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Reevaluation of Prescription Strategies for Intermittent and Prolonged Renal Replacement Therapies

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KEYWORDS

• Extracorporeal renal replacement therapy • CRRT • IHD • PIRRT

KEY POINTS

- Renal replacement therapies have become the advanced standard for the management of acute and chronic kidney failure.
- Conventional guidelines for the prescription and outcomes assessment of discontinuous therapies have become outdated, are not universally applicable across current delivery platforms and are in need of reassessment.
- Delivered urea clearance, derived from the simplified mathematical relationship between fractional patient urea clearance, and urea reduction ratio, is proposed as a unifying link to the prescription and outcome assessment of discontinuous renal replacement therapy across currently available delivery platforms and modalities.

INTRODUCTION

Extracorporeal renal replacement therapy is now acknowledged as the advanced standard of care for animals with acute and chronic kidney failure and has become increasingly available worldwide. During the past 25 years, these therapies transitioned from the exclusive purview of nephrologist and now are provided equally by nephrologists and criticalists. Dialysis equipment has expanded in veterinary therapeutics to include both intermittent and continuous platforms, and each has been exploited beyond their conventional designs to provide a broad spectrum of dialytic modalities therapeutically adapted to the requirements of animal patients [1]. Despite the evolution of these modalities of therapy, delivered on fundamentally diverse extracorporeal platforms, there has been no recent attempt to reevaluate current prescription criteria or to provide a unifying approach to prescription across these differing platforms.

Standard, catheter-based, venous dialytic techniques include intermittent hemodialysis (IHD) and intermittent hemodiafiltration and continuous renal replacement therapy (CRRT), including continuous hemodialysis, continuous hemofiltration, and continuous hemodiafiltration [1–10].

More recently, modifications of these standard IHD and CRRT therapies have emerged to better accommodate patient needs and practical constraints of veterinary therapeutics. These discontinuous therapies provided over variable ranges of time have been

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described variously in the veterinary literature as slow low-efficiency dialysis or prolonged intermittent renal replacement therapy (PIRRT, includes H, HD, and hemodiafiltration [HDF] modalities). Other variant modalities have emerged, including dialysate-based IHD treatments in which dialysate flow (below the operational parameters of the machine) controls treatment intensity, and IHD bypass treatments in which dialysis intensity is controlled by discontinuous pulses of "no dialysis" and "dialysis" by placing the IHD machine alternatively "in" and "out" of bypass, respectively, while maintaining a variable blood flow [1–3,6,7]. Each of these various terminologies embrace an alteration of the configuration or prescription of dialysis with regard to the modality of therapy, intensity of treatment, and duration of the treatment session. Collectively, variations from traditional IHD or CRRT therapies are designated simply as "hybrid therapies" with attendant descriptors to identify the modification(s).

The necessity for veterinary IHD hybrid treatments emerged at a time when CRRT platforms were not available widely, and the existing IHD platforms had to be adapted to mimic features of CRRT by providing less intensive and more prolonged treatments. Similarly, the evolution of hybrid modalities delivered on continuous platforms arose from the constraints to provide expert staffing for continuous sessions and the requirements for a single CRRT machine to span a broader spectrum of dialytic indications [1]. Compared with standard IHD treatments, hybrid treatments are configured to provide considerably decreased intensity for urea clearances (K• t) on the order of 0.3 to 0.8 L/kg delivered over extended treatment sessions of 6 to 12 hours. Similarly, compared with standard CRRT treatments delivered continuously spanning multiple days, a hybrid treatment on a CRRT platform is delivered discontinuously over a 6- to 12-hour treatment shift on sequential days.

A veterinary renal replacement center may embrace both IHD and CRRT delivery platforms and prescribe a variety of treatment modalities on any given day. Alternatively, a center may be established with a singular platform required to provide a spectrum of therapies. Current guidelines for veterinary IHD prescriptions were derived empirically more than 30 years ago and have remained relatively unchanged [1–8]. CRRT prescription, although more contemporary, is founded on recommendations exclusive of hybrid therapies, which are more typical in veterinary therapeutics [9,10]. An updated unifying approach to the prescription and delivery of these varied modalities of therapy would facilitate the establishment of comparable treatment guidelines and benchmarks for outcomes assessments across all platforms.

Renal replacement prescription must be tailored to the unique requirements of individual patients and adapted to changing requirements on sequential dialysis sessions. The delivery platform must accommodate the size diversity of veterinary patients (from <1 to >100 kg) and simultaneously accommodate the requirements for different phases of kidney failure and differing degrees of azotemia, fluid balance, and electrolyte and acid–base dysregulation.

The foundation of blood purification by dialytic modalities is based on the capacity to transfer dysregulated or toxic solutes from the patient into the dialysate or effluent across the membrane of the extracorporeal filter. Uremia is characterized by a broad classification of retained solutes, but dialysis intensity and efficacy generally are characterized by the transfer of small solutes and prescribed in terms of the clearance of urea. In human medicine, prescription standards and guidelines for human patients are based on the fractional clearance of urea from the patient (Kt/V_{urea}) derived from formal urea kinetic modeling [11–14] and for CRRT are based on the intensity of urea clearance, defined as the normalized effluent volume (in milliliters per kilogram per hour) [14].

Both of these standards have been described for veterinary dialysis, but guidelines based on formal kinetic modeling may be less applicable or valid for veterinary patients, where acute kidney injury is the most frequent indication [14,15]. For acute kidney injury, the assumptions of the steady-state nitrogen balance, constant urea generation, and a uniform distribution volume for urea (V_{urea}) required for kinetic modeling are not likely present; nor is the analytical rigor to define these outcomes in veterinary therapeutics readily applied. Consequently, treatment intensity and efficacy outcomes have been relegated to a more indirect standard, the urea reduction ratio (URR; see Equation 1a). Although the URR is mechanistically linked to urea clearance (Box 1, Formula 1b), it oversimplifies solute transfer and ignores many of the complexities inherent with solute clearance. Despite these deficiencies and the simplicity of URR as a basis for prescribing and quantifying dialysis delivery, it is highly ingrained in veterinary therapies and likely will not be replaced by more rigorous clearance-based standards. It is the authors' intent to broaden the understanding of the inherent relationship between URR and fractional clearance (Kt/V_{urea}) across renal replacement platforms and modalities of therapy. From this understanding, we

BOX 1
Equations

$$URR = (BUN_{pre} - BUN_{post}) / BUN_{pre}; \text{URR}(\%) = [(BUN_{pre} - BUN_{post}) / BUN_{pre}] \times 100 \quad \text{1-a}$$

$$\frac{Kt}{Vurea} = -\ln(1 - target\ URR) \quad \text{1-b}$$

$$Kd_{urea} = Q_b(BUN_{in} - BUN_{out}) / BUN_{in} \quad \text{1-c}$$

propose a reprised approach to the prescription of discontinuous therapies with applicability across all currently used delivery platforms and modalities of therapy. The unifying link to prescription across these diverse modalities of therapy is the urea clearance delivered to the patient. In this article, we hope to expose the limitations of current prescription patterns and explore the practicality and rational to standardize prescriptions based on delivered clearance. To this goal, we have established a clinical strategy and prescription calculator to facilitate a uniform and cross-platform approach to the delivery of extracorporeal renal replacement therapy.

CURRENT INTERMITTENT HEMODIALYSIS AND INTERMITTENT HEMODIALYSIS HYBRID PRESCRIPTION AND DELIVERY ASSESSMENTS

The prescription intensity for IHD-based dialysis treatments for dogs and cats with acute or chronic kidney failure has been founded on URR predictions from the "total blood processed" through the hemodialyzer during a treatment session ($Qb \bullet t$), where Qb is the average blood flow rate (in milliliters per minute) during the treatment, and t is dialysis time (in minutes) (Fig. 1). This empiric basis for prescribing IHD was founded on the direct relationship between Qb and urea clearance of the hemodialyzer (Kd) (see Box 1 Equation 1c) and the observational correlation between "total blood processed" and the intensity of the treatment as predicted by URR for specific hemodialyzers [1,3,6,8]. "Total blood processed" became the de facto operational parameter to guide dialysis prescription and delivery for a desired URR treatment outcome. The usefulness of this simple relationship was adopted widely owing to the flow dependency of clearance at low blood flow rates and the time dependency of total clearance at faster blood flow rates. At a low Qb used during the initial dialysis treatments for acute kidney injury, urea extraction across the dialyzer approaches 100%, and urea clearance (Kd) is approximately equal to Q_b and independent of hemodialyzer selection. Under these conditions, $Qb \bullet t$ becomes a reasonable surrogate for patient clearance, $Kd \bullet t$. At the faster blood flow rates used for maintenance treatments, the relationship between Qb and clearance flattens, because Kd is influenced to a greater extent by membrane characteristics dependent on hemodialyzer selection and to a lesser extent from increasing Qb. Under these conditions, the relationship between $Qb \bullet t$ and the URR also flattens reflecting contributions to patient clearance owing to an increased t (see Fig. 1). Published URR prediction charts based on "blood processed" became widely used despite their applicability to only specific hemodialyzers and species [1,3,6,8]. As a result, practice patterns for prescribing and quantitating IHD dosing promoted little recognition or understanding of clearance beyond URR.

For hybrid therapies including IHD bypass and low-intensity IHD dialysate–based techniques, treatment prescriptions also have been based on the same total blood processed–URR outcome predictions used for more intensive treatments. For these low-intensity treatments, the blood processed projections reflect the volume of blood to be dialyzed during the "out of bypass" intervals for IHD bypass modalities or the volume of dialysate required for low-intensity dialysate-based IHD modalities, respectively. For these low-intensity treatments, the predicted blood processed is essentially equivalent to the total dialyzer clearance ($Kd \bullet t$) and patient urea clearance during the treatment session. For IHD bypass modalities, the prescribed volume is distributed over small intervals of the treatment time (t) when the machine is out of bypass. It is important to distinguish this effective volume of processed blood from the total blood volume passed through the hemodialyzer during both bypass and out of bypass

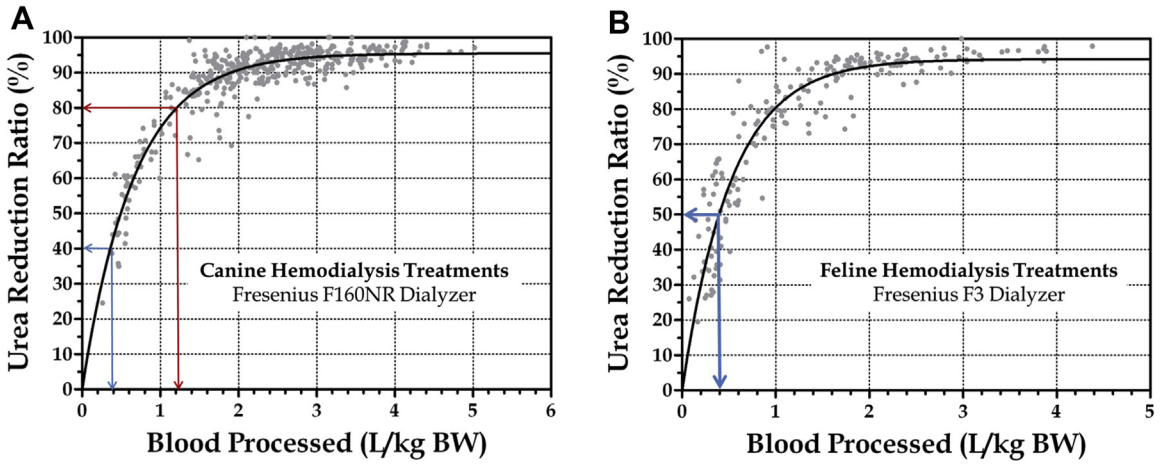

FIG. 1 IHD treatment nomograms to predict the required volume of blood to process in liters per kilogram of body weight (L/kg BW) through a Fresenius F160 NR hemodialyzer for dogs (**A**) and cats treated using a Fresenius F3 hemodialyzer (**B**) to achieve a prescribed URR outcome for a treatment session. The *arrows* illustrate the estimated volume of blood to be dialyzed ($Qb \bullet t$) to achieve specific URR outcomes of 40%, 50%, and 80%.

intervals. For low-intensity dialysate-based IHD modalities, this effective volume of blood to process (see Fig. 1), divided by the appropriate treatment time, predicts the required *Qd* for the URR outcome. Again, the actual volume of blood passing through the hemodialyzer will be many times greater than this URR predicted volume. The slow *Qd* also will be equivalent to *Kd* if it is saturated completely during transit through the hemodialyzer. As can be seen from these examples, the common prescription and outcome link through the varied modalities delivered on a IHD platform is patient clearance.

Patient urea clearance also functions as the delivery link for the prescription of hybrid therapies delivered on a CRRT platform. For a low-intensity $PIRRT_{HD}$ treatment, *Qd*, not *Qb*, controls the delivery of the desired URR for the treatment. Currently, that parameter commonly is predicted from blood processed URR nomograms derived for IHD treatments or empirically derived effluent versus URR nomograms rather than more universal predictions from the URR–clearance relationships.

A REASSESSED PARADIGM FOR DIALYSIS PRESCRIPTION AND DELIVERY

A shift from the historical paradigm of prescribing the delivery of dialysis based on the processed blood volume to a strategy based on patient clearance, would establish a more uniform and rational strategy for prescribing renal replacement treatment applicable to either IHD or CRRT platforms. For a unifying strategy, the URR likely would remain the outcome measure of treatment efficacy, given its conceptional simplicity and deep roots in veterinary dialysis. However, the fractional clearance of urea (Kt/V_{urea}) over the session would define the delivery of therapy necessary to achieve the prescribed URR outcome.

For example, consider a hybrid prescription for a cat with an historical weight of 4.6 kg presented for dialysis with a blood urea nitrogen of 285 mg/dL (102 mmol/L) and current weight of 4.9 kg. For the first hybrid treatment, a URR treatment outcome of 50% over an 8-hour treatment session is elected with a plan to remove approximately 7 mL/kg/h of fluid to resolve the fluid burden. From the relationship between URR and Kt/V_{urea} (see Box 1, Equation 1b; Fig. 2), it is necessary to clear 70% of the urea burden from the cat ($Kt/V_{urea} = 0.7$) to achieve the 50% URR outcome for the treatment. Predicting the urea distribution volume, *V*, is approximately 65% of the cat's body weight owing to the 300 g weight gain; the urea volume of the cat is 3185 mL (4.9 kg × 0.65 × 1000 mL/kg), and the treatment requires approximately 2208 mL (3185 mL × 0.7) of total clearance ($Kd \bullet t$) or 276 mL of clearance per hour of treatment. Because ultrafiltration for the fluid removal contributes 35 mL/h (7 mL/kg/h) of clearance to the treatment goal, an additional 240 mL/h of diffusive and/or convective clearance is required to achieve the outcome URR. This component of the treatment

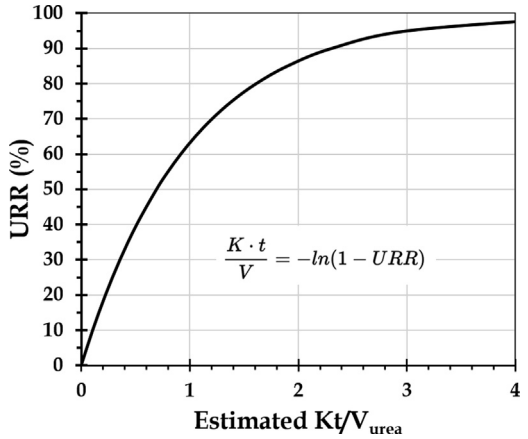

FIG. 2 Graphical nomogram relating the URR and fractional clearance of urea (Kt/V_{urea}) estimated from the simplified single pool kinetic modeling of urea removal (Equation 1b, insert) in the absence of urea generation, G, and changes in the urea distribution volume, V.

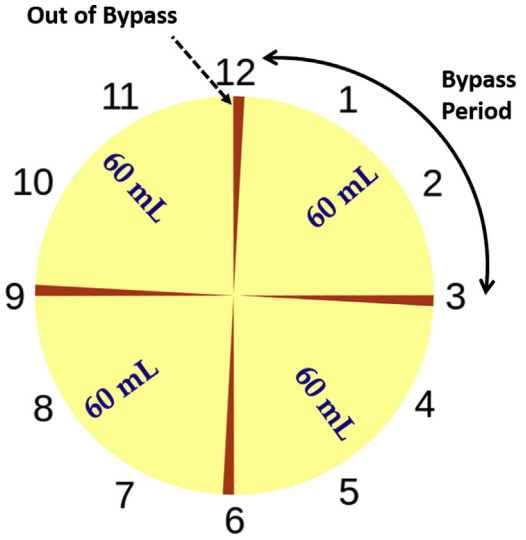

FIG. 3 Schematic representation of the IHD bypass modality to deliver low-intensity treatments on an IHD hemodialysis platform. The illustration depicts an hour of treatment performed with a Fresenius F3 hemodialyzer. At the beginning of the hour, the delivery system briefly is "taken out of bypass" mode (*red area*) to establish 30 to 40 seconds of dialysate flow sufficient to refresh the dialysate compartment of the hemodialyzer with the blood pump temporarily stopped. When the delivery system is placed into bypass mode (*yellow area*), the refreshed dialysate is entrapped in the dialyzer as the blood flow is reestablished. For the Fresenius F3 hemodialyzer, the dialysate compartment contains 60 mL of dialysate, which becomes progressively saturated with urea during 10 to 15 minutes of bypass, establishing 60 mL of blood clearance. When this process is repeated at 15-minute intervals the process delivers 240 mL/h of diffusive clearance. If a greater hourly clearance is required, brief periods (2–5 minutes) of dialysis at a reduced *Qb* can be delivered between the bypass intervals.

could be delivered by any hybrid method over the 8-hour session (t = 480 minutes) by providing 4 mL/min (1928 mL/480 min) or 240 mL/h of clearance as an appropriate treatment intensity for this degree of azotemia. This predicted clearance is essentially the same as the 4.2 mL/min (249 mL/h) *Qb* predicted from Fig. 1B for the Fresenius F3 hemodialyzer, but was derived independent of empirical nomograms as a direct clearance projection applicable universally on any delivery platform.

Procedurally, the treatment could be delivered using an IHD bypass modality with a Fresenius F3 hemodialyzer and a *Qb* of greater than 30 mL/min (Fig. 3) simply by stopping the blood pump and taking the machine out of bypass for 30 to 60 seconds to refresh the dialysate compartment, and then placing the machine back in bypass and restarting the blood pump. The F3 hemodialyzer provides approximately 60 mL of clearance as the dialysate compartment containing approximately 60 mL of new dialysate at the start of the interval reequilibrates with plasma water during the bypass period. When the procedure is repeated every 15 minutes, it provides the 240 mL of hourly clearance, and the prescribed 1920 mL of diffusive clearance would be delivered in an 8-hour session. The convective component of the treatment for the fluid removal would be prescribed independently at 35 mL/h. The urea profile for a treatment of this intensity is illustrated by the graph depicted in Fig. 4 (see Prescribing Tool, elsewhere in this article).

For a low-intensity $PIRRT_{HD}$ treatment on either an IHD platform (using an external dialysate controller) or on a CRRT platform, the treatment is achieved simply by setting *Qd* to 4 mL/min (240 mL/h) for the duration of the 8-hour treatment and prescribing ultrafiltration at 35 mL/h. On a CRRT platform, the treatment alternatively could be delivered by a purely convective prescription of 240 mL/h of postfilter replacement fluid, or any desired combination of convection and diffusion providing 240 mL/h of saturated effluent flow in addition to the 35 mL/h of ultrafiltration for a total effluent flow of 275 mL/h.

For treatments on a CRRT platform or low-intensity IHD dialysate-based treatments, it generally is accepted

PIRRT Calculator

Patient	72-29-35 Prince
Date	
BW (kg)	4.9
Estimated V (%)	65
V (ml)	3185
Starting BUN (mg/dL)	285
PCV (%)	33

Treatment URR target (%):	50%	Time (hours)	8
KT/V_{urea}	0.69	*Kt* (mL)	2208
		K (mL/h)	276

	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 7	Hour 8	
Prescription									
Qb (mL/min)	65	65	65	65	65	65	65	65	
Qd (mL/hr)	240	240	240	240	240	240	240	240	
Qd (mL/min)	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	
Qrep pre (mL/h)	0	0	0	0	0	0	0	0	
Qrep pre (mL/min)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Qrep post (mL/h)	0	0	0	0	0	0	0	0	
Qrep post (mL/min)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Qpfr (mL/h)	35	35	35	35	35	35	35	35	
Qpfr(mL/min)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	
Qeff (mL/h)	275	275	275	275	275	275	275	275	
Saturation ratio (%)	100%	100%	100%	100%	100%	100%	100%	100%	
Caculated values									
Filtration fraction	1%	1%	1%	1%	1%	1%	1%	1%	
Qb/Qd	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	
PFR Rate (mL/kg/h)	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	
Volume of distribution	3150	3115	3080	3045	3010	2975	2940	2905	
Calc.clearance (mL/h)	275	275	275	275	275	275	275	275	
Calc. Clearance (mL/min)	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	
							Total Effluent	2200.0	
Treatment Time (min)	0	60	120	180	240	300	360	420	480
Predicted BUN	285	261	240	219	201	183	167	153	139
%hourly URR	8%	8%	8%	9%	9%	9%	9%	9%	9%
Overall URR	0%	8%	16%	23%	30%	36%	41%	46%	51%

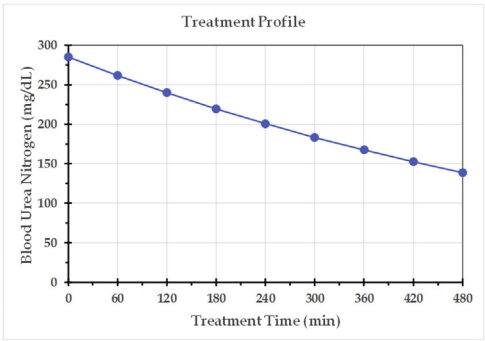

FIG. 4 Illustration of a prescription tool developed to generate clearance delivery targets (Kt/V, Kt, and K) from prescription inputs to achieve a defined URR outcome goal. The example demonstrates prediction of the hourly clearance required for a 50% URR outcome in a 4.9 kg patient requiring 300 mL of ultrafiltration over an 8-hour $PIRRT_{HD}$ session (see text). The prescription could be delivered on a CRRT platform or as a low-intensity IHD dialysate–based treatment. The calculator also plots the expected treatment profile. Box 2 provides the formulas for the treatment projections.

that 1 mL of effluent or dialysate is equivalent to 1 mL of clearance. This concept is true if the effluent (or dialysate) is fully saturated, meaning the urea concentration of the dialysate or effluent are the same as the inlet blood water concentration. This assumption may not hold when delivering more intensive treatments over shorter treatment times and higher *Qd* prescriptions (Fig. 5). Effluent (and dialysate) typically is considered saturated if *Qb* is at least 3 times faster than *Qd*, but this generalization does not consider dialyzer size or membrane performance and may not be valid universally.

As illustrated in Fig. 5, at a *Qb* of 100 mL/min using a Prismaflex HF20 blood set, the effluent will become undersaturated when the *Qd* exceeds 1.5 L/h, even at a Qb/Qd ratio of greater than 3. To ensure greater accuracy in the delivery of PIRRT treatments, it is important to consider the concept of saturation ratio, the ratio between effluent (or dialysate) and inlet urea concentrations. When the saturation ratio is less than 100%, the effluent flow will not equal the *Kd*, but the effective *Kd* can be estimated as the product of effluent flow and saturation ratio.

Prescribing standard or hybrid treatments based on delivered clearance permits the formulation of treatment parameters independent of patient size, degree of azotemia, available platform, and duration of the treatment session. It fosters a consistent understanding of treatment prescription and delivery across distinctly different delivery platforms, which otherwise can be confusing.

THERAPEUTIC AND PRESCRIPTION PRESUMPTIONS

The URR is likely to remain the prescription and outcome standard for veterinary dialysis for the foreseeable future, based on current treatment indications and the inherent difficulties to validate more rigorous outcome standards in animal patients. Prescribing and delivering treatment based on fractional clearance using simplified assumptions for the estimation of Kt/V_{urea} (see Fig. 2; Equation 1b) may differ from its more rigorous estimation by formal urea kinetic modeling. Formally modeled Kt/V_{urea} more accurately predicts the required and delivered fractional clearance by consideration of nutritional intake and catabolic status of the patient, urea distribution, compartmentation, and sequestration, fluid removal, filter kinetics, residual kidney function, and access flow [16–21]. Failure to consider the influence of these variables in the

BOX 2
PIRRT Calculator Formulas

$$V(mL) = BW(kg) * \%Vd * 1000$$

$$\frac{Kt}{Vurea} = -\ln(1 - target\ URR)$$

$$\text{Kt} = \frac{Kt}{V} * \text{V}$$

$$\text{Qeff} = \text{Qd} + \text{Qreppre} + \text{Qreppost} + \text{Qpfr}$$

$$\text{FF} = \frac{(Qd + Qreppre + Qreppost + Qpfr)}{Qreppre + Qb\left(\frac{1-PCV}{100}\right)}$$

$$\text{PFR rate} = \frac{Qpfr}{BW}$$

$$\text{Calculated clearance } K = SR * \frac{Qeff}{1 + \frac{Qreppre}{Qb}}$$

$$\text{URR} = 1 - e^{-\frac{Kt}{V}}$$

formulation of the treatment can result in substantial deviations from expected outcomes [17–21]. Exaggerated urea appearance from excessive dietary intake or a high nitrogen turnover in catabolic patients causes an apparent undertreatment and a higher than expected URR outcome. The urea distribution volume (V) is not quantitated readily by clinical assessment, and inaccurate estimates of hydration, lean body mass, or fat mass can cause the underestimation or overestimation of the V and corresponding undertreatment and overtreatment prediction by URR. Similarly, overestimates of Kd owing to inaccurate Qb measurements, clotting of the filter, access recirculation, or incomplete dialysate or effluent saturation can overpredict actual

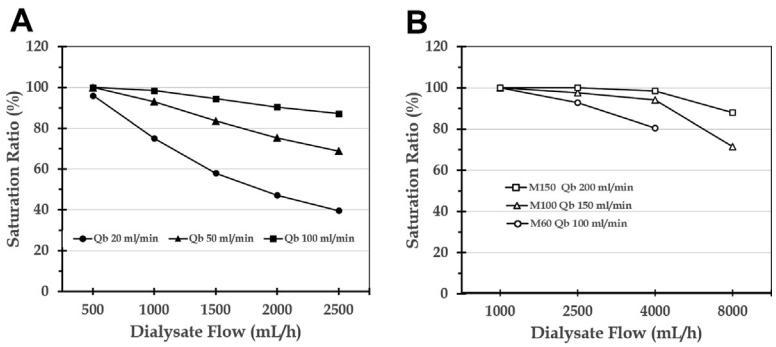

FIG. 5 Influence of dialysate and blood flow rates on effluent saturation ratio. Saturation ratios are calculated from manufacturer's clearance estimations for the Baxter HF20Set (**A**) during continuous hemodialysis treatments at blood flow rates (Qb) of 20, 50, and 100 mL/min and (**B**) the Baxter M150, M100, and M60 Sets at blood flow rates of 200 mL/min, 150 mL/min, and 100 mL/min, respectively. Note that significant effluent undersaturation is possible with small hemofilters and Qb/Qd ratios of less than 3.

delivery of the treatment. Any influences affecting the true treatment delivery can be expected to alter actual outcome from projected outcome.

The application of the *URR* versus Kt/V_{urea} relationship to establish clearance delivery targets ignores many important assumptions incorporated into Kt/V_{urea} quantitation by formal urea kinetic modeling. However, the relationship is sufficiently robust to direct the prescription of therapies that are inherently subject to clinical and treatment variables that positively or negatively bias treatment outcomes. Clearance targets stand on more theoretic validity across all delivery platforms than conventional prescriptions formulated from the URR normograms derived for specific treatment platforms and specific hemodialyzers with their own inherent variance (see Fig. 1).

The precise estimation of the Kt/V_{urea} requires documentation of residual renal clearance (*Kr*); ultrafiltration volume; dialysis time (*t*); measurement of pretreatment, post-treatment, and the subsequent pretreatment urea concentrations; average clearance of the filter (*Kd)*; *Qb*; *Qd*; and iterative estimation of urea appearance (*G*) and urea distribution volume (*V*) for a treatment session [7,12,17–20]. For practical and economic considerations, this degree of precision is not likely to direct veterinary dialysis. The precision of URR outcomes from the delivery prescriptions based on Kt_{urea} will be dictated by the same clinical uncertainties that influence all dialysis outcome analyses. Parameters determined with reasonable certainty include only *Qd* and *t*. All other determinants of treatment outcome are subject to variable errors of clinical assessment or cannot be assessed directly.

Residual urea clearance, *Kr*, rarely is assessed in animal patients undergoing acute or maintenance dialysis and typically is considered negligible over the treatment session. However, even low rates of *Kr* can contribute to total session clearance and promote a lower than predicted post-treatment urea concentration and increased URR [12,13].

Similar to *Kr*, filter clearance, *Kd*, rarely is measured. Most commonly, *Kd* is overestimated owing to filter clotting, inaccurate *Qb* measurements, access recirculation, periods of dialysate bypass, or excessive periods of pump stoppage owing to poor access performance. The overestimation of *Kd* results in less treatment than prescribed and a lower URR outcome than predicted [18,20]. During IHD bypass treatments, total patient clearance may be underestimated significantly if the clearance produced by dialysate equilibration during bypass intervals is ignored. Patient clearance will be increased from the prescribed clearance, and URR will be greater than prescribed for the session. Ionic dialysance can help to predict real-time *Kd* and unexpected decreases owing to clotting, access recirculation, or blood flow inaccuracies [22–25].

Dialysis time, *t*, can be overestimated if the session time or clock time is used to deliver the treatment rather than actual treatment time. Discrepancies between session time and treatment time occur if the session is burdened with excessive alarm conditions during which treatment does not occur, or during prolonged or continuous treatments if the patient is disconnected temporarily for procedural necessities. These situations promote underdialysis from decreased delivered clearance and lower URR outcomes.

URR outcomes can deviate from prescribed projections owing to errors in post-treatment blood sampling. A delay in post-treatment sampling by even several minutes causes an increase in the urea concentration from rebound compared with samples taken immediately after treatment [20]. A 5% to 25% increase in the urea concentration owing to delayed sampling would cause a corresponding decrease in the session URR and a seemingly inadequate treatment. In contrast, dilution of the post-treatment sample by access recirculation would decrease the measured urea concentration and artificially increase the measured URR for the session [20].

Urea distribution volume, *V*, and urea appearance, *G*, directly influence urea kinetics and patient clearance for all modalities of renal replacement, but cannot be measured directly or predicted accurately by clinical assessment. Estimates of *V* and *G* are derived by iterative calculation using urea kinetic modeling to compute Kt/V_{urea} [12,18,20,25]. Simplified algorithms to estimate the Kt/V_{urea} incorporating adjustment of the *V* owing to ultrafiltration during the treatment, and estimates of *G* have been derived for human patients but have not been explored or validated in animals [17,26,27]. Until these compensations have been defined, and in the absence of formal urea kinetic modeling, Equation 1b provides a reasonable surrogate for the prescribed intensity (*Kt*) and efficacy (Kt/V_{urea}) of the delivered therapy to meet URR goals for individual treatments.

When formulating a clearance-based prescription, consideration should be given to the variable influences of the *G* and *V* and the caveats for the other influences, as described elsewhere in this article, to better match the clearance requirements to the patient's clinical state.

For normally hydrated animal patients, the *V* generally is estimated as 60% (53%–66%) of body

weight; however, *V* changes according to hydration status and directly influences both the required and delivered patient clearance [28]. In an overhydrated patient, the *V* is predictably more than 60% of the body weight. The prescription should be adjusted for a greater estimate of *V* to provide greater patient clearance, *Kt*, than predicted for normal hydration and body condition. Because the fluid burden is corrected with ultrafiltration, fractional clearance may increase, leading to a higher than predicted URR outcome. Obese patients have a relatively lower *V* as a percentage of body weight, and may have greater URR outcomes when the *V* is estimated for a normal body composition.

Urea appearance rate (*G*) from hepatic urea generation generally is ignored in both the prescription and outcomes assessment of renal replacement therapies in animals.

The extremes of urea generation and nitrogen balance significantly influence URR outcomes, and should be considered when formulating the prescription. Infectious or inflammatory causes or comorbidities associated with kidney injury generally cause a catabolic state and increased urea appearance rate that increase the requirement for delivered clearance and URR outcome. Urea appearance also increases as patients are provided enteral or parenteral nutrition. Increases in the blood urea nitrogen by more than 25 mg/dL/d between renal replacement sessions suggest a hypercatabolic state that may require the prescription of increased patient clearance.

REPRISED UREA REDUCTION RATIO APPROACH AND PROLONGED INTERMITTENT RENAL REPLACEMENT THERAPY CALCULATOR TO DELIVER RENAL REPLACEMENT BY FRACTIONAL UREA CLEARANCE

With the increased application of renal replacement therapy in veterinary medicine over the past 25 years, it is timely to reassess prescription strategies to provide a unifying approach applicable across all conventional platforms and modalities of delivery. The vast majority of renal replacement treatments are provided discontinuously rather than as continuous modalities, so we have limited this discussion to discontinuous therapies. Despite its inherent shortcomings, we also have reprised URR as the operative outcome parameter, owing to its simplicity and engrained foothold in veterinary medicine. However, conventional URR prescriptions based on "processed blood volume" nomograms are not universal to all dialysis modalities and should be respectfully retired [3,6–8]. In its place the fractional urea clearance (Kt/V_{urea}) is proposed as a prescription delivery target, as it is universally applicable to all renal replacement platforms and modalities of therapy. It has been validated as the standard of therapy for human patients and has a practical mathematical relationship to URR (see Fig. 2). [11–14,18,21]. This kinetic relationship provides an opportunity to maintain the current URR heritage while embracing patient clearance as a more appropriate operational parameter to prescribe and deliver renal replacement therapies.

We propose an approach and calculating tool to facilitate a transition for the operational delivery of renal replacement therapies (see Fig. 4). The calculating tool provides opportunity to perform "what if" manipulations of URR, URR/h, *t*, *Qb*, *Qd*, *UF*, effluent saturation, filtration fraction, prefilter versus postfilter replacement, and *Qb*/*Qd* ratio to establish treatment parameters appropriate across platforms and modalities. Therapy delivered on the basis of clearance is logical and imposes less confusion when confronting differing platforms and modalities of therapy. Without the calculating tool, the prescription requirements can be configured from a simple strategic approach.

Step 1: From the patient weight and clinical estimate of hydration status, *V* is estimated as a percentage of the patient weight subject to the caveats and uncertainties as discussed elsewhere in this article. A value of 60% of body weight can be used for euhydrated patients, and proportionate adjustments used for dehydrated (50%–59% of body weight) or overhydrated (61% to $\geq$70% of body weight) patients as predicted from historical weight or clinical judgment.

Step 2: The desired URR outcome and appropriate treatment time (*t*) are determined to define the treatment goals for the patient during the session.

Step 3: The operational Kt/V_{urea} for the selected URR outcome for the treatment (Step 2) is determined from Equation 1b (see Fig. 2), or the calculating tool. From the operational Kt/V_{urea}, the required patient clearance (*Kt*) is determined by multiplying the unitless Kt/V_{urea} value by the estimated *V* determined in Step 1.

Step 4: Dividing the total patient clearance (*Kt*) by time (*t*) provides the hourly clearance required to establish the treatment goals by hemodialysis, hemofiltration, or hemodiafiltration independent of the treatment platform (IHD, $PIRRT_{HD}$, IHD-bypass, or low-intensity IHD dialysate–based modalities on an IHD platform; or $PIRRT_{H}$, $PIRRT_{HD}$, or $PIRRT_{HDF}$ using hemofiltration, hemodialysis, or hemodiafiltration on a CRRT platform, respectively).

For treatment modalities delivered on an IHD platform, the hourly treatment goals are delivered as follows.

Standard or $PIRRT_{HD}$

The hourly and session urea clearance goals are delivered by the selection of the hemodialyzer and the prescribed *Qb*. Establishing the appropriate *Qb* requires some understanding of the performance characteristics of the selected hemodialyzer. Its instantaneous urea clearance, *Kd* (mL/min), at typical dialysate flow rates of more than 300 mL/min, is predicted by *Qb* times the extraction ratio at the selected *Qb*. For nearly all hemodialyzers, at a *Qb* less than 50 mL/min, the extraction ratio approaches 100% and the *Kd* is approximately equal to the *Qb*. The prescribed hourly clearance equals the *Qb* (mL/min) times 60 minutes. At faster blood flow rates, the *Kd* increases exponentially, and the instantaneous *Kd* and hourly clearance must be predicted from its mass transfer area coefficient (KoA), historical or real-time measurements of *Kd* or ionic dialysance at the selected Qb, or manufacturer's references. If the initially prescribed hourly clearance cannot be delivered owing to limitations of access flow or performance of the hemodialyzer, the clearance goals for the session can only be achieved by extension of the treatment time, such that the product of *Kd* and session time (*t*) matches the prescribed patient clearance goal (*Kt*).

IHD bypass modality

The IHD bypass technique was conceived to enable the delivery of a very slow, low-efficiency treatment, especially in small patients on an IHD platform ill-designed to deliver such therapies. The strategy is to provide small discontinuous intervals of diffusive clearance within the platform's capabilities of *Qb* and *Qd* followed by prolonged intervals of no clearance while maintaining the *Qb* as fast as possible to prevent clotting in the extracorporeal circuit. Cumulatively, over the session, these intervals of clearance sum to achieve the prescribed patient clearance goal (*Kt*). The diffusive clearance is interrupted by placing the IHD platform in bypass to stop delivery of dialysate to the hemodialyzer. To deliver the treatment, the desired hourly URR is divided into the URR goal to determine the required session time in hours. For example, a 50% URR treatment goal providing 6% URR per hour would require an 8-hour treatment. The hourly clearance is determined next by dividing the calculated session clearance goal (*Kt*)by the treatment time (see Fig. 4).

Because the *Kd* will be very low for these treatments, one component of the hourly clearance is determined by the product of *Qb* (mL/min) and the number of minutes the system is out of bypass. However, during bypass, there is additional clearance equivalent to the volume of the refreshed dialysate contained in the hemodialyzer during the bypass interval, as this fluid equilibrates with flowing blood. This component of clearance must be configured into the total hourly clearance to prevent overtreatment of the patient. Fig. 3 illustrates the IHD bypass method providing 240 mL of hourly diffusive clearance (4 mL/min) delivered during bypass alone. Equilibration of the refreshed dialysate during bypass contributes 1900 mL of cumulative clearance as a component of the total 2208 mL of clearance required for a 4.9 kg patient over an 8-hour session (see example in Fig. 4). In this example, the equilibrating static dialysate provides the entire diffusive clearance while the system is in bypass. There is no requirement to provide additional clearance out of bypass. Ultrafiltration for fluid removal provides the small additional component to the total clearance. This prescription will deliver the 0.7 Kt/V_{urea} required to achieve the 50% URR outcome for the treatment. As discussed elsewhere in this article, the prescription can be delivered simply by equilibrating the 60 mL of dialysate retained in the hemodialyzer (Fresenius F3) during the bypass intervals to achieve 60 mL of clearance. Repeating this procedure every 15 minutes for the 8-hour session provides both the required hourly and cumulative session clearances, respectively, while maintaining the *Qb* within machine capabilities sufficient to prevent clotting in the circuit. If a greater hourly clearance is required, brief periods (2–5 minutes) of dialysis at a decreased *Qb* can be delivered between the intervals bypass.

Low-intensity IHD dialysate–based modalities

This hybrid technique also was conceived to enable the delivery of a very slow, low-efficiency diffusive treatment to small patients on an IHD platform. Much like on a CRRT platform, dialysis intensity is controlled by delivering a very slow *Qd* rather than a slow *Qb*. At *Qb*/*Qd* ratios of greater than 3, the dialysate approaches 100% saturation, and the *Kd* will be equivalent to the *Qd*. The treatment is delivered simply by providing a dialysate flow equal to the prescribed hourly clearance at a *Qb* at least 3 times this flow. IHD platforms are not designed to deliver

dialysate at such slow flows, so an external pump can be configured to divert a small portion of the bulk dialysate flow to the hemodialyzer at the desired rate (Fig. 6).

The configuration and delivery of hybrid treatments based on clearance are more intuitive on CRRT platforms, because the components of the effluent volume are more predictably equivalent to clearance.

Prolonged Intermittent Renal Replacement Therapy with Hemofiltration

For purely convective modalities, the total clearance required for a given URR outcome is determined by setting the effluent rate (*Qeff*) to the required hourly clearance (postfilter replacement) or to the adjusted effluent rate to accommodate dilution from prefilter replacement and/or net ultrafiltration. The delivery of these effluent rates must be prescribed with consideration of the obtainable *Qb* and appropriate filtration fraction.

Prolonged Intermittent Renal Replacement Therapy with Hemodialysis

A purely diffusive treatment on a CRRT platform is analogous to a low intensity IHD-dialysate-based modality, as described elsewhere in this article. Typically, the *Qd* will be sufficiently slow to promote a *Qb*/*Qd* ratio of greater than 3 to provide saturation of the effluent. Under these conditions, the *Qd* will approximate the prescribed hourly clearance. The *Qd* should be decreased by the rate of ultrafiltration for net fluid removal to prevent an increased treatment intensity and excessive URR outcome.

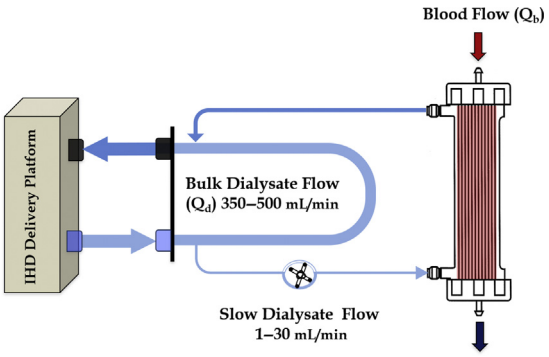

FIG. 6 Schematic illustration of a low-intensity IHD dialysate–based circuit designed for use on a conventional IHD platform. The bulk dialysate flow from the IHD platform circulates in a loop, and a variable slow flow is diverted by an external pump and delivered to the hemodialyzer. The equilibrated dialysate (including any ultrafiltration) is returned to the bulk dialysate stream. The slow dialysate flow controls the intensity of the treatment and generally is equivalent to Kd_{urea}. This configuration does not require modification to the IHD platform and does not interfere with any of the monitoring alarm or systems functions of the platform. (*Courtesy of* Dr. LD Cowgill.)

Prolonged Intermittent Renal Replacement Therapy with Hemodiafiltration

For this modality, clearance is provided by both diffusion and convection, and the required patient clearance can be achieved by variable distribution of among these modalities. Once the total (*Kt*) and hourly clearances are determined the different combinations of filtration, diffusion, and ultrafiltration, can be configured to determine the best combination to maximize effluent saturation, Qb/Qd ratio, filtration fraction, prefilter versus postfilter replacement, and fluid removal. Commonly, the distribution is arbitrarily set to 50% diffusion and 50% convection, in which the *Qd* and *Qrep* would each contribute one-half of the hourly clearance, presuming conditions permitting complete effluent saturation prevail (see Fig. 5).

SUMMARY

As veterinary renal replacement therapy completes its first 50 years of inception, establishment, and evolution, it is opportune to reflect on its impact to advanced veterinary therapeutics. It is also opportune to look to our past and current guidelines for the delivery of these therapies to assess their future applicability and relevance. We have exploited the mechanistic relationship between the URR and the fractional urea clearance of the patient (Kt/V_{urea}) in an attempt to provide greater uniformity of understanding dialysis across the diversity of platforms for its delivery. From this understanding we propose reevaluating the approach to the prescription of standard and hybrid extracorporeal therapies with applicability across the current modalities of therapy.

CLINICS CARE POINTS

- Prescribing dialysis intensity and outcomes based on "blood processed" nomograms provides a highly generalized and indirect estimate of the required clearance for a delivered URR outcome, but such nomograms are specific to a targeted filter, blood flow rates, species, IHD modality, and solutes and should not be generalized to therapeutic conditions beyond their defined characteristics.

- Blood processed nomograms to predict URR outcomes predict clearance only at relatively slow blood flow rates and low URR goals when the extraction ratio for urea approximates 100%. At progressively faster blood flow rates and progressively higher URR outcome goals, the predicted blood volume to process is more significantly influenced by treatment time as blood flow rate (*Qb*) becomes limiting.
- The *Kt/V* versus URR relationship (see Box 1, Equation 1b) proposed to prescribe dialysis treatment intensity and delivered URR outcome also generalizes this complex relationship and oversimplifies the influences of urea distribution volume, generation rate, compartmentation, and treatment schedule, among other clinical factors.
- The *Kt/V* versus URR relationship (see Box 1, Equation 1b) proposed to prescribe dialysis treatment intensity and delivered URR outcome promotes a reasonably simplified yet generalizable approach for dose prescription and outcomes monitoring of discontinuous renal replacement therapies within the inherent clinical and technical variabilities of these therapies.
- The treatment session clearance estimated from the Kt/V versus URR relationship (see Box 1, Equation 1b) can be delivered by variable combinations of diffusive or convective modalities independent of the delivery platform.
- Clinical estimates of urea distribution volume based on hydration status and body composition and predictions of the catabolic status of the patient should be incorporated into dose prescription for discontinuous renal replacement treatments.
- For bypass-based hybrid treatments, the clearance provided during the bypass intervals must be included in the prescription of the total clearance provided to the patient during the treatment session.

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