



Extracorporeal renal replacement therapy and blood purification in critical care

Larry D. Cowgill, DVM, PhD, DACVIM and Julien Guillaumin, Doct. Vet., DACVECC

Abstract

Objective – To review indications methods of renal replacement therapies (RRT) and practical considerations for the creation of a RRT program.

Data Sources – Current human and veterinary literature review with a focus on advanced renal physiology and clinical experience in RRT and acute/chronic kidney diseases.

Data Synthesis – Renal replacement therapies encompass intermittent hemodialysis, continuous renal replacement therapy as well as some “hybrid” techniques. Each method of RRT has practical and theoretical advantages but currently there is no evidence that one technique is superior to the other.

Conclusions – RRT is a valuable therapeutic tool for treatment of acute kidney injury and chronic kidney disease. The implementation of an RRT program needs to take into consideration multiple parameters beyond the choice of an RRT platform.

(J Vet Emerg Crit Care 2013; 23(2): 194–204) doi: 10.1111/vec.12028

Keywords: acute kidney injury, hemodialysis, hemoperfusion, kidney failure, therapeutic plasma exchange

Introduction

Extracorporeal renal replacement therapy (RRT) has evolved over the past 40 years to become the advanced standard of care for the management of acute kidney injury (AKI) in veterinary medicine.^{1,2} The demand for RRT in veterinary therapeutics and especially in veterinary critical care has expanded rapidly in the past 10 years. Today, the availability of renal replacement modalities for companion animals has flourished throughout the world but particularly in the United States. The expansion of RRT also has resulted in a transition in the perspective of dialytic therapies from the purview of nephrologist to the attraction of the criticalist or intensivist. The paradigm also has caused a transition away from utilization of intermittent extracorporeal modalities established by nephrologists to continuous modalities embraced by some criticalists. In human medicine, this has prompted spirited debate and encampment of advocates for each

Abbreviations

AKI	acute kidney injury
CRRT	continuous renal replacement therapy
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
CVVHDF	continuous veno-venous hemodiafiltration
IHD	intermittent hemodialysis
RRT	renal replacement therapy
PIRRT	prolonged intermittent renal replacement therapy
TPE	therapeutic plasma exchange

approach.^{3–8} Acknowledging specific benefits associated with each modality, overall there appears to be no obvious evidence-based advantages in outcomes of human patients with AKI when comparing intermittent versus continuous modalities.^{9–19} Consequently, when establishing a veterinary RRT program it is important to consider beyond specific therapeutic modalities based on specialty orientation established in human medicine to therapeutic considerations, practicalities, and economic realities specific to veterinary medicine. It also is important to consider provision of broader extracorporeal procedures such as hemoperfusion and therapeutic plasma exchange in addition to RRT as forms of extracorporeal blood purification. Our aim

From the Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA 95616 (Cowgill), and the Emergency and Critical Care Service, Veterinary Medical Center, The Ohio State University, Columbus, OH 43210 (Guillaumin).

The authors declare no conflict of interest.

Address correspondence and reprint requests to Dr. Larry D. Cowgill, Department of Medicine and Epidemiology, 2108 Tupper Hall, School of Veterinary Medicine, University of California, Davis, CA 95616, USA. Email: ldcowgill@ucdavis.edu

Submitted August 14, 2012; Accepted January 26, 2013.

is to provide an overview and perspective on the benefits, differences, and potential similarities afforded by divergent extracorporeal platforms to nephrologists and criticalists considering establishing an extracorporeal blood purification program.

Dogs and cats equally share the demand and utilization for RRT, and techniques and equipment for the delivery extracorporeal RRT are safe and effective for animals as small as 1.5 kg or as large as 600 kg.²⁰ The primary therapeutic applications for extracorporeal blood purification in animals is to support the consequences and homeostatic disorders associated with acute uremia as a RRT, but there are equally important applications of blood purification following acute poisoning and drug overdoses and for the management of fluid overload (Table 1).²⁰ Conventional medical therapies cannot reproduce the efficacy of extracorporeal procedures for correction of the cumulative azotemia, biochemical alterations, and the acid-base, endocrine, and fluid disorders associated with kidney failure or the intoxication of an acute poisoning. Generally, delay or inopportunity to initiate RRT in patients with AKI or acute poisoning leads to greater uremic symptomology, morbidity, recruitment of additional organ dysfunction, and less favorable outcomes.^{2,19,21}

Modalities and Principles of Renal Replacement Therapies

Currently applied extracorporeal RRT modalities are broadly categorized into intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). Extending from these, broad categories are a variety of modified procedures that better serve particular therapeutic goals and patient needs. Both IHD and CRRT share common features that blood is circulated in an extracorporeal circuit, and its composition is modified by the mass transfer of solute and water by diffusive and/or convective forces across an interfacing semipermeable membrane. The magnitude and spectrum of the solute transfer is predicated by the nature of the force(s) imposed across the membrane, on the chemical and physical characteristics of the solute, and the structural properties of the porous membrane. Water and low molecular weight solutes (<500 daltons) 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. The composition of the blood returning to the patient is further influenced by the prescribed composition of the dialysate solution used in diffusive hemodialysis procedures or the replacement solution used in convective dialysis.

Diffusive transfer of solutes used for hemodialysis 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. Net solute transfer is directed from the solution at higher concentration to the solution at lower concentration or thermodynamic potential.^{1,20,22} 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. The diffusive potential for every solute varies under differing physiologic condition. Molecular weight is the main determinant of kinetic motion and contributes inversely to the rate of diffusion for individual solutes. Small solutes such as urea (60 daltons) diffuse faster than larger solutes such as creatinine (113 daltons), and generally the plasma concentration of small solutes decrease faster than those of larger solutes during the course of dialysis.^{20,22} The intrinsic permeability of a membrane for each solute is determined by its thickness, its effective surface area, and the number, size, and shape of its pores or diffusion channels.²³ In addition to these intrinsic membrane characteristics, net transfer of solutes is influenced further by its molecular charge, protein binding, volume of distribution, and cellular seclusion.

Convective transport of solutes used in hemofiltration procedures is achieved by the process of ultrafiltration, in which water is driven through the membrane by hydrostatic pressure gradients (rather than diffusive concentration gradients). Diffusible solutes dissolved in the water are swept through the membrane by solvent drag.^{20,22,24} Convective transport does not require a concentration gradient across the membrane and does not generate diffusive gradients or alter serum concentrations. The transmembrane hydrostatic pressure gradient, hydraulic permeability, and the surface area and sieving coefficient of the membrane determine the rate of ultrafiltration and solute transfer. During hemofiltration, the transmembrane pressure generated by the blood and effluent pumps initiate and control the rate and volume of ultrafiltrate that is transferred to a waste container. Convective transport has a greater capacity to transfer middle and large molecular weight solutes that have limited diffusibility. The solute concentration of blood returning from the hemofilter (and ultimately the patient's blood composition) is modified or corrected by the composition of a replacement solution infused into the returning blood before (prefilter) or after

(postfilter) ultrafiltration at the filter. Hemodiafiltration is a hybrid treatment modality that is used in both IHD and CRRT procedures combining both diffusive dialysis and large-volume hemofiltration to achieve better small and large molecular weight solute removal and greater fluid removal than achieved by either technique alone.^{24,25}

Adsorption of solutes is a third mechanism of blood purification and occurs to a small extent on the membranes of both hemodialyzers and hemofilters but is maximized in the process of hemoperfusion. Hemoperfusion is an adsorptive extracorporeal therapy used to manage endogenous and exogenous intoxications that are not cleared efficiently by hemodialysis or hemofiltration. Adsorption is the principle of molecular attachment of a solute to a material surface. In contrast to the physical separation between blood and dialysate that occurs during hemodialysis, during hemoperfusion blood is exposed directly to an adsorbent with the capacity to selectively or nonselectively bind solutes or toxins of defined chemical composition within the blood path. Hemoperfusion is an important adjunct to other extracorporeal blood purification therapies and should be integrated into veterinary RRT programs.^{26–29} Hemoperfusion is effective at eliminating high-molecular weight, protein-bound, or lipid-soluble toxins or drugs that are cleared poorly, if at all, by hemodialysis or hemofiltration (ie, diffusion and convection). Ideally, hemoperfusion adsorbents should have a high adsorptive capacity for target solutes, be nontoxic and hemocompatible, minimally adsorptive for normal blood constituents, sterile, free of endotoxins, noncarcinogenic, and maintain a stable composition when exposed to blood. Activated charcoal has been the adsorbent used most commonly to eliminate endogenous and exogenous toxins *in vivo*.^{28–30} 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 to greater than 21,000 daltons.³⁰

Delivery of Extracorporeal Therapy

All extracorporeal modalities share a requirement for vascular access and the delivery of a large, continuous flow of blood to the extracorporeal device. Typically, vascular access is provided by a temporary or permanent, dual-lumen catheter placed surgically or transcutaneously in the jugular vein by interventional techniques.^{31–33} Each extracorporeal procedure requires anticoagulation to prevent clotting of blood in the extracorporeal circuit. Most importantly, all extracorporeal

real modalities require a team of highly dedicated, exceptionally well-trained and experienced professionals (nephrologists, intensivists, and technicians), and an appropriately equipped facility to provide critical patient care. Both IHD and CRRT demand the same degree of technical expertise, dedicated experience, and understanding of extracorporeal therapies, nephrology, and critical patient care.

The emergence of new RRT programs in veterinary therapeutics has been entangled by the debate associated with which RRT delivery platform is most appropriate for human critical care nephrology. Consequently, nephrology-based or critical care-based veterinary programs have tended to align with their counterpart human discipline for selection of an RRT platform. There are, however, fundamental differences in the type and characteristics of the patients, the etiologies and clinical manifestations of disease, therapeutic indications, facilities, professional staffing, and economics between human and veterinary RRT programs. Consequently, the therapeutic platforms and treatment modalities used to deliver extracorporeal RRT to animal patients should not be based exclusively on discipline (nephrology versus intensivist) preference or bias, latest trends, or marketing hype. Rather, decisions should be based on realistic and considered understanding of veterinary therapeutics, animal diseases, veterinary practice patterns, and veterinary economics.

Intermittent Hemodialysis

Intermittent hemodialysis technically incorporates all modalities (diffusion, convection, and adsorption) of solute and fluid removal but is primarily a diffusive process with convection and adsorption contributing only to a minor extent depending on the capabilities of the delivery system, the degree of ultrafiltration for fluid removal, and the membrane type. Intermittent hemodialysis has been used for 40 years in veterinary therapeutics and has an established history of safety and efficacy. Intermittent hemodialysis typically is provided for 3–6 hours per daily session and repeated on a variable daily schedule (usually 3 times weekly) after an initial period of patient management that may include 2–3 consecutive daily sessions. The overall efficiency of IHD permits near normalization of body fluid composition and volume during a single treatment session, but its efficiency and intermittent delivery, results in large, “saw tooth” excursions in solute concentration and fluid volume during and between treatments that are nonphysiologic.^{34,35} These rather drastic excursions are generally tolerated in patients with chronic kidney disease and in hemodynamically stable AKI, but may be tolerated poorly in patients with severe or

hemodynamically unstable AKI associated with sepsis, shock, hypoxia, and severe fluid overload.³⁶ The innate efficiency for solute and fluid removal of IHD platforms currently used for animal dialysis also may predispose very small and severely azotemic animals to potentially fatal complications associated with dialysis disequilibrium syndrome and hypovolemia if used inappropriately by inexperienced personnel.²⁰

Currently used IHD platforms have been designed and certified for adult human (and not animal) use, but their sophisticated design, monitoring systems, and inherent safeguards have made them safe, reliable, appropriate, and flexible enough for use in animal RRT. The most fundamental differences between animal and human dialysis are the relative size of animal patients and their requisite volume for the extracorporeal circuit. The volume of the extracorporeal circuit is established by disposable bloodlines and the hemodialyzer that are not necessarily specific or intrinsic to the IHD platform per se and can be configured independently to the requirements of the animal patient.

Intermittent hemodialysis platforms and treatment prescriptions also can be configured to perform “hybrid therapies” in which the conventional modality is adjusted to mimic a continuous modality if desired or appropriate for the needs of the patient. Prolonged (or extended) intermittent renal replacement therapy, (PIRRT) also termed sustained low-efficiency daily dialysis is a modality performed on an IHD platform in which the duration of the dialysis session is extended to 8–12 or more hours. The intensity of the solute clearance and ultrafiltration rate is minimized to facilitate more gradual correction of solute and volume disturbances, to provide greater protection from dialysis disequilibrium, and enhanced hemodynamic tolerance. PIRRT promotes efficacy and outcomes comparable to CRRT.^{36–40} (Figure 1).

Intermittent hemodialysis platforms generate an ultrapure dialysate solution on-line from highly purified water and concentrated salt solutions. Dialysate composition, temperature, and flow rate are actively programmable components of the dialysis prescription. Dialysate is formulated to maximize elimination of uremia toxins, prevent depletion of normal blood solutes, replenish depleted solutes, and minimize physiologic and metabolic perturbations during and after the dialysis sessions. The countercurrent flow of warmed dialysate in the hemodialyzer compensates for thermal losses from the blood in the extracorporeal circuit and helps to prevent hypothermia in the patient. The requirement for an external purified water treatment system is often regarded as a deterrent to IHD platforms; however, small, self-contained, and portable water purification systems that require a minimum of operational expertise, maintenance, and

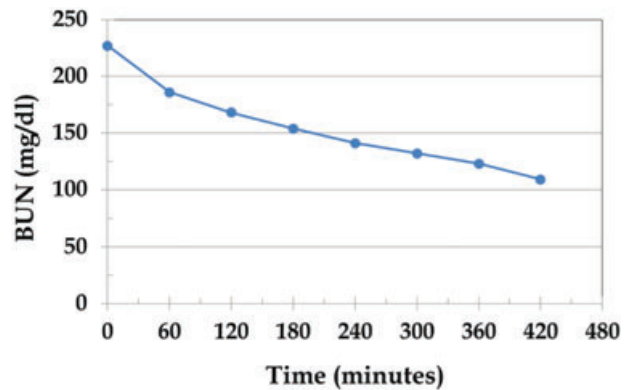


Figure 1: Changes in BUN before and during 420 minutes extended dialysis performed on a 2.9 kg cat with AKI secondary to ureteral obstruction. The dialysate based, diffusive treatment was performed on a Gambro Phoenix IHD hemodialysis platform modified with a slow-dialysate bypass adaptor to provide a dialysate flow (and urea clearance) of 3 mL/min.

monitoring can supply the water requirements for multiple IHD systems with relative portability.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy encompasses a variety of dialytic modalities depending on the prescribed treatment to provide a slow and continuous rate of solute and water removal over a prolonged period approaching 24 hours per day.^{3,6,24,34,41} These therapies have evolved to embrace the increasing severity of AKI recognized in critically ill human patients in the ICU setting who may not tolerate the physiologic and hemodynamic excursions associated with IHD.^{8,42} A variety of continuous modalities are used singularly or in combination to achieve the therapeutic goals. CRRT also incorporates all principles of solute and fluid removal but is founded primarily as a convective process with diffusion and adsorption contributing variably depending on the modality of therapy. The basic modality, continuous veno-venous hemofiltration (CVVH), is a purely convective therapy in which a fraction (usually 15–30%) of the blood volume passing through the hemofilter is ultrafiltered removing water and toxic solutes to a waste container at a rate between 20 and 45 mL/h/kg. The composition and volume of the blood (and body fluid volume and composition) are normalized by variable replacement of the ultrafiltered volume by a sterile commercially produced replacement solution of defined composition to achieve the net removal of toxic solutes and desired balance of normal solutes and water over the course of the treatment. The replacement solution can be added before the ultrafiltration process to minimize hemoconcentration and clotting in the hemofilter

or after the ultrafiltration process to maximize efficiency of the treatment. Continuous veno-venous hemodialysis (CVVHD) is a purely diffusive process conceptually similar to IHD using relatively slow blood and dialysate flow rates to promote continuous solute and water removal over an extended 24-hour period. Continuous veno-venous hemodiafiltration (CVVHDF) uses a combination of convective and diffusive modalities to exploit the removal of water and larger molecular weight solutes by the convective component and the efficiency of the diffusive component for small molecular weight solutes.

In distinction to IHD, CRRT modalities use sterile dialysate or replacement solutions that are commercially prepackaged rather than generated on-line. This eliminates the need for a source of purified water that makes the platform self-contained and generally portable. However, the requirement for large volumes of dialysate or replacement solution can be an economic constraint for some modalities and for treatment of large dogs.

Indications for RRT in Critical Care

The major application of dialytic therapy is the elimination of innumerable and unspecified solutes and fluid retained during renal failure that would otherwise be cleared by healthy kidneys. The management of AKI is the most common indication for RRT.^{1,20} The rapid accumulation of retained solutes with AKI intensifies expression of the clinical signs and metabolic disturbances compared to the uremia of chronic kidney disease. Prescriptions for RRT are prioritized to resolve hyperkalemia, profound azotemia, fluid imbalance, metabolic acidosis, persisting nephrotoxins, and to accommodate on-going therapies (eg, parenteral feeding) (Table 1).

In many circumstances, the therapeutic efficiency of RRT must be applied judiciously to prevent overtreatment. Correction of severe azotemia too rapidly heightens the risk of dialysis disequilibrium syndrome that may be fatal.²⁰ The risk of dialysis disequilibrium is especially accentuated in small animals with severe azotemia whose depuration volume (ie, the volume subjected to purification or clearance) is small relative to the efficiency or clearance capacity of extracorporeal therapy. With CRRT correction of the azotemia is performed gradually over a protracted 24–48-hour treatment interval. Delivery systems typically used for IHD are intrinsically more efficient than CRRT platforms and sometimes difficult to adapt to small animals requiring inefficient treatment. Nevertheless, it is possible to provide extended convective or diffusive hemodialysis sessions (8–12+ hours) equivalent to CRRT rates of clearance on a conventional human IHD platform. A dialysis treatment

Table 1: Indications for dialytic and extracorporeal therapies in animals

Acute kidney injury

1. Anuria or severe oliguria
2. Failure of conventional medical therapy to initiate an adequate diuresis
3. Failure of conventional therapy to control the azotemia, biochemical, or clinical manifestations of acute uremia
4. Life-threatening fluid overload
5. Life-threatening electrolyte (hyperkalemia, hyponatremia, hypernatremia) or acid-base disturbances
6. Severe azotemia—BUN > 80 mg/dL; serum creatinine > 8 mg/dL
7. Clinical course refractory to conservative therapy for 12–24 hours

Chronic kidney disease

1. Indefinite intermittent renal replacement therapy
2. Support for acute decompensation of chronic kidney disease
3. Finite renal replacement therapy for client transition to irreversible disease status
4. Bridge to and/or from staged kidney surgery (ie, ureteral obstruction, renal transplantation)

Miscellaneous

1. Severe overhydration, pulmonary edema, congestive heart failure
2. Acute poisoning/drug overdose (dialysis, hemoperfusion), ethylene glycol, NSAIDs, caffeine
3. Endogenous intoxications, ie, liver failure (hemoperfusion, MARS®)
4. Immune-mediated disease (therapeutic plasma exchange), myasthenia gravis, polymyositis, polyneuropathy, IMHA, ITP, rapidly progressive glomerulonephritis
5. Hyperproteinemia, ie, multiple myeloma (therapeutic plasma exchange)

promoting a urea reduction of less than 5% per hour of treatment has proven safe for animals of all sizes to prevent the adverse effects rapid correction of the azotemia when the blood urea nitrogen (BUN) concentration is > 107 mmol/L [300 mg/dL]^{20,43} When the BUN concentration is < 107 mmol/L [300 mg/dL], a schedule promoting 10% urea reduction per hour can be delivered safely. Consequently, the azotemia could be controlled completely and safely in 20–24 hours of continuous therapy or comparably in 2 sequential intermittent sessions of 8–10 hours on the first day to establish a urea reduction of 40–50% (Figure 1) followed with 3–6 hours of dialysis on the second daily session to eliminate the residual urea burden. It must be emphasized that evidence-based outcomes data are not available in animals to support the equivalency of these treatment regimens or the superiority of one over the other, but they can provide equivalent solute correction despite differences in treatment delivery. Regardless of the RRT platform, there is no alternative to providing a gradual and controlled rate of solute clearance delivered over an extended time interval for these high-risk patients.

A decision of considerable importance is when to transition from continuous to intermittent therapy for patients who remain dependent on RRT while the renal

injury is repairing. It can be challenging for patients to remain on continuous therapy for extended periods of time, and it is uncommon for animals with typical etiologies of AKI to recover sufficiently during a 1–3-day window of therapy that might be provided practically with continuous therapies. It is imperative the RRT program have practical and cost-effective contingencies for this transition, otherwise patients may be denied renal support of sufficient duration to permit repair of the renal injury and potential for recovery. To this end, a RRT program emphasizing CRRT for the initial (critical) phase of the AKI must also maintain a platform and personnel to provide intermittent therapy for all sizes of animals for indefinite periods of time. If only a single platform is to be available in an RRT program, it must be capable of providing practical and cost-effective modalities of renal replacement that are safe and efficient for all stages of the disease. In other words, is the available equipment equally capable to treat the critically azotemic and hemodynamically unstable cat and St. Bernard from presentation to discharge?

A fundamental requirement for all RRT indications is the ability to provide ultrafiltration to correct fluid overload produced by medical therapies to manage the AKI, fluids to support hemodynamics in critically ill animals, or fluids to support other comorbidities or multiorgan failure. Symptomatic hypotension during the delivery of RRT lingers as a persistent threat due to the small size of animal patients as well as the increasing requirement to treat animals with critical comorbidities. Better maintenance of hemodynamic stability is one of the expressed and historical foundations supporting selection of CRRT for critically ill human patients requiring RRT and fluid removal.^{3–8} This perception, however, has not been demonstrated convincingly, and many observational and randomized clinical human trials consistently failed to document such superiority.^{9,11–13,15–17,36} The maintenance of hemodynamic stability may not discriminate IHD versus CRRT platforms per se but rather reflect the prescription and delivery of therapy for the management of solute removal and fluid balance by ultrafiltration. The susceptibility to hypotensive events is influenced by body size, hydration status, the severity of the uremia, the presence of cardiac disease or comorbid conditions (eg, hemorrhage, anemia, sepsis, pancreatitis), and concurrent medications (eg, antihypertensives, diuretics). For cats and small dogs, the volume of the extracorporeal circuit should be as small as possible but may exceed 25–30% of the intravascular volume and cause hypovolemia as the circuit is filled. Once the extracorporeal circuit is established, however, the rate of blood flow through the circuit per se has little impact on blood pressure but will influence the intensity of diffusive and convective solute removal.

The rapid removal of plasma solutes in the early stages of a dialysis treatment can decrease intravascular volume and opposes refilling of the vasculature by fluid from the extravascular space. More importantly, excessive or rapid ultrafiltration that exceeds vascular refilling is the most frequent cause of hypovolemia and transient hypotension during RRT. Consequently, the intensity of the dialysis and ultrafiltration prescription has important influences on the hemodynamic stability of the patient. These influences are not necessarily the consequence of the RRT platform but rather the intensity of the prescription for ultrafiltration and solute removal formulated by the nephrologist or criticalist. Both platforms can be configured to provide appropriate and equivalent therapies if time and intensity of solute and fluid correction are recognized as critical operational parameters.

An indication of increasing importance is detoxification of animals subjected to accidental or malicious poisoning or acute drug over dosage. This use of extracorporeal therapy 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. An RRT modality is often suitable and effective if the toxicant has a low molecular weight (<1500 daltons), a small volume of distribution and minimal protein binding. For toxicants that do not match this profile, dialytic procedures may be minimally effective and should be combined or substituted with charcoal hemoperfusion or a selective adsorbent. Consideration also should be given to the efficiency of the extracorporeal platform used for the detoxification. For the majority of intoxications, the most expeditious elimination of the toxin is desired which may be constrained by CRRT modalities. For acute life-threatening intoxications (exogenous or endogenous, ie, hyperkalemia), IHD is the most appropriate and efficient blood purification modality. A partial list of removable toxins is outlined in Table 1 and elsewhere.^{29,33,44} Ethylene glycol (ie, antifreeze poisoning) is a common intoxication in companion animal practice, and it generally is possible to eliminate 90–95% or more of the toxin with a single intensive hemodialysis treatment.¹ Many other candidate toxins are emerging including barbiturates, salicylates, antimicrobials, antidepressants, chemotherapeutics, and especially nonsteroidal anti-inflammatory drugs (NSAID) that may be removed poorly by dialytic therapies and are more susceptible to hemoperfusion. Hemoperfusion represents an important extension of the extracorporeal therapies that can be provided when there are no effective or efficient therapeutic alternatives.

Extracorporeal removal of inflammatory mediators or endogenous toxins associated with sepsis or immune-mediated processes are potential indications for selective hemoperfusion techniques or therapeutic plasma

exchange (TPE). In veterinary medicine, preliminary efficacy has been demonstrated for myasthenia gravis and immune-mediated hemolytic anemia as examples for immune-mediated disorders.^{45–48} Acute liver failure, and more specifically hepatic encephalopathy also can benefit from extracorporeal procedures including charcoal hemoperfusion and molecular adsorbent recirculating systems (MARS) that provide “artificial liver” support.⁴⁹ In sepsis, Systemic Inflammatory Response and Multi-Organ Dysfunction Syndrome, RRT has been used for cytokines removal, although the indications and outcome benefit in humans are unclear⁵⁰ and there are no data in veterinary medicine. It is important to contact individual manufacturers about the possibility of TPE as specific CRRT and IHD platforms may have capacities for these options.

Programmatic Considerations for a New Program

Important issues to confront at the outset of establishing a RRT program are the components required to get the program operational and sustainable. Many times the decision to initiate a RRT program is based on frustrations associated with the existing gap in the ability of conventional medical therapy to adequately support the immediate or ongoing needs of the acutely uremic or intoxicated patient. This desire is bolstered by the attraction of available hardware and the exciting opportunities to embrace new and sophisticated therapies. Beyond these incentives, it is important to formulate a realistic plan that is programmatically sound, functional, and medically proficient.

A RRT program has impact on the entire hospital, including the ICU, the internal medicine and surgery services, the interventional radiology service (if available), and supportive services including radiology, nutrition, ultrasound imaging, laboratory services, pharmacy, and client services. It should be recognized also, that the calling for extracorporeal therapies typically occurs on a “feast or famine” basis. When active, a RRT programs may do > 300 treatments a year, whereas, at other times, a program may not be utilized for weeks at a time. Creation of a RRT program requires a hospital-wide commitment, as it is considerably more complex than the selection of a suitable extracorporeal platform and the acquisition of the equipment to process blood. A series of critical issues must be considered before the program is launched.

Therapeutic Goals

All decisions fundamentally must be directed to the therapeutic goals of the program. AKI is the most common indication for RRT, but these patients present sporad-

ically, and the program with the broadest therapeutic scope has the most potential to be programmatically sound and economically viable. Dialysis patients carry an overall poor prognosis associated with a 50–60% mortality for some etiologies of AKI in dogs and cats.^{21–24} These outcomes have potential to create a low morale and overall sense of futility among the general hospital staff. However, without RRT the 40–50% who survive would have been included among the mortality statistics. Other indications for extracorporeal blood purification including acute intoxications and immune-mediated diseases appear to have better prognoses and promote a sense of “magic” regarding the procedures. Programs should have the capacity to effectively and safely treat patients from 2 to 70 kg that represent the size spectrum presented to small animal practice. In addition, capability for indefinite extracorporeal support beyond the initial 2–3 days of critical presentation must be available for patients presenting for AKI. The calling for finite periods of intermittent hemodialysis for animals with chronic kidney disease is uncommon but provides important opportunities to refine and extend the therapeutic expertise of the program, bolsters revenues, and should be considered in program development. Beyond the management of uremia, the value of an extracorporeal therapy program increases if it is equally capable to support multiple modalities of blood purification including hemoperfusion and potentially therapeutic plasma exchange for acute intoxications and immune-mediated diseases, respectively.

Professional Expertise

There have been profound technological advances in the design of equipment for RRT in the past 2 decades to facilitate safety and the interface between the doctor, the patient, and the delivery system. Yet, extracorporeal therapies remain technically complex, professionally demanding, and physiologically and metabolically challenging for the patient. The delivery of extracorporeal RRT is not readily mastered by the untrained, self-taught, or the casual RRT practitioner, regardless of the perceptive simplicity of the platform or the provided in-service training. Operational familiarity with the setup and functionality of the delivery system, whether it is a CRRT or an IHD platform, can be learned sufficiently in a matter of a few practice sessions. However, this is the least complicated and least important aspect of the delivery of extracorporeal therapy. Beyond operation of the machine, one must also master the establishment and maintenance of vascular access, understanding of materials biocompatibility, anticoagulation, dialysis efficiency and kinetics, and critical care nephrology. The clinician supervising a new RRT program should seek

training opportunities at an established extracorporeal program to more fully understand the complexities of this sophisticated therapeutic modality and to acquire the therapeutic standards and quality assurance required for the delivered care. Unfortunately, formal training opportunities are sparse and may require commitments from 6 months to 2 years. Many authorities in veterinary RRT programs recommend active participation in at least 100 RRT treatments as the minimum experience for competency with these procedures. Beyond the mechanics and procedures of prescribing RRT, the attending clinician must have an advanced understanding of nephrology that is generally beyond the training and expertise of the internal medicine or critical care specialists. Be assured, the stewards of extracorporeal RRT take great delight in the current recognition, perceived need, and increasing demand for this discipline; however, the increasing number of evolving RRT programs throughout the world has raised real concerns about the consistency of the expertise and quality of *de novo* programs that have not been exposed to critical training or a minimum of experience. There is increasing recognition that quality assurance standards should be established for the delivery of RRT in combination with certification to recognize individuals and programs that have acquired an advanced standard of expertise.

During RRT sessions performed on critically ill and unstable patients, a clinician is usually warranted in attendance during the entire treatment to consult on the indications, timing, and modality of treatment; to establish vascular access; to generate the dialysis prescription and implement the treatment plan; and troubleshoot both the patient and the equipment. In case of CRRT, clinical coverage extends for 24 hours per day, and minute-to-minute monitoring is required. Beyond active treatments, a RRT program must maintain contingencies for 24-hour emergency coverage for every day of the year. These clinical demands mandate a professional team of at least 2 clinicians with appropriate expertise and experience in the discipline.

Technical expertise

The hemodialysis technician is the cornerstone of every RRT program. Programmatic commitment to technical expertise should be established at the outset of starting any program. Next to the professional expertise, the dialysis technician is the most important component of the program and will require comparable competency and patient experience. The safety and minute-by-minute monitoring of the treatment as well as the overall management and maintenance of the delivery systems is overseen by the dialysis technician. These are responsibilities that require extensive training, experience,

and on-going practice. They cannot be assigned justifiably to technicians (students or house officers) with primary competencies in other areas of nursing or critical care. This has considerable relevance to the delivery of CRRT where the treatment will likely span multiple shifts of nursing staffing, all of whom should share comparable competency.

If the RRT platform is part of the “regular” ICU, the ICU technicians who help run the platform with the clinician must all possess appropriate competencies to perform the dialytic procedures and maintain a technician/patient ratio of 1:1. This likely will increase the need for an “on-call” schedule to cover subsequent dialysis shifts and the remainder of the ICU responsibilities and the overall number of technicians needed for the ICU. The CRRT nursing staff must be prepared for consecutive 24-hour shift commitments to deliver a treatment that is likely to extend continuously over multiple days. The “demand” on manpower probably doubles, requiring 2–3 technicians, some of whom may be paid extra due to overnight or overtime rates. The same issue is relevant to a lesser extent for PIRRT treatments delivered on IHD sessions that may extend beyond 6–8 hours for the first treatment. A PIRRT treatment can be delivered reasonably by a single technician with a slightly prolonged initial shift who still can be prepared for a subsequent treatment and normal shift the following day. There also is unquestioned need for a training and certification requirement for IHD and CRRT technicians to assure competency for the skill set required for the discipline.

Physical space

The dialysis environment should be quiet and distinct from the fast pace, intermittent loud noises, and risk for infectious agents associated with the ICU if possible. As the spectrum of patients requiring RRT shifts to those with more critical care requirements, the proximity of the “dialysis unit” to the ICU will become more important and may warrant appropriate accommodation of space within the ICU.²² The IHD platform generally requires a dedicated space to accommodate the piping for the inlet water and drain requirements. Additional space with inlet water and a drain is required for the water purification system that is preferably located in an isolated location in close proximity to the treatment area. The CRRT platform theoretically is portable and can be used at the “cageside” but is bulky enough to mandate a dedicated space when in use.

Storage space is a consistently overlooked requirement of any RRT program. All RRT platforms require ready access to a variety of bulky and heavy supplies (multiple dialysate concentrates, CRRT replacement

solutions, dialyzers and tubing sets, and CRRT cartridges), and adequate storage should be provided a high priority in program planning.

Ancillary equipment

The RRT program requires its own dedicated patient monitoring and ancillary equipment as required in the "classic" ICU. If the ICU monitoring equipment is "shared" with the RRT program, it will not be available for the rest of the ICU when utilized for RRT necessitating duplication of these equipment requirements. Although some equipment sharing by the RRT program and the ICU (eg, blood gas machine or point-of-care chemistry analyzer) is effective, it requires a means to transfer specimens if the programs are not colocated. Guidelines for equipment requirements for an the RRT program have been published.⁵¹ Some equipment requirements distinctive or specialized for RRT include: a patient-side coagulation monitor (ACT II by Medtronic, Coag DX) and inline blood volume monitoring (CritLine, HemaMetrics).^{1,51}

Extracorporeal RRT Platform

Perhaps the most polarizing and controversial decision concerning a veterinary RRT program is the appropriate platform or machinery to acquire. Veterinary RRT evolved from the historical foundations of IHD that has suited the needs of veterinary critical care nephrology at its current state-of-the-art for nearly a half century. The evolving attraction of veterinary critical care programs to follow lockstep with counterpart human programs and embrace CRRT needs thoughtful and unemotional consideration. CRRT has evolved in the human ICU as a niche RRT therapy to address unique and precise therapeutic requirement associated with the changing pathogenesis and clinical presentation of AKI in the ICU associated with sepsis, shock, and multiple organ dysfunction.^{3,8,42} In light of the lack of documented superiority of this platform the question must be asked, is the scope of veterinary critical care nephrology equivalent to critical care nephrology experienced in the human ICU? There is little doubt veterinary therapeutics are becoming more complex and sophisticated, and the pathogenesis of AKI in animals is broadening to include sepsis, shock, and hemodynamic instability. Yet, in total, these represent a small minority of animal patients requiring RRT that today mostly involves infectious, toxic, obstructive, and metabolic pathogeneses.

Ideally, a veterinary RRT program should incorporate the professional expertise, staff, commitment, and equipment to appropriately address these traditional indications for RRT, simultaneously prepare and meet the

emerging trends in veterinary critical care nephrology, and embrace other forms of blood purification including hemoperfusion and therapeutic plasma exchange. For regional programs, and especially those without an academic mandate, the resources to acquire and maintain the multiple platforms required to provide these disparate therapies are extremely problematic. For programs operating a singular extracorporeal platform, it should be one with the greatest flexibility for the spectrum of veterinary therapeutics while maintaining compatibility with the infrastructure of the hospital.

Intermittent Hemodialysis Platform

For some authorities, IHD currently represents the most appropriate choice for a singular extracorporeal platform for veterinary medicine. Current IHD equipment has been uniquely applicable for the routine nephrological indications that include AKI, chronic kidney disease, broad-spectrum intoxications, fluid overload, and hemoperfusion. In addition, the current systems on most IHD machines can be configured to perform intermittent dialytic and convective prescriptions on all sizes of animal patients. Creative prescription of the dialysis treatment, facilitated by an understanding of the fundamentals of dialysis kinetics and the systems design and operation of the delivery system, permit the safe, and effective delivery of dialysis for any clinical presentation. The IHD platform also can be configured to perform consistent and exceedingly slow (CRRT-like) dialysate-based diffusive treatments with urea clearances as low as 1.0 mL/min at any appropriate rate of ultrafiltration for extended session lengths required for critical patients with addition of a simple, external slow dialysate bypass modifications to the machine (Cowgill, personal observation) (Figure 2). This slow dialysate bypass loop, maintains all the functionality, safety, and patient monitoring configured into the IHD systems and permits PIRRT or sustained low-efficiency daily dialysis treatment intensities while maintaining fast blood flow rates to minimize clotting and anticoagulation requirements of the in the extracorporeal circuit. As the patient emerges from extended dialysis requirements, it can be transitioned to an indefinite IHD protocol on the same platform. The IHD machine is not designed to perform convective prescriptions as precisely as a CRRT machine in CVVH modality, but a purely convective, PIRRT treatment could be provided if there were indication for such therapy.

Conventional IHD platforms have a variety of circuit configuration, monitoring and operational modalities generally not available with CRRT machines including: blood volume monitoring, dialysate, and ultrafiltration profiling, on-line ionic dialysance for real-time kinetic modeling and performance monitoring, and

- patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant* 2009; 24:512–518.
14. Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163.
 15. Misset B, Timsit JF, Chevret S, Renaud B, Tamion F, Carlet J. A randomized cross-over comparison of the hemodynamic response to intermittent hemodialysis and continuous hemofiltration in ICU patients with acute renal failure. *Intensive Care Med* 1996; 22:742–746.
 16. Rauf AA, Long KH, Gajic O, Anderson SS, Swaminathan L, Albright RC. Intermittent hemodialysis versus continuous renal replacement therapy for acute renal failure in the intensive care unit: an observational outcomes analysis. *J Intensive Care Med* 2008; 23:195–203.
 17. Uehlinger DE, Jakob SM, Ferrari P, et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20:1630–1637.
 18. Vinsonneau C, Jakob SM, Ferrari P, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006; 368:379–385.
 19. Zarbock A, Singbartl K, Kellum JA. Evidence-based renal replacement therapy for acute kidney injury. *Minerva Anestesiol* 2009; 75:135–139.
 20. Cowgill LD, Francey T. Hemodialysis and extracorporeal blood purification, In: SP DiBartola ed. *Fluid Therapy in Small Animal Practice*, St. Louis, MO: Elsevier; 2011.
 21. Cowgill LD, Langston C. Acute kidney disease, In: J Bartges, Polzin D. eds. *Nephrology and Urology of Small Animals*, Hoboken, NJ: Wiley-Blackwell; 2011.
 22. Depner TA. Hemodialysis adequacy: basic essentials and practical points for the nephrologist in training. *Hemodial Int* 2005; 9:241–254.
 23. Sargent JA, Gotch F. Principles and biophysics of dialysis, In: Maher JF. ed. *Replacement of Renal Function by Dialysis: A Textbook of Dialysis*, Boston, MA: Kluwer Academic Publishers; 1989, pp. 87–143.
 24. Acierno MJ. Continuous renal replacement therapy in dogs and cats. *Vet Clin North Am Small Anim Pract* 2011; 41:135–146.
 25. Huang Z, Letteri J, Ronco C, Clark WR. Basic principles of solute transport, In: Kellum J, Bellomo R, Ronco C, eds. *Continuous Renal Replacement Therapy*, New York, NY: Oxford University Press; 2009, pp. 25–32.
 26. Borkan SC. Extracorporeal therapies for acute intoxications. *Crit Care Clin* 2002; 18:393–420, vii.
 27. Holubek WJ, Hoffman RS, Goldfarb DS, Nelson LS. Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int* 2008; 74:1327–1334.
 28. Shalkham AS, Kirrane BM, Hoffman RS, Goldfarb DS, Nelson LS. The availability and use of charcoal hemoperfusion in the treatment of poisoned patients. *Am J Kidney Dis* 2006; 48:239–241.
 29. Smith JP, Chang JJ. Extracorporeal treatment of poisoning, In: Taal MW, Marsden PA, Skorecki K, Yu ASL, Brenner BM. eds. *Brenner and Rector's The Kidney*, Philadelphia, USA: Elsevier/Saunders; 2012, pp. 2411–2431.
 30. Chandy T, Sharma CP. Activated charcoal microcapsules and their applications. *J Biomater Appl* 1998; 13:128–157.
 31. Chalhoub S, Langston CE, Poeppel K. Vascular access for extracorporeal renal replacement therapy in veterinary patients. *Vet Clin North Am Small Anim Pract* 2011; 41:147–161.
 32. Cowgill LD, Francey T. Hemodialysis, In: SP DiBartola ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*, Philadelphia, PA: Saunders/Elsevier; 2006, pp. 650–677.
 33. Fischer JR, Pantaleo V, Francey T, Cowgill LD. Veterinary hemodialysis: advances in management and technology. *Vet Clin North Am Small Anim Pract* 2004; 34:935–967, vi–vii.
 34. Ronco C, Ricci Z. Renal replacement therapies: physiological review. *Intensive Care Med* 2008; 34:2139–2146.
 35. Yeun JY, Ornt DB, Depner TA. Hemodialysis, In: Taal MW, Marsden PA, Skorecki K, Yu ASL, Brenner BM. eds. *Brenner and Rector's The Kidney*, Philadelphia, PA: Elsevier/Saunders; 2012, pp. 2294–2346.
 36. Vanholder R, Van Biesen W, Hoste E, Lameire N. Pro/con debate: continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish? *Crit Care* 2011; 15:204.
 37. Fieghen HE, Friedrich JO, Burns KE, et al. The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury. *BMC Nephrol* 2010; 11:32.
 38. Kielstein JT, Schiffer M, Hafer C. Back to the future: extended dialysis for treatment of acute kidney injury in the intensive care unit. *J Nephrol* 2010; 23:494–501.
 39. Kumar VA, Craig M, Depner TA, Yeun JY. Extended daily dialysis: a new approach to renal replacement for acute renal failure in the intensive care unit. *Am J Kidney Dis* 2000; 36:294–300.
 40. Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK. Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 2001; 60:777–785.
 41. Ricci Z, Ronco C. Dose and efficiency of renal replacement therapy: continuous renal replacement therapy versus intermittent hemodialysis versus slow extended daily dialysis. *Crit Care Med* 2008; 36(4 Suppl):S229–S237.
 42. Bobek I, Ronco C., History and rationale for continuous renal replacement therapy, In: Kellum JA, Ronco C. eds. *Continuous Renal Replacement Therapy, USA: Oxford University Press; 2009, pp. 11–17.*
 43. Langston CE, Cowgill LD, Spano JA. Applications and outcome of hemodialysis in cats: a review of 29 cases. *J Vet Intern Med* 1997; 11:348–355.
 44. Cutler RE, Forland SC, Hammond PG, Evans JR. Extracorporeal removal of drugs and poisons by hemodialysis and hemoperfusion. *Annu Rev Pharmacol Toxicol* 1987; 27:169–191.
 45. Matus RE, Gordon BR, Leifer CE, Saal S, Hurvitz AI. Plasmapheresis in five dogs with systemic immune-mediated disease. *J Am Vet Med Assoc* 1985; 187:595–599.
 46. Matus RE, Schrader LA, Leifer CE, Gordon BR, Hurvitz AI. Plasmapheresis as adjuvant therapy for autoimmune hemolytic anemia in two dogs. *J Am Vet Med Assoc* 1985; 186:691–693.
 47. Bartges JW, Klausner JS, Bostwick EF, Hakala JE, Lennon VA. Clinical remission following plasmapheresis and corticosteroid treatment in a dog with acquired myasthenia gravis. *J Am Vet Med Assoc* 1990; 196:1276–1278.
 48. Palm CA, Cowgill LD, Dickinson PJ, Sturges BK. Therapeutic apheresis: a novel treatment for myasthenia gravis in dogs. In: *Proceedings ACVIM Forum; 2011: Denver, CO, USA.*
 49. Shinozaki K, Oda S, Abe R, Tateishi Y, Yokoi T, Hirasawa H. Blood purification in fulminant hepatic failure. *Contrib Nephrol* 2010; 166:64–72.
 50. Joannidis M. Continuous renal replacement therapy in sepsis and multisystem organ failure. *Semin Dial* 2009; 22:160–164.
 51. Poeppel K, Langston CE, Chalhoub S. Equipment commonly used in veterinary renal replacement therapy. *Vet Clin North Am Small Anim Pract* 2011; 41:177–191.
 52. Berbece AN, Richardson RM. Sustained low-efficiency dialysis in the ICU: cost, anticoagulation, and solute removal. *Kidney Int* 2006; 70:963–968.
 53. Faese S, Jakob SM, Kalicki R, Frey FJ, Uehlinger DE. Treatment of acute renal failure in the intensive care unit: lower costs by intermittent dialysis than continuous venovenous hemodiafiltration. *Artif Organs* 2009; 33:634–640.