VETERINARY
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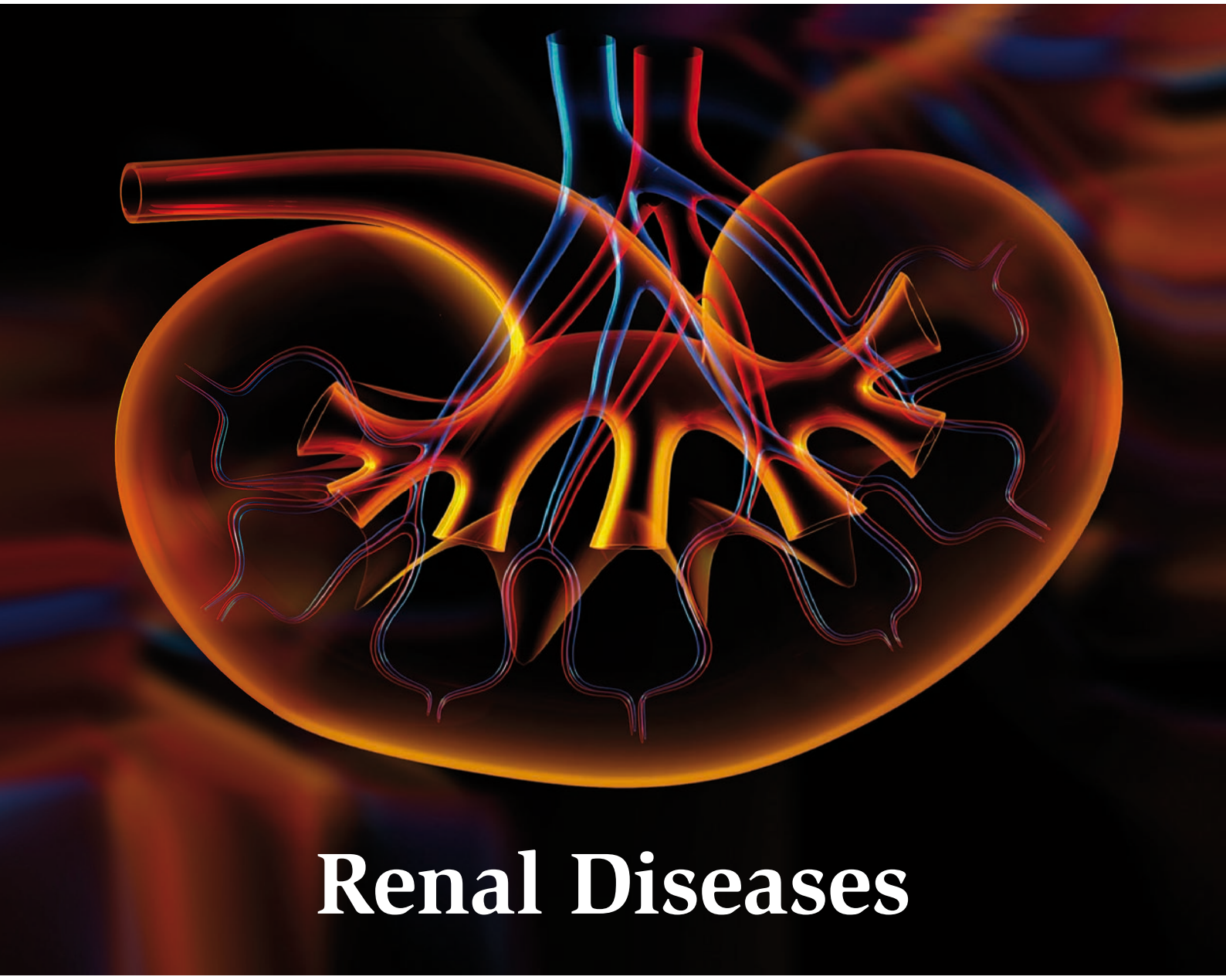
The worldwide journal for the companion animal veterinarian



Renal Diseases

Hemodialysis in dogs • Feline genetically-linked renal disease • Dealing with ureteral obstructions • Epidemiology of CKD • Infectious renal disease in dogs • Biomarkers for early diagnosis of feline chronic kidney disease • Nutritional management in feline kidney disease • Diagnostic implications of proteinuria

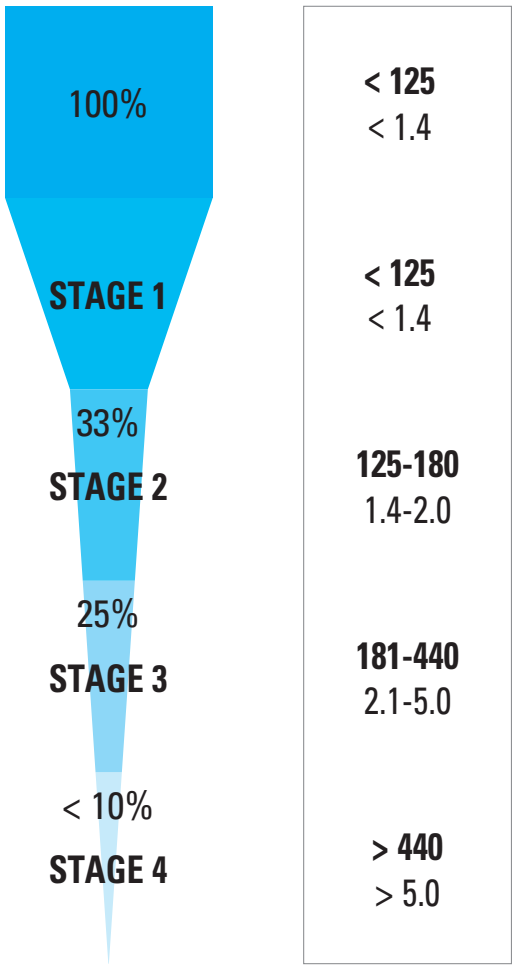
ROYAL CANIN

IRIS International Renal Interest Society

DOGS

Staging system for chronic kidney disease (CKD)

STEP 1. Staging is initially based on fasting blood creatinine assessed on at least two occasions in the stable patient. Blood creatinine concentrations apply to average size dogs - those of extreme size may vary.



Comments

History suggests the animal is **AT RISK** of developing CKD in the future due to a number of factors (*e.g.,* exposure to nephrotoxic drugs; breed; high prevalence of infectious disease in the area).

Nonazotemic. Some other renal abnormality present (*e.g.*, inadequate urinary concentrating ability without identifiable nonrenal cause, abnormal renal palpation or renal imaging findings, proteinuria of renal origin, abnormal renal biopsy results, increasing blood creatinine concentrations in samples collected serially).

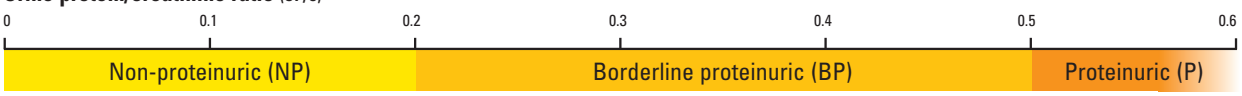
Mild renal azotemia (lower end of the range lies within reference ranges for many laboratories, but the insensitivity of creatinine concentration as a screening test means that animals with creatinine values close to the upper reference limit often have excretory failure). Clinical signs usually mild or absent.

Moderate renal azotemia.
Many extrarenal clinical signs may be present.

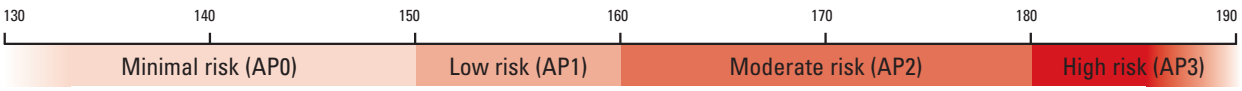
Severe renal azotemia.
Increasing risk of systemic clinical signs and uremic crises.

STEP 2. Cases are then sub-staged based on proteinuria and blood pressure.
Note that UP/C and blood pressure vary independently of each other and the stage of CKD, so that any level of proteinuria or hypertension can occur at any stage of CKD *i.e.,* at any level of azotemia.

Urine protein/creatinine ratio (UP/C)



Risk of end organ damage from hypertension (Systolic blood pressure mmHg)



Adapted from the Manual of Canine & Feline Nephrology & Urology (Fig: 5.5) 2nd Edition edited by J. Elliott & G. Grauer (2006) in accordance with IRIS Staging of CKD, 2013.
*The relative percentages of residual function are conceptual estimates only.

Supported by Novartis Animal Health Inc.

Based on IRIS Staging of CKD, 2013.

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20070002-01

VETERINARY focus

ROYAL CANIN

EDITORIAL

Recognition of the importance of the kidney for normal physiological function is a relatively recent event, although there is perhaps a pleasing correlation that the body's main organ tasked with purifying the blood was chosen specifically as a sacrificial offering for cleansing in Biblical times. The Old Testament also notes that the kidneys were regarded as the site of temperament, emotions, prudence, vigor, and wisdom, and the kidneys and heart were thought to be the organs examined by God to judge an individual.

However, other ancient civilizations seem to have taken the kidneys to be not only less important than the heart but also the liver, lungs and intestines. Scholars may argue that this was because, with their retroperitoneal location, the kidneys were not easily visualized, or simply because their function was obscure. This seems to concur with the teachings of Aristotle, the Greek philosopher and polymath, who treated the organs dismissively - from his observations on animals he concluded that the kidneys were not essential to life, and believed that their function was to anchor the blood vessels in the body, and to secrete, rather than eliminate, fluid. Nevertheless he realized that they could be the source of disease - he considered renal fat to be the cause of cancer and gangrene, and in his text *De Partibus Animalium* (*On the Parts of Animals*), written around 350 BC, he noted that "very often the kidneys are found to be full of stones, growths, and small abscesses". More than two thousand years later we know a bit more about kidney structure, function and pathology, and recognize that they are indeed vital to an animal's well-being, and whilst this issue of *Veterinary Focus* does not claim to have the authority of Biblical teachings or a philosopher's insight, we anticipate that it will offer the reader wisdom and learning regarding the kidney and its diseases.

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Printed in the European Union
ISSN 1354-0157
Circulation: 80,000 copies
Legal deposit: November 2013
Cover: Shutterstock

Veterinary Focus is also published in French, German, Chinese, Italian, Polish, Spanish, Japanese & Russian.

ROYAL CANIN

A practical approach to hemodialysis for canine renal disease

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Dr. Lippi graduated with first-class honors from the University of Pisa in 2006 and was the recipient of the SCIVAC-Pfizer Animal Health award the following year; this allowed her to spend some time with the Feline Internal Medicine Service at Bristol University in the UK before moving to UC Davis in 2010 for hemodialysis training. She was awarded her PhD in 2011 for a research project on early diagnostic and prognostic markers of CKD in cats and dogs. Dr. Lippi currently works in the Hemodialysis and Blood Purification Service (CEPEV) of the Department of Veterinary Sciences at Pisa University. Her main areas of interest are nephrology, urology and hemodialysis.

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KEY POINTS

- **Modern technology means that hemodialysis is now not only feasible but is safe, efficacious, and indispensable for the management of animals with life-threatening uremia.**
- **Hemodialysis may be provided either as intermittent or continuous therapy. In both situations azotemic blood is pumped through a dialyzer, where solute and water exchange occurs, before clean blood is returned to the patient.**
- **The movement of molecules across the dialysis membrane is primarily driven by two forces: diffusion and convection.**
- **Various factors must be considered when selecting a dialysis protocol for each patient.**
- **It is essential to ensure blood coagulation does not occur during dialysis; various methods may be employed to prevent this from happening.**

Introduction

Although considered the standard of care in human medicine, hemodialysis (HD) as a management option for animals with significant kidney disease continues to have limited availability. Only within the last decade has hemodialysis become increasingly available and it is now offered in many countries. Traditionally, intracorporeal dialytic therapies (*i.e.* peritoneal dialysis) have been used to manage patients with severe acute kidney disease. However, where available, extracorporeal renal replacement therapies (ERRT) are now preferred due to improved patient outcomes as well as logistical factors (1,2). Although patient size may be a limiting factor, as it employs equipment designed for humans ***(Figure 1)***, ERRT hemodialysis is now a successful therapy within veterinary medicine (2).

ERRT may be provided as intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT) ***(Figure 2)***. Although they differ in execution, both methods rely on the same physiologic principles. Once vascular access has been established, typically via a jugular catheter, the patient is connected to the extracorporeal circuit. The dialysis machine regulates the flow of blood

within the closed circuit, so that the azotemic ("contaminated") blood is pumped from the patient and through the dialyzer, where solute and water exchange occurs before the "clean" blood is returned to the patient ***(Figure 3)***. The amount of blood passing through the dialyzer is dictated by various factors; during a typical dialysis session, the patient's entire blood volume may be processed many times (3).

Principles of hemodialysis

The dialyzer (artificial kidney) represents the cornerstone of ERRT. Within the dialyzer, blood and dialysate are separated by a semi-permeable membrane, which allows the free passage of water and small size molecules (typically < 500 Da). The movement of molecules across the membrane is primarily driven by two forces: diffusion and convection.

- Diffusive transfer of solute relies on particle movement through the membrane from higher to lower concentration. Once equilibrium has been achieved, there is no net change in the solute concentration on either side of the membrane (1); however, constant replenishment of fresh dialysate within the dialyzer prevents equilibrium from being established, thus maintaining active diffusion (3). The efficiency of diffusion is further increased by using a countercurrent system between blood and dialysate flow that maximizes the concentration gradient (4). A major factor in the process is a compound's molecular weight, which is inversely related to the rate of diffusion, so that small solutes like urea (60 Da) diffuse more readily than larger molecules such as creatinine (113 Da). The size of the membrane pores limits the movement of larger solutes, plasma proteins, and cellular components of blood.

- Convective transfer of solute uses ultrafiltration, whereby water is driven through the dialyzer membrane using hydrostatic gradients. Solutes dissolved in the water are swept through the membrane by a process called solvent drag (1,5,6). Although convective transport influences the clearance of large molecules with limited diffusibility, during standard hemodialysis its contribution to total solute removal is usually < 5%. The main reason for using ultrafiltration during standard hemodialysis is the regulation of fluid removal; if it is used as the primary method of blood purification the process is known as hemofiltration. To achieve adequate solute clearance using convection, ultrafiltration can be significantly increased (> 35 mL/kg/h), while maintaining the patient's blood volume with replacement intravenous

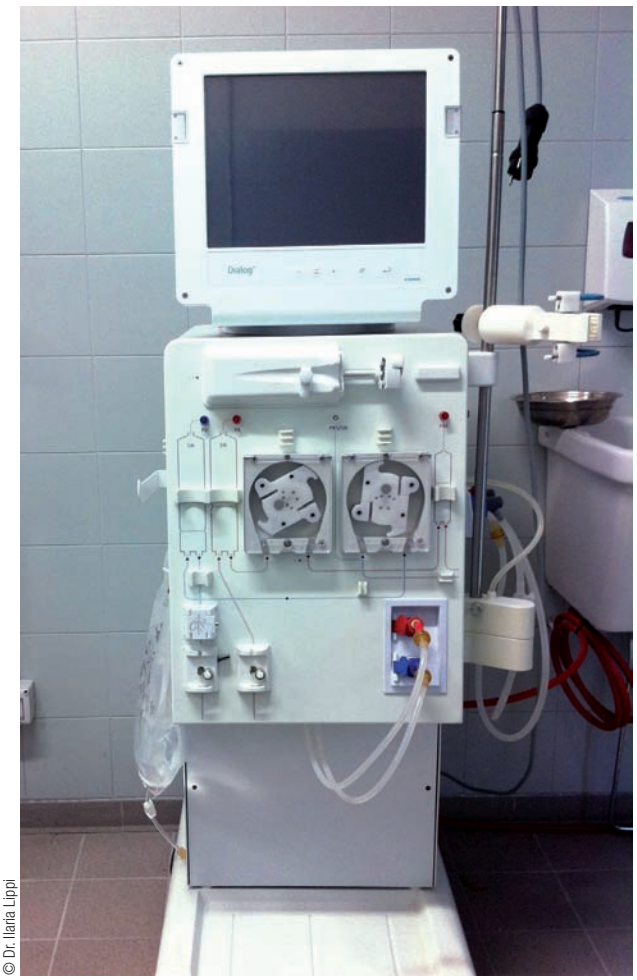

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Figure 1. A typical renal dialysis unit suitable for IHD therapy.

Figure 2. A CRRT machine is a very flexible platform for extracorporeal therapies, offering a wide spectrum of different treatment options.

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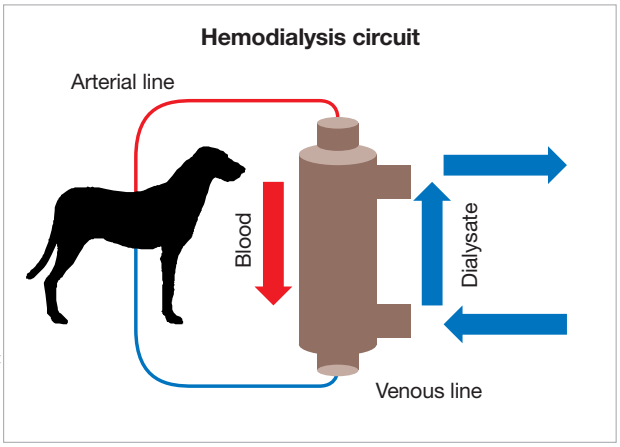

Figure 3. Schematic representation of a hemodialysis circuit.

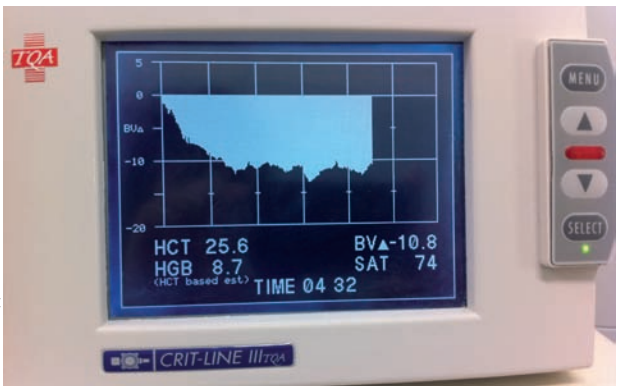

Figure 4. Blood volume must be monitored during hemodialysis treatment.

fluids ***(Figure 4)*** which can either be administered separately or within the dialyzer circuit (1-6).

Convective transport does not require a concentration gradient across the membrane and does not generate diffusion gradients or alter serum concentrations. The transmembrane hydrostatic pressure gradient, the hydraulic permeability, and the surface area of the membrane determine the rate of ultrafiltration and solute transfer. During ultrafiltration the transmembrane pressure generated by the blood pump initiates and controls the rate and volume of ultrafiltrate.

Overall, the net removal of uremic solutes is influenced by: (i) the concentration gradient for diffusion, (ii) the diffusivity of the solute, (iii) the permeability characteristics and surface area of the membrane, (iv) the blood and dialysate flow within the dialyzer, (v) the duration of dialysis, (vi) the distribution volume of the solutes, and (vii) the amount of ultrafiltration.

Very large or protein-bound molecules cannot be removed by standard hemodialysis, but may be eliminated using hemoperfusion (4) which involves passing blood through a device containing absorbent particles (most commonly activated charcoal) which removes molecules from circulation by competing with plasma proteins. This technique is much more efficient than HD in clearing protein-bound compounds and lipid-soluble drugs. A list of drugs and molecules that can be cleared by hemodialysis is available online (7).

Indications for hemodialysis

Acute kidney injury

In veterinary medicine the most frequent indication for hemodialysis is acute kidney injury (AKI); there are various etiologies, but exposure to exogenous and endogenous nephrotoxins causes most AKI in dogs. The majority of animals presented for HD are acutely uremic and non-responsive to attempted diuresis with intravenous fluids and pharmacologic manipulation; many are volume overloaded from attempted diuresis in the face of oliguria and may have life-threatening hyperkalemia. HD rapidly mitigates hyperkalemia and can restore fluid balance, thus stabilizing the patient and allowing time for renal function to recover. HD should be initiated when the clinical consequences of the uremia cannot be managed effectively with medical therapy alone.

Chronic kidney disease

Hemodialysis is also effective for the management of animals with end-stage chronic kidney disease (CKD), although cost and limited availability restricts its use. Hemodialysis can ameliorate the azotemia, electrolyte, mineral and acid-base disorders, and systemic hypertension that complicate CKD, and such animals really require HD indefinitely, but many owners desire short periods of dialytic support to adjust emotionally to the inevitability of the animal's disease. Animals supported with hemodialysis still require comprehensive medical therapy, but the prolonged survival it affords will often promote other manifestations of chronic kidney disease (hyperkalemia, fluid retention, renal osteodystrophy, and refractory hypertension) rarely identified in animal patients managed solely with medical therapy.

Hemodialysis is also used frequently in the peri-operative management of candidates for renal transplantation, as many such animals have complicated factors such as

Table 1. Comparison of intermittent hemodialysis and continuous renal replacement therapy.

Intermittent hemodialysis	
Advantages • Suitable for the management of acute and chronic patients • Relatively short treatment time • Low cost of disposables	**Disadvantages** • Higher risk of hemodynamic disturbances • High cost of water treatment system • Need for high blood flow rates • Trained medical staff required for duration of treatment
Continuous renal replacement therapy	
Advantages • Hemodynamically well tolerated • Better physiologic control of azotemia, electrolyte and acid-base disorders • Separate water purification system not required • Portable machines allow cage-side therapy	**Disadvantages** • High cost of pre-packaged dialysate • High cost of disposables • Long (or continuous) treatment time • Trained medical staff required for duration of treatment • Not suitable for the management of chronic patients

anemia, and metabolic disorders that would preclude surgical success. Brief pre-surgical hemodialysis sessions will help manage the uremia and stabilize the recipient while an appropriate donor animal is sought, whilst post-transplantation hemodialysis can support the recipient during periods of delayed graft function, revision of technical or surgical complications, acute rejection, or pyelonephritis (3).

Acute intoxications

Dialytic techniques are uniquely suited to the management of specific acute toxicoses. Drugs and chemicals with physical characteristics that permit passage through dialyzer membrane pores and which are not bound to plasma proteins can be quickly and efficiently removed from the bloodstream, often with a single HD session. The benefits include the ability to remove toxins that are already absorbed from the gut lumen, removal of substances that do not adhere to enteric activated charcoal, and the fact that both the parent compound and active toxic metabolites can be removed. Hemodialysis is indicated for the treatment of common poisonings including ethylene glycol, methanol, salicylate, ethanol, phenobarbital, acetaminophen, theophylline, aminoglycosides and many others.

Fluid overload

Overhydration, resulting in systemic hypertension, ascites, peripheral and pulmonary edema, plural effusion, and congestive heart failure is a common complication of aggressive fluid therapy in animals with kidney injury. Circulatory overload may be life-threatening and may not resolve with conventional therapy in oliguric animals. Overhydration is a consistent feature of end-stage renal disease when animals have insufficient excretory ability to eliminate intravenous or subcutaneous fluid treatments, oral fluid supplements, or dietary water. These excessive fluid loads can be readily removed by the ultrafiltration capability of hemodialysis.

IHD *versus* CRRT

The pros and cons of both systems are set out in ***Table 1***. By definition, IHD is based on intermittent treatments of limited duration (generally 4-5 hours 2 to 3 times a week) which may be adjusted according to the patient's requirements. IHD is used in the treatment of both AKI and CKD patients and can be utilized for correcting many other pathological conditions such as electrolyte disorders and fluid overload. CRRT is mainly indicated for treating AKI patients. Whereas traditional IHD primarily uses diffusion for solute clearance, CRRT utilizes both diffusion and convection. CRRT is generally more efficient in removing larger molecules but relies upon a slow continuous treatment for a more physiologic reduction of uremic toxins (4,6). The patient must be attached to the machine almost continuously (23+ hours each day).

Vascular access for HD

Regardless of the method used, an appropriate and well-functioning vascular access is essential for delivery of a large and continuous flow of blood through the extracorporeal circuit. The choice of catheter, placement,

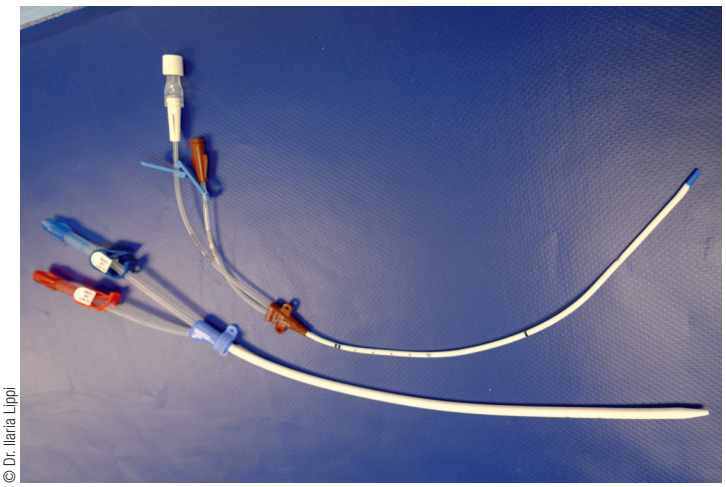

Figure 5. Temporary central venous catheters designed for hemodialysis.

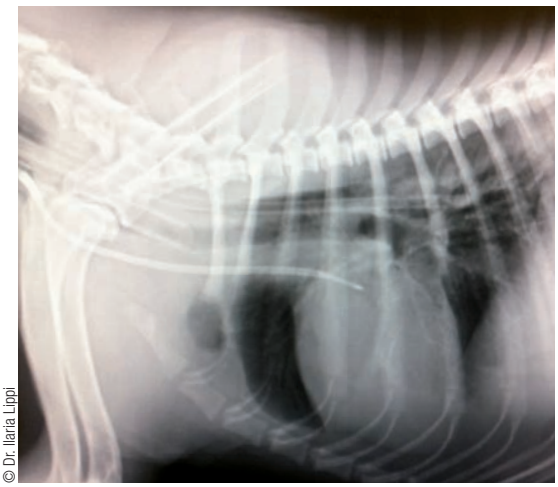

Figure 6. Placement of the hemodialysis catheter must be assessed by radiography.

and long-term management can affect the catheter performance, which directly influences the ability to deliver high quality treatment.

Catheter choice

Catheter choice is strongly influenced by a patient's size, the catheter material and the expected duration of use. As a general rule, it is advisable to use the largest catheter that may be safely placed in the jugular vein; blood flow, which is proportional to the catheter diameter and inversely proportional to its length, should be maximal (3). A 7-8 Fr catheter is generally suitable for a small dog, whereas a 12-14 Fr will suit a medium or large dog; the catheter should be composed of a material that is minimally thrombogenic and non-irritant for the vessel.

Dual-lumen catheters are the most common design used in dogs, allowing simultaneous removal and return of blood to the patient. The most popular catheter configuration is a double-D design, which provides the highest lumen volume with the lowest surface area in contact with blood, thus reducing shear stress (8) ***(Figure 5)***. Although both lumina open within the same vessel, by convention the lumen that aspirates blood from the patient is referred to as the arterial port, and the lumen that returns the processed blood to the patient is known as the venous port. The arterial lumen normally opens more proximally on the catheter in order to reduce re-aspiration (recirculation) of purified blood returning to the patient via the venous lumen. In some instances the degree of recirculation may be significant, which can dramatically reduce treatment efficiency. There is often more than one opening along the catheter to minimize the risks of obstruction and the possibility of vessel wall irritation from jet lesions through the ports (3).

Catheter placement

The external jugular veins are typically used for ERRT due to accessibility, size and blood flow. Catheters may be temporary or permanent. Temporary catheters are designed with a tapered tip, which facilitates placement using a percutaneous Seldinger technique. Although designed for temporary use such catheters, with strict asepsis and careful maintenance, may remain functional for several weeks. Placement usually requires sedation or general anesthesia and full aseptic technique is essential. A standard over-the-needle peripheral catheter inserted into the vein allows introduction of a guidewire; as this is advanced along the vein the electrocardiogram must be monitored for changes (*e.g.* premature complexes) which may occur if the guidewire touches the myocardium ***(Figure 6)***. The vessel is then gently dilated before the catheter is advanced over the wire into the vein and sutured in place; note that the catheter should be pre-filled with heparinized saline before placement. If the patient is severely overhydrated or the jugular vein cannot be visualized, a cut-down technique may be necessary (8).

Permanent catheters are preferred if the patient is likely to require chronic therapy. Ideally placement of these catheters should be done with fluoroscopic guidance and full sterile technique. A tunneling technique

is employed, so that the point of entry into the vein is some centimeters from the cutaneous exit. Many catheters have a cuff positioned midway between the skin and jugular vein which acts both as a barrier to minimize infection and an anchoring device. Although typically more expensive and difficult to place, long-term catheters can be used for months or even years with appropriate care (8).

Catheter management

Catheters should only be used for HD and not employed for anything else (*e.g.* intravenous fluids, medications, blood sampling, parenteral nutrition) to minimize the risk of contamination. They should be protected by a sterile dressing between treatments ***(Figure 7)*** and closely inspected for defects and inflammation at the insertion site before each use. Strict asepsis should be followed at the beginning and end of each dialysis treatment. Between treatments the catheter is filled with an anticoagulant locking solution, generally unfractionated heparin (1000-5000 U/mL). As a precaution, antibiotics (*e.g.* cefazolin at 10 mg/mL) may be added to the heparin, or sodium citrate may be used (high citrate concentrations (> 30%) have been shown to exhibit antimicrobial properties (9,10)). Locking solutions must be removed prior to dialysis; sometimes clotting or catheter malfunction can make this difficult, but flushing the solution into a patient may result in profound anticoagulation or (with high citrate concentration) severe hypocalcemia. Most patients undergoing hemodialysis should also receive systemic anticoagulation between treatments, typically oral aspirin (0.5-2 mg/kg SID), to minimize catheter-associated thrombosis (8).

Hemodialysis preparation

The goals of individual HD treatments may vary significantly between and within patients. Selection of the dialyzer should consider factors such as the priming volume of the extracorporeal circuit, patient size (expressed as surface area) and the biocompatibility and other characteristics of the filtration membrane. Smaller and low-flux dialyzers are more appropriate when a low-efficiency treatment is required (*e.g.* severe azotemia to avoid disequilibrium syndrome) and for smaller patients. Conversely, high-flux dialyzers are generally preferred if high convective clearance or more intense treatment is required.

Treatment intensity is another key factor; this is a function of the total volume of blood to be processed during the dialysis session and is expressed differently for IHD and CRRT. With IHD the total volume of blood processed is related to the urea reduction ratio (URR), so that the URR can be used as an operative parameter to guide treatment intensity (1). With CRRT the dialysis capability is estimated using the ratio K_t/V, where K_t is a measurement of instantaneous urea clearance and V is the volume of distribution (6). Once the total blood volume to be processed is established, appropriate combinations of blood flow rate and treatment time are determined. If moderate to severe azotemia is present, it is advisable to plan a longer dialysis session with a slower blood flow. Short treatment periods and rapid blood flow can induce dramatic changes in serum BUN and predispose the patient to life-threatening conditions such as dialysis disequilibrium syndrome (DDS). In small patients with severe azotemia it may not be possible to maintain a blood flow slow enough to reduce BUN safely because of the risk of clotting in the extracorporeal circuit. In these patients it is advisable to prolong treatment time by alternating the dialysis with bypass periods (where blood continues to move throughout the circuit but the dialysate flow is stopped).

Other important factors to consider include the dialysate composition and temperature. Conventional dialysate formulations for small animals contain a mix of different electrolytes, and the composition may be adjusted during the treatment according to patient's needs. For example, the sodium concentration may be increased or decreased gradually; an increased sodium profile (from hyponatremic or isonatremic to hypernatremic) is typically used to minimize the risk of DDS in severely azotemic

Figure 7. Indwelling catheters should be protected by a sterile dressing between treatments and the insertion site closely inspected for defects and inflammation before each use.

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patients, but the high dialysate sodium concentrations may result in post-dialysis thirst and volume overload. Another frequently manipulated component is bicarbonate; low bicarbonate concentration in the dialysate (25 mmol/L) is generally preferred in patients with severe metabolic acidosis to prevent rapid correction of the acidosis, which could cause paradoxical cerebral acidosis.

Occasionally, certain additions to the dialysate may be required; *e.g.,* in patients with ethylene glycol intoxication, ethanol (a competitive inhibitor for alcohol dehydrogenase) may be added, slowing the metabolism of ethylene glycol and allowing for a more complete removal with dialysis. The temperature of the dialysate is regulated by the dialysis machine and may have a significant effect on the hemodynamic stability of the patient; warmed dialysate may promote vasodilation and hypotension, while a cooler temperature can result in vasoconstriction and hypertension (1).

Anticoagulation

During ERRT, blood is exposed to various surfaces (*i.e.,* the catheter, blood tubing and dialyzer components) which have differing degrees of thrombogenicity; in particular, arterial and venous pressure chambers are highly thrombogenic as they present a wide air-blood interface, and blood turbulence and shear stress during dialysis may result in platelet activation. Clotting within the extracorporeal circuit may significantly reduce treatment efficacy. Visual inspection of the circuit is the simplest method to assess for clotting, but even if clots are not visible, they should be suspected if the blood is very dark or if fibrin is present at the blood-air interface.

Anticoagulants are therefore routinely used during dialysis, typically heparin due to its low cost, short biologic half-life and ease of administration. In humans, administration can cause heparin-induced thrombocytopenia (HIT) syndrome (11) but to date this has not been reported in veterinary medicine. The standard heparin protocol for hemodialysis is the administration of a single bolus (10-50 U/kg) five minutes before starting treatment, followed by a constant rate infusion (CRI) at 10-50 U/kg/h into the arterial side of the extracorporeal circuit, discontinued 20-30 minutes before ending the procedure. As an alternative to CRI, heparin boluses (10-50 U/kg) may be administered every 30 minutes (12).

Citrate may be used as an alternative to heparin; citrate exerts its effect by chelating calcium, which prevents coagulation, and although the majority of calcium-citrate complexes are lost into effluent dialysate, some citrate returns to the patient. In order to prevent systemic hypocalcemia, calcium should be given as a CRI. Careful monitoring is essential to minimize the risk of significant hypo- or hyper-calcemia and metabolic alkalosis (6).

Factors that may contribute to clotting during a dialysis treatment are generally categorized as blood-related, circuit-related and anticoagulation-related. Among blood-related factors, the most important include slow flow rate, frequent interruption of bloodflow due to machine alarms or catheter malfunction, rapid ultrafiltration rate, high patient hematocrit and the administration of blood transfusions during the treatment. Circuit-related factors include the presence of air within the dialyzer and the biocompatibility of the dialyzer membrane. Finally, anticoagulation-related factors include an inadequate loading dose of heparin, or underdosing or early discontinuation of the heparin CRI.

Some patients may be at increased risk of bleeding (*e.g.,* from gastrointestinal hemorrhage, active bleeding from other sites, or if other invasive procedures such as surgery or biopsy have been performed within 48 hours of dialysis) and may require more involved anticoagulation protocols. Here regional anticoagulation of the extracorporeal circuit may be used to minimize the risk. This involves the constant infusion of heparin into the arterial side of the extracorporeal circuit and the simultaneous infusion of protamine (to bind to and neutralize heparin) into the venous side.

There are many risks associated with this approach, including the possible side effects of protamine (dyspnea, bradycardia and hypotension) and rebound anticoagulation (as heparin and protamine are metabolized at different rates). A more common method of regional anticoagulation involves the continuous infusion of trisodium citrate into the circuit, adding calcium to neutralize the citrate immediately before the blood is returned to the patient (12); this is reported to be better at reducing the risk of bleeding (13) although complications related to the patient's calcium levels and concurrent metabolic disorders may occur.

No-heparin treatment is the most common protocol in high-risk human patients and involves pre-treating the extracorporeal circuit with heparin during the recirculation phase before the patient is dialyzed. Heparin is then flushed from the circuit before connecting the

patient. During the hemodialysis treatment, frequent saline boluses are required to flush fibrin strands from the circuit and minimize clotting, with the activated clotting time measured every 15-30 minutes in order to maintain adequate anticoagulation (12).

Conclusion

With modern technology, hemodialysis is not only feasible but is safe, efficacious, and even indispensable for the management of animals with potentially fatal azotemia, often permitting life-saving treatment for patients with renal injury when no other therapeutic options exist. It is important that owners understand that dialysis does not repair damaged kidneys but that it does replace many of the normal renal functions, so that the patient may have a good quality of life. Usually it is impossible to determine at the outset how long dialysis therapy will be needed; in general, with severe acute tubular necrosis, clients should be prepared (both financially and emotionally) to see their animal undertake 2-4 weeks of therapy, although some patients can recover more quickly.

Conversely, some patients have recovered renal function only after many months of dialysis and some patients never recover. Prognosis and duration of therapy vary tremendously from patient to patient and depend on the etiology and degree of renal insult, as well as patient condition and comorbidities.

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Feline hereditary and congenital kidney diseases

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Introduction

Congenital diseases are structural or functional diseases which are present at birth, although they may only become clinically obvious during the first few years of an animal's life. Etiologies vary; a range of external factors can affect development *in utero*, or random or inherited genetic abnormalities may be responsible.

Some congenital diseases may also be inherited (*i.e.* passed from parents to offspring via a variety of inheritance patterns) as a result of DNA mutation, which alters protein structure and hence affects the functional biology (1,2).

There are a limited number of inherited diseases for which the inheritance pattern and the underlying specific mutations are definitively known. Other than polycystic kidney disease (PKD), congenital renal disorders are relatively uncommon in cats; fortunately tests are available for the early identification of PKD (3).

KEY POINTS

- **With the exception of polycystic kidney disease, congenital renal disorders are uncommon in cats.**
- **There are a limited number of renal diseases for which the inheritance pattern and the specific mutations behind them are definitively known.**
- **The majority of inherited renal diseases affect purebred cats, although they can appear sporadically in any animal.**
- **Some affected animals may not develop clinical signs for years, and there can be individual variation in terms of disease severity and rate of progression.**
- **The clinical pathology of congenital renal disorders follows the general syndrome of chronic kidney disease and its different stages.**

Clinical characteristics

The true frequency of congenital renal diseases and their full range of clinical signs are yet to be fully characterized, but recognized familial and hereditary nephropathies are shown in ***Table 1***. For practical purposes, the majority of congenital disorders are included under the syndrome of chronic kidney disease (CKD) with the typical hematological, biochemical, urinary and clinical signs seen with renal failure.

The age at onset and the clinical signs of congenital renal disorders vary depending on the severity of the disease. Clinical signs tend to appear insidiously and are progressive, and may not be observed by owners until the disease is significantly advanced, although identification as part of a breeding program can assist in early detection. Some diseases can lead to death at only a few months of age, following signs such as anorexia, polyuria/polydipsia (PU/PD), growth retardation, renal osteodystrophy, anemia, lethargy, and various gastrointestinal clinical signs.

With other diseases, such as PKD or amyloidosis, either due to partial penetrance or the disease characteristics themselves, renal function is initially normal and affected

cats may live for years, eventually progressing to renal failure with the appearance of clinical signs such as PU/PD (1,2).

Renal failure at an early age tends to indicate a congenital etiology, although young animals can also be affected by acquired conditions; and terminal structural renal changes can develop within a period as short as two months. In addition, with many inherited diseases the kidneys can be normal at birth, with no signs appearing until the animal is older.

The presumptive diagnosis can be established by an appropriate clinical investigation including the history, laboratory tests and imaging techniques ***(Table 2)***. Definitive diagnosis usually requires detection of characteristic kidney lesions in samples obtained via biopsy or necropsy. Ideally biopsies should be performed on all animals with renal disease, especially where familial studies are planned, but this may not be justifiable in advanced stage patients (since all remaining functioning kidney parenchyma is required) and clinical evaluation usually allows for a presumptive diagnosis and appropriate medical care. Furthermore, many patients are diagnosed at a very advanced stage, when the main causative lesions cannot be identified and secondary changes common to terminal stages, such as fibrotic, degenerative and inflammatory lesions, tend to predominate (1,2).

Molecular diagnostic techniques have allowed great progress to be made in the study of these diseases, but specific genetic testing cannot be carried out on all cases as it is often unknown what gene is responsible for certain conditions. Where available, molecular diagnosis allows confirmation of the disease and also allows for early identification of affected asymptomatic animals so they can be excluded from any breeding program (3).

There is no effective treatment for congenital kidney diseases. The same benefits offered by CKD treatment strategies may be achieved (reduction in uremic clinical signs and kidney protection measures), but there is the added difficulty that specific renal diets do not meet all nutritional requirements for growth in very young animals. Consultation with a nutritionist is recommended. The administration of phosphate binders is possibly a more useful and appropriate suggestion (2).

Polycystic kidney disease

Polycystic kidney disease (PKD), or autosomal dominant polycystic kidney disease, is the most common inherited renal disease in the feline species (4). It is

Table 1. Familial and hereditary nephropathies in cats.

Disease	Breed affected
Amyloidosis	• Abyssinian • Siamese
Kidney dysplasia	• Persian • Norwegian forest
Polycystic disease	• Persian • American shorthair • British shorthair • Burmilla • Himalayan • Longhair crosses (Persian, Angora, Himalayan, Manx, Maine Coon)
Immune-mediated glomerulonephritis	• Abyssinian

Table 2. Diagnostic tools for standard kidney imaging.

Methodology	Indications
Radiography	• Allows determination of the shape, size and position of kidneys. • Allows anomalies of the kidney outline to be assessed but does not differentiate between fluid and solid structures. • Allows detection of radio-opaque nephroliths.
Ultrasound	• Allows kidney size to be determined. • Allows evaluation of the kidney parenchyma structure. • Allows obstructive conditions to be identified. • Allows detection of radiolucent nephroliths. • Allows differentiation between solid and fluid lesions.

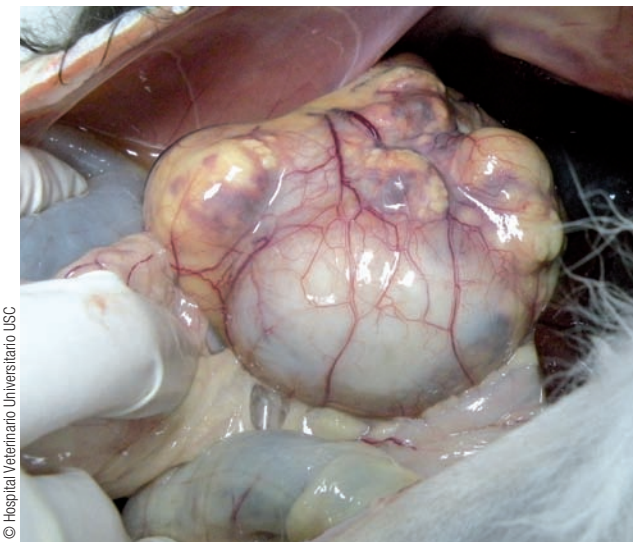

Figure 1. Gross appearance of an enlarged kidney from a Persian cat with PKD at *post-mortem* examination.

mainly observed in Persian cats and in breeds which have included Persians in a breeding program to acquire certain characteristics, but PKD is also seen sporadically in other breeds (5,6).

The disease has a worldwide distribution, with an estimated prevalence in the Persian of 37-49% (7,8). This high prevalence, along with the popularity of the breed, makes it one of the most common and well-known inherited diseases in the cat. A prevalence of up to 16% has been described in other breeds, such as the American shorthair, Siamese, American curl and Scottish fold (9).

PKD is a monogenic disorder characterized by the presence of multiple kidney cysts ***(Figure 1)*** leading to the destruction of kidney parenchyma (1-3), although progression varies between individuals. It can also occasionally cause formation of cysts in other organs such as the liver, but the percentage of cats where this occurs has not been studied in detail; one report suggested that almost 48% of cats with PKD can have liver cysts, but the study population only comprised 23 cases (4).

PKD is inherited as an autosomal dominant trait with complete penetrance, *i.e.*, only one gene mutation is necessary to cause the disease, and given that no cat with two alleles has been identified to date, the homozygote combination is considered to be lethal. When it comes to breeding, this means that if one progenitor is affected, the kittens will have a 50% chance of inheriting the mutated gene. If both parents have the mutated gene the probability rises to 66%, as embryos homozygous for the gene will die before birth (4,10).

The same mutation – identified in all affected Persian cats – is simple; a cytosine base is substituted for an adenine base (a transversion mutation). This single base change leads to insufficient production of polycystin, which is vital for normal renal function (4). Polycystin is a membrane glycoprotein, located in the cilia of epithelial cells that cover the renal tubules, responsible for controlling cell proliferation and maintaining the tubule cells in a differentiated state. If polycystin levels drop below a critical point cell changes develop; these include the inability to maintain cellular polarity, an increase in cell proliferation and apoptosis, the expression of a secretory phenotype, and the remodeling of the extracellular matrix, such that macroscopic cysts begin to develop (11).

The development of kidney cysts begins in the embryo and continues throughout an individual's life. As with humans, it is possible that different stages of cystogenesis occur, for example an initial stage (which is mutation-dependent), and a growth stage (which is mutation-independent). It has been suggested that genetic and modifying environmental factors may be responsible for the individual variability observed when it comes to the severity of the condition (10).

Histologically, the cysts originate as focal dilations of the renal tubules, with the connection between them being lost. Initially the parenchyma appears relatively normal, but eventually the kidneys enlarge with numerous fluid-filled cysts, with isolated areas of relatively normal parenchyma surrounded by abundant fibrous tissue (4).

An autosomal recessive form of PKD exists in humans, causing severe changes in both the kidneys and the biliary tracts. A similar disease has been reported as a familial problem in cats, with affected kittens showing obvious abdominal distension and death before 7 weeks of age. Histology showed PKD and cysts in the biliary tracts (12).

Cats with PKD may not show clinical signs related to the disease, or may present with a range of signs. Kidney cysts are responsible for many complications such as hematuria, urinary tract infections or sepsis (due to secondary infection of the cysts), but renal failure is the most serious problem due to the progressive destruction of the parenchyma as the cysts enlarge ***(Figure 2)*** (13). Kidney disease can occur at any age, but the majority of

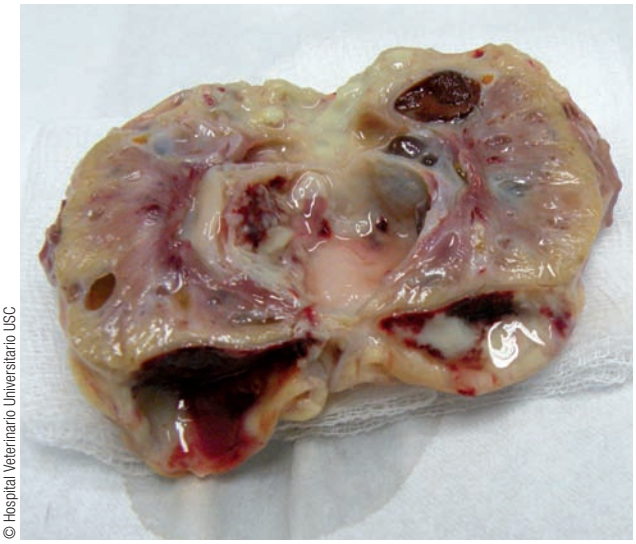

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Figure 2. Section of the kidney in **Figure 1** demonstrating multiple variable-sized cysts in both cortex and medulla, completely altering the normal architecture. Some of the cysts showed hemorrhagic areas.

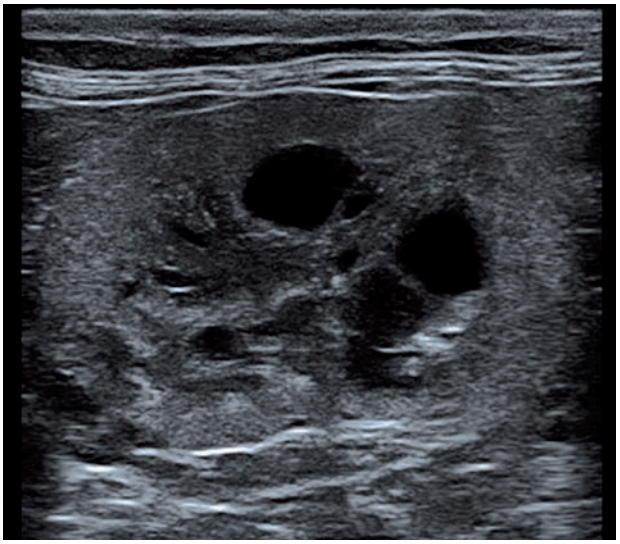

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Figure 3. Ultrasound images of PKD demonstrating multiple well-defined, circular anechoic structures throughout the renal parenchyma, consistent with renal cysts.

animals present between the ages of 3-7 years. Many humans with PKD show hypertension-derived complications, but this appears to be uncommon in the feline species (1-4,13).

Diagnosis

Two subsets of patients can be considered here; those presented for early detection of the disease, and those where clinical signs have already developed.

The main methods employed for early diagnosis are ultrasound examination and genetic testing. Studies indicate that ultrasound examination for PKD has a sensitivity as high as 95% in cats at 10 months of age. False negatives may occur with very small cysts, operator inexperience, or (rarely) the presence of small medullary cysts with similar echogenicity (7). Animals are considered PKD positive when at least one of the kidneys is identified to have an anechoic structure > 2 mm in diameter ***(Figure 3)***. Advances in equipment have led to better diagnostic sensitivity, with identification as early as 6-8 weeks of age, but even when there is no evidence of cyst formation the condition may still develop at a later date (8,14-16).

Despite the ultrasound sensitivity and its usefulness in evaluating progression in affected individuals, genetic studies offer greater advantages by establishing an early diagnosis in potential breeding cats, given that young cats can easily be checked via a buccal swab or a blood sample. The gene responsible for feline PKD was identified in 2005 using PCR techniques, and because the mutation remains unchanged the gene can be detected in all affected individuals (3). However the test cannot identify all forms of PKD; recent studies have reported that a small percentage of cats with ultrasound abnormalities and histologies compatible with PKD had a normal genotype (6).

Regardless of whether or not an animal is clinical sign-free, once identified with PKD it must be monitored once or twice yearly (depending on how badly affected the individual is) for disease progression, and this is best done by ultrasound examination (10).

In humans, the increase in kidney size and the number of cysts are the most significant predictive factors of a decline in kidney function, although in some individuals vascular resistance appears to play a significant role, which may explain why functional failure is not always proportional to the severity of cyst formation (17).

In cats rapid progression of cysts may hasten the development of clinical signs; severity may be increased due to both the development of a larger number of cysts at a young age and a faster growth rate of the cysts. It is estimated that if > 75% of the tissue is cystic, PKD can potentially cause CKD, although other factors in older

animals may also contribute to the loss of functional tissue (10).

As well as the development of the characteristic signs of CKD (which can be classified via the IRIS staging system; see inside back cover for more information), a bilateral increase in kidney size detected on abdominal palpation or radiography ***(Figure 4)*** should increase suspicion of PKD in any cat that is unwell ***(Table 3)***. Identification of cystic structures on ultrasound allows a presumptive diagnosis to be made, and although renal cysts can occur for other reasons, they are extremely rare ***(Figure 5)***.

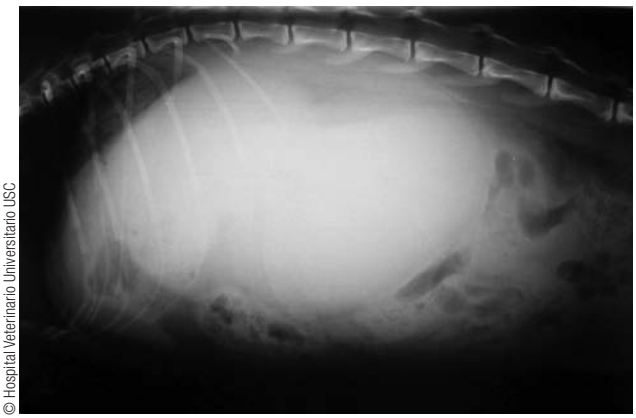


Figure 4. Lateral abdominal radiograph of a cat with palpably enlarged kidneys. Large, oval overlapping soft tissue opacities are evident within the abdomen, displacing the intestines ventrally and caudally. The differential diagnoses should include PKD, perinephric pseudocyst, severe hydronephrosis, and (less likely) a neoplastic process such as lymphoma.

Treatment

Cyst drainage does not slow the progression to kidney failure and there are few studies on the efficacy of ACE inhibitors in cats with PKD (13); there is no real evidence that this drug should be recommended for all cats with PKD. The use of renal diets follows the same principles as the treatment of CKD, and should be initiated as soon as IRIS stage 2 is reached (18). Hematuria episodes may abate spontaneously, but analgesia may be necessary to alleviate any pain. If infection is suspected, a culture of the cyst content should ideally be undertaken, with treatment based on sensitivity tests, but since not all antibiotics will penetrate the cystic structure adequately, lipophilic antibiotics (such as quinolones, *e.g.* marbofloxacin at 2.75-5.5 mg/kg PO once daily) are preferred, with a treatment duration of 4-6 weeks. Any possible urinary infection must also be treated, as sepsis from secondary infection of the cysts is a risk.

Breeding recommendations

The increased feasibility of identification, whether via genetic or ultrasound tests, leads to a significant dilemma when it comes to breeding with affected individuals. Complete elimination of all affected Persians from breeding programs would reduce the diversity of the breed by almost 40% and may lead to other undesirable characteristics appearing. Given that mating an affected progenitor with a healthy individual will result in 50% of the descendants being free of the disease, this type of crossing is one method to avoid losing a particular genetic line whilst also conserving the genetic diversity of the breed. Bear in mind, however, that typically 50% of the descendants will be affected (10).

Table 3. Main differential diagnoses for patients with renomegaly.

Unilateral	Bilateral
• Primary kidney tumor • Compensatory hypertrophy • Hydronephrosis • Pyelonephritis • Perinephric cysts	• Acromegaly • Amyloidosis • Glomerulopathy • Hydronephrosis • Renal lymphoma • Granulomatous nephritis (due to feline infectious peritonitis) • Pyelonephritis • Perinephric cysts • PKD

The number of patients for whom PKD is the true cause of death is unknown. Experience demonstrates that some cats never develop kidney failure (and eventually die from an unrelated illness) and so breeding from animals in this category may produce offspring that are minimally affected, thus avoiding a loss of genetic diversity (10).

Amyloidosis

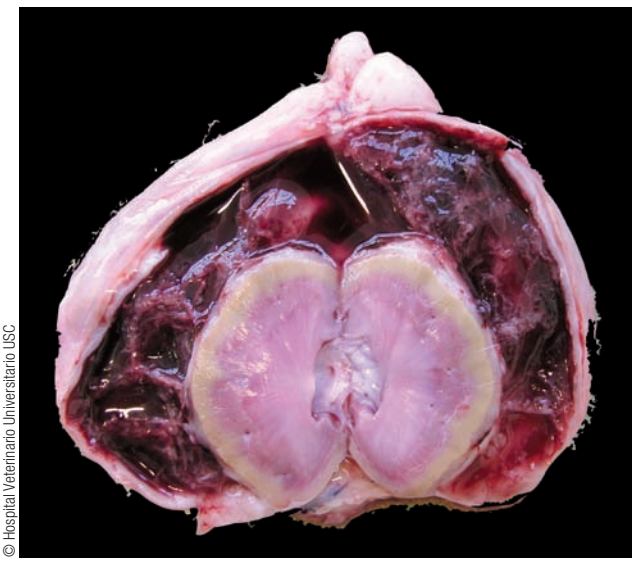
Amyloidosis is characterized by protein deposition in the extracellular space, specifically by polymerization of protein subunits into a specific conformation known as β-pleated sheets. Reactive amyloidosis is the most common form in domestic animals, where an acute-phase serum protein (amyloid A) is deposited in tissues as a response to inflammatory disease or chronic neoplasia. It is uncommon in cats, with the majority of cases involving Abyssinian, Oriental and Siamese cats, and is considered to have a familial predisposition.

Amyloidosis in Abyssinian cats is likely to be an autosomal dominant inheritance, with variable penetrance without gender predilection (19). In severely affected patients the renal amyloid deposition occurs mainly at the level of the medulla at around 9-24 months of age, causing papillary necrosis, myelofibrosis, and chronic kidney disease. The lack of cortical amyloid deposits explains why proteinuria is uncommon, and the most common pathological sign is renomegaly and rapid, progressive chronic kidney disease. The majority of patients show advanced clinical signs by 3 years of age. Some animals can show incomplete penetrance and have a normal life expectancy (1,2,9,19).

In Oriental and Siamese cats with familial amyloidosis the amyloid deposits tend to occur in the liver, and abdominal hemorrhage due to organ rupture can be the main sign, although CKD can develop in some individuals (20). The amyloid identified in these breeds is slightly different to that in Abyssinians, which may explain the differing deposition sites.

Whilst the veterinarian may be suspicious of amyloidosis on clinical examination, the diagnosis can only be confirmed by biopsy, with the sample stained using Congo red and examined using a polarizing microscope to identify the apple-green birefringence, characteristic of amyloid. The main problem with biopsying these patients is that the amyloid shows preferential medullary deposition, and since biopsy collects cortical tissue no histopathological changes may be detected. Amyloidosis is a progressive disease and in the author's opinion the suggested treatments with dimethyl sulfoxide and colchicine are unlikely to give good results. Once the disease is identified, the only possible treatment options are the same as those employed for CKD.

Figure 5. A large pseudo-hemorrhagic fluid-filled lesion surrounding a cat's kidney; this was a perinephric pseudocyst.



Other genetic diseases

In conclusion, congenital feline renal disorders, with the exception of PKD, are rare, but a brief mention of other unusual abnormalities is worthwhile to complete the topic.

Renal dysplasia, whereby the kidney parenchyma develops in a disordered fashion due to abnormal differentiation, can lead to early onset renal failure. At birth, immature non-differentiated tissues (glomeruli, fetal tubules and mesenchymal tissue, and possible cartilaginous metaplastic tissue) are present in the kidneys and complete their normal development in the first two months of life. In affected individuals, however, the undifferentiated tissues remains present throughout life, and affected animals develop kidney failure, usually before two years of age. The reasons behind this abnormal nephrogenesis are not fully defined. It may be due to damage during the fetal development or neonatal periods, and panleukopenia virus infection has been suggested as a potential cause (2). An isolated case has been identified in a 5-month-old Norwegian forest cat which developed polyuria, anorexia and laboratory abnormalities indicative of CKD (21). A definitive diagnosis can only be obtained histologically and at least three of the following criteria must be present: asynchronic nephron differentiation, persistent metanephric ducts, mesenchymal tissue, atypical tube epithelium, and/or dysontogenetic metaplasia (22). The abnormalities may affect the entire kidney, or simply one section, meaning some individuals do not show clinical signs. Although they may sometimes be normal macroscopically, affected kidneys are generally smaller than usual and have cyst structures distributed either segmentally or diffusely throughout the cortex (21).

A possible **hereditary glomerular nephritis** has been described in a family of Abyssinian cats; all littermates (of both genders) developed variable levels of hematuria and proteinuria between the ages of 5-36 months (23). Only one patient had biomarker levels indicative of renal failure at the time of presentation, and six of the eight affected animals developed nephrotic syndrome with peripheral edema. Although genetic studies were not

undertaken, the pedigree analysis suggests an autosomal recessive inheritance. Histology demonstrated changes consistent with focal proliferative glomerulopathy, although more in-depth investigations (*e.g.* immunohistochemical and ultra-structural studies) are required for better categorization of this disorder.

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HOW I APPROACH...

Ureteral obstructions in dogs and cats

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Introduction

An increasing incidence of problematic nephroliths and ureteroliths has been seen in veterinary practice over the past decade (1-6). The invasiveness and morbidity associated with traditional surgical techniques (*e.g.*, nephrotomy, ureterotomy, ureteral re-implantation, and ureteral resection and anastomosis) can pose a management dilemma (2-4) and recently interventional radiologic (IR) and interventional endoscopic (IE) techniques have enabled clinicians to simultaneously diagnose and treat upper tract stone disease in a much more effective and minimally invasive manner (1,5,6), although special equipment and operator training are essential. Developments in human endourology have almost eradicated the need for open surgery for upper urinary tract disease (*e.g.* stones, strictures, tumors, congenital anomalies (7-10)), and veterinary medicine is following the same trend. More than 98% of feline, and 50% of canine upper tract stones are composed of calcium oxalate, meaning that they will not dissolve medically (2-5,11,12) and they must either be passed spontaneously, be removed, or bypassed to allow a continued flow of urine. This review will focus on the application of endourology for the management of problematic nephroliths and ureteroliths; traditional therapeutic options will be only briefly reviewed, and more detail on surgical methods is beyond the scope of this paper. Note that most of the data pertaining to IR/IE treatment is solely the experience of the author, some of which has only been published and/or presented in abstract form.

KEY POINTS

- **Ureteral obstructions are underdiagnosed but can pose a major dilemma for veterinarians.**
- **Newer interventional treatment options have decreased the morbidity and mortality often seen with more traditional surgical interventions.**
- **Nephroliths are rarely problematic in dogs and cats, with the majority not requiring intervention.**
- **Endoscopic placement of a ureteral stent for the treatment of canine ureteral obstructions is effective in almost all patients and is typically an outpatient procedure.**
- **Ureteral obstructions cause a dramatic decline in renal function over a short period of time and should be treated quickly and effectively.**
- **All cats with an acute onset azotemia should be evaluated for a ureteral obstruction prior to a presumptive diagnosis of chronic interstitial nephritis or CKD.**

Nephrolithiasis

Nephroliths are rarely problematic (< 10%) in dogs and cats, but complicated nephroliths can result in progressive renal insufficiency, intractable pyelonephritis, intermittent ureteral outflow obstructions, progressive hydronephrosis, chronic pain, or chronic hematuria. If problematic, intervention may be needed to avoid permanent nephron damage but nephrotomies, pyelotomies or

salvage ureteronephrectomy can be prolonged, invasive, and complicated surgeries, potentially resulting in significant morbidity and progressive decline in the glomerular filtration rate (GFR) (13-15). These procedures do not prevent future obstruction in animals prone to stone formation, so recurrence should always be discussed and considered.

Complications after traditional surgery can be severe and life-threatening, and include hemorrhage, decreased renal function, post-operative ureteral obstruction by remaining fragments, and uroabdomen development (14-15). One study in normal cats noted that GFR decreased by 10-20% after a nephrotomy, which was considered clinically insignificant (16), but in a clinical patient with maximally hypertrophied nephrons, the significance could be dramatic. Cats with an already compromised GFR from chronic stone disease, and a 30% chance of developing renal azotemia with age, may therefore develop a significant decline in renal function after nephrotomy and cannot tolerate a further 10-20% decline in GFR. It is generally agreed that a nephrotomy should be avoided whenever possible, especially for animals that have existing renal disease or stones in the contralateral kidney (16).

Figure 1. A dog under anesthesia undergoing extracorporeal shockwave lithotripsy (ESWL) to treat a large nephrolith. Note this is a dry unit, with a water bag placed directly over the kidney.

In humans, various minimally invasive options are employed for nephrolithiasis, including extracorporeal shockwave lithotripsy (ESWL) for nephroliths < 1-2 cm in size and percutaneous nephrolithotomy (PCNL) for larger stones. Open surgery and laparoscopy are rarely necessary and are usually considered only if other, less invasive options, have failed or are inappropriate. Studies have shown ESWL and PCNL to have minimal effects on GFR in clinical stone-forming people, particularly when compared with nephrotomy (11-13) and both methods (and particularly PCNL) are highly effective in removing all stone fragments. Endoscopic calyceal inspection with PCNL is superior to all other procedures for visualization and fragment retrieval (17).

In dogs, ESWL can be considered to remove upper tract calculi in the renal pelvis or ureters. The technique utilizes external shockwaves passed through a water medium and directed under fluoroscopic guidance ***(Figure 1)***. The stone is shocked between 1,000-3,500 times at different energy levels and fragments into small (typically ~1mm) pieces, the debris being allowed to pass down the ureter into the bladder over a 1-2 week period, although it can take 3 months for full stone clearance. This procedure can be safely performed for nephroliths < 10 mm and ureteroliths < 5 mm; however, because the fragments are rarely less than 1 mm, and the feline ureter is 0.3 mm in diameter, this is not an effective treatment for cats.

For large stone burdens an indwelling double pigtail ureteral stent (see paragraph "Minimally invasive options" on page 21) is typically placed prior to ESWL to help prevent ureteral obstruction during stone passage (10). However this can hinder ureteral peristalsis, meaning that the fragments can take longer to pass (18).

ESWL is believed to be safe and well tolerated by canine kidneys (13), with minimal decreases in GFR and return to baseline within 1 week (13,19) of treatment, and is reported as successful in ~85% of dogs with calcium-containing nephroureteroliths (14). Successful fragmentation of renal stones was achieved in 90% of dogs, but some required more than one treatment (13). The newer dry units are more powerful, with a more focused beam, resulting in fewer repeated treatments (15-20% in my experience) when used appropriately. Success with ESWL is highly stone- and patient-dependent; stone size and composition seem to play a major role and

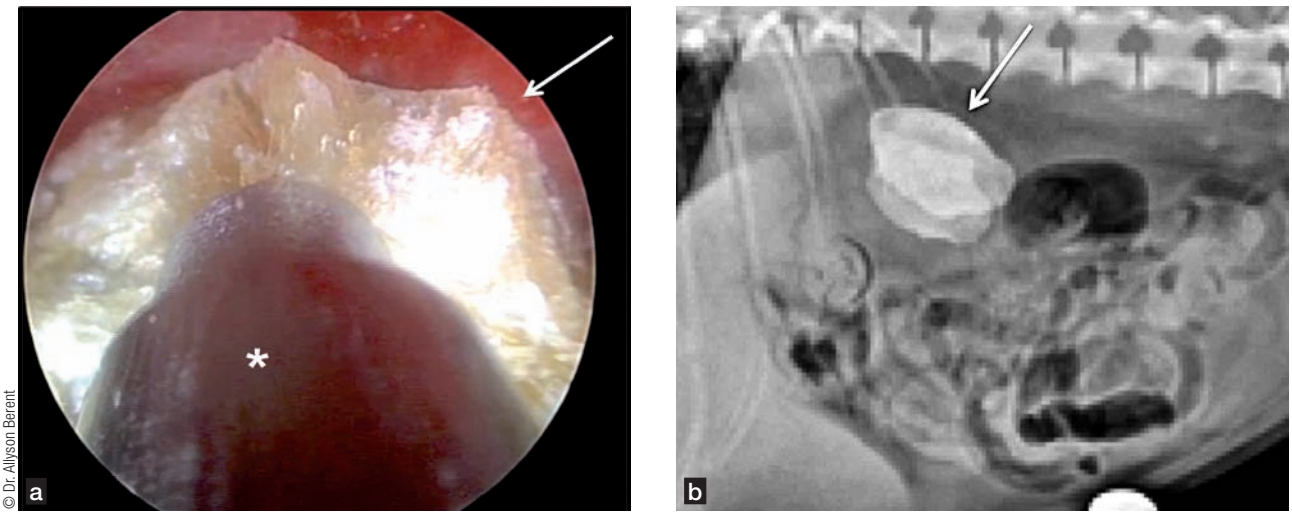

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Figure 2. PCNL in a dog.
(a) Endoscopic image during nephroscopy; a lithotripter (starred) has been passed through the working channel and is breaking down the stone (arrowed) within the renal pelvis.
(b) Bilateral large calcium oxalate nephroliths (arrowed) can be seen on a lateral abdominal radiograph prior to PCNL.

struvite, urate and calcium oxalate stones are considered more amenable to ESWL than cystine stones.

PCNL is typically considered for large or impacted nephroliths (> 15-30 mm) in humans (20). In small animals I consider PCNL or surgically-assisted endoscopic nephrolithotomy (SENL) when ESWL fails, if cystine stones are present or if the stone is > 15 mm in size ***(Figure 2)*** (10, 21). A combination of ultrasound, nephroscopy, and fluoroscopy allows access into the renal pelvis and guides nephroscopic intracorporeal lithotripsy (via electrohydraulic, ultrasonic, and/or laser means). Patient size is not typically a factor for PCNL – we have performed this technique on a dog weighing 3.1 kg, and PCNL/SENL is currently performed routinely in dogs with problematic nephroliths at the Animal Medical Center.

Ureterolithiasis

Ureteroliths are the most common cause of ureteral obstructions in both dogs and cats (2-5), although ureteral strictures (22) and trigonal neoplasia (23) have also been reported. The physiologic response to a ureteral obstruction is known to be very complex; after a complete ureteral obstruction there is an immediate increase in renal pelvic pressure and the renal bloodflow diminishes by 60% over the first 24 hours, and 80% within 2 weeks (24,25). This excessive pressure decreases the GFR (24) and the contralateral kidney (if it is normal and has the potential for hypertrophic compensation) will increase its GFR in response. The longer the ureter remains obstructed, the more progressive the damage; studies show that after 7 days the GFR can permanently diminish by 35%, and after 2 weeks by 54% (24,25), but these figures apply to normal dogs and a poorer outcome might be expected in a patient once the hypertrophy mechanisms are exhausted. Additionally, since > 30% of all adult cats will eventually develop renal azotemia (26), leaving less than 25% of renal function, any preventable loss in GFR should be avoided. Note that partial obstructions have been shown to result in less severe and slower nephron destruction, giving more time for intervention when needed (24), but aggressive management and obstruction relief is recommended for both partial and complete situations as soon as possible.

In human medicine, ureteroscopy is the first choice to evaluate and treat ureteral calculi > 5 mm in size. Small stones (< 5 mm) have a 98% chance of spontaneous passage with medical management alone (*e.g.*, alpha-blocking agents), whilst for larger stones, or those that do not pass spontaneously, ESWL is effective in 50-67% of cases. Ureteroscopy is almost always successful when laser lithotripsy is used in humans, but this is only possible in dogs over 18-20 kg in my experience, and since most dogs with ureterolithiasis are small terrier or toy breeds this is an uncommon procedure.

Ureteral stenting was first introduced for management of people with malignant ureteral obstructions (8), and is still widely used in a variety of situations. In veterinary

medicine, stents are considered a long-term solution, and are far better tolerated than in humans; at the AMC various minimally invasive endourologic modalities are now employed to manage ureteral obstructions (1,5,6).

Feline patients with ureteral obstruction typically present with vague signs associated with vomiting, lethargy, weight loss and inappetence (4). Unless there are concurrent bladder or urethral stones, dysuria is rare. Note that cats with a unilateral ureteral obstruction may be asymptomatic and continue to urinate normally, as they have one non-obstructed ureter and a normal urethra, and monitoring progress by clinical signs alone is difficult. Concurrent urinary tract infections (UTI) are documented in approximately 33% of cats and 77% of dogs (2-4) when a ureteral obstruction is present. Pain on palpation of the affected kidney is more commonly seen in acute obstructions and in dogs with severe pyelonephritis, but absence of pain does not mean that a ureteral obstruction is not present.

Biochemical parameters

Cats are often anemic (48%) at diagnosis and this is either due to concurrent CKD, chronic disease, or excessive blood sampling during previous hospitalizations (2). Dogs often have a moderate to severe neutrophilia associated with concurrent pyelonephritis and 44% of dogs with ureterolithiasis-induced obstructions were reported to have some degree of thrombocytopenia (which can be severe, *i.e.*,< 40,000 platelets/μL), either from sepsis or immune-mediated disease (4). Azotemia is common at the time of diagnosis, even with a unilateral obstruction (83-95% of cats and 50% of dogs (2-5)), but the degree of azotemia does not appear to be associated with outcome if successful decompression occurs (27). Hyperphosphatemia (54%), hyperkalemia (35%), hypercalcemia (14%), and hypocalcemia (22%) were reported in a large series of cats with ureteral obstructions (2); on urinalysis 29% of cats had crystals, most commonly calcium oxalate or an amorphous composition.

Imaging

Bilateral ureteral obstructions occur in about 20-25% of cats (1-3,5,6) and 12% of dogs (4). Radiographic evaluation is mandatory during a work-up, as radiopaque calculi are typically identified, and stone size, number, location and the presence of concurrent nephrolithiasis (reported as 60-86% in cats and 50% of dogs (1-6)) can be documented, but ultrasound examination is also essential to identify any hydroureter or hydronephrosis, and the exact location of the most proximal obstruction.

If there is a hydroureter very proximally, with no evidence of a stone at the junction of normal and abnormal ureter, then a stricture may be present. In a recent study 60% of cats with a ureteral stricture had evidence of peri-ureteral hyperechoic tissue at the stricture site on ultrasound, most commonly seen on the right side associated with a circumcaval ureter (22). Knowing the exact diameter of the dilated renal pelvis (via ultrasound) and identifying concurrent nephroliths/ureteroliths are vital for therapeutic decision-making.

When hydroureter and hydronephrosis are located to a specific area of the ureter, a ureteral obstruction (partial or complete) is present. Knowing the cause of the obstruction is very important if opting for a traditional surgical method; no stone should be left within the ureter, whereas resection and anastomosis can be anticipated if a stricture is present. If interventional management (*e.g.* stenting or a bypass device) is planned, these details are used to decide which device and approach is best, but both can safely treat most ureteral obstructions. With interventional treatments pre-operative intravenous pyelography, antegrade pyelography or CT-pyelography are not typically necessary.

Most ureteroliths in dogs (~50%) and cats (> 98%) are calcium oxalate (11,12). Because these stones cannot be dissolved medically, they must pass spontaneously, remain in place, be removed, or urine must be diverted. Dissolution of obstructive ureteroliths is contraindicated, regardless of the composition, because the time required will result in excessive kidney damage. The traditional approach to a partial ureteral obstruction has been medical management as detailed below. If this approach is unsuccessful many clinicians previously opted for conservative monitoring due to the presumed poor risk:benefit ratio of attempted surgical removal; although the literature indicates that surgical intervention provides a higher success rate than medical management alone (2,3) in cats, the morbidity and mortality rates associated with traditional surgery are still considerable.

Less-invasive alternatives that result in immediate ureteral decompression, fewer major complications and a decreased recurrence of ureteral obstructions are very promising. With medical management being effective in some feline cases (8-17%), and traditional surgery being associated with relatively high post-operative complication (~20-40%) and mortality rates (~20-30%) (2-4), medical therapy should be considered for 24-48 hours before any intervention, but in my experience interventional

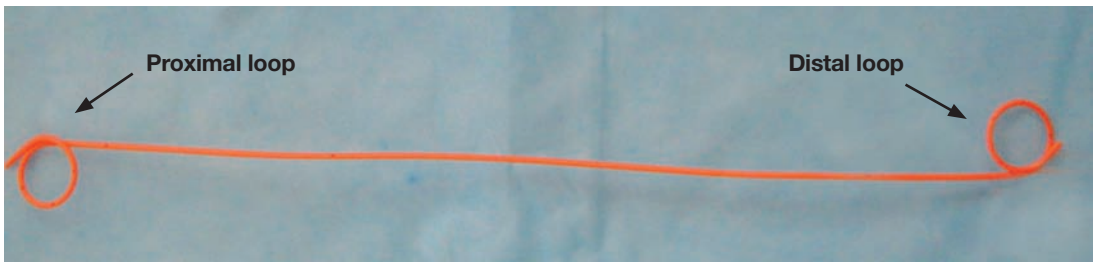

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Figure 3.
A double pigtail ureteral stent.

options (as discussed below) have a lower morbidity and mortality rate. I find that beyond this period the chance of stone passage is low, and the risk of permanent renal damage is high.

Treatment

Medical management is clinician-dependent and should consist of IV fluid therapy (4 mL/kg/h) while monitoring central venous pressure, bodyweight, electrolyte concentrations and hydration status. In patients without cardiac compromise, mannitol (as a bolus at 0.25-0.5 g/kg over 20-30 minutes, followed by continuous rate infusion (CRI) at 1 mg/kg/min for 24 hours) and low dose prazosin given orally (0.25 mg/cat BID or in dogs 1 mg/15 kg bid) can be considered. If, after 24 hours, there is no evidence of improvement based on imaging and serial blood work, this is discontinued.

Other medical alternatives include amitriptyline or glucagon therapy but these are less effective in my experience. If medical management fails, or the patient is unstable *(e.g.*, hyperkalemic, excessively overhydrated, oliguric/anuric, or developing progressive hydronephrosis), immediate renal decompression involving a surgical or interventional option should be considered. If this is not possible, or the patient is too unstable, then intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT), when available, should be considered. During these few days of stabilization, there is a possibility that the ureterolith may pass spontaneously, making an intervention unnecessary. Note that many patients with ureteral obstructions have concurrent UTI, and broad-spectrum antimicrobial therapy is recommended for all patients, with urine culture and sensitivity testing part of the work-up.

Surgical intervention has traditionally included ureterotomy, neoureterocystostomy, ureteronephrectomy, or renal transplantation (2-4). In a small study of dogs, results after ureterotomy for stone disease were associated with a mortality rate of 25%, and 17% required additional surgery for re-obstruction within 4 months (4). In cats, the procedure-associated complication and mortality rates are reported to be over 30% and 18%, respectively. Complication rates may be higher where operating microscopes and microsurgical expertise are not available. Many of the surgical complications are due to site edema, recurrence of stones that pass from the renal pelvis to the surgery site, stricture formation, persistent obstruction, missed ureteroliths, and surgery- or nephrostomy tube-associated urine leakage.

It is important to realize that ureteronephrectomy is not ideal in any stone-forming patient, especially in those with concurrent renal azotemia (2-6). A recent study noted 97% of cats were azotemic at the time of ureteral obstruction diagnosis, even when unilateral (5). Persistent azotemia is a common problem, even after successful intervention (40-70% of cats), but is often minor and remains stable for many years (2-6). In one study, 40% of cats developed a second ureteral obstruction after traditional stone removal (3) and 85% had evidence of nephrolithiasis documented at the time of the first surgery. Nephroliths have the potential to pass into and obstruct the ureter during a post-obstructive diuresis, and can occur immediately after surgery, but a concurrent nephrotomy increases the risks for postoperative complications and will likely worsen renal function. Due to these high morbidity, mortality and re-obstruction rates, alternative options were investigated and have been deemed safe and highly effective.

Minimally invasive options

Ureteral stents

Double pigtail ureteral stents suitable for veterinary use are now available ***(Figure 3)*** and offer many benefits: they allow immediate decompression of the renal pelvis and passive ureteral dilation to allow urine and stone passage around the stent; stenting avoids the complications that can develop with other forms of treatment;

and also prevents ureteral obstruction after ESWL (1,5,22,23,27).

Placement of a stent, which is achieved by fluoroscopy and surgical assistance (usually in cats - ***Figure 4)*** or endoscopy and fluoroscopy (usually in dogs - ***Figure 5)*** avoids many of the surgical peri-operative complications and results in expedited stabilization. Prior to considering this option, the risks need to be understood and discussed with the owners, but with an experienced operator, stent placement is highly successful. The main complications, typically seen months or years after placement, include dysuria, stent migration, stent occlusion (most commonly with ureteral strictures in cats), and stent encrustation, but they are not usually life-threatening and most can be addressed on an outpatient basis.

In cats, access is either attempted via retrograde cystoscopy (successful in < 20% of female cats) or by surgery using fluoroscopy with antegrade placement of a nephrostomy needle (successful in > 95% of all cats). Again extensive training is necessary, and whilst this procedure is not recommended for all obstructed patients, we now achieve a 95% success rate despite the fact that many cases are considered poor surgical candidates (due to stone number, stricture location, concurrent nephroliths and patient stability).

A review of our caseload reveals a median of 4 stones per ureter, with most cases (86%) having concurrent nephroliths. About 25% of cats had a ureteral stricture (with or without a stone). 95% of cases had significant improvement in their azotemia following treatment, and whilst peri-operative mortality was 7.5%, none of the deaths were from surgical complications or ureteral obstruction. The short-term complication rate (< 1 month) was 9% (*e.g.*, stent misplacement, a ureteral tear, and urine leakage at the concurrent ureterotomy site) and the

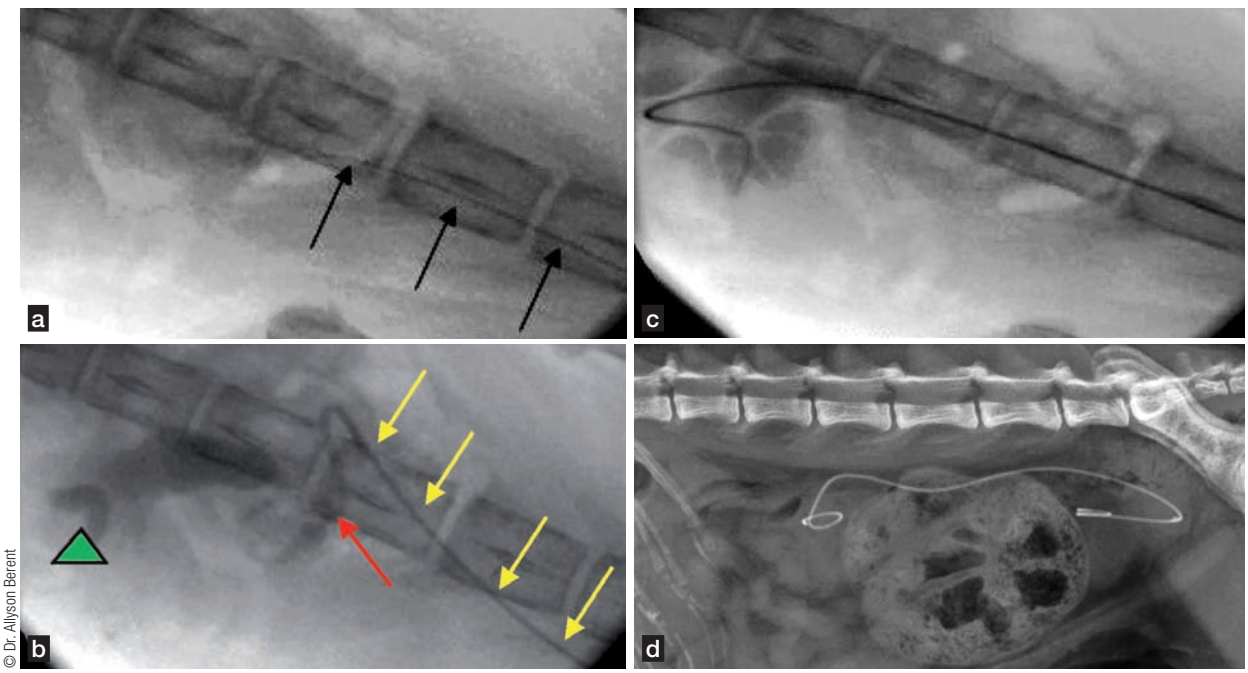

Figure 4. Fluoroscopic-guided retrograde ureteral stent placement in a female cat under general anesthesia.

(a) A guidewire (black arrows) is advanced up the ureteral lumen through the ureterovesicular junction (UVJ) via endoscopic guidance.
(b) An open-ended ureteral catheter/dilator (yellow arrows) is then advanced over the guidewire to the level of the stones (red arrow) before the wire is removed and a retrograde ureteropyelogram performed; the renal pelvis is seen filled with contrast (green arrowhead).
(c) The guidewire is then re-advanced through the catheter and into the renal pelvis; the ureteral stent is then advanced over the wire into the renal pelvis.
(d) A lateral radiograph demonstrates the ureteral stent in place; note how one loop is within the renal pelvis and the other loop in the urinary bladder.

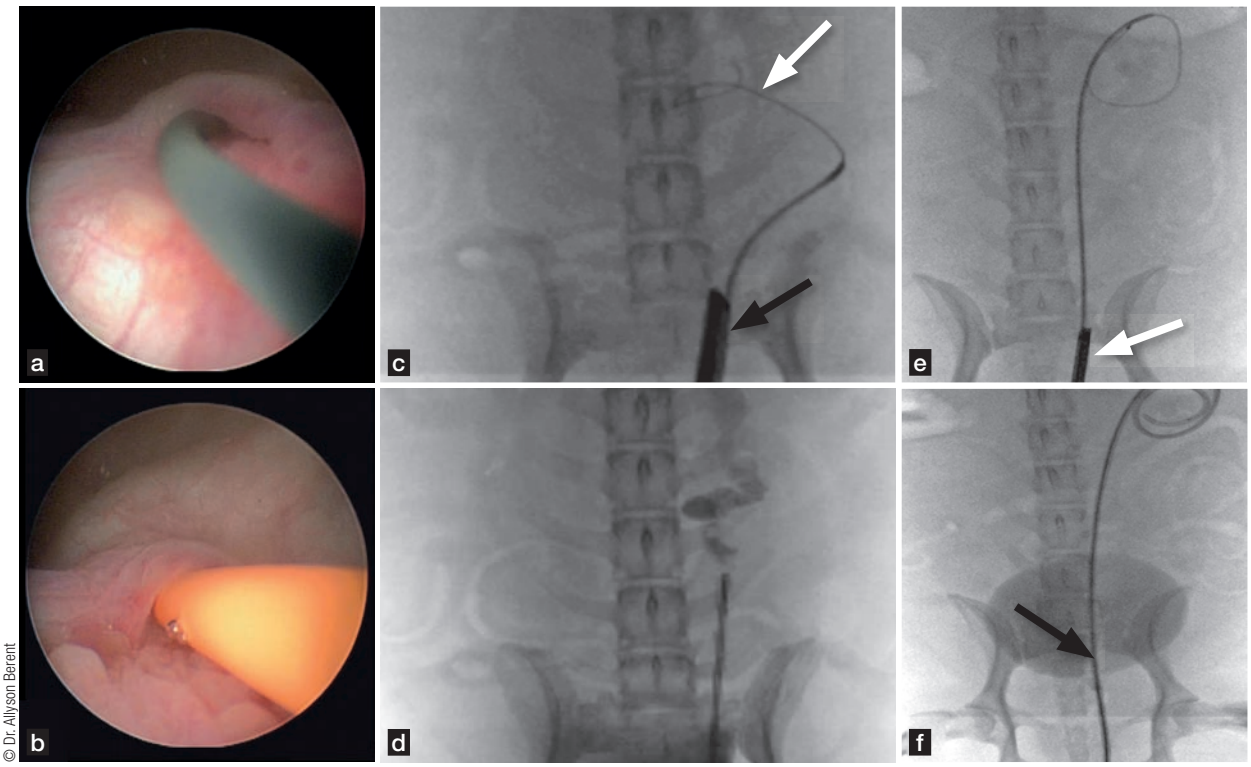

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Figure 5. Cystoscopic- and fluoroscopic-guided retrograde ureteral stent placement in a female dog.

(a) A guidewire is advanced into the ureteral lumen from the UVJ by endoscopy.

(b) An open-ended ureteral catheter is then advanced over the guidewire into the ureteral lumen.

(c) Under fluoroscopy the guidewire (white arrow) and open-ended ureteral catheter (black arrow) can be seen being advanced in a retrograde manner up the ureter.

(d) The wire is then removed; the catheter remains in the ureter and a retrograde ureteropyelogram is performed to outline the ureteral obstruction.

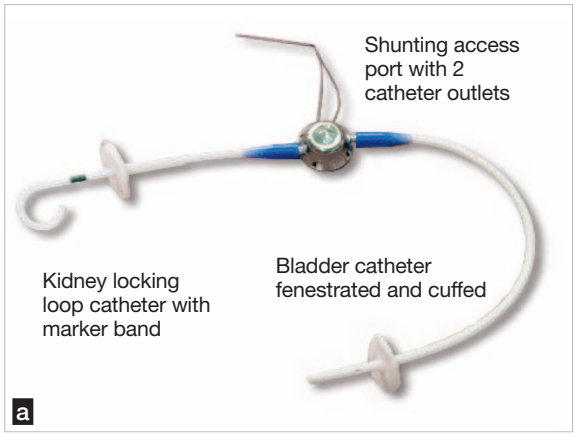
(e) The guidewire is then re-advanced through the ureteral catheter (white arrow) and into the renal pelvis.

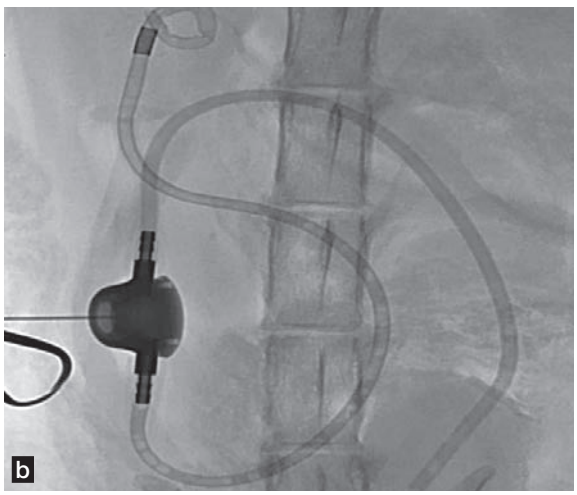
(f) The bladder is filled with contrast to identify the UVJ under fluoroscopy, and the stent, supported by a catheter (black arrow), is advanced over the guidewire into the renal pelvis.

The guidewire is then retracted and the distal end of the stent pushed into the urinary bladder.
Once the stent is within the bladder the pushing catheter and wire are completely removed; patency is verified if fluid can be seen draining through the stent fenestrations.

long-term complications (> 1 month) were less severe (dysuria (35%, with 4% persistent), stent migration (6%), ureteral stent reaction (3%), and scar tissue around the stent (11%)). Scar tissue is typically associated with a concurrent ureterotomy or a previous stricture and can occur 3-6 months post-placement; 57% of all cases that developed scar tissue had a previous stricture in their ureter at the time of stent placement. These strictures have also been associated with a circumcaval ureter (1,5,22). For strictured cats, we typically recommend the placement of a subcutaneous ureteral bypass (SUB) device rather than a ureteral stent, which avoids the risk of re-obstruction (1,5,6,27).

In dogs with ureterolithiasis, stenting is almost always performed via endoscopic and fluoroscopic guidance ***(Figure 5)***, in a retrograde manner, and is considered an outpatient procedure. We achieve ~98% success with fewer complications than in cats over all time periods (peri-operative, short- and long-term). These included recurrent UTI (< 20%, with over 75% having infection present pre-stent), proliferative tissue growth around the distal





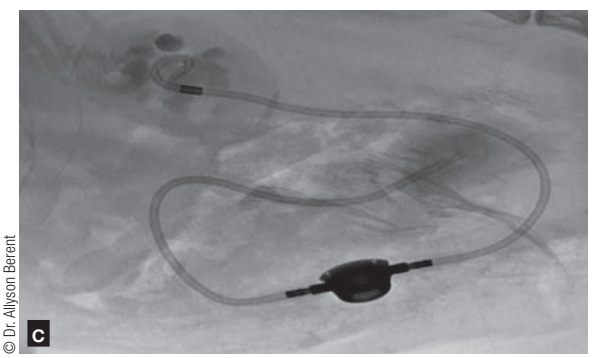


Figure 6. A subcutaneous ureteral bypass device in a cat. This allows urine to flow from the kidney through the shunting port and into the bladder, bypassing the ureter.

(a) The device labeled to identify the components.

(b) VD fluoroscopy image showing the nephrostomy and cystostomy catheters connected to the shunting port.

(c) Lateral fluoroscopy image showing contrast in the renal pelvis after the system has been flushed via the port.

loop of the stent at the ureterovesicular junction (~15%), stent migration (< 5%), occlusion (< 5%), and encrustation (< 5%). Dysuria is much less common in dogs than in cats after stent placement (< 1%), and both species are typically glucocorticoid responsive if resolution is not spontaneous.

Preliminary data (1,5,6,22,27) suggest that ureteral stenting in both dogs and cats is safe and effective, resulting in immediate decompression of the renal collection system. There are few major procedural or perioperative complications reported, and most are not life-threatening and can be managed medically, but owners should be prepared for "stent upkeep". The equipment has dramatically improved recently, making stenting less complicated and faster, but is still technically challenging. In cats, stent replacement or manipulation may be necessary if a complication develops and because of this I prefer the SUB devices for most cats and stents for most dogs.

Subcutaneous ureteral bypass device

The use of a SUB device ***(Figure 6)*** has recently been described (6); this involves an indwelling long-term nephrostomy catheter placed into the renal pelvis linked by a port to a cystostomy catheter placed into the bladder, effectively bypassing the ureteral obstruction, and remaining completely intracorporeal. The shunting port, secured subcutaneously to the ventral abdominal wall under the skin, allows the device to be flushed every 3 months to prevent occlusion and also permits collection of urine samples for culture, and has met with considerable success (28).

At the AMC we have performed this procedure in over 100 ureters (95% in cats) to date for various reasons, initially for proximal ureteral strictures or ureteral stent failure, but more recently as the first choice for feline ureteral obstructions. Performed with surgical assistance and fluoroscopic guidance, it shows excellent long-term results, with good tolerance of the device and patency maintained in ~94% of cats and 90% of dogs over a median of 2 years. Six devices were found to obstruct with stone debris, 4 of which needed replacement, whilst the others were treated with serial flushing.

The main complication was leakage at the nephrostomy tube site, but recent design developments have led to 97% of patients surviving to discharge (deaths being unrelated to ureteral obstruction or surgical complication); the biggest risk post-operatively in all cats with ureteral obstructions is the development of pancreatitis or complications from fluid overload.

Conclusion

In general, the minimally invasive management of veterinary upper tract urolithiasis is following the trend seen in human medicine. Over the past 5-10 years great strides have been made in adapting human technology for veterinary patients. Small adjustments to various devices have allowed many hurdles to be crossed, and we can currently treat patients that would have been considered unsuitable for surgical intervention in the past. These newer treatment options are still considered investigational and most are only currently available at a few institutions around the world, but the outcomes are promising and the use of such devices is growing.

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Clinical findings in cats and dogs with chronic kidney disease

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Introduction

Chronic kidney disease (CKD), formerly referred to as chronic renal failure, is common in elderly pets; 7.9% of cats and 1.5% of dogs > 10 years of age seen at Banfield Pet Hospitals in 2012 were diagnosed with the disease, and the progressive and irreversible nature of kidney damage threatens the longevity and quality of life for affected pets. It is therefore important to understand the demographic and clinicopathologic characteristics typical of pets first diagnosed with CKD in general veterinary practice.

Method of analysis

Canine and feline patients at 815 Banfield Pet Hospitals were considered eligible for the study when they had a first-ever diagnosis of CKD at some point in 2011 or 2012. Included patients were required to have had at least one other recorded consultation prior to the visit when CKD was diagnosed. Variables recorded at time of CKD diagnosis included age and bodyweight, sex, reproductive status, and breed size (dogs only). Other variables extracted closest to (before or after) the CKD diagnosis were as follows: serum creatinine, phosphate, calcium, and potassium concentrations; urine specific gravity; diagnosis of overweight, obesity, or underweight; and type of diet fed (wet, dry or mixed). It was also noted if there was a prior or existing diagnosis of periodontal disease, cystitis, hyperthyroidism, hypertension, or diabetes mellitus.

Summary statistics were calculated as percentages and mean ± SD when normally distributed or as median (range) when not normally distributed. The Chi square test was used to compare the proportions of pets with CKD with those in the general population with respect to reproductive status, breed size and diet types and with those in the general geriatric pet population (*i.e.,* ≥ 10 years of age) regarding prevalence of various diseases. Values of $P < 0.01$ were considered significant.

Results

A total of 11,752 cats and 7,293 dogs met the study inclusion criteria. The mean ± SD age of cats with CKD was 13.5 ± 4.2 years, with 81.0% (9,516/11,752) ≥ 10 years of age. The mean age of dogs was 10.9 ± 4.1 years, with 65.3% (4,762/7,293) ≥ 10 years of age.

Comparisons with the general patient population showed spayed female (6,022/11,752; 51.3%) and neutered male (5,266/11,752; 44.8%) cats to be over-represented ($P < 0.001$) among cats with CKD (general population values, 36.6% and 36.5%, respectively). The same was true for spayed female dogs (3,630/7,293; 49.8% *vs* 36.5% in general population) but not for neutered males (2,590/7,293; 35.5% *vs* 36.6% in general population). Intact males and females were under-represented in both species with CKD. No significant differences were evident in the distribution of breed sizes in dogs with CKD, as compared with the distribution in the general population, nor was any difference evident between cats and dogs with CKD and the general population in type of food consumed.

The prevalence of cats and dogs with CKD that were also underweight and had periodontal disease was much higher than in the general population > 10 years of age ***(Table 1)***. Cats and dogs with CKD were also more likely to have cystitis, hyperthyroidism, diabetes mellitus and/or hypertension.

According to the IRIS staging system (1) (for more information, see inside front and back covers), which recommends use of plasma creatinine values to stage disease progression, the distribution of cats newly diagnosed

Table 1. Distribution of comorbidities in cats and dogs with CKD.

Diagnosis	No. (%) of all cats with CKD (n = 11,752)	% in general geriatric cat patient population (n = 162,102)	No. (%) of all dogs with CKD (n = 7,293)	% in general geriatric dog patient population (n = 420,203)
Overweight	813 (6.9)[a]	23.5	705 (9.7)[a]	26.0
Underweight	1,212 (10.3)[b]	5.5	396 (5.4)[b]	1.8
Periodontal disease	3,312 (28.2)[b]	19.6	3,006 (41.2)[b]	27.4
Cystitis	1,838 (15.6)[b]	6.8	1,081 (14.8)[b]	3.7
Hyperthyroidism	1,081 (9.2)[b]	6.3	13 (0.2)[b]	0.1
Diabetes mellitus	406 (3.5)[b]	3.2	120 (1.7)[b]	1.1
Hypertension	122 (1.0)[b]	0.3	81 (1.1)[b]	0.2

[a] Value is significantly ($P < 0.01$) lower than in the general population. [b] Value is significantly higher than in the general population.

Table 2. Values of clinicopathologic variables in cats and dogs with CKD.

Variable	No. of cats with results	Value	Reference interval (2)	No. of dogs with results	Value	Reference interval (2)
Serum creatinine (mg/dL)	9,285	3.2 (0.4-33.6)	0.9-2.2	6,372	2.6 (0.4-36.0)	0.5-1.7
Urine specific gravity	6,046	1.019 ± 0.038	1.020-1.040	3,804	1.018 ± 0.010	1.016-1.060
Serum potassium (mEq/L)	6,106	4.3 ± 1.0	3.7-6.1	3,939	5.0 ± 1.8	3.9-5.1
Total calcium (mg/dL)	9,302	10.3 ± 1.0	8.7-11.7	6,432	10.8 ± 1.3	9.1-11.7
Serum phosphate (mg/dL)	9,316	5.3 (0.1-32.2)	3.0-6.1	6,435	5.9 (0.2-30.4)	2.9-5.3

Normally distributed data are reported as mean ± SD, and non-normally distributed data are summarized as median (range).

with CKD in each stage of disease for which creatinine values were available (n = 9,285) was as follows: nonazotemic (< 1.6 mg/dL), 366 (3.9%); mild renal azotemia (1.6-2.8 mg/dL), 3,121 (33.6%); moderate renal azotemia (2.9-5.0 mg/dL), 3,403 (36.7%); and severe renal azotemia (> 5.0 mg/dL), 2,395 (25.8%). The distribution of dogs with available creatinine values (n = 6,372) was as follows: nonazotemic (< 1.4 mg/dL), 506 (7.9%); mild azotemia (1.4 to 2.0 mg/dL), 1,492 (23.4%); moderate azotemia (2.1-5.0 mg/dL), 3,221 (50.5%); and severe azotemia (> 5.0 mg/dL), 1,153 (18.1%). Values of these and other clinicopathologic values for cats and dogs were summarized ***(Table 2)***.

Discussion

This basic analysis revealed some interesting findings that may aid clinicians in formulating their index of suspicion of CKD in cats and dogs, particularly in those ≥ 10 years old that are underweight and have other diseases. Clinical signs associated with kidney disease (*e.g.*, lethargy, dehydration, vomiting, or polyuria/polydipsia), though nonspecific, are also useful to raise the suspicion of CKD. The range of values for serum creatinine concentration and the high prevalence of cats with apparently normal values at the early stages of CKD reinforce the potential for mistakes to be made if reference limits are used to rule out the disease. Additional research is needed to better understand the natural history of CKD and the percentage change in analytes that can be expected for pets in the early stages when appropriate interventions may slow disease progression and make patients more comfortable.

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Infectious renal disease in dogs

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Introduction

Acute kidney injury (AKI), leading to severe uremia, is associated with high morbidity and mortality (1,2). AKI has multiple etiologies, including infectious agents, nephrotoxicity, ischemia and others. Infectious diseases are both important and common causes of renal injury, as the kidneys may be directly damaged by an infecting agent itself (as in leptospirosis or pyelonephritis) or secondary to systemic diseases or complications (*e.g.*, following sepsis or pyometra) (3-6). Immune complex deposition in the kidneys subsequent to immune system stimulation by an infectious agent is an additional intrinsic cause for acute, or more commonly, chronic glomerular kidney damage (*e.g.,* leishmaniasis). The prevalence for infectious agents as a cause for renal damage does vary between different geographical areas, but in a recent retrospective study infectious diseases were identified as the etiological cause in approximately one third of dogs with acute kidney injury (1).

KEY POINTS

- **Infectious diseases are important and common causes of renal injury. An infective agent may directly damage the kidneys or may be secondary to systemic diseases or complications; damage can also be caused by immune-mediated reactions.**
- **The prevalence of renal damage from infectious causes varies between different geographical areas.**
- **Leptospirosis is a re-emerging disease, diagnosed with increased frequency over the past decade, in both humans and animals. Any dog with acute kidney injury of unknown cause should be tested for leptospirosis.**
- **Many infectious agents have been associated with stimulation of the immune system leading to glomerulopathies caused by immune complex deposition within the kidneys.**

Leptospirosis

Leptospirosis is a worldwide zoonosis resulting from infection with pathogenic species and serovars of the bacterium *Leptospira interrogans sensu lato* ***(Figure 1)***. This bacterium is an obligate aerobic spirochete that shares features of both gram-negative and gram-positive bacteria. Each *Leptospira* serovar has a specific primary host that also serves as its reservoir. The bacterium remains in the host species within the renal tubules and is shed to the environment mostly via the urine. The dog is the reservoir host for the pathogenic *Leptospira interrogans* serovar Canicola.

Leptospirosis is a re-emerging disease, diagnosed with increased frequency over the past decade in both humans and animals (3,4). In the past, *Leptospira interrogans* serovars Canicola and Icterohaemorrhagiae were responsible for most leptospiral infections in dogs, but with the introduction of bivalent vaccines the incidence of these serovars as the causal agent for canine leptospirosis has decreased. Recent studies suggest that the most common serovars now diagnosed in dogs with leptospirosis are Grippotyphosa, Pomona, Autumnalis, and Bratislava (5-7). Consequently, new vaccines containing

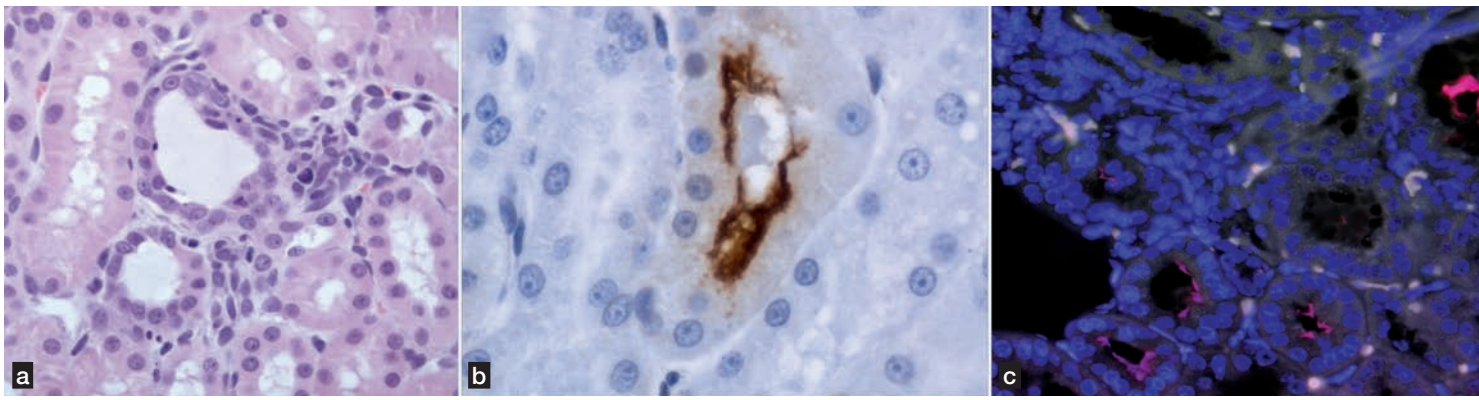

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Figure 1. Histological sections (light microscopy **(a)**, immunohistochemistry **(b)** and fluorescence *in situ* hybridization (FISH) **(c)**) taken from a dog with leptospirosis infection. The bacteria can be identified by the brown staining in **(b)** and pink staining in **(c)**.

the serovars Grippotyphosa and Pomona have now been introduced in many countries.

Dogs can be infected with *Leptospira* organisms when exposed to a contaminated environment or, less commonly, through venereal routes, placental transfer, bite wounds, or ingestion of infected tissues. Both the prevalence of leptospirosis and the distribution of the different serovars varies among geographical areas (5,8-12). Risk factors for infection in dogs as identified by a recent review include contact with rodents or slow-moving/stagnant warm water, free roaming in rural areas, living in developing countries, and raw meat ingestion. Intact male working dogs are at high risk (13). However leptospirosis may occur in any dog.

Clinical signs of the disease may be mild to severe, and are often non-specific; the severity may vary substantially, from subclinical infection to peracute infection and death. Common signs include vomiting, lethargy and anorexia, and the clinical presentation often resembles that of acute kidney injury. Liver involvement or failure is being reported less frequently with the decreasing incidence of infection with the serovar Icterohaemorrhagiae. Other affected organs and systems may be involved, including the lungs, the blood coagulation system, and (less commonly) the central nervous system. There is some evidence to suggest that the severity of the disease is influenced by the infecting serovar, with the Pomona serovar being responsible for the most severe disease and associated with the highest mortality rate (5).

The diagnosis of leptospirosis is based on clinical presentation and confirmed via laboratory tests. Any dog with acute kidney injury of unknown cause should be tested for leptospirosis, and a definitive diagnosis should always be attempted due to the zoonotic potential of the disease and the possibility that an infected dog may serve as a reservoir. The most common diagnostic method for leptospirosis is the microscopic agglutination test (MAT), although PCR is becoming readily available and will likely be employed more frequently in the future. Despite its widespread use the MAT serologic test has many disadvantages; it is subjective, the results are discordant across different laboratories (14), it lacks sensitivity (as the immune response may not have had sufficient time to develop in the early phase of the disease), and its specificity is hampered due to vaccinal antibodies.

Therefore high titers, or preferentially convalescent titers, (*i.e.,* 4-fold increase in MAT titers) are required to confirm the diagnosis. A single titer may be reliable when greater than 1:3,200 for a vaccinal serovar or greater than 1:1,600 for a non-vaccinal serovar. It was previously suggested that the infecting serovar is the one which presents the highest MAT titer, but during the course of the disease individual dogs may show varying titer levels to different serovars, making it difficult to predict which is the actual infecting serovar (14). Fortunately, and despite its importance from an epidemiologic point of view, this fact does not affect therapy, which does not vary between serovars. PCR can be used to identify the organism in the blood or in the urine in early stages of the disease, and earlier than with the MAT (15), but it is vital that samples are obtained before initiating antibiotic therapy.

Treatment of leptospirosis is aimed at bacterial elimination using antimicrobials, along with supportive care to control clinical signs and the clinicopathologic abnormalities associated with kidney injury. Early identification of

the disease and early initiation of treatment decrease the zoonotic risk; antimicrobial therapy should therefore be commenced in suspected cases as soon as possible, even before laboratory test results are available. Shedding is usually terminated within 24 hours of antibiotic initiation, but owners and staff should be cautious when handling dogs suspected of having leptospirosis.

For the acute phase, penicillins (*e.g.*, ampicillin, 20 mg/kg IV q8hr) are often used. Doxycycline (10 mg/kg PO q24hr) for 3 weeks is recommended to obtain bacterial clearance from the tissues and to prevent a carrier state. With the recent shift in the incidence of different leptospiral serovars, acute kidney injury, rather than severe liver injury, is usually the main clinical feature and supportive treatment should include rapid rehydration, promotion of urine production using diuretics (*e.g.*, mannitol, furosemide), maintaining homeostasis (*i.e.*, correcting blood pressure, electrolytes and acid-base balance as necessary), and controlling other clinical signs until recovery is achieved.

Leptospirosis is associated with reversible kidney injury and has a relatively high survival rate (~80%) compared with other etiologies of acute kidney injury (16). Nevertheless, and despite the potential for recovery, dogs may die due to the consequences of uremia or other disease-associated complications. When medical management fails, dialytic intervention is indicated to control clinical signs and clinicopathologic abnormalities. It has been shown that even when the injury is severe enough to necessitate dialysis, recovery rates still approximate 80% (1). Due to the relatively fast recovery, approximately four hemodialysis treatments may be required before dogs become dialysis-independent.

Pyelonephritis

Pyelonephritis is defined as an inflammation of the renal pelvis, and is most commonly caused by an ascending lower urinary tract bacterial infection.

Vesicoureteral reflux occurs when the intravesicular pressure increases above intraureteral pressure, which predisposes to pyelonephritis. Normally, as the urinary bladder fills, the intravesicular pressure compresses the ureters, due to their oblique course through the bladder wall (*i.e.*, the vesicoureteral valve), thereby preventing urine reflux. The length and diameter of the ureteral submucosal portion, its peristaltic action, the pressure gradient between the urinary bladder and the ureters, and detrusor muscle integrity all influence the vesicoureteral valve function. Vesicoureteral reflux is documented in 10% of clinically normal adult dogs (more commonly in females) and is usually bilateral (17).

Apart from the vesicoureteral reflux, other predisposing factors for pyelonephritis include compromised immune status (*e.g.*, diabetes mellitus, hyperadrenocorticism) and chronic kidney disease. Since most lower urinary tract infections (with the exception of prostatic infection) do not cause systemic illness, pyelonephritis should be suspected in any dog presenting with a urinary tract infection and systemic signs (*e.g.*, fever, lethargy, anorexia). Pyelonephritis should also be considered in any dog with acute kidney injury and a positive urine culture. Nevertheless, in a study evaluating 182 dogs with acute kidney injury requiring hemodialysis, pyelonephritis was rare, occurring in only ~2% of the cases (16).

Conversely, pyelonephritis is a relatively common etiology for acute exacerbation of static chronic kidney disease (*i.e.*, “acute on chronic”), and therefore should be considered when a dog with a stable chronic kidney disease presents with a sudden unexpected worsening of azotemia. Moreover, urine cultures should be performed routinely in dogs with chronic kidney disease since infection limited to the urinary bladder is often asymptomatic in such cases, and if left untreated, infection may ascend to the renal pelvis. This approach should also be implemented in dogs with diabetes mellitus or hyperadrenocorticism, as bacterial cystitis is common but often asymptomatic in these cases.

It is possible that pyelonephritis is underdiagnosed, because clinicians often expect the disease to be associated with severe clinical signs. Nonetheless, it is important to be aware that pyelonephritis may not always be accompanied by systemic illness, and the absence of signs should not exclude the possibility that disease is present. Pyelonephritis should also be suspected in dogs with persistent or relapsing chronic urinary tract infections. The definitive diagnosis of pyelonephritis is challenging, and is based on compatible clinical signs, imaging modalities and a positive urine culture. Ultrasonographic signs consistent with pyelonephritis include a hyperechoic, dilated pelvis, and blunting of the renal pelvis papilla ***(Figure 2)***; however, these changes are variable and should not be considered pathognomonic.

Treatment of pyelonephritis varies, based on the severity of the disease. Acute pyelonephritis often requires

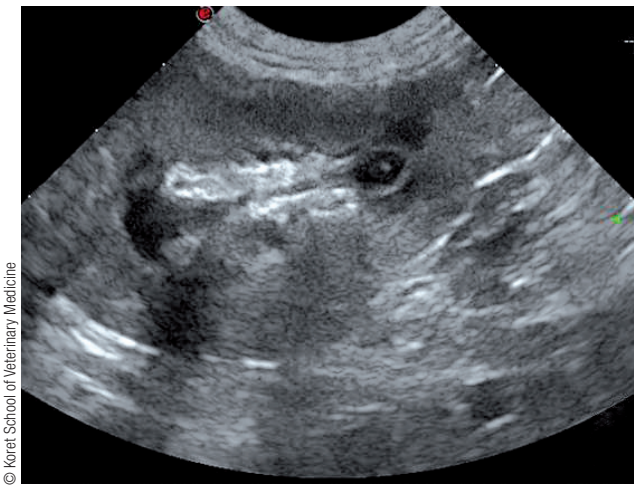

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Figure 2. Ultrasonographic signs consistent with pyelonephritis include a hyperechoic, dilated pelvis and blunting of the renal pelvis papilla.

hospitalization for parenteral antimicrobial treatment and supportive therapy when azotemia is present. Antimicrobial choice should be based on culture and sensitivity results, and treatment should be continued for a minimum of 4-8 weeks. It is also important to select an antibiotic (such as a quinolone) with good penetration to the renal parenchyma, but if the chosen drug is excreted renally the dose should be adjusted when azotemia has developped. Urine culture should be performed before initiation of antibiotic therapy, during the treatment (to assure *in vivo* efficacy and to exclude persistent infection), before its discontinuation (to rule out superinfection) and several days after the end of treatment (to exclude relapse). When pyelonephritis is present in the face of ureteral obstruction, treatment should be aggressive and immediate, with the aim of removing the obstruction or achieving urine diversion, as severe kidney damage may occur very rapidly in such cases.

The prognosis for acute kidney injury due to pyelonephritis is favorable, since specific therapy can be applied based on culture and sensitivity results. The survival rate of dogs with pyelonephritis is probably high, as has been shown in cats with acute pyelonephritis (18), but available data are limited.

Systemic infections commonly affecting the kidneys

Some bacterial diseases in dogs commonly affect the kidneys, including pyometra and sepsis. Pyometra has been associated with kidney dysfunction in dogs through a variety of mechanisms, including formation of circulating immune complexes and direct tubular damage.

A recent study evaluating kidney damage in dogs with pyometra using biomarkers suggests that the prevalence of pyometra-associated kidney injury is substantially higher than previous estimations had suggested (19). In this study a third of the dogs had increased serum creatinine concentration at presentation and 2 out of 25 dogs developed overt acute kidney injury based on routine biomarkers. However, 68% of the non-azotemic dogs also had evidence of kidney damage, based on elevation of other biomarkers, suggesting that kidney injury should be considered in any dog with pyometra, even if routine markers (*e.g.*, serum creatinine and urea) are within the reference intervals (19).

This study also demonstrated that the evaluation of kidney damage using routine biomarkers probably underestimates its true prevalence in a variety of systemic conditions (see article "Biomarkers for early diagnosis of feline chronic kidney disease" on page 34 for more information).

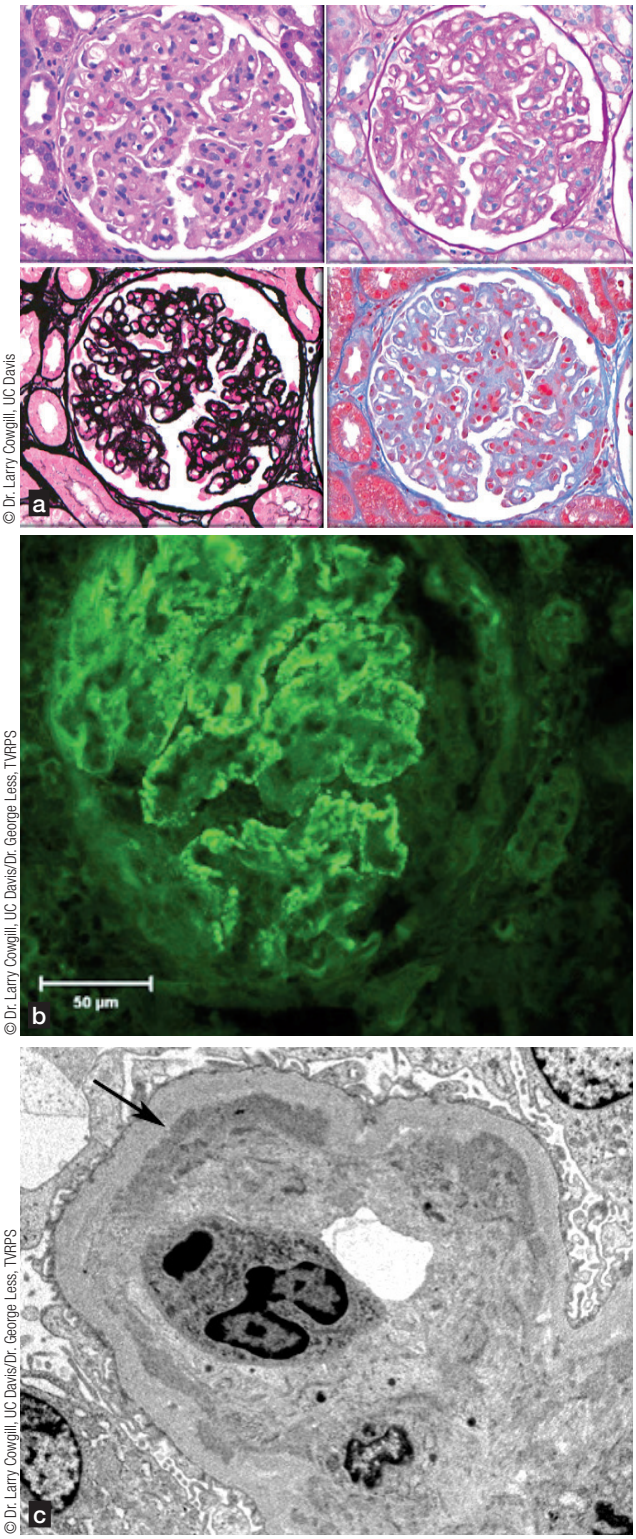
Sepsis is one of the most common causes of acute kidney injury in human patients hospitalized in intensive care units, and this may be true in dogs as well, although its true prevalence in this species is currently unknown. The pathophysiology of sepsis-associated acute kidney injury is likely multi-factorial and includes ischemia, vasoconstriction, reperfusion injury, apoptosis, and the presence of reactive oxygen species.

Treatment of sepsis-associated acute kidney injury should be aggressive and directed towards eliminating the underlying cause, as well as appropriate supportive treatment of the uremic-based clinical consequences. There are no data regarding the prognosis of sepsis-associated acute kidney injury in dogs, but in human patients the mortality rates are as high as 70%.

Fungal infections

Fungal infections in the urinary system have been reported infrequently in dogs. Primary fungal urinary tract infections are most commonly caused by *Candida spp.* (20). Affected animals typically have local or systemic compromised immune status which predisposes them to infection. Other agents that can cause fungal pyelonephritis include *Aspergillus* and *Cryptococcus spp.* (21). Fungal infection may be suspected from routine urine sediment examination, but culture is required to confirm the diagnosis. Treatment consists of administering antifungal

Figure 3. Immune complexes within the kidneys can be demonstrated by light microscopy (using a variety of stains) **(a)**, immune-fluorescent antibody technique **(b)**, or electron microscopy **(c)** – the arrow in the latter image indicates an immune complex.



agents that are excreted via the kidneys (*e.g.*, fluconazole) and eliminating the underlying cause wherever possible. Treatment should be continued for at least 4-6 weeks and repeated urine sediment examinations should be performed to confirm successful elimination.

Immune-mediated diseases

Many infectious agents have been associated with stimulation of the immune system, leading to immune complex deposition in the kidneys and glomerulopathies ***(Figure 3)***. These immune-mediated injuries can manifest as acute kidney injury but more often induce progressive chronic renal damage. The hallmark of glomerular disease is proteinuria, and therefore persistent proteinuria should raise the suspicion of glomerular disease, and possibly an underlying infectious cause. There is growing evidence in both veterinary and human literature suggesting that proteinuria is associated with a more rapid progression of chronic kidney disease, higher frequency of uremic crises, and an increased mortality rate (22). It has also been shown that the prognosis for a favorable long-term outcome decreases if there is marked proteinuria (23).

When glomerular disease is suspected, a diagnostic work-up should be performed, directed towards detecting the origin of the proteinuria and the underlying disease, including possible infectious agents. The work-up includes obtaining a complete history and performing a full physical examination as well as diagnostic investigations such as serologic and PCR testing for infectious disease. It is important to rule out the presence of any infectious agent, as some types of glomerular disease require immunosuppressive therapy which may worsen any undiagnosed infection.

Lyme-associated nephritis is an example of a disease presumably of infectious etiology (*Borrelia burgdorferi*) that has been associated with rapidly progressive membranoproliferative glomerulonephritis with concurrent severe tubular necrosis, corticointerstitial inflammation, and acute uremia. It has been suggested that the main pathogenesis of the disease is immune complex formation. Prognosis in these cases is considered grave due to the rapid, progressive nature of the disease, although adjunctive management using immunosuppressive therapy might be helpful (24).

Conclusion

In summary, the kidney can be affected by infectious diseases through a variety of mechanisms. In some cases

the kidney is the primary target of the infecting agent, whilst in other situations the kidneys can be affected by systemic infection or damaged following an abnormal immune response. In many cases of infection-associated acute kidney injury, specific antimicrobial therapy can be employed to eliminate the cause; this offers a more favorable prognosis when compared with other forms of acute or chronic kidney disease, which are often progressive in nature and frequently have an unknown etiology that cannot be eliminated.

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Biomarkers for early diagnosis of feline chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is highly prevalent in cats and increases with advancing age, with over 30% of cats > 15 years of age being affected (1). It can be a significant cause of morbidity and mortality; one study following cats with CKD where no attempt was made to control management of the condition reported a median survival time of only 233 days (2). Routine diagnosis of feline CKD is based on taking a patient's history, clinical examination, plasma or serum urea and creatinine measurements, measurement of urine specific gravity (USG) and quantification of proteinuria. It is commonly reported that 75% of nephron function is lost before azotemia develops, but many cats do not show obvious clinical signs of CKD even when azotemia has developed. Prompt diagnosis of CKD allows the clinician to commence management strategies such as renal diet, which has been shown to improve survival time in azotemic patients (3,4). The ability to identify cats in the early stages of CKD would allow clinicians to monitor these cases closely and detect azotemia as soon as it develops. It may also facilitate earlier intervention to treat the underlying cause of the CKD if one can be found.

KEY POINTS

- **Chronic kidney disease (CKD) is very prevalent amongst older cats and causes significant morbidity and mortality.**
- **Prompt diagnosis allows for earlier intervention and treatment of the disease in an attempt to improve survival time.**
- **Biomarkers for non-invasive early diagnosis of CKD are sought after and this is an active area of current research.**
- **Biomarkers of tubular damage or dysfunction, endogenous markers of GFR and hormonal biomarkers have all been explored, but the "perfect" biomarker for feline CKD has not yet been identified.**
- **Current recommendations to detect early CKD include serial measurements of serum creatinine, USG and UPC during screening of apparently healthy middle-aged to geriatric cats.**

CKD can be the result of inflammatory, infectious, neoplastic or genetic conditions. However, in the majority of cases, feline CKD results from chronic tubulointerstitial nephritis of unknown cause, characterized by tubular dilatation and atrophy, and interstitial inflammation and fibrosis (5). Regardless of the underlying etiology, loss of nephrons results in a reduction in the glomerular filtration rate (GFR), which ultimately leads to an inability to concentrate urine and the development of azotemia.

Tools to help diagnose CKD in its earlier stages, without employing invasive renal biopsies, are sought after and this is an active area of research. Techniques that have and are being investigated include those which focus on estimating or measuring GFR, and those which look for markers of kidney damage/injury. Biomarkers can be objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (6). This article will discuss biomarkers that have been and are currently being investigated to facilitate early diagnosis of feline CKD, and review current recommendations for

veterinarians using biomarkers in practice. Techniques for measuring GFR are outside the scope of this article, but have been covered elsewhere (7).

Endogenous markers of GFR

Measurement of GFR is generally accepted to be the most useful tool for identifying and staging CKD and an estimated GFR formula (eGFR) is routinely used for this purpose in humans; the formula takes into account plasma creatinine concentration and a number of other factors including age, sex and race. Despite numerous markers and sampling methods being explored for measuring GFR in the cat, there is no current consensus for the optimal protocol to follow and no available feline-specific eGFR formula. As a result, in veterinary medicine the IRIS staging system (for more information, see inside back cover) uses serum creatinine as a surrogate marker of GFR.

Azotemia refers to increased concentrations of non-protein nitrogen wastes, such as creatinine and urea, in the blood. Creatinine is a suitable biomarker for GFR because it is produced at a constant rate in the body from breakdown of creatine phosphate in muscle tissues, is freely filtered at the glomerulus, and is not reabsorbed by the renal tubules. The relationship between creatinine and GFR is exponential; creatinine doubles when GFR decreases by half and is not elevated above the reference range until GFR has reduced by 75%. Serum creatinine does increase as GFR declines in the early stages of CKD, but because of the exponential relationship this change is small and will typically be "hidden" within the reference range, thus limiting the use of creatinine as a biomarker for early renal disease. An additional limitation in the use of serum creatinine as a biomarker for early CKD is the inconsistency in laboratory reference ranges, which vary greatly. However, serum creatinine is an independent predictor of cats that will develop azotemia within 12 months (8).

Care must be taken when interpreting measurements of serum creatinine in cats; patients should be fasted and well hydrated prior to blood sampling, measurements should be repeated for confirmation prior to staging under the IRIS system, and assessment of changes in body muscle mass should be taken into account. It should be noted that cases should only be staged under IRIS once a diagnosis of CKD has been made (*i.e.,* creatinine has been documented to be persistently above the laboratory reference range in a well-hydrated cat, ideally with concurrent demonstration of a USG < 1.035) or if an abnormality has been detected that puts a cat at a high risk of developing azotemia, such as persistent proteinuria or an abnormal renal biopsy.

Urea is produced in the liver from breakdown of ammonia. Serum urea concentration is another endogenous marker of GFR but is a much poorer indicator of GFR than creatinine. Urea is freely filtered at the glomerulus but is also reabsorbed by the collecting duct under the control of antidiuretic hormone. It is trapped in the medullary interstitium to form part of the concentrating mechanism of the kidney, therefore in the face of dehydration, serum urea increases in the absence of kidney disease even though GFR is maintained. Serum urea also increases when protein catabolism is induced, can increase after food intake, and can decrease with severe hepatic failure; serum urea concentration should therefore only be interpreted alongside serum creatinine concentration for assessment of renal function. Studies examining alternative endogenous markers of GFR in the cat are lacking.

Urinary Biomarkers

Urine is an easily obtained bodily fluid which can be of great use to the clinician when evaluating a patient with possible renal disease. Since the majority of cases of feline CKD are due to tubulointerstitial nephritis, the most useful biomarkers for identifying early feline CKD are those which indicate tubular damage or dysfunction.

Urine specific gravity (USG) also gives an indication of tubular function and is easily measured in practice using a refractometer ***(Figure 1)***. Measurement of USG ≥ 1.035 in a cat suggests the kidneys have adequate urine-concentrating ability. One study showed that cats that go on to develop azotemia within 12 months have significantly lower USG than cats that remain non-azotemic (8).

Figure 1. USG gives an indication of tubular function and is easily measured in practice using a refractometer.

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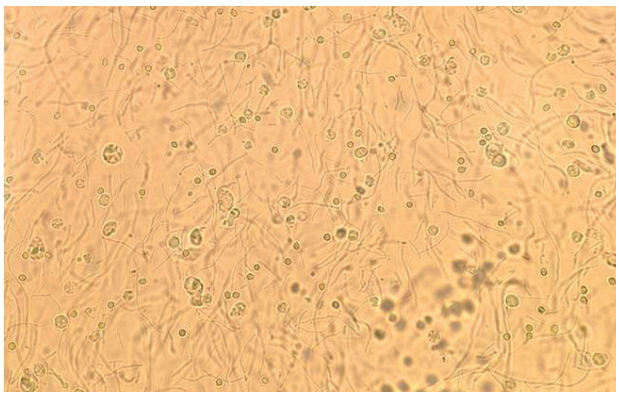


Figure 2. A urine sample taken by cystocentesis containing *E. coli* and numerous white blood cells (x40 magnification). The presence of a urinary tract infection should always be ruled out before interpreting UPC.

However, in this study, more than half of the cats that developed azotemia within 12 months had a USG ≥ 1.035 at baseline, therefore documenting concentrated urine in a cat does not rule out the presence of early CKD.

Measurement of USG < 1.035 may be indicative of renal damage in a non-azotemic cat, especially in a dehydrated animal. Note that cats fed solely on wet food may have a low USG, and care should be taken to rule out other causes of decreased urine concentrating ability (*e.g.,* diabetes mellitus or the use of diuretics). Biomarkers of tubular damage or dysfunction that have been researched in the cat are discussed below.

Proteinuria

In the healthy kidney, low and intermediate-molecular weight proteins are freely filtered at the glomerulus and reabsorbed by cells in the proximal tubules, so that the concentration of protein in the urine is low. Causes of proteinuria can be pre-renal, renal (functional or pathological) and post-renal (for more information, see Cut-out and keep on page 47). Sequential steps to help identify the origin of proteinuria have been published (9), and if these are followed, then diagnosis of persistent renal proteinuria indicates the presence of CKD.

Proteinuria can be measured semi-quantitatively during routine urinalysis, either by determination of urine protein: creatinine ratio (UPC) or by the assay of urine albumin, which can also be corrected by creatinine concentration to give urine albumin:creatinine ratio (UAC). Measurement of UPC is readily available in practice, but these measurements are invalid if a urinary tract infection (UTI) is present ***(Figure 2)***. It should also be noted that severe hemorrhage and inflammation can affect UPC. Mild proteinuria can be the result of glomerular or tubular damage, but tubular causes are more prevalent in the cat. Causes of moderate to severe proteinuria associated with UPC measurements ≥ 1.0 are uncommon in cats, but should make the clinician suspicious of glomerular disease if a UTI has been ruled out. It is advised that investigation into the cause of the proteinuria should be carried out in any non-azotemic patient with a UPC ≥ 1.0 (9).

Low concentrations of proteinuria are predictive of the development of azotemia within 12 months in geriatric cats (8). In this study healthy cats that went on to develop azotemia within 12 months had significantly higher UAC and UPC at baseline compared to cats that remained non-azotemic. In the multivariable analysis, which included age and measurements of USG, systolic blood pressure, creatinine, N-acetyl-β-D-glucosaminidase (NAG) activity (see below) and UPC or UAC, only creatinine and either UAC or UPC were independent predictors for the development of azotemia. The use of UAC offered no additional benefit in predicting azotemia development over UPC, which is more readily available in practice. This study was unable to clarify if proteinuria was a cause of renal injury or simply a marker of impending azotemia.

NAG activity

NAG is a lysosomal enzyme present in the epithelial cells of the proximal convoluted tubule. It is released into the urine following tubular damage and is therefore a possible biomarker for tubular injury.

There are two different isoenzymes; NAG A and NAG B. NAG A is continuously excreted and can be up-regulated during protein processing, whereas NAG B is only released during proximal tubular cell damage. NAG can be measured using an enzymatic assay, which allows easier adaptation to different species than many immunoassays which require the use of species-specific antibodies. A non-automated colorimetric technique has been validated for use in cats with and without CKD (10). Once NAG activity has been measured, this can be converted to the so-called NAG index by calculating the ratio of urinary NAG activity to grams of urinary creatinine. No correlation has been found between feline NAG index and plasma creatinine concentration, but NAG index is correlated with proteinuria severity (10) and is a predictor of the development of azotemia within a 12-month period in geriatric cats (8). This correlation is lost once the model is corrected for UPC, therefore

measuring NAG index currently offers no benefit over measurement of UPC for predicting impending azotemia. Future studies are required to ascertain if the isoenzyme activities of NAG A and B can be measured separately to aid use of NAG as a biomarker of tubular damage in early CKD.

Cauxin

Cauxin is a feline urinary protein produced in the proximal tubules and is present in particularly high concentrations in intact male cats (11). The function of cauxin has not been fully elucidated, but it is known to be involved in the production of a feline pheromone, felinine. Cauxin expression has been demonstrated to be reduced in feline kidneys with tubulointerstitial nephritis and azotemia (12). An immunoassay has been validated for the measurement of cauxin in feline urine, but the assay appears to measure denatured cauxin, which requires all samples to be stored for a minimum of 7 days at -20°C before measurements can be performed (13). Using this assay, the urinary cauxin:creatinine ratio (UCC) was found to be significantly different between geriatric cats with differing severities of proteinuria, and was significantly higher in healthy geriatric cats that went on to develop azotemia within 12 months, compared to cats that remained non-azotemic (13). However, the overlap of UCC between cats that remained non-azotemic and those that became azotemic during the 12-month period was substantial, making cauxin a poor biomarker to predict development of azotemia when used alone (13). Further studies are required to confirm if this marker may be of use when combined with the measurement of other biomarkers.

Retinol binding protein (RBP)

RBP is a low molecular weight protein produced in the liver which acts as a carrier for lipophilic vitamin A (retinol). Unbound RBP can be filtered at the glomerulus and is completely reabsorbed by the proximal tubules. As tubular function decreases, reabsorption of RBP also decreases, causing increased concentrations of RBP in urine and thereby allowing RBP to be a biomarker of tubular dysfunction. RBP has been demonstrated to be increased in cats with CKD and with hyperthyroidism (14). Urinary RBP reduces with radioiodine treatment of hyperthyroid cats, unless the cats become azotemic following treatment. It has, however, no predictive value for which cats will develop azotemia following treatment (15). No studies to date have examined the predictive value of RBP for the development of azotemia in healthy geriatric cats.

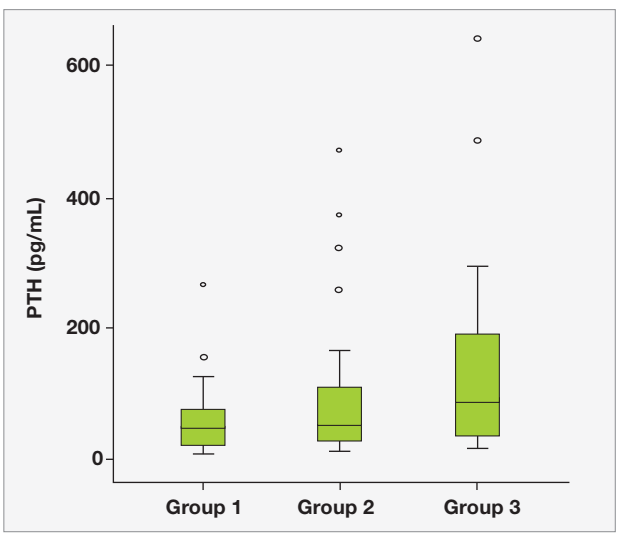
Proteomics

Proteomics is the analysis of expressed proteins in tissues, cells or biological fluids. This technique uses mass spectrometry to simultaneously identify multiple potential biomarkers which could then be used to help detect cats at risk of developing azotemia on an individual basis. A very recent study investigated feline proteomics and involved urine samples from 10 cats which remained non-azotemic after 12 months and 10 cats which developed azotemia within 12 months. This study identified 6 “clusters” on the output traces, which may represent 6 potential biomarkers that could help to identify cats at risk of developing azotemia (16). This technique is currently in its infancy and further studies are now required to identify these potential biomarkers and assess their usefulness in diagnosing early CKD in cats.

Plasma hormonal biomarkers

Parathyroid hormone (PTH) is secreted by the parathyroid gland primarily in response to plasma ionized hypocalcemia, and acts to increase plasma calcium

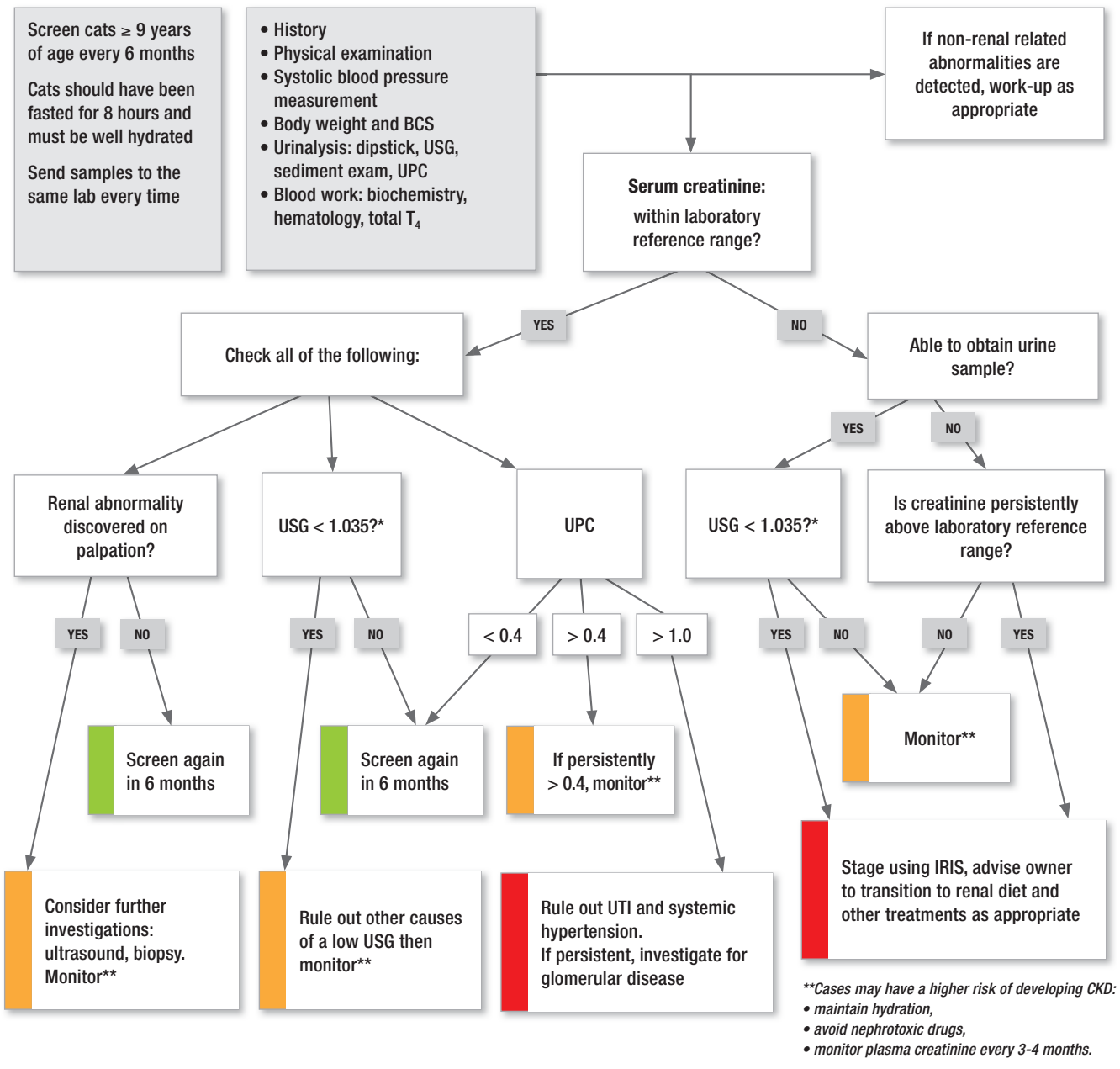
Figure 3. Box-and-whiskers plot illustrating the PTH concentrations in geriatric cats with various degrees of renal function at enrolment prior to being followed for 12 months (17). All cats were non-azotemic at baseline, then were grouped according to their renal function at the end of the 12-month study: Group 1 (n = 35) had plasma creatinine concentration ≤ 1.6 mg/dL (≤ 140 µmol/L), Group 2 (n = 52) had plasma creatinine concentration > 1.6 mg/dL (> 140 µmol/L) but had not been diagnosed with azotemic CKD and Group 3 (n = 31) had been diagnosed with azotemic CKD. PTH concentrations for Group 3 were significantly higher than Group 1 ($p < 0.017$), but not Group 2. However, the PTH concentrations overlapped greatly between Group 3 and Groups 1 and 2, limiting the usefulness of PTH as a biomarker for predicting the development of azotemia.



concentration by increasing calcium absorption from the gut and bone and decreasing plasma phosphate re-absorption in the kidney. A number of PTH assays have been validated and used in previous studies examining PTH in the cat, but unfortunately many of these assays are no longer available. One study found that PTH is increased in non-azotemic cats that go on to develop azotemia within 12 months, when compared to cats that remain non-azotemic (17) ***(Figure 3)***. Unfortunately, measurements of PTH overlapped greatly between cats that became azotemic and those that did not, limiting its use as a biomarker for impending azotemia in individual cats. Additionally, the assay employed in this study is no longer available.

Fibroblast growth factor 23 (FGF-23) is a hormone which acts on the sodium-phosphate cotransporters in the proximal tubules of the kidney to decrease phosphate

Figure 4. A logical approach using biomarkers to identify feline CKD as early as possible.



*Cats fed solely on wet food may have a low USG.

reabsorption from the urine. It is secreted by osteocytes and osteoblasts in response to increased plasma phosphate concentration, but as a low molecular weight protein it is also freely filtered by the glomerulus and therefore increases as GFR decreases (18). A human ELISA has been validated for use with feline plasma samples (19), but FGF-23 measurement is currently not available in commercial laboratories. Initial studies of this hormone indicate that it is increased in azotemic cats (19), correlates to GFR (20) and is further increased in cats with higher plasma phosphate concentrations (19). FGF-23 is also increased in non-azotemic cats that go on to develop azotemia within 12 months when compared to cats that remain non-azotemic (20), but again, there is substantial overlap of FGF-23 measurements between these different groups of cats. At the moment the use of FGF-23 as a biomarker for cats at risk of developing azotemia is therefore limited.

Current best practice

A variety of different biomarkers have been examined as indicators of impending azotemic CKD in cats, but there is currently no "perfect" biomarker that can be used to diagnose early CKD in an individual cat. A number of the biomarkers discussed in this article have been shown to be predictors of the development of azotemic CKD in the cat on a population basis, and are therefore of use in trying to diagnose feline patients in early CKD. Use of the routinely available biomarkers in combination, particularly with repeated measurements over time, is currently the best way of assessing kidney function without directly measuring GFR. ***Figure 4*** shows a logical approach to using biomarkers currently available in general practice to help identify feline patients with CKD as early as possible.

Conclusion

Prompt diagnosis of CKD in the cat allows for intervention to slow progression of the disease and improve survival time. Biomarkers of early CKD in cats are an active area of current research, and although no ideal biomarker has been identified in the cat to date, new biomarkers may be identified in the near future with the use of proteomics. The most useful biomarkers for use in practice at the moment to identify early feline CKD are serial measurement of serum creatinine concentration in conjunction with USG and measurement of UPC.

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Nutritional management of feline chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is a frequent disease of older cats, although it can occur in younger animals as a congenital (*e.g.,* renal dysplasia) or acquired (*e.g.,* sequel to acute kidney injury) disease. In a recent study, 26% of cats > 9 years of age that were healthy at initial evaluation developed azotemia within a year (1). While CKD is ultimately progressive, the veterinarian plays a key role in delaying the inevitable; firstly by detecting CKD at an early stage, and secondly by instituting appropriate dietary changes (along with fluid and medical therapy) which can improve quality and life expectancy of cats with CKD.

KEY POINTS

- **Dietary modifications are key to slowing progression of renal disease and alleviating its metabolic consequences.**
- **The four objectives of nutritional management are to provide sufficient energy to maintain a good body condition, alleviate the clinical manifestations of uremia, minimize the fluid, electrolyte and acid-base disturbances, and slow the disease progression.**
- **A renal diet should be implemented early in the disease to maximize both its benefits and acceptance by the cat.**
- **Assisted enteral feeding helps deliver the appropriate diet and maintain body condition in dysorexic patients.**

Nutritional management has four objectives: to provide sufficient energy to maintain a good body condition, to alleviate the clinical manifestations of uremia, to minimize the fluid, electrolyte and acid-base disturbances, and to slow the disease progression. These objectives are more or less critical and challenging to reach depending on the stage of CKD, and can be achieved by feeding the appropriate diet as well as employing adjunct therapy, such as phosphate binders, if needed.

Key nutrient modifications, why and when?

The whole set of nutrient modifications usually applied in so-called "renal diets" serve different purposes (the four goals mentioned above) at different stages of CKD ***(Figure 1)***. While slowing down the disease is important as early as IRIS* stages 1 and 2, alleviating the clinical signs and metabolic disturbances is more critical in stages 3 and 4 when these disorders are more likely to be present. Likewise, meeting energy needs becomes more challenging as the disease progresses.

Slowing CKD progression

Protein

High levels of dietary protein were historically linked to faster progression of experimentally induced kidney disease in rats, as well as in cats (2). However, the effect of protein in these studies was confounded with that of caloric intake, as low protein diets had a lower consumption, probably because of poorer palatability. Subsequent studies in cats to investigate the role of protein

*IRIS, International Renal Interest Society. For more information on renal disease staging in cats, see inside back cover.

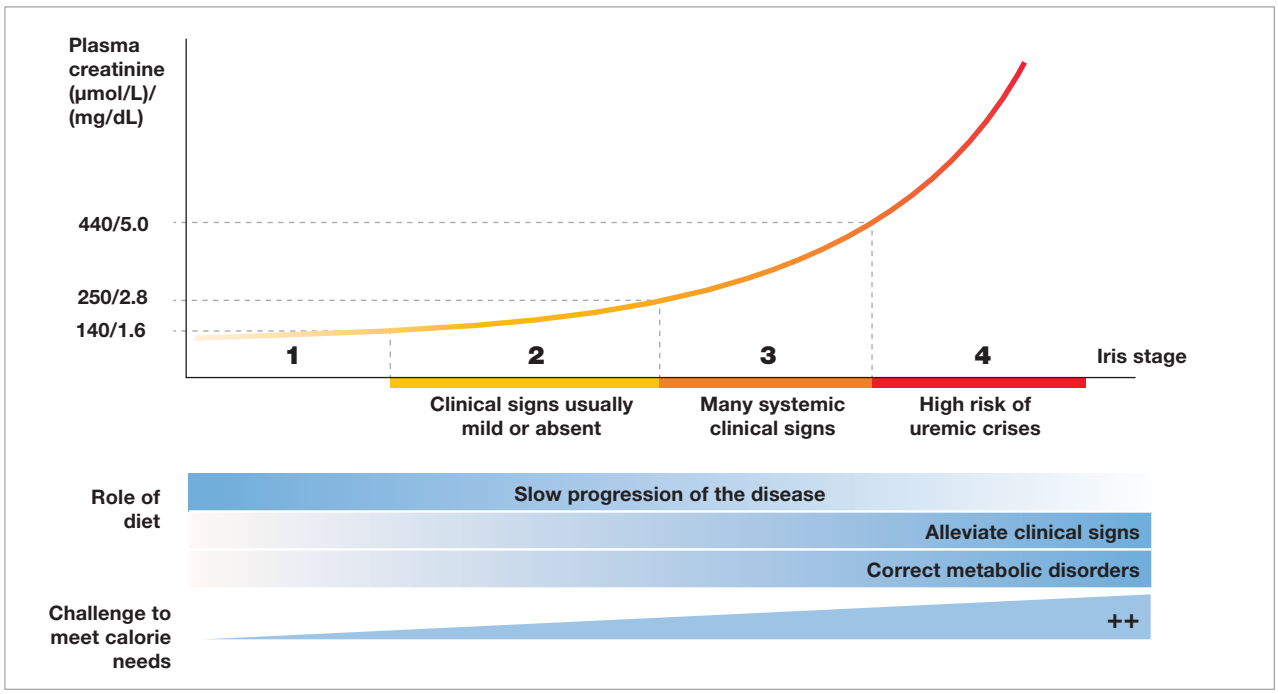

Figure 1. Role of nutrition in feline chronic kidney disease based on IRIS staging.

versus calorie restriction showed that calorie – and not protein – restriction was responsible for the protective effect on renal morphology and proteinuria (3). Therefore protein restriction is not useful to slow the progression of tubulointerstitial renal disease in cats; it may be useful to limit proteinuria in severe glomerulopathy, as shown in dogs, but this renal disorder is rarer in cats.

Phosphorus

Phosphorus retention (secondary to decreased glomerular filtration) and the ensuing hyperphosphatemia leads to renal secondary hyperparathyroidism, and is more prevalent as the CKD stage increases (1); this in turn can lead to renal osteodystrophy or soft tissue calcification. High plasma phosphate concentrations have also been associated with shorter survival times in cats with CKD (4,5). It is now well established that dietary phosphorus restriction is key to slowing renal disease progression, by lowering plasma parathyroid hormone (PTH) (6) and preventing renal lesions (such as mineralization and fibrosis) (7). Restriction early in the stage of the disease is recommended as PTH may already be elevated.

EPA and DHA

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 long chain polyunsaturated fatty acids (LC-PUFA) only found in marine sources (fish). Once incorporated in the cell membranes, they compete with the omega-6 LC-PUFA arachidonic acid for their enzymatic degradation, leading to the production of a class of eicosanoids (leukotrienes, prostaglandins, thromboxanes) that are less inflammatory and promote vasodilation. Most studies show that EPA and DHA have a beneficial effect, slowing the decline in renal function; the research has been done in rats and dogs but there is no reason to believe that this effect would be different in cats.

Antioxidants

A recent study showed that, as with humans, oxidative stress is present in cats with CKD (8). Oxidative damage is believed to play an important role in the progression of renal disease by triggering glomerulosclerosis and interstitial fibrosis. Reactive oxygen species may be generated by glomerular hyperfiltration and tubular hypermetabolism following the loss of functioning nephrons, hence the rationale for supplementing renal diets with antioxidants.

Alleviating clinical consequences of CKD

Protein

While the role of dietary protein in the progression of kidney disease has been controversial (see above), it is on the other hand clearly established that limiting

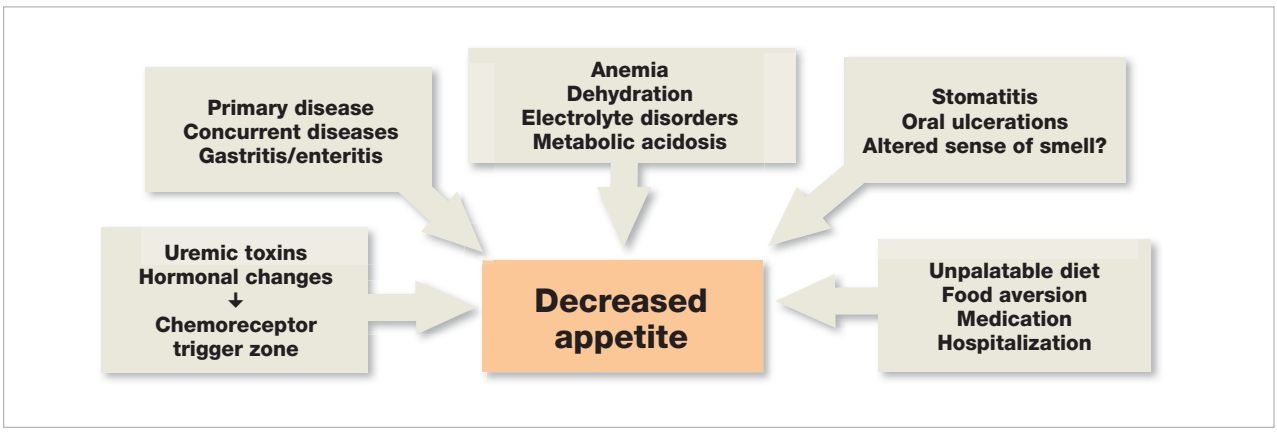

Figure 2. Decreased food intake is multifactorial in CKD. All the causes listed above should be addressed to maximize the chances of improving the cat's appetite.

protein intake alleviates some of the clinical signs related to uremia. Feeding protein well in excess of the minimum requirements leads to generation of nitrogen waste products, which accumulate in body fluids when renal excretory capacities are reduced. Thousands of different uremic toxins exist, but measuring the concentration of blood urea nitrogen (BUN), an innocuous form of nitrogen excretion, is considered to offer a good estimation of toxin levels.

BUN and the BUN:creatinine ratio both rise as dietary protein increases (among other causes) and a high protein intake in cats with CKD is correlated with higher morbidity and frequency of uremic crises (9). The central question is to what extent protein should be restricted. Cats with early stage CKD (1 and 2) are likely to tolerate higher amounts than those with more advanced CKD (3 and 4). Most maintenance commercial diets provide protein well in excess of the minimum requirements. However, these minimum requirements have been determined for healthy animals, and they may be higher in patients with CKD (10), and so the question is important, as excessive protein restriction can lead to protein malnutrition and morbidity. Protein quality (essential amino acid profile and digestibility) is also important to avoid essential amino acid deficiency or unnecessary nitrogen loads.

Sodium

Systemic hypertension is common in cats with CKD and contributes to the progression of the disease. It has been suggested that high dietary sodium (> 1.5 g/1000 kcal) could promote renal disease progression with no effect on blood pressure in cats with early stage of CKD (11). In another study, sodium up to 2.0 g/1000 kcal did not affect blood pressure or GFR in cats with surgically induced renal disease, although it was only tested for a short duration (7 days) (12). On the other hand, excessive sodium restriction led to the activation of the renin angiotensin aldosterone system in these cats. The current consensus is therefore to avoid both excessively low and high sodium levels in diets for renal disease. Transitioning patients with advanced CKD to a renal diet (usually mildly restricted in sodium) should be progressive, as their ability to adjust sodium excretion in response to the intake becomes severely impaired.

Potassium

Cats with CKD can become hypokalemic and experience total body potassium depletion as a result of decreased intake and increased diuresis (13), and potassium supplementation is warranted to avoid signs of potassium deficiency (*e.g.,* generalized muscle weakness). As a general rule, every patient with CKD should have regular monitoring of serum potassium in order to adjust the dietary prescription accordingly; commercial renal diets can differ in their potassium content. Drugs that can influence potassium excretion (*e.g.,* ACE inhibitors, which can cause potassium retention) must also be taken into account.

Acid-base

Kidneys play an important role in maintaining blood pH, notably through a net reabsorption of bicarbonate and the excretion of hydrogen ions. Metabolic acidosis can therefore result from CKD, usually in late stages (14). This increases skeletal muscle protein catabolism, disrupts intracellular metabolism, and promotes long-term

bone mineral dissolution. Ensuring the provision of alkalinizing agents in the diet (bicarbonate, carbonate, citrate) in order to correct or prevent metabolic acidosis is therefore recommended.

B vitamins

Losses of water-soluble B vitamins may ensue from increased diuresis in CKD patients. While there is no strong evidence that it is a necessary intervention, B vitamins show no (or marginal) toxicity and are therefore often supplemented in excess of the requirements in renal diets.

In summary, studies (mostly in animals with experimentally induced kidney disease) have shown that the following nutrient modifications have been beneficial in delaying disease progression and alleviating the clinical consequences of CKD: protein and phosphorus restriction, EPA/DHA supplementation, moderate sodium restriction, potassium supplementation, and alkalinization. The combination of all these dietary strategies has been validated in clinical studies in cats with naturally occurring kidney disease (9,15), where patients receiving a "renal diet" had an improvement in both quality and the duration of life.

Practical implementation of nutrition

Before nutritional therapy is initiated, any fluid, electrolyte and acid-base disorder should be corrected by medical therapy if the patient is experiencing a uremic crisis in order to maximize the chances of acceptance of the renal diet.

Meeting the energy requirement

Weight loss in cats with CKD is driven by insufficient caloric intake, which is multifactorial ***(Figure 2)***: causes include nausea from nitrogen waste product accumulation, anemia, dehydration, electrolyte and acid-base disorders, buccal and gastrointestinal mucosal ulcerations (in advanced stages of the disease), possible altered sense of smell, and the lower palatability of low protein and low phosphorus diets.

The goal is to provide enough calories for the cat to reach and maintain an ideal BCS (5/9). While predictive equations can be used as a starting point to determine the daily caloric intake, this caloric allowance should be regularly revisited based on weight and BCS changes, due to the high variability of energy needs in the population. Likewise, the target for hospitalized cats is to reach resting energy requirement (RER = 70 kcal x weight(kg)$^{0.75}$), with subsequent weight reassessments.

Selecting administration route

Parenteral nutrition, available in some veterinary hospitals, can be used in cats that do not tolerate enteral feedings (*e.g.,* with intractable vomiting in severe uremia), but the diet formula should be discussed with a nutritionist to ensure that the amino acid, electrolyte and fluid levels provided are adequate for uremic patients.

The preferred and most common route to feed CKD patients is enteral. Most cats with stage 3 and 4 CKD fail to consume enough calories to maintain their weight. Commercially available renal diets are usually high in fat, which increases their caloric density and reduces the volume that needs to be eaten, but this is not always sufficient. Force-feeding should be proscribed, as it increases the risks of food aversion and creates stress that compromises the cat's well-being. Appetite-stimulating drugs can be tried, but usually fail to sustain caloric intake sufficient to maintain body weight over the long term. The antidepressant mirtazapine has been shown to increase ingestion in young healthy cats at 1.88 mg/day PO (16); it may need to be given every other day to CKD cats due to the longer half-life of the drug in these patients (17).

Assisted enteral feeding should be discussed when continuous weight loss is documented (sooner in underweight cats) after attempts to offer various renal diets have failed. Since CKD is ultimately a progressive disease, a sudden improvement in caloric intake is unlikely in animals with stage 3 or 4 CKD (provided that there is no important metabolic disturbance that can be readily corrected).

Nasoesophageal, esophagostomy (E-) or gastrostomy (G-) tubes all have pros and cons, which will not be discussed here, but the latter two can be used successfully in the long term to improve BCS as well as the medical condition of the cat, since appropriate diet, fluid and medical therapies can be administered through the devices after minimal client education ***(Figures 3 and 4).***

Selecting the diet

Several commercial diets formulated for renal disease are available, in various forms (dry, canned, morsels in gravy, etc.). While most are restricted in protein and phosphorus below levels found in maintenance (including senior) diets ***(Table 1)***, degrees of restriction and palatability vary, as well as other nutritional factors which can be of importance for the patient. Updated

Table 1. Key nutritional characteristics of feline renal diets compared to maintenance diets. Note that the composition of commercial diets can vary widely and that individual patients may benefit from different nutrient levels.

	Most renal diets	Most maintenance diets
Protein	20-27% ME*	> 27% ME
Phosphorus	< 1.2 g/Mcal**	> 1.3 g/Mcal
Sodium	< 1.0 g/Mcal	> 1.0 g/Mcal
Potassium	> 2.0 g/Mcal	Variable
EPA+DHA	Increased	Variable
Acid-base balance	Neutral or alkalinizing	Acidifying

*% ME = % metabolizable energy (% of calories provided by protein, fat or carbohydrate). It is a better way to compare diets than % as fed (impacted by moisture, fiber and ash content) or % dry matter (impacted by fiber and ash content), and can be obtained from the manufacturer.
**1 Mcal = 1,000 kcal.

nutrient information should be obtained from manufacturers as diet reformulations occur over time.

For hospitalized cats with nasoesophageal tubes in place ***(Figure 4 and 5)***, liquid diets specifically formulated for cats with renal disease may be available in some countries. Any commercial canned diet can be blenderized and administered through larger diameter tubes (E or G-tubes) as described in ***Table 2***.

Transitioning the patients from their current diet to a therapeutic renal diet can be done gradually (over several weeks to months at home) in order to limit the risk of refusal. Implementing the new diet at an early stage of the disease is also more likely to be successful, as cats in stages 3 or 4 experience more nausea and food aversion.

Homemade diets can be formulated for animals that refuse all available commercial diets, if there are specific additional conditions (*e.g.,* adverse food reaction), or where the owner prefers this option. However, the diets should be formulated by veterinary nutritionists as

Table 2. Implementing a nutritional plan in a cat with a feeding tube.

• Select the renal diet appropriate for the patient, and determine the caloric content of a can or a pouch (information from the manufacturer). *e.g.,* 200 kcal/can.
• Put a given amount of diet in the blender (*e.g.,* 1 can) and add sufficient water to achieve a blend consistency that can be easily pushed through the patient's feeding tube. The volume of water added must be taken into account in the overall fluid plan.
• Measure the final volume of the blend and calculate the energy density of the final blend. *e.g.,* 50 mL of water added to 1 can (200 kcal) to reach adequate consistency to be pushed through a 14 FG E-tube. If the total volume is 220 mL and the caloric density is 200 kcal/220 mL, this calculates to 0.9 kcal/mL.
• From RER calculation and feeding plan, calculate the volume the patient should receive per day, and at each meal *e.g.,* RER of a 3.0 kg cat = 160 kcal/day during hospitalization, equivalent to 160/0.9 ≈ 180 mL/day of the slurry, or 45 mL at each meal if fed 4 times per day.
• After each feeding, the tube must be flushed with sufficient water (a few mL) to prevent clogging.
• The blended food should be stored in a refrigerator (for a maximum of 24 hours). Stir and warm to body temperature before administering a new meal.

Figure 3. Cat with an E-tube in place.

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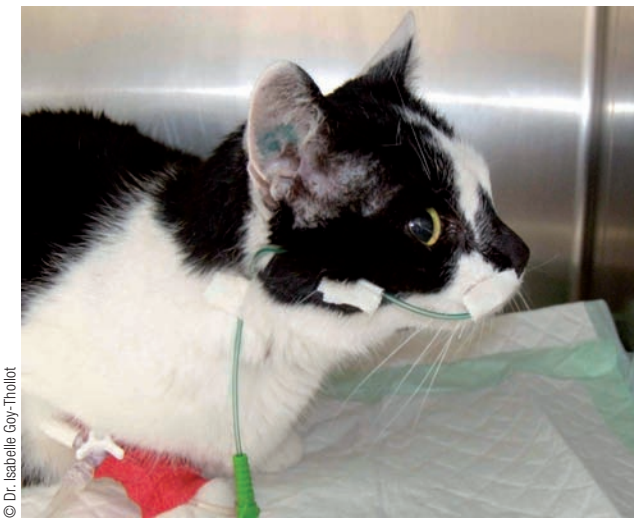

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Figure 4. Nasoesophageal tubes allow liquid diets specifically formulated for renal disease to be administered, but are usually for short-term (days) use.

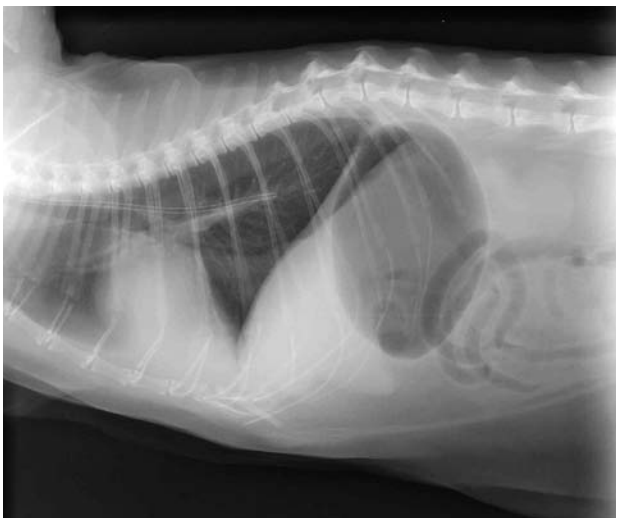

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Figure 5. Correct placement of a nasoesophageal tube can be confirmed by radiography.

generic recipes found in books or online are often inadequate (18), and acceptance by the cat can be really challenging in the author's experience.

Use of intestinal phosphate binders

Maintaining serum phosphate levels within a target range (available in IRIS guidelines) is a goal of CKD management. If dietary phosphorus restriction alone is insufficient, phosphorus binding agents should be added, and their dose titrated to effect. These binders must be administered with (or very close to) each meal to be effective, which may decrease palatability; this problem is however circumvented when using a feeding tube. The cation contained in these agents binds phosphate in the intestinal lumen, making an insoluble, non-absorbable complex which is eliminated in the feces.

Several phosphate binders are available ***(Table 3)***, but there is only limited information published on their clinical efficacy or safety in cats. Aluminum-containing binding agents (*e.g.,* aluminum hydroxide) are cheap, effective and appear relatively safe in cats, although aluminum toxicity manifested by neurological signs has been reported with high dosage in dogs. Liquid aluminum hydroxide can be quite unpalatable, but is much more easily accepted when compounded by certain pharmacies as a powder, which may then be mixed with a dry or canned diet.

Calcium-based agents (calcium acetate, calcium carbonate) are also used, but their optimal binding capacity may depend on pH and they usually require higher doses to be effective, putting some cats at risk for hypercalcemia, especially if concurrent calcitriol therapy is in place. A binder containing calcium carbonate and chitosan has been shown to be effective in reducing serum phosphorus and PTH in cats with reduced renal mass fed a maintenance diet, although this benefit seemed to disappear after 9 months (19).

Table 3. List of intestinal phosphate-binding agents and typical recommended doses. To limit the potential adverse effects of some of these agents (*e.g.,* hypercalcemia, aluminum toxicity), a combination of agents can be given at a lower dosage level. Administration should be divided and given with meals, and must be titrated to effect.

Aluminum hydroxide	60-90 mg/kg daily
Calcium acetate	60-90 mg/kg daily
Calcium carbonate	60-90 mg/kg daily
Calcium carbonate + chitosan	200 mg/kg twice daily
Sevelamer hydrochloride	50-160 mg/kg daily
Lanthanum carbonate	12.5-25 mg/kg daily
Lanthanum carbonate octahydrate	400 mg per cat once or twice daily

Other aluminum- and calcium-free options include sevelamer hydrochloride and lanthanum carbonate. The latter has been shown to be safe and effective in reducing phosphorus absorption in healthy cats fed a maintenance diet over a two-week period (20).

Monitoring

Once the nutritional plan is implemented, the patient should be re-evaluated after 2-3 weeks, and then two to four times a year (depending on the stage of the disease) to readjust medical and nutritional therapy as needed, and to ensure owner compliance. The amount of food truly eaten, rather than offered, and any treat or supplement given, should be documented. Body weight and BCS curves are easy and valuable follow-up tools which can help determine the moment to implement new feeding strategies (*e.g.,* feeding tube placement). Blood work provides insight as to the appropriateness of the dietary plan (*e.g.,* serum phosphate or potassium, acid-base status, BUN etc.).

Conclusion

Appropriate nutrition is the cornerstone of treatment for feline CKD: it delays the progression of the disease and improves the quality of life for the patients. Nutritional modifications should be initiated early during the disease, and subsequently adjusted to an individual patient's needs, based on close monitoring of physical and laboratory parameters.

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CUT-OUT AND KEEP GUIDE...

Diagnostic implications of proteinuria

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Proteinuria can be:

Functional

Associated with

- Hyperthermia/fever
- Strenuous exercise

Functional proteinuria

- History and physical examination generally indicate recent exertion or hyperthermia
- Usually mild and transient

OR

Pathological

Which can be

- Pre-renal (increased amount of small size plasma proteins, *e.g.,* hemoglobin, myoglobin, immunoglobulin "Bence Jones" light chains)
- Renal (glomerular, tubular and/or interstitial)
- Post-renal (protein enters the urine from the urinary tract)

Pathological proteinuria

- Firstly, identify the most likely source of the proteinuria, *i.e.,* exclude post-renal origins and look for indications of a pre-renal source
- Secondly, determine if it is persistent (the hallmark of renal proteinuria) and then the magnitude of the proteinuria, preferably using a urinary protein:creatinine ratio (UPC) test

Pre-renal proteinuria

- Urinalysis is not usually prioritized in patients suspected of hemolysis or significant muscle damage, so proteinuria is typically a coincidental finding in these cases
- Patients with plasma protein disorders resulting in altered globulins are rare and not easily identified clinically. Routine "dipstick" methods are satisfactory to detect most proteinurias but since they detect predominantly albumin some abnormal proteins (*e.g.,* "Bence Jones" proteins from plasma cell tumors) will go undetected. Protein (plasma and/or urine) electrophoresis can be used to detect such plasma protein disorders

Post-renal proteinuria

- History may indicate abnormal micturition (*i.e.,* pollakiuria). Systemic signs of illness are rare but if present suggest involvement of the upper urinary or genital tract
- Physical examination should include abdominal palpation with special attention paid to the bladder (assessing bladder size and content) as well as inspection of genitalia and a rectal examination
- Urine sediment will commonly show erythrocytes and/or inflammatory cells combined with large numbers of epithelial cells. Cystocentesis is the preferred method of sampling for bacteriological examination

Renal proteinuria

The primary considerations for a patient with established persistent renal proteinuria are:

- To identify a (treatable) cause; *e.g.,* infectious, endocrine or neoplastic disorders
- To assess the sequelae; especially azotemia, hypoalbuminemia and hypertension
- To balance costs and risks of various diagnostic procedures against possible benefits for the patient

Approach

- Signalment, which should consider breed predilections
- History may be indicative of predisposing factors (*e.g.*, foreign travel) and underlying disease, and is useful for assessing duration and extent of illness
- Physical examination should at a minimum include an assessment of the urogenital tract as well as blood pressure measurements, and preferably also retinal examination
- Urinalysis will repeatedly show UPC > 0.5; bacteriological examination is usually negative; specific gravity, sediment and chemistry will vary but can be informative for involvement of *e.g.,* the tubular system
- Blood examination: CBC will provide clues regarding cause as well as consequences. A biochemistry profile generally includes renal values, electrolytes and albumin, but can be tailored to fit with history, physical exam and urinalysis. Other tests, *e.g.* for infectious diseases, other immune-mediated disorders, DNA mutations, and/or assessment for bleeding disorders and risk of thrombosis can be considered, and indeed may be essential in some cases
- Imaging techniques such as radiography and ultrasound can provide structural information on kidneys and other abdominal organs (liver, adrenals, GI tract) and can also detect cardiac changes, but are rarely solely diagnostic for protein-losing nephropathies

Renal biopsy

- Is essential for diagnosing a suspected primary glomerulopathy
- Will help decide on therapeutic options
- May not be essential to assess prognosis; *e.g.,* an animal with end-stage chronic renal disease (IRIS CKD stage 4) is unlikely to benefit
- Should consist of cortex samples appropriately processed for light microscopy as well as ultrastructural examination and immunostaining (specific renal biopsy kits are available)
- The technique requires experienced personnel to minimize the risk for the patient and involves considerable costs
- Consider a biopsy if:
  - The work-up does not indicate end-stage renal disease
  - Renal proteinuria remains high despite conventional therapy
  - Hypertension is controlled and hemostasis is adequate
  - Cost and time are not limiting factors; in particular electron microscopy ultrastructural examination is time-consuming, and the biopsy may indicate the need for immunosuppressive treatment, which is generally ongoing and costly in terms of medication and follow-up requirements

Further reading and useful websites

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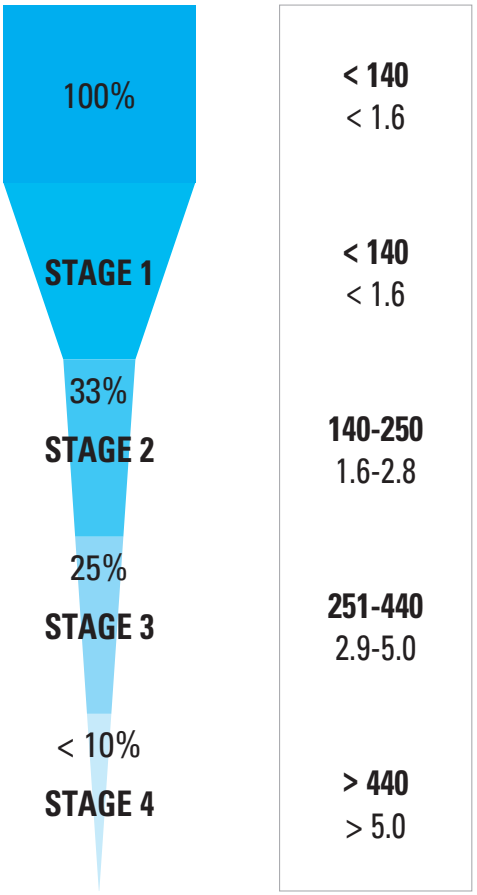
- www.iris-kidney.com
- www.wsava.org/educational/renal-standardization-project
- http://research.vet.upenn.edu/WSAVA-LabSearch

IRIS International Renal Interest Society

CATS

Staging system for chronic kidney disease (CKD)

STEP 1. Staging is initially based on fasting blood creatinine assessed on at least two occasions in the stable patient.



Comments

History suggests the animal is **AT RISK** of developing CKD in the future due to a number of factors (*e.g.,* exposure to nephrotoxic drugs; breed; high prevalence of infectious disease in the area).

Nonazotemic. Some other renal abnormality present (*e.g.,* inadequate urinary concentrating ability without identifiable nonrenal cause, abnormal renal palpation or renal imaging findings, proteinuria of renal origin, abnormal renal biopsy results, increasing blood creatinine concentrations in samples collected serially).

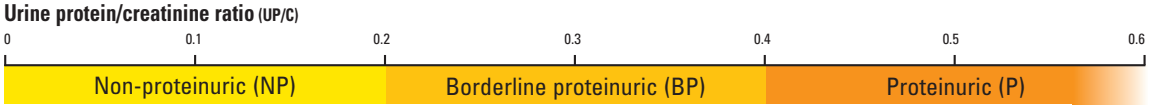
Mild renal azotemia (lower end of the range lies within reference ranges for many laboratories, but the insensitivity of creatinine concentration as a screening test means that animals with creatinine values close to the upper reference limit often have excretory failure). Clinical signs usually mild or absent.

Moderate renal azotemia.
Many extrarenal clinical signs may be present.

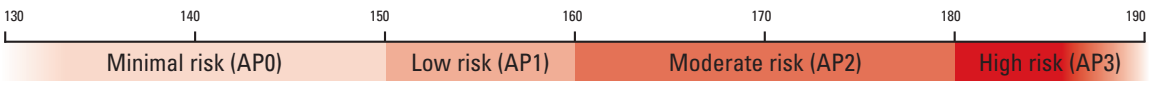
Severe renal azotemia.
Increasing risk of systemic clinical signs and uremic crises.

STEP 2. Cases are then sub-staged based on proteinuria and blood pressure.
Note that UP/C and blood pressure vary independently of each other and the stage of CKD, so that any level of proteinuria or hypertension can occur at any stage of CKD *i.e.,* at any level of azotemia.

Urine protein/creatinine ratio (UP/C)



Risk of end organ damage from hypertension (Systolic blood pressure mmHg)



Adapted from the Manual of Canine & Feline Nephrology & Urology (Fig: 5.5) 2nd Edition edited by J. Elliott & G. Grauer (2006) in accordance with IRIS Staging of CKD, 2013.
*The relative percentages of residual function are conceptual estimates only.

Supported by Novartis Animal Health Inc.

Based on IRIS Staging of CKD, 2013.

www.iris-kidney.com

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