.[36,39,125,128] Conversely, decreasing the frequency of dialysis to 2 treatments per week would require extension of each treatment to almost 24 hours to achieve an equivalent $_{std}$Kt/V. These quantitative predictions illustrate the marked benefits to increased frequency of therapy and conversely indicate the difficulty to compensate for decreased frequency of therapy with longer treatment times.[29,30,76]

The intermittent kinetics of hemodialysis can be converted to a continuous equivalent clearance as an alternative to $_{sdt}$Kt/V for comparing the equivalency of intermittent and continuous therapies, including residual renal function.[29,99,129] This concept is more intuitive for clinicians because the relative contribution of dialysis can be compared directly to residual renal function and to other intermittent or continuous dialytic therapies (see Appendix 1; Equation 11). Total patient clearance (renal clearance, Kr, and dialyzer clearance, EKR) is expressed in the familiar term (milliliter per minute) of clearance, similar to glomerular filtration rate, and the resulting total clearance can be used to predict the expected uremic morbidity, comparable to an earlier stages of kidney disease.

Future Considerations for Outcomes Assessment

A prerequisite for the validity of most urea kinetic modeling algorithms is the presumption of steady-state urea metabolism (ie, constant food intake [quality and quantity]), constant endogenous nitrogen metabolism and catabolism, stable body weight, and a regular dialysis schedule. These conditions rarely exist for most veterinary applications prescribed for acute kidney failure; however, classic double-pool, equilibrated and EKR analyses appear valid under these conditions in human patients if careful attention is paid to the accuracy of all input variables.[130–132]

The rationale to scale dialysis dose to the nebulous index (V) that cannot be readily measured has kinetic justification and historical acceptance. The first-order kinetics of

urea removal by dialysis proceeds with an elimination constant equal to K_d/V, which is a measure of the intensity of the treatment. Even though V is not measured directly, it can be derived mathematically to yield the expression, Kt/V, with kinetic modeling. Recently, however, the universality of scaling dialysis dose to the urea distribution volume has been questioned in human patients as the distribution volume varies independently of body size, between genders, and in patients of differing body composition.[133] Consequently, scaling dialysis dose to V may promote undertreatment in some individuals and relative overtreatment in others. The comparative significance of this issue has not been addressed in animals, but it is likely that the diversity of size, species, and breed in addition to gender in animal patients could impose even greater variance in the relative urea distribution volume than seen in humans.

The effect of dose of dialysis on outcome has been demonstrated in humans with end-stage chronic kidney disease in several large-scale clinical studies.[20–23,28,120] The dose of dialysis that is adequate to manage dogs and cats with either acute or chronic kidney failure needs to be established using appropriate tools for treatment quantification. However, until these parameters are established, routine application of UKM extends the therapeutic insights of dialysis delivery far beyond reliance on routine chemistry tests and provides insight into the assessment and clinical management of uremic animals. Kinetic parameters and quantitation of dialysis delivery are important tools for quality assurance of dialytic therapy in animals, but they are not therapeutic goals per se. The provision of a yet-to-be-defined minimal dose of dialysis is only one of the requirements of therapeutic adequacy, and management of uremia necessitates an individually tailored global approach to the animal.

SUMMARY

The establishment of hemodialysis and extracorporeal therapies in animal patients has had a long and sluggish evolution from experimental curiosity to therapeutic mainstream. Currently, hemodialysis stands as a novel and technically complex therapy with narrowly targeted clinical indications and regional availability. Intermittent hemodialysis serves a vital role in the therapeutic stratification of dogs and cats with uremia that remain nonresponsive to conventional medical therapy. Hemodialysis improves survival for animals with AKI beyond what would be expected with conventional management of the same animals. Clinical evidence and experience in human patients suggests a role for earlier intervention with renal replacement to avoid the morbidity of uremia and to promote better metabolic stability and recovery. For a large population of animal patients, it is the advanced standard for the management of acute and chronic uremia, life-threatening poisoning, and fluid overload for which there is no alternative therapy.

APPENDIX 1: MATHEMATICAL EQUATIONS USED FOR DIALYSIS QUANTIFICATION

Equation 1: urea reduction ratio

$$\text{URR}\ (\%) = \frac{{}_{\text{pre}}\text{BUN} - {}_{\text{post}}\text{BUN}}{{}_{\text{pre}}\text{BUN}} \times 100$$

or

$$\text{URR}\ (\%) = \left(1 - \frac{{}_{\text{post}}\text{BUN}}{{}_{\text{pre}}\text{BUN}}\right) \times 100$$

Equation 2: creatinine reduction ratio

$$\text{CrRR}\ (\%) = \frac{{}_{\text{pre}}\text{Crea} - {}_{\text{post}}\text{Crea}}{{}_{\text{pre}}\text{Crea}} \times 100$$

or

$$\text{CrRR}\ (\%) = \left(1 - \frac{{}_{\text{post}}\text{Crea}}{{}_{\text{pre}}\text{Crea}}\right) \times 100$$

Abbreviations: Crea, creatinine concentration (mg/dl); CrRR, creatinine reduction ratio (%); pre, predialysis; post, postdialysis.

Equation 3: time-averaged urea concentration

$$\text{TAC} = \frac{\text{AUC}}{(t_d + t_i)}$$

Abbreviations: AUC, area under the BUN-Time profile curve (mg/dl x min); TAC, time-averaged urea concentration (mg/dl); t_d, time on dialysis (min); t_i, duration of the interdialytic interval (min).

Equation 4: instantaneous hemodialyzer urea clearance

$$\text{Kd} = Q_b \cdot \frac{\text{BUN}_{in} - \text{BUN}_{out}}{\text{BUN}_{in}}$$

Abbreviations: BUN_{in}, BUN concentration at the dialyzer inlet (mg/dl); BUN_{out}, BUN concentration at the dialyzer outlet (mg/dl); Kd, hemodialyzer urea clearance (ml/min); Qb, blood flow rate through the hemodialyzer (ml/min).

Equation 5: residual renal clearance

$$\text{Kr} = \frac{U_{urea} \cdot V}{\text{BUN}}$$

Abbreviations: Kr, residual renal clearance for urea (ml/min); U_{urea}, urinary urea nitrogen concentration (mg/dl); V, urine flow rate (ml/min).

Equations 6–10: Kinetics of urea using a single-pool fixed-volume model and resulting dose of dialysis: intradialytic and interdialytic BUN concentration (equation 6), urea generation rate (equation 7), and urea distribution volume (equation 8). In equation 6, the interdialytic BUN concentration is obtained by setting Kd as 0. The mathematical solution of equations 7 and 8 requires iterative simultaneous calculations as G is a function of V and reciprocally. The transformation of the dose of dialysis in standard Kt/V (equation 10) allows comparison of different dialysis schedules and modalities.

Equation 6: BUN concentration at time t

$$C_t = C_0 \cdot e^{-(Kr + Kd)t/V} + \frac{G \cdot \left[1 - e^{-(K_r + K_d)t/V}\right]}{K_r + K_d}$$

Equation 7: urea generation rate

$$G = K_r \cdot \left[\frac{C_3 - C_2 \cdot e^{-K_r T_i / V}}{1 - e^{-K_r T_i / V}} \right]$$

Equation 8: volume of distribution of urea

$$V = \frac{(K_r + K_d) \cdot T_d}{\ln \left[\frac{G - C_1 (K_d + K_r)}{G - C_2 (K_d + K_2)} \right]}$$

Equation 9: single-pool Kt/V

$$spKt/V = K_d \cdot T_d / V$$

Equation 10: standard Kt/V

$$stdKt/V = \frac{10080 \cdot \left(1 - e^{-Kt/V}\right)}{T_d \cdot \left[\frac{\left(1 - e^{-Kt/V}\right)}{Kt/V} + \frac{10080}{N \cdot T_d} - 1 \right]}$$

Abbreviations: C_t, BUN concentration at time t (mg/ml), where t = 0 at the beginning of the interval analyzed, t = 1 predialysis, t = 2 postdialysis, t = 3 predialysis for the next session; G, urea generation rate (mg/min); Kd, dialyzer urea clearance (ml/min); Kr, residual renal urea clearance (ml/min); $_{sp}$Kt/V, single-pool Kt/V; $_{std}$Kt/V, standard Kt/V; N, number of dialysis treatments per week; T_d, duration of the dialysis session (min); T_i, duration of the interdialytic interval (min); V, urea distribution volume (ml).

Equation 11: continuous equivalent of intermittent clearance

$$EKR = G/TAC$$

Abbreviations: EKR, continuous equivalent of urea clearance (ml/min); G, urea generation rate (mg/min); TAC, time-averaged BUN concentration (mg/ml).

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