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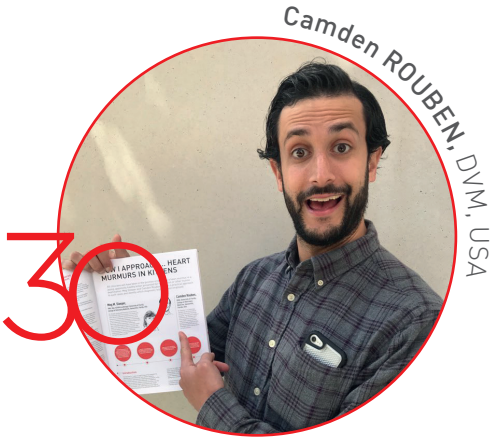

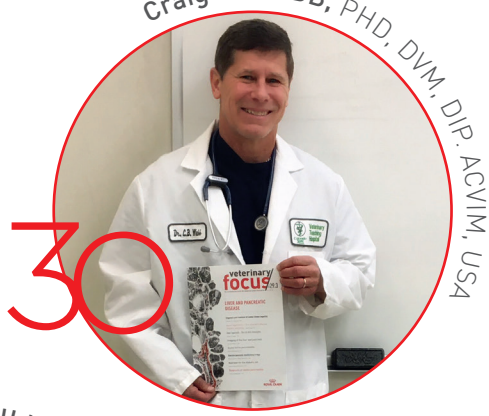

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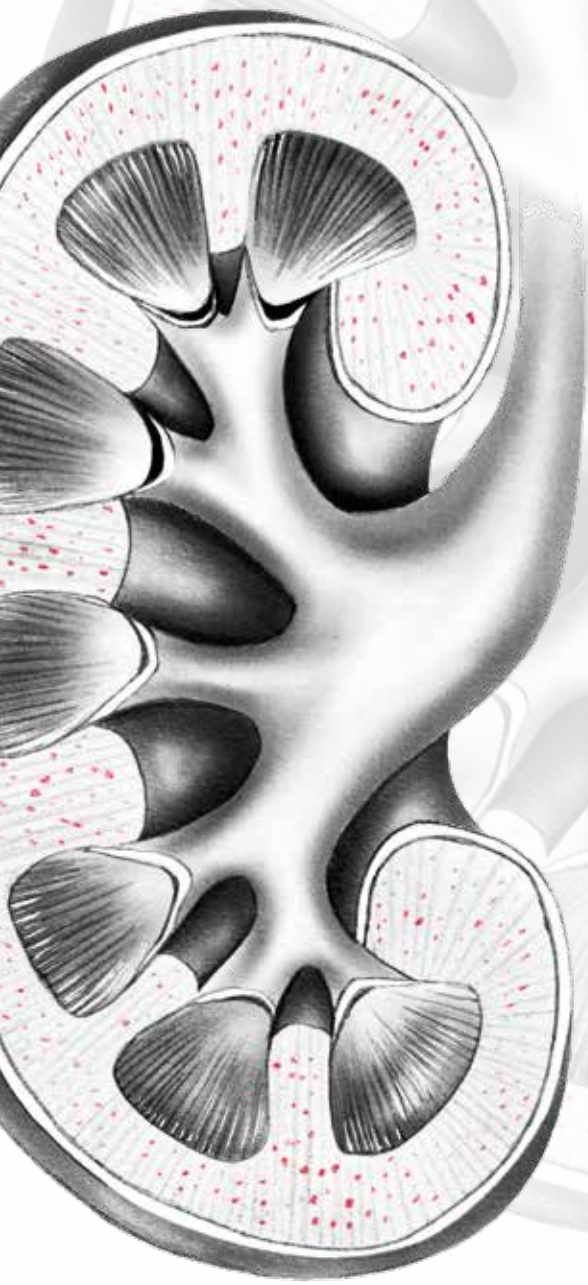

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COMING UP...

In our next issue we will look at how we can make a better world for pets.

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  Dana Novara and Kimberly-Ann Therrien, USA
- **Non-accidental injury in animals**
  Nienke Endenburg, The Netherlands
- **Child development and the human–animal bond**
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ROYAL CANIN

Editorial

THE BEST PHYSICIANS ARE ALSO PHILOSOPHERS

"The physician is only nature's assistant" **–** Galen of Pergamon

Any association between Roman gladiators and the science of modern nephrology is not, at first sight, an obvious one. But the juxtaposition – although tenuous – is possible, and the pivotal figure is Galen, the Greek physician and philosopher who lived in the 2nd century AD. Regarded as perhaps the most accomplished of all scientific researchers in the ancient world, Galen was a great proponent of experimental methods to test his theories. Although some of his assertions were far from the truth – he was inspired by the then-current belief in the four humors (the balance between black bile, yellow bile, blood, and phlegm) – in other ways he was well ahead of his time. As a medical teacher Galen encouraged his students to observe dead gladiators to further their knowledge of anatomy – human dissections being strictly prohibited at the time – and it was he who proved that urine was formed in the kidney, challenging the common belief that it was produced in the bladder. Thus it can be argued that these were the first steps towards modern nephrology.

Not only did Galen's influence reach down over the centuries – his theories dominated and influenced Western medical science until medieval times – he was a true adherent to the idea that everything is connected. A great writer, he authored a treatise entitled *That the Best Physician Is Also a Philosopher*, and he was a major protagonist for the concept that disease was natural, encouraging the move away from supernatural ideas about cause and cure of illness. And not only did he give us the words that head this editorial, he also had definite opinions about communication, saying "The chief merit of language is clearness". This issue of *Veterinary Focus*, which looks at one of Galen's favorite subjects, would, one assumes, meet with his approval.

Ewan McNEILL
Editor-in-chief

• **Focus on** *Veterinary Focus*

Primary hypertriglyceridemia, or familial idiopathic hypertriglyceridemia, is a common yet under-recognized condition in **Miniature Schnauzers**; affected dogs are at risk of developing proteinuria and are also predisposed to hypertension, pancreatitis and gallbladder mucoceles.

p02

Renal transplantation is very much a specialty, but the front-line clinician should nevertheless know the pros and cons of the procedure in order to best advise owners who enquire if it is an option for their cat.

p07

p30

Chronic kidney disease is estimated to have a prevalence of up to 32% in older cats and is one of the most common causes of death; early detection of the disease is therefore a major target in preventative care.

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PEFC 10-31-1668

Origine du papier : VIRTON (Belgique)
Taux de fibres recyclés : 0%
Certification : 100% PEFC
Impact sur l'eau : 0.012 P tot kg/tonne

Deputy publisher: Buena Media Plus Bernardo Gallitelli 11-15, quai De Dion-Bouton 92800 Puteaux, France
Phone: +33 (0) 1 72 44 62 00
Editor-in-chief: Ewan McNeill, BVMS, Cert VR, MRCVS
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Artwork
• Pierre Ménard

Printed in the European Union
ISSN 2430-7874
Legal deposit: March 2020
Cover: Shutterstock

Veterinary Focus is published in Brazilian Portuguese, Chinese, English, French, German, Italian, Japanese, Polish, Russian, Spanish and Korean.

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ROYAL CANIN

HYPERTRIGLYCERIDEMIA-ASSOCIATED PROTEINURIA IN MINIATURE SCHNAUZERS

Proteinuria secondary to primary hypertriglyceridemia is a common yet under-recognized metabolic disorder of Miniature Schnauzers; Eva Furrow describes the diagnostic process and treatment options.

KEY POINTS

1. Primary hypertriglyceridemia is common in Miniature Schnauzers and is associated with proteinuria, glomerular lipid thromboemboli, and other glomerular pathology.
2. Affected dogs do not typically have azotemia or hypoalbuminemia; if these abnormalities are present, other causes of glomerular disease should be investigated.
3. Hyperadrenocorticism is a differential for hypertriglyceridemia and proteinuria and should be ruled out if consistent clinical signs or physical exam abnormalities are present.
4. Treatment involves dietary fat restriction and, if necessary, lipid-lowering drugs; proteinuria is managed with drugs that inhibit the renin-angiotensin-aldosterone system.

Introduction

Primary hypertriglyceridemia, also known as familial idiopathic hypertriglyceridemia, is a common yet under-recognized condition in Miniature Schnauzers. This metabolic disorder has an age-dependent manifestation, with a prevalence that increases from 15% of Miniature Schnauzers less than 3 years of age to more than 75% of dogs older than 9 years of age (1).

Hypertriglyceridemia is typically associated with increased risk for pancreatitis, gallbladder mucoceles, and elevated liver enzymes (2-4); more recently, hypertriglyceridemia has also been found to be associated with proteinuria and glomerular pathology in Miniature Schnauzers (5-7).

Approximately 50% of Miniature Schnauzers with primary hypertriglyceridemia have proteinuria, and fasting serum triglyceride concentrations have a strong positive correlation with urinary protein-to-creatinine ratios (UPC) in the breed (5,6). Furthermore, renal biopsies of proteinuric Miniature Schnauzers with hypertriglyceridemia contain lipid thromboemboli **(Figure 1)** (7). These findings suggest that hypertriglyceridemia is the cause rather than the consequence of glomerular disease. This paper presents the features and consequences of hypertriglyceridemia-associated proteinuria in Miniature Schnauzers and provides information on how to diagnose and manage the condition.

Clinicopathologic features

The clinical presentation of hypertriglyceridemia-associated proteinuria is outlined in **Table 1**. As noted above, the condition is most common in middle aged and older Miniature Schnauzers (5). Males and females are affected at similar frequency; no sex predisposition has been reported. Unless comorbidities are present, affected dogs do not have any clinical signs (5,6); for example, polyuria and polydipsia have not been reported. There are also no physical examination findings specifically associated with the condition, although hypertriglyceridemia can result in ocular lipid deposits (8). Thus, hypertriglyceridemia-associated proteinuria is often detected incidentally when urinalysis is performed for routine health screening or for comorbidities.

The laboratory findings seen with hypertriglyceridemia-associated proteinuria are also presented in **Table 1**. The extent of proteinuria is strongly correlated to fasting serum triglyceride concentrations (5,6). Proteinuria occurs in 25-41% of Miniature Schnauzers with mild hypertriglyceridemia (100-400 mg/dL, 1.1-

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Dr. Furrow qualified from the University of Pennsylvania and after completion of a small animal internship at the same establishment she moved to the Midwest for a residency in internal medicine followed by a PhD on metabolic and genetic risk factors for urinary stones in dogs, both at the University of Minnesota. She is currently an assistant professor of internal medicine and genetics at the University of Minnesota, where her primary interests include genetic, urinary, endocrine and metabolic disorders.

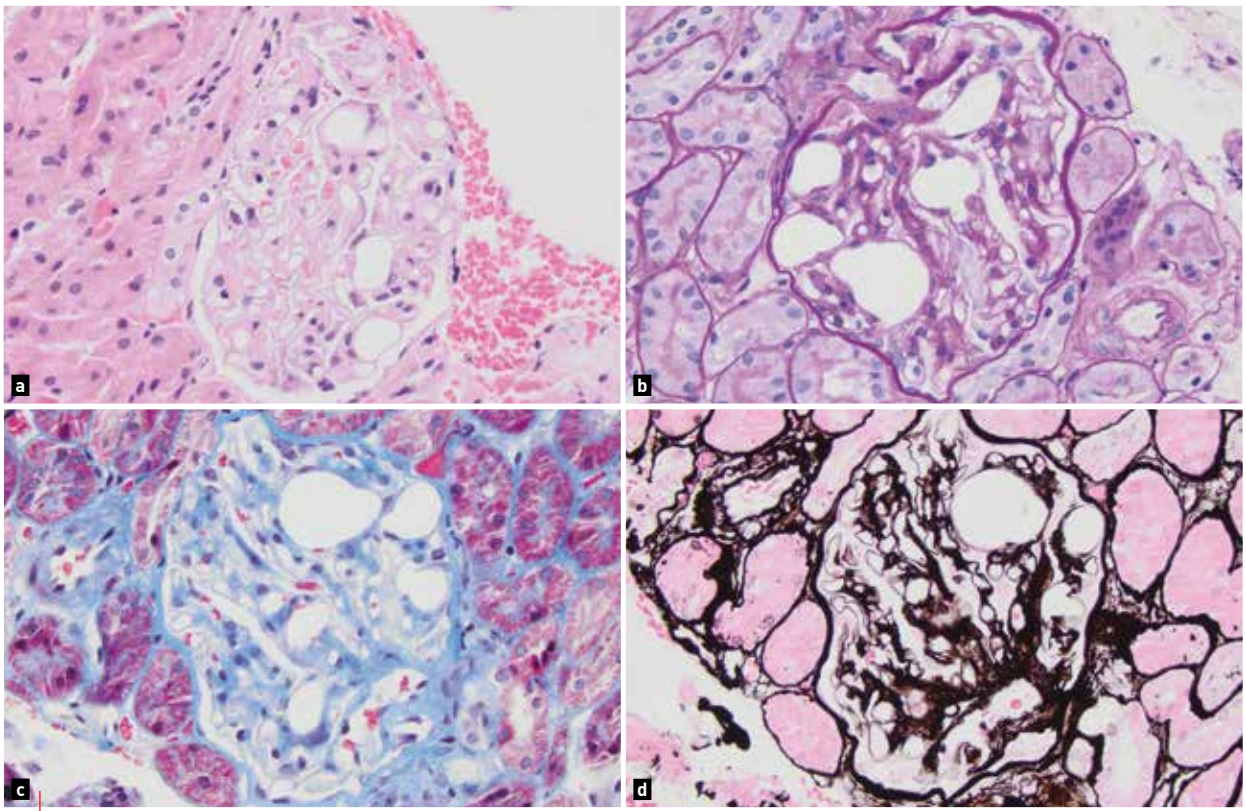

Figure 1. Glomerular lipid thromboemboli in a 10-year-old male neutered Miniature Schnauzer with primary hypertriglyceridemia and subclinical proteinuria. The lipid thromboemboli are visualized as intracapillary non-staining circular structures; **(a)** hematoxylin and eosin. **(b)** Periodic acid–Schiff. **(c)** Masson's trichrome. **(d)** Jones's methenamine silver. Images were captured at 40x magnification.

4.5 mmol/L), and the degree of UPC elevation is generally mild (*i.e.*, < 2). In contrast, proteinuria occurs in 85-88% of Miniature Schnauzers with moderate to severe hypertriglyceridemia (> 400 mg/dL, > 4.5 mmol/L), and the UPC is greater than 2 in most dogs, with values > 5 reported. Urine specific gravity (USG) is variable and similar to age-matched Miniature Schnauzers without hypertriglyceridemia-associated proteinuria. The urine sediment is inactive on examination.

Hypertriglyceridemia-associated proteinuria is not associated with hypoalbuminemia or azotemia (6). It is important to note that there are inter-breed differences in serum creatinine concentration, and the median in healthy Miniature Schnauzers is < 1.0 mg/dL, < 88 µmol/L (6,9).

Hypercholesterolemia is rare in Miniature Schnauzers with mild primary hypertriglyceridemia, but common in those with moderate to severe hypertriglyceridemia, at around 40% of dogs where the serum triglyceride level is > 400 mg/dL, > 4.5 mmol/L (1). Moderate to severe hypertriglyceridemia is also associated with elevations in liver enzymes; 60% of Miniature Schnauzers with serum triglyceride > 400 mg/dL, > 4.5 mmol/L show elevation in alkaline phosphatase plus at least one other enzyme (4). This is thought to be due to hepatic lipid accumulation. No hematologic abnormalities have been associated with hypertriglyceridemia-associated proteinuria, but mild thrombocytosis (platelet count of 400-500 x 10^3/µL) is common in older Miniature Schnauzers (6).

Table 1. Clinicopathologic features of hypertriglyceridemia-associated proteinuria in Miniature Schnauzers.

	What fits?	What doesn't?
Urinalysis	• USG variable (isosthenuric to concentrated, median 1.021) • Inactive sediment • Dipstick proteinuria*	• Persistent isosthenuria or hyposthenuria • Hematuria, pyuria
UPC	• Correlated to degree of hypertriglyceridemia: - Fasting triglyceride concentrations of 100-400 mg/dL (1.1-4.5 mmol/L) are associated with mild proteinuria, UPC < 2 - Fasting triglyceride concentrations > 400 mg/dL (> 4.5 mmol/L) are associated with glomerular-range proteinuria, UPC > 2	• UPC elevations in the absence of hypertriglyceridemia or disproportionate to the fasting triglyceride concentration (*e.g.*, UPC > 2, with fasting triglyceride concentration < 200 mg/dL, < 5.2 mmol/L)
Serum chemistry	• Albumin within reference interval (median 3.6 g/dL, 54 µmol/L) • Creatinine within reference interval (median 0.7 mg/dL, 61 µmol/L) • Hypercholesterolemia with moderate to severe hypertriglyceridemia (> 400 mg/dL, > 4.5 mmol/L) • Alkaline phosphatase elevations are common; mild elevations in other liver enzymes can also be present	• Hypoalbuminemia • Azotemia • Hypercholesterolemia without hypertriglyceridemia • Hyperbilirubinemia • Hepatocellular leakage pattern predominant (alanine aminotransferase > alkaline phosphatase)
Complete blood count	• Mild thrombocytosis is common in geriatric Miniature Schnauzers with or without hypertriglyceridemia-associated proteinuria	• Anemia • Thrombocytopenia • Inflammatory leukogram

*Dipstick proteinuria is not a reliable predictor of UPC, and even trace proteinuria is suggestive of a pathologic state when present in dilute urine (10).

Diagnosis

The presence of hypertriglyceridemia and proteinuria in a Miniature Schnauzer is necessary for a diagnosis of hypertriglyceridemia-associated proteinuria, but in itself not sufficient to confirm the disorder; other causes of these disturbances must first be ruled out. A simple diagnostic approach is presented in **Table 2**. A serum biochemistry profile **(Figure 2)** and urinalysis are critical to exclude pre- and post-renal causes of proteinuria and for detecting abnormalities (*e.g.*, hypoalbuminemia, azotemia) that could indicate that a more severe form of glomerular disease is present (11,12). It is also important to rule out treatment with medications associated with hyperlipidemia (*e.g.*, corticosteroids, phenobarbital) and to evaluate for metabolic disorders that can cause secondary hyperlipidemia (13). These include diabetes mellitus, hyperadrenocorticism, and hypothyroidism, all of which can also be associated with proteinuria (14-16).

Hyperadrenocorticism can be particularly difficult to differentiate from primary hypertriglyceridemia, as similar patterns of liver enzyme elevations occur with both conditions. If clinical signs (*e.g.*, polyuria, polydipsia, polyphagia) and physical exam findings (*e.g.*, alopecia, abdominal distension, hyperpigmentation) consistent with hyperadrenocorticism are present, a low-dose dexamethasone suppression test is recommended as a diagnostic test for hyperadrenocorticism (17). If signs are absent, a urine cortisol-to-creatinine ratio can be used to rule out hyperadrenocorticism. Obesity, pancreatitis, and cholestasis are also associated with mild hypertriglyceridemia in dogs (13,18).

Ultimately, hypertriglyceridemia-associated proteinuria is a diagnosis of exclusion. The final step in the diagnostic process is the evaluation of a renal biopsy with comprehensive examination of the tissue by thin sections, special stains, and transmission electron microscopy **(Figure 1)** (7). Glomerular lipid thromboemboli with or without focal segmental glomerulosclerosis are characteristic for lipid-induced injury. If no lipid deposits are present, or if other lesion types are detected, the dog's proteinuria should be assumed to have another origin. Importantly, one in five Miniature Schnauzers

Table 2. Diagnostic algorithm for diagnosing hypertriglyceridemia-associated proteinuria in Miniature Schnauzers.

Step 1. Evaluate for pre- and post-renal causes of proteinuria (11)
- Hyperglobulinemia – if present, consider serum and/or urine protein electrophoresis to evaluate for a neoplastic gammopathy.
- Pyuria and/or bacteriuria – if present, consider a urine culture to rule out infection.
- Hematuria – if present, consider imaging of the urinary tract to evaluate for uroliths or neoplasia; also consider urine culture to rule out infection.

Step 2. Evaluate for evidence of other more serious forms of glomerular disease (12)
- Hypoalbuminemia, renal azotemia, and loss of urine concentrating ability are not consistent with hypertriglyceridemia-associated proteinuria and warrant further diagnostic investigation.

Step 3. Evaluate for other conditions associated with hyperlipidemia (17)
- Post-prandial (sample drawn less than 12 hours post-feeding)
- Diabetes mellitus
- Hyperadrenocorticism*
- Hypothyroidism
- Obesity
- Treatment with corticosteroids* or phenobarbital

***Note:** Dogs with hyperadrenocorticism (spontaneous or iatrogenic) and primary hypertriglyceridemia can present with identical clinicopathological disturbances (hyperlipidemia, elevations in alkaline phosphatase and other liver enzymes, and proteinuria). A thorough history and exam are important for differentiating the conditions.

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Figure 2. Lipemic serum on blood sampling may be an indicator of hypertriglyceridemia. Gross lipemia indicates triglyceride elevations of at least 200 mg/dL.

undergoing renal biopsy for proteinuria are found to have immune-complex mediated glomerulonephritis (7) and could benefit from treatment with immunosuppressive therapy (19). The decision to proceed with a renal biopsy in a dog with presumed hypertriglyceridemia-associated proteinuria should weigh the likelihood of another disease process against the risk of complications from the biopsy, such as severe hemorrhage (20).

Treatment

No studies have investigated the optimal therapy for Miniature Schnauzers with hypertriglyceridemia-associated proteinuria. However, based on data from humans and rodents, management of the hypertriglyceridemia is important. Dietary management should first be instituted, and feeding a low-fat diet (containing less than 25 grams of total fat per 1,000 kcal) is recommended (13). Reduced dietary protein intake is recommended for dogs with glomerular disease (21), but it is unknown if this is beneficial for dogs with hyperlipidemia-associated proteinuria. If the fasting serum triglyceride concentration remains elevated after two months of exclusively feeding this type of diet, a fibrate should be administered. This is especially important if the serum triglyceride concentration is > 400 mg/dL (> 4.5 mmol/L), as the risks for proteinuria and pancreatitis are greatest with this degree of hypertriglyceridemia (2,5,6). Bezafibrate is effective at normalizing triglyceride concentrations in dogs within 30 days of treatment (22) and has a recommended dose of 50 mg PO q24H for dogs weighing < 12 kg, 100 mg for 12.1-25 kg, and 200 mg for > 25 kg. Bezafibrate is manufactured as a 200 mg sustained-release tablet; although it must be split for dogs weighing less than 25 kg, it

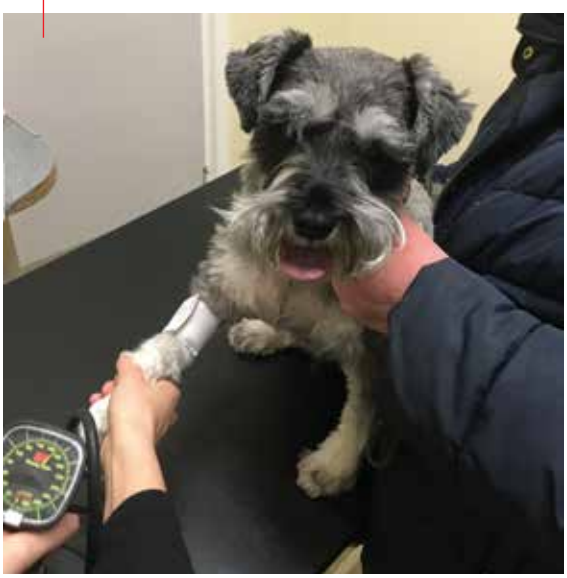
"The presence of hypertriglyceridemia and proteinuria in a Miniature Schnauzer is not in itself sufficient for a diagnosis of hypertriglyceridemia-associated proteinuria; other causes of these disturbances must first be ruled out."

Eva Furrow

remains effective at treating hypertriglyceridemia in animals under this weight. If bezafibrate is not available, other options include fenofibrate at 2-4 mg/kg q24H (23), or clinofibrate at 10 mg/kg q12H (24). In humans, major side effects of fibrates include myopathy and hepatotoxicity, but these have not yet been reported in dogs at the dosages recommended above. Other proposed medications for hyperlipidemia in dogs are omega-3 fatty acids and niacin, but evidence of efficacy is lacking (13).

Treatment of proteinuria with an inhibitor of the renin-angiotensin-aldosterone system is recommended for dogs with a UPC consistently > 0.5 (21). Examples include angiotensin converting enzyme inhibitors such as enalapril or benazepril (both given at 0.5 mg/kg q24H), or angiotensin receptor blockers such

Figure 3. It may be prudent to perform a blood pressure measurement in any Miniature Schnauzer that is diagnosed with renal proteinuria; antihypertensive therapy should be prescribed for all dogs with persistent hypertension.



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as telmisartan (1 mg/kg once daily). The UPC, serum creatinine, serum potassium, and blood pressure should be rechecked 1-2 weeks after starting these drugs (21). Antithrombotic agents are also a component of the general recommendations for dogs with proteinuric glomerular disease, but a prothrombotic tendency was not found in a limited evaluation of Miniature Schnauzers with hypertriglyceridemia-associated proteinuria (6). Given the paucity of data, the decision to start an antithrombotic agent can be made at the discretion of the clinician. Antihypertensive therapy should be administered to dogs with persistent hypertension (> 150 mmHg) according to consensus guidelines for management of glomerular disease **(Figure 3)** (21).

Prognosis

Longitudinal data on Miniature Schnauzers with hypertriglyceridemia-associated proteinuria is limited to one study that followed 8 affected dogs for a median of 18 (range 3-31) months (6). During this time there was no evidence of progressive renal disease, and no deaths were attributed to the hypertriglyceridemia-associated proteinuria. Dogs with hypertriglyceridemia-associated proteinuria also have no evidence of cardiac damage or hypercoagulability, as assessed by antithrombin III activity (6).

CONCLUSION

Primary hypertriglyceridemia is prevalent in middle-aged and geriatric Miniature Schnauzers and often associated with glomerular-range proteinuria. There is evidence that the proteinuria is a consequence of lipid-induced glomerular injury, and glomerular lipid emboli have been detected in renal biopsies obtained from hypertriglyceridemic, proteinuric Miniature Schnauzers. The disease is subclinical, and serious consequences of glomerular disease (hypoalbuminemia, azotemia, or thromboembolic disease) have not been reported. When hypertriglyceridemia and proteinuria are detected concurrently in this breed, other possible causes, such as hyperadrenocorticism, should be ruled out before making the presumptive diagnosis of hypertriglyceridemia-associated proteinuria. Treatment consists of management of hypertriglyceridemia with diet, and if needed, fibrate administration. Inhibition of the renin-angiotensin-aldosterone system is also recommended to reduce proteinuria. Based on limited data, prognosis is excellent, but if hypoalbuminemia, azotemia, or persistent isosthenuria develops, other underlying disease processes should be investigated.

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FELINE RENAL TRANSPLANTATION

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After completing veterinary school and an internship at the University of Pennsylvania, Dr. Aronson undertook a small animal surgical residency at the University of California, Davis (UCD). From 1994-1996 she was the coordinator of the renal transplantation program for animals at UCD. Following her residency, she joined the faculty at the University of Pennsylvania – where she is currently Professor of Surgery – and started their renal transplantation program. Her clinical interests include all areas of soft tissue surgery, but in particular microvascular surgery and complex urinary tract surgery (including renal transplantation), and treatment of urolithiasis. As well as frequently lecturing in her specialist fields, she is the author of a textbook on small animal surgical emergencies.

Kidney transplantation has been pioneered in the USA as an option for treating feline renal disease and is still very much a specialist procedure, but Lillian Aronson reviews the technique, the ethics and the possible pitfalls in a paper that will be of benefit to all first-line small animal clinicians.

KEY POINTS

1. Kidney transplantation may be a viable option for some cats suffering from acute and chronic renal failure.
2. Stringent case selection is a critical part of patient evaluation to prevent serious, life threatening complications.
3. Lifelong immunosuppression post-surgery consists of a combination of the calcineurin inhibitor, cyclosporine, and the glucocorticoid, prednisolone.
4. For ethical reasons, the owner of the transplanted cat commits to adopt the donor.

Introduction

Renal transplantation for cats continues to gain acceptance as a treatment option for patients presenting with early, decompensated chronic renal failure as well as those with acute irreversible renal failure. Since its introduction to veterinary medicine in 1987, it is estimated that between 600-700 cases of feline renal transplantation have been performed at various centers in the USA. The ability to successfully perform the technique in cats has been attributed to a number of factors, including the use of the drug cyclosporine for immunosuppressive therapy, the development and refinement of specific microsurgical techniques for the procedure, and the use of an allograft from an unrelated or related donor (1). Successful transplantation can result in the disappearance of clinical signs previously associated with the patient's kidney disease, weight gain, an overall improvement in the quality of life and prolonged survival time compared to medical management of the condition (2).

Client education

It is important for owners to understand that kidney transplantation in cats involves a long-term financial (and often emotional) commitment, as well as an obligation to ongoing postoperative

management that should not be underestimated. The goal of the procedure is to improve the quality of life for the patient, but it is not a cure and complications can occur. Additionally, although medical treatments – including subcutaneous fluids, a renal diet, hormonal therapy to stimulate red blood cell production, phosphate binders, hypertension medication and gastrointestinal protectants – can often be discontinued following transplantation, lifelong immunosuppressive therapy is necessary to prevent rejection of the allograft. The owner needs to be informed about the risks of the procedure and should be alerted to the fact that their pet may be turned down as a potential candidate if the patient is fractious or if it fails any aspect of the medical screening process. Financial commitments include the costs incurred from both the recipient and donor during their initial hospitalization, as well as additional expenses once the patient leaves the transplant facility. These include repeated veterinary visits to perform routine blood work and wellness examinations, and also the cost of treating potential complications if they arise. Prior to the procedure, the owner should identify a veterinarian and facility committed to performing long-term follow-up and willing to provide 24-hour care should complications develop. Additionally, regardless of the outcome, the owner is responsible for adopting the donor cat and providing the animal with a lifelong home.

Recipient and donor screening

Recipient

Thorough screening of a potential recipient can prevent complications from occurring following the procedure, and is typically performed by the referring veterinarian in conjunction with the transplant team. Cats should be free of other disease conditions including recurrent urinary tract infections, significant heart disease, feline leukemia virus [FeLV] or feline immunodeficiency virus [FIV] positive status, and underlying neoplasia. Note that calcium oxalate urolithiasis, inflammatory bowel disease and/or a history of an upper respiratory infection are not contraindications to performing this procedure, as cats diagnosed with these conditions have been successfully transplanted at the author's facility (3).

Although the exact time to intervene is still up for debate, the author recommends surgical intervention for patients with irreversible acute renal failure or those with chronic disease showing signs of decompensation, including continued weight loss and worsening of the azotemia and anemia in the face of medical management (4,5). It is important to note that clinically stable patients can rapidly deteriorate and die without prior evidence that decompensation was present. Although there is no set age limit for the procedure, recipient age has been associated with survival following discharge, with one study identifying cats older than 10 years of age having a higher-mortality rate during the first 6 months after surgery and another study identifying a decrease in median survival time with increasing age (2,6).

Current evaluation of a potential recipient involves laboratory testing (blood type and cross-match, complete blood count [CBC] and biochemistry, and thyroid evaluation), urinary tract evaluation (urinalysis, urine culture, urine protein:creatinine ratio, abdominal radiography, and abdominal ultrasonography), cardiac evaluation (thoracic radiography, electrocardiography, echocardiography and blood pressure) and screening for infectious disease (FeLV, FIV), as well as serologic testing for toxoplasmosis [IgG and IgM]) **(Table 1)**. If a patient is traveling from a significant distance, a blood sample can be sent for cross-matching to potential donors prior to travel to determine if a compatible donor is available.

Donor

The author's facility maintains a donor colony that consists of healthy young (typically 1-3 years old) cats adopted from a regional shelter. Once a donor is identified for a specific recipient, the owner of the recipient is responsible for adopting the donor cat and giving him/her a lifelong home. The wellbeing of the donor cat is of the utmost importance to the transplant team. Those who work in the field of transplantation understand the ethical implications of the procedure, including concerns that have been raised by ethicists regarding possible harm and suffering that could be inflicted from the procedure, as well as any effect on long-term survival. Because of these concerns, a large retrospective study was performed at the author's facility in 2016 looking at perioperative morbidity and long-term outcome following unilateral nephrectomy in 141 kidney donors (7). The study identified an acceptably low perioperative morbidity, and the median time from nephrectomy to hospital discharge was 3.6 days. Long-term follow-up was available for 99 cats; the

Table 1. Preoperative evaluation for a potential feline renal transplant recipient.

- Complete blood count
- Serum biochemistry profile
- Feline leukemia virus (FeLV)/Feline immunodeficiency virus (FIV) status
- *Toxoplasma gondii* serology, IgG and IgM
- Thyroid hormone (thyroxine)
- Blood type and major and minor cross-match to donor
- Urinalysis and urine culture
- Urine protein:creatinine ratio
- Abdominal and thoracic radiography
- Abdominal ultrasonography
- Electrocardiography
- Echocardiography
- Blood pressure measurement

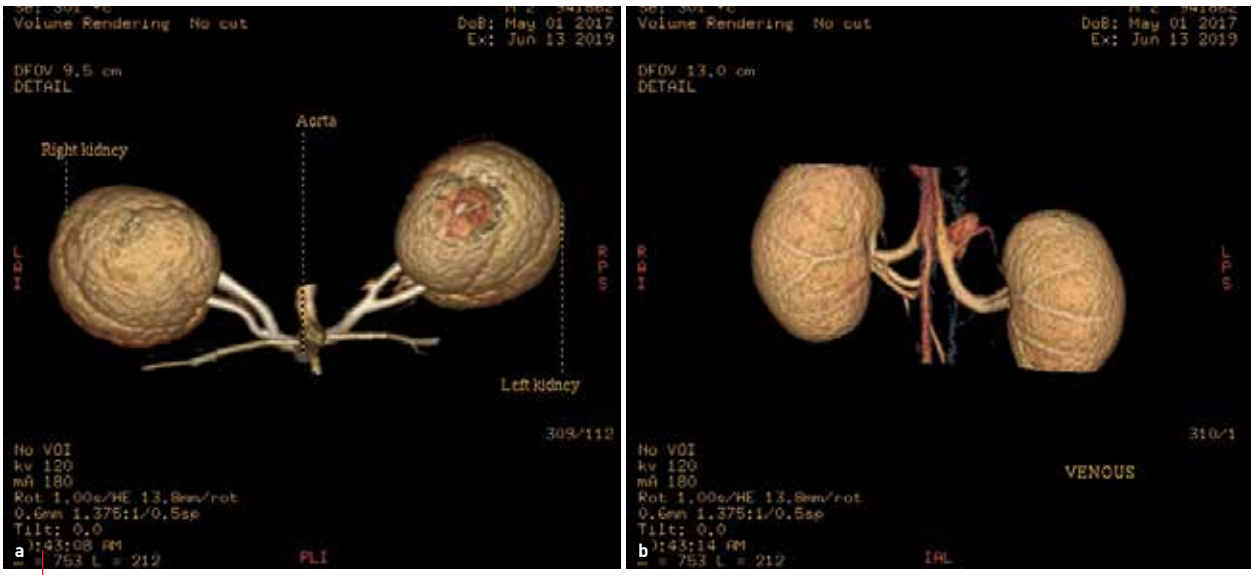

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Figure 1. CT angiography of a potential feline renal transplant donor. The arterial phase **(a)** identifies a single renal artery on both the right and left at the level of the aorta. Both arteries bifurcate prior to entering the kidney. The left kidney is more suitable for donation because the common artery leaving the aorta is greater than 0.5 cm in length. The venous phase **(b)** identifies a single vein on the left with a short bifurcation just prior to entering the kidney. Three veins are identified on the right side.

median age at the time of follow-up was 12.2 years. Three cats had a history of stable chronic kidney disease (median 6.2 years post-operatively) and two cats were treated successfully for acute kidney injury, 4 and 6 years following surgery. Two cats died of chronic renal failure 12 and 13 years following surgery and four cats developed an acute ureteral obstruction from calcium oxalate urolithiasis a median of 7 years following surgery. Because of this latter finding, routine abdominal radiographs are performed during yearly wellness visits to identify any new stone formation so that it can be addressed accordingly before resulting in morbidity or mortality.

Standard donor evaluation includes CT angiography to assess the renal vasculature as well as to evaluate the renal parenchyma for any abnormalities **(Figure 1)**. Other mandatory tests include a complete blood count and blood type, serum biochemistry profile, urinalysis and culture, FeLV and FIV testing and serologic testing for toxoplasmosis (IgG and IgM). A suitable home is found for any potential donor that fails the screening process.

Preoperative treatment

Medical management – including an appropriate renal diet, fluid therapy, blood products, gastrointestinal protectants, phosphate binders and antihypertensive therapy – will vary depending on the stability of the recipient. If the patient is anorectic, a nasogastric tube is placed to administer nutritional support and prevent hepatic lipidosis. However, because of complications encountered with esophagostomy tubes in some recipients receiving chronic immunosuppressive therapy, such tubes are no longer recommended by the author in this population of patients unless absolutely necessary.

Two immunosuppressive protocols currently exist to prevent rejection of the allograft. The protocol currently used at the author's facility includes a combination of the calcineurin inhibitor cyclosporine (CsA) and the corticosteroid, prednisolone. An oral liquid formulation of cyclosporine is used so that the dose can be titrated for each individual cat. Cyclosporine is typically begun 72-96 h prior to transplantation whilst prednisolone administration is started on the

"Successful renal transplantation can result in the disappearance of clinical signs previously associated with the patient's kidney disease, weight gain, an overall improvement in the quality of life and prolonged survival time compared to medical management of the condition."

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morning of surgery. A 12-hour whole-blood cyclosporine trough concentration is obtained the day before surgery to adjust the oral dose for surgery. Vitamin B_{12} (given by intramuscular injection) has been used in some patients to aid cyclosporine absorption from the gastrointestinal tract. Another option for immunosuppression used by some transplant surgeons combines ketoconazole with cyclosporine and prednisolone, allowing for once daily administration of medication (8,9). With this protocol, cyclosporine trough concentration is measured every 24 hours. If signs of hepatotoxicity are identified, ketoconazole administration should be discontinued. If the cat is positive on IgM and IgG serology for *Toxoplasma gondii*, clindamycin is administered in conjunction with immunosuppressive therapy and continued for the lifetime of the cat.

Surgery

At the author's facility, the transplant procedure takes approximately 6-7 hours and involves a team of 3 surgeons. The donor kidney is prepared for nephrectomy. The left kidney is preferred because it has a longer vein, however the right kidney can be used if necessary. The renal artery and vein are cleared of fat and adventitia and the ureter is dissected free to the point where it joins the bladder. It is critical, however, to harvest a donor kidney with a single renal artery, with a minimal length of 0.5 cm at the point where the artery joins the aorta (10). The nephrectomy is performed when the recipient's vasculature is prepared to receive the kidney.

An operating microscope is used to perform the majority of the recipient's surgery. The allograft is flushed with a phosphate-buffered sucrose organ preservation solution or heparinized saline solution; the donor renal artery is anastomosed end-to-side to the abdominal aorta using 8-0 nylon in a simple continuous pattern, and the donor renal vein is anastomosed end-to-side to the caudal vena cava using 7-0 silk in a simple continuous pattern **(Figure 2)** (10). Once complete, the hemostat clamps are removed; a small amount of hemorrhage usually occurs at this point and is controlled with pressure, but any significant leaks may need to be repaired with the placement of additional sutures.

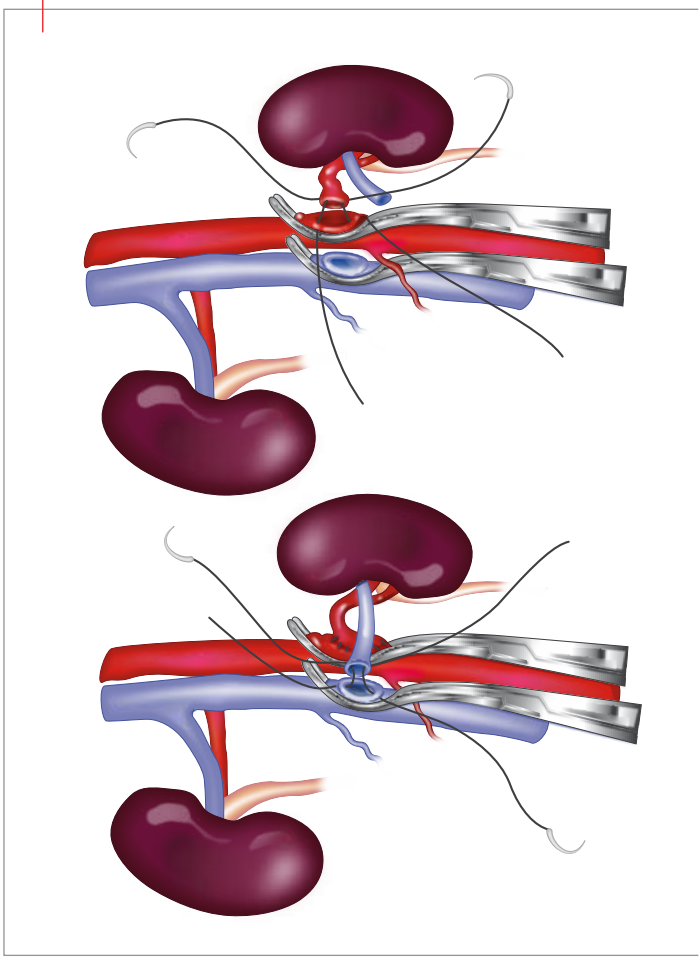
An alternative surgical technique uses hypothermic storage to preserve the donor kidney until the recipient surgery is performed. This technique reduces personnel and resources needed for the transplantation procedure.

Following the vascular portion of the procedure, the donor ureter is attached to the urinary bladder using one of three techniques. At the author's facility, a ureteroneocystostomy is performed using an intravesicular mucosal apposition technique. A ventral midline cystotomy is performed and then the end of the ureter is brought directly into the bladder at the apex. The end of the ureter is spatulated and the ureteral mucosa is sutured to the bladder mucosa using either 8-0 nylon or synthetic absorbable suture material in a simple interrupted pattern **(Figure 3)**. Prior to closure, the allograft is attached to the abdominal wall to prevent torsion. The recipient's native kidneys are usually left in place to act as a reserve in case graft function is delayed **(Figure 4)**. Because patients are on immunosuppressive therapy, non-absorbable suture (polypropylene) is used for abdominal wall closure to prevent incision dehiscence.

Postoperative care

Postoperative care is tailored for each individual patient, but typically includes intravenous fluid therapy until the patient is eating and drinking, antibiotic therapy, blood products as needed, and pain control. Minimal stress and handling and prevention of hypothermia are critical during the early postoperative period. The packed cell

Figure 2. A diagram depicting an end-to-side anastomosis of the renal allograft to the recipient's abdominal aorta and vena cava. The renal artery (upper image) is anastomosed end to side to the aorta with 8-0 nylon, and the renal vein (lower image) is anastomosed end to side to the vena cava with 7-0 silk.



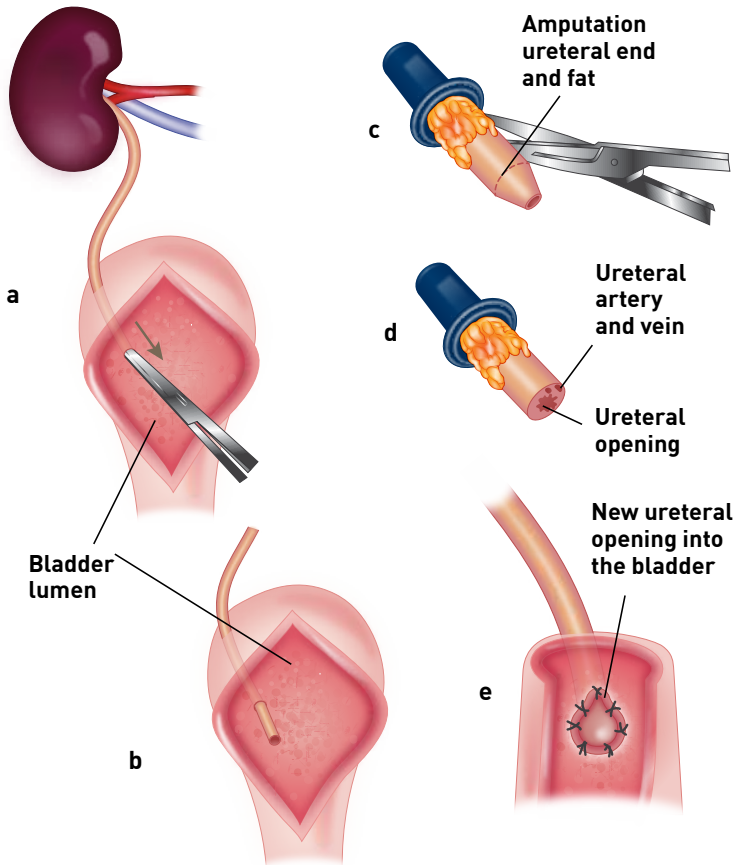


Figure 3. A diagram showing ureteroneocystostomy using an intravesicular mucosal apposition technique. A ventral midline cystotomy is performed and the donor ureter is brought directly into the bladder at the apex **(a,b)**. The end of the ureter that had been traumatized from pulling it into the bladder is then resected back to healthy tissue and periureteral fat is removed from the end of the ureter to aid in suturing **(c)**. Following amputation, the ureteral opening is visualized. Uncommonly, the ureteral artery may need to be ligated **(d)**. The end of the ureter is then spatulated; this involves placing microvascular scissors in the lumen of the ureter and making a small (5 mm) cut to fillet it open. The ureteral mucosa is then sutured to the bladder mucosa in a simple interrupted pattern **(e)**.

volume, total protein, electrolytes, blood glucose and acid base status are initially evaluated 2-3 times daily for the first few days and then daily until discharge. Indirect blood pressure is monitored every 2-4 hours for the first 48-72 hours to monitor for the development of hypertension. A renal panel is checked every 24-48 hours, and a cyclosporine level checked every 3-4 days and dosage adjusted accordingly. If needed, a full blood biochemistry and complete blood count is performed. Voided urine is collected daily to assess urine specific gravity. If the procedure is successful, azotemia typically resolves within the first 24-72 hours following surgery. If improvement is not identified, an ultrasonographic examination of the allograft is recommended to assess blood flow as well as for any signs of a ureteral obstruction. If graft perfusion is adequate and no signs of obstruction are present, then delayed graft function should be considered. In these cases, improvement in function often occurs within the first few weeks following the procedure. If the transplanted kidney fails to function, the kidney should be biopsied prior to re-transplantation.

Long-term management and complications

Patients are confined either to a room without furniture or in a larger dog crate during the early postoperative period to prevent any catastrophic injury to the allograft. Weekly evaluations for the first 6-8 weeks are recommended, and then visits are extended to longer intervals depending on the animal's stability. Long-term patients are evaluated by their veterinarian 3-4 times a year. During each exam, body weight and blood pressure are recorded. Clinical pathological evaluation should include a renal panel, packed cell volume, total protein, cyclosporine level and urinalysis if a free-catch urine sample is available. If indicated, a complete blood count and serum biochemistry panel is performed. Evaluation by a cardiologist is recommended every 6-12 months if the patient had been diagnosed with underlying cardiac disease prior to transplantation.

Complications from the procedure include those related to the allograft and those associated with chronic immunosuppressive therapy. Technical

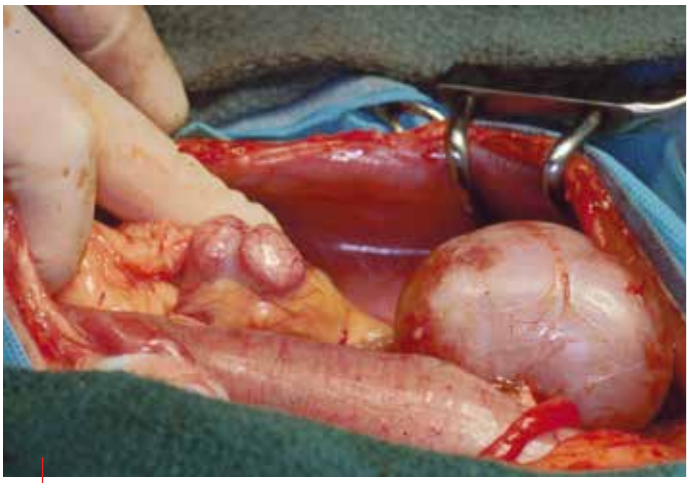


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Figure 4. An intra-operative picture showing the native kidney (left) and donor allograft (right). The recipient's native kidneys are usually left in place to act as a reserve in case graft function is delayed.

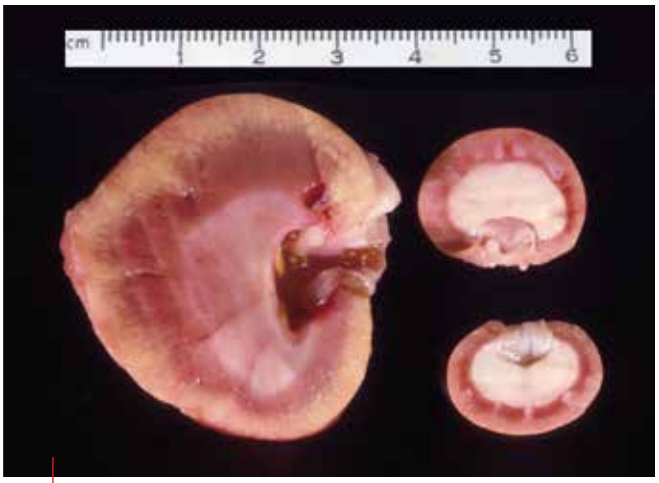

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Figure 5. Cross sections of an allograft (left) and native kidney (right) at necropsy from a 7-year-old female spayed domestic shorthair cat that developed a proximal ureteral obstruction from calcium oxalate urolithiasis two years following transplantation.

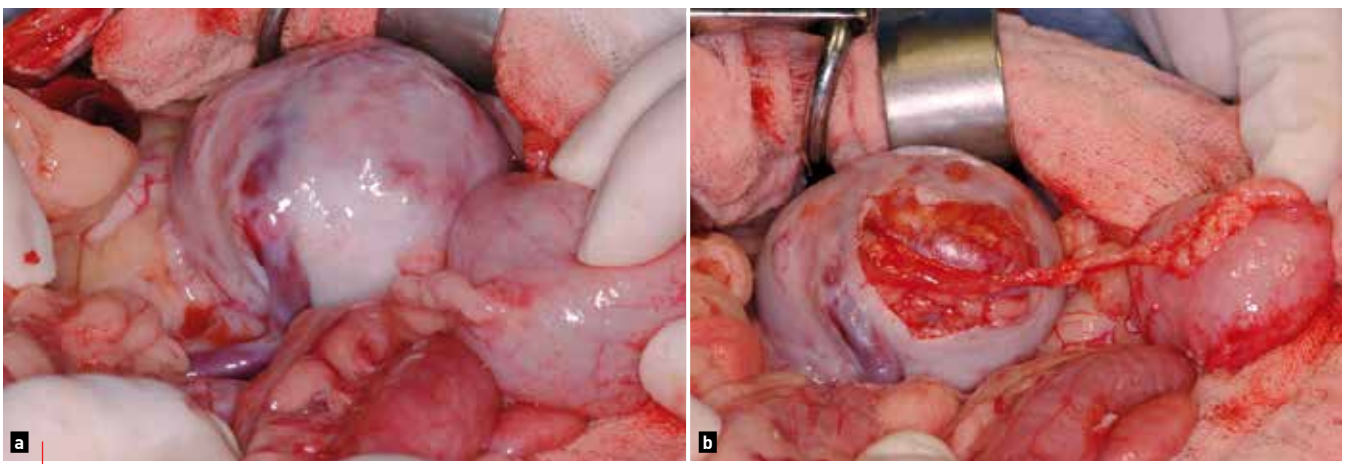

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Figure 6. Retroperitoneal fibrosis. Note the white scar tissue along the caudal pole of the allograft and the shortened length of the ureter because it is encased in fibrotic tissue **(a)**. Surgical dissection and partial resection of the fibrotic tissue surrounding the allograft ureter releases the ureter from being obstructed **(b)**.

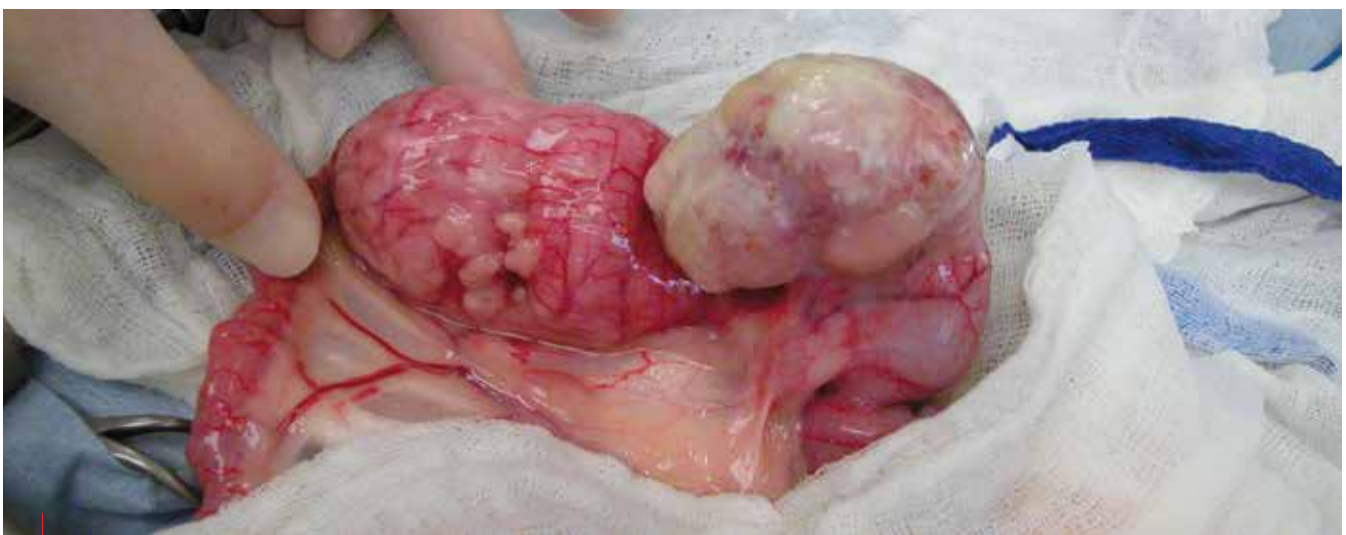

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Figure 7. A 1.5-year-old female spayed domestic shorthair that developed gastrointestinal lymphoma two years following renal transplantation. Surgery was performed to resect the tumor.

complications at surgery can occur with the vascular pedicle and ureteral reimplantation, resulting in the need for further procedures. Other complications directly related to the allograft include delayed graft function, acute rejection, calcium oxalate nephrosis **(Figure 5)**, and retroperitoneal fibrosis **(Figure 6)** (3,11,12). Patients experiencing a rejection episode can be treated successfully with the administration of IV immunosuppressive therapy. Surgical intervention may be necessary for patients developing calcium oxalate urolithiasis of the allograft and is always indicated for cats developing retroperitoneal fibrosis in order to remove scar tissue that has resulted in a ureteral obstruction. Complications secondary to chronic immunosuppressive therapy include the development of infection (including opportunistic infections), diabetes mellitus (DM) and lymphoma **(Figure 7)** (13-20). Successful treatment of infectious complications is directed towards the specific infectious agent. For patients developing DM secondary to chronic immunosuppressive therapy, treatment involves an attempt to decrease the immunosuppressive drugs, dietary management and, in some cases, insulin administration. Unfortunately, treatment for patients who develop lymphoma following immunosuppressive therapy and transplantation has not been successful, and the prognosis is considered guarded.

CONCLUSION

Currently at the author's facility 92% of cats (154/168) have been discharged following surgery with a mean and median survival time of 994 and 595 days respectively. Ongoing clinical experience with short- and long-term management, as well as the ability to identify specific risk factors both pre- and post-operatively, will hopefully continue to improve long-term outcome in these patients. Whilst not an option for all cats with CKD, renal transplantation is becoming more widely available and the first-opinion practitioner should be aware of the pros and cons of the procedure, as well as the ethical and financial considerations that come with it.

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PROTEIN RESTRICTION FOR CATS WITH CHRONIC KIDNEY DISEASE

Feeding protein-restricted diets to cats with kidney disease has been a mainstay of the therapeutic approach to such cases for many decades, but controversies still remain; Meredith Wall and Nick Cave review the current state of knowledge and offer some advice for the clinician.

KEY POINTS

1. Current knowledge indicates that protein restriction close to minimum requirements is warranted in cats with IRIS CKD Stage 2 or 3, or earlier if proteinuric.
2. Benefits of feeding a reduced protein diet may include reducing accumulation of nitrogenous wastes and harmful uremic toxins, reducing proteinuria and decreasing renal oxidative stress.
3. Home-prepared or raw meat-based diets can be very high in protein, and a specialist in nutrition should be consulted to ensure such diets are appropriate.
4. Careful attention should be given to monitoring appetite, caloric intake, body weight, body condition and muscle condition, in order to minimize the risk of protein-energy wasting.

Introduction

Chronic kidney disease (CKD) is a commonly encountered problem in feline practice (1-2), and the prevalence of the condition in cats over 15 years of age has been shown to be more than 30% (3). In the majority of cases an underlying etiology is not identified at the time of diagnosis, even when histopathological examination is performed (1). While CKD in all species is often progressive in nature, it is also a surprisingly dynamic and heterogenous disease process, being influenced – particularly in cats – by multiple factors, many of which remain to be discovered (1,4).

Despite this variability, dietary therapy has remained the cornerstone of management for feline CKD for the past 60 years (4-7). Feeding a renal diet (either a diet formulated by a veterinary nutritionist or manufactured specifically for managing animals with kidney disease) to cats with International Renal Interest Society (IRIS) CKD stages 2-4[1] **(Table 1)** is currently considered the standard of care (8). In fact, nutritional management is regarded as the therapeutic intervention most likely to enhance the long-term survival and quality of life for cats with IRIS CKD stages 3 and 4 (8). Renal diets also help to ameliorate or prevent the clinical consequences of CKD and uremia, slow the progression of the disease, minimize electrolyte, mineral, and acid-base balance abnormalities, and maintain adequate body weight, body condition and muscle condition. Initiating therapy with a renal diet is also considered part of the standard of care for management of proteinuria in cats **(Table 2)** (8).

Despite its widely accepted role, there is controversy surrounding the use of renal diets for cats, and in particular the restriction of dietary protein. The increasing popularity of feeding raw and protein-rich, grain-free diets has reduced public interest in the use of protein-restricted renal diets, and there is also increased awareness of the potential risks, such as protein-energy wasting. It is a challenge to evaluate the potential benefits of protein restriction and whether they outweigh any risks, as there is insufficient research in cats, and some reference to studies in dogs, humans or other species is required, which is obviously not ideal. There are therefore three main questions that need to be answered;

1. Should we restrict dietary protein intake for cats with CKD?
2. If yes, how much should we restrict protein intake?
3. When should we restrict protein intake?

[1] http://iris-kidney.com/guidelines/index.html

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To answer these questions, we need to consider the benefits versus the risks of protein restriction, the protein requirements of both healthy cats and cats with CKD, and a range of individual factors such as the pet's appetite, concurrent medical conditions and their associated prognoses, as well as the cat's age.

What are the benefits of protein restriction?

Limiting protein intake to ameliorate the clinical signs of uremia has been considered best practice for many years and is well-supported by evidence for cats with advanced renal disease. Multiple studies have demonstrated that feeding a renal diet to cats with CKD is associated with a reduction in blood urea nitrogen and observable clinical benefit, along with an increased survival time, although whether protein restriction (rather than other features of a renal diet) contributes to this increase in survival is the subject of ongoing and sometimes heated debate. It is uncertain how toxic urea is in cats, whilst in humans, though once thought of as being biologically inert, it is now considered to be directly toxic at concentrations seen in CKD (9). Altered insulin sensitivity, increased free radical production and induction of apoptosis have been directly attributed to the concentration of urea, although urea-derived metabolites may also contribute. Whether the concentration of urea in plasma reaches sufficient concentrations to have a direct effect in cats with CKD remains to be shown (2,4,7,10).

Protein restriction may also be of benefit if proteinuria is present, although even this is controversial. Restricted dietary protein is thought to alter glomerular hemodynamics and permselectivity, thus reducing glomerular filtration pressure and protein loss into the filtrate. In other species a linear relationship between reduction in dietary protein intake and a decrease in proteinuria has been demonstrated (11). However, in a study where cats with naturally occurring stage 2 and 3 CKD were fed either a protein-restricted renal diet or a maintenance diet, there was no difference in proteinuria levels (7). It may be that the renal hemodynamic response is over-ridden as renal function declines, or that it depends on the specific amino acids in the proteins, or other as yet unknown factors.

Table 1. Staging of feline CKD based on blood creatinine concentration (according to IRIS Staging of CKD (modified 2017)).

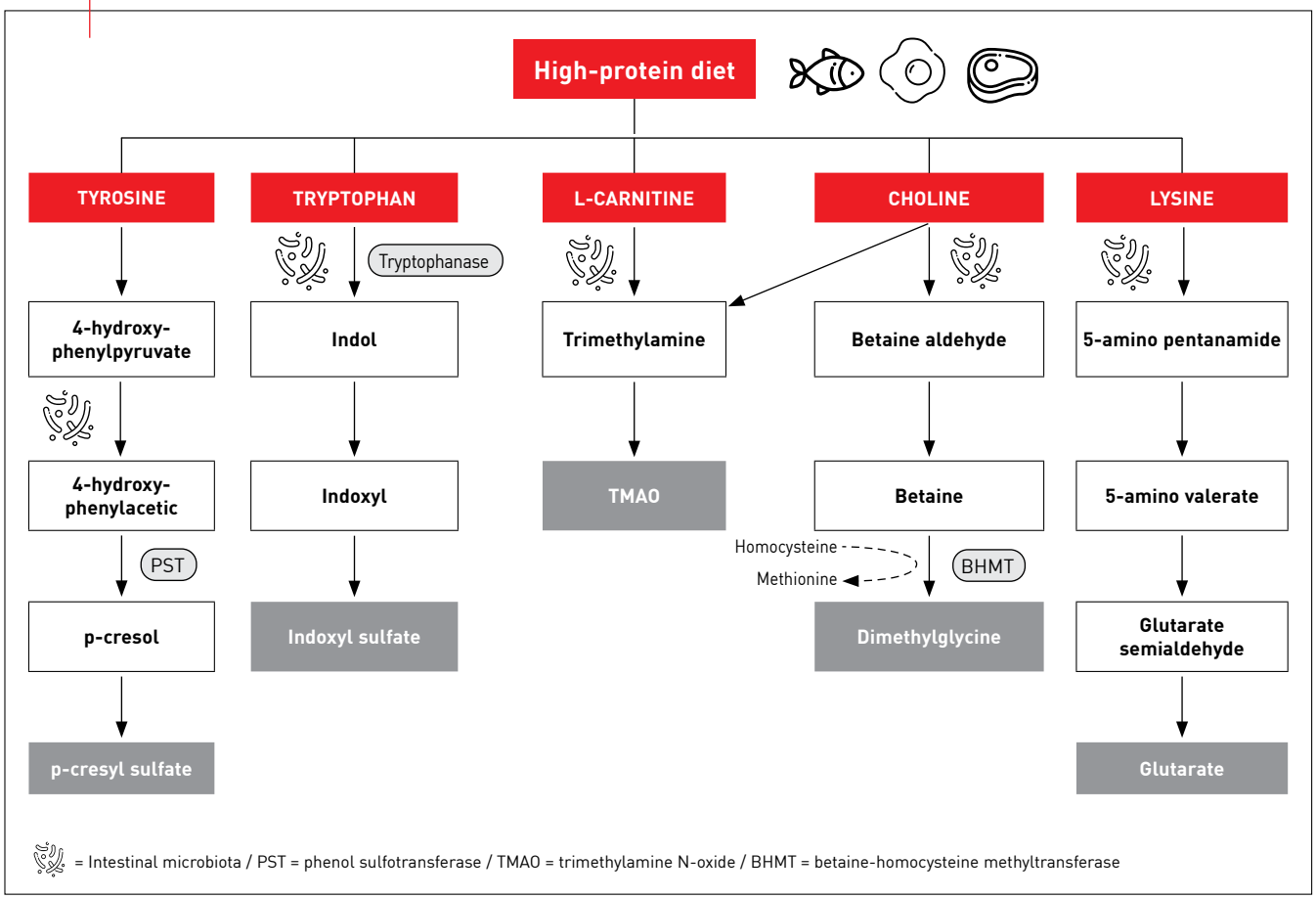
Stage	Blood creatinine µmol/L (mg/dL)
At risk*	< 140 (< 1.6)
1	< 140 (< 1.6)
2	141-250 (1.6-2.8)
3	251-440 (2.9-5.0)
4	> 440 (> 5.0)

* At risk as the history suggests the cat may develop CKD in the future because of a number of factors (*e.g.*, exposure to nephrotoxic drugs, breed, old age, etc).

Table 2. Substaging of feline CKD by proteinuria (according to IRIS Staging of CKD (modified 2017)).

Urine protein to creatinine ratio	Substage
< 0.2	Non-proteinuric
0.2-0.4	Borderline proteinuric
> 0.4	Proteinuric

Figure 1. Pathways of some uremic toxins produced from dietary-derived nutrients.



Dietary protein restriction has been shown experimentally to reduce the gene expression of several proteins believed to play an important role in the progression of chronic kidney disease, such as platelet-derived growth factor and transforming growth factor β within the glomerulus (12). It is unknown whether this decreased gene expression is a direct consequence of an improvement in proteinuria, or due to some other effect of dietary protein restriction such as reduced renal ammoniagenesis (13).

What about uremic toxins?

Most interestingly, recent research has focused on the benefits of protein restriction with respect to reducing uremic toxin formation. Uremic toxins are solutes normally excreted by the kidneys that accumulate in patients with CKD and have detrimental effects. Uremic toxins have been associated with accelerated progression of renal disease, the development or progression of cardiovascular disease, bone disorders and neurological complications, both in humans and in many other species.

Urea was the first toxin identified and is now known to have both direct and indirect toxic effects (14), but to date over 130 different uremic toxins have been identified. Ingested nutrients, such as L-carnitine, tryptophan and tyrosine, can be metabolized by the gut microbiota to generate uremic toxins, or precursors that are metabolized to toxins in the body **(Figure 1)**. Trimethylamine N-oxide, p-cresyl-sulfate, and indoxyl sulfate are important uremic toxins that originate from dietary-derived nutrients. Methylguanidine (a nephro- and neurotoxin) has been shown to increase oxidative stress and accelerate neutrophil apoptosis in dogs (15).

Indoxyl sulfate is produced by hepatic sulphation of indole, which is absorbed from the gut where it is produced by bacterial metabolism of dietary tryptophan, and has been extensively studied. It has been reported to induce mitochondrial dysfunction, leading to increased production of reactive oxygen species and oxidative damage in the renal vasculature (16). This results in induction of inflammation and renal tubular cell injury, promotion of renal fibrosis, and progression of glomerular sclerosis (17). In addition accumulation of indoxyl sulfate can contribute to sarcopenia; therefore, feeding more protein in an attempt to maintain lean mass may actually promote and worsen sarcopenia, contributing to patient morbidity and ultimately mortality (18). However, the production of indole is dependent

on both the mass of available tryptophan, and the number of indole-producing bacteria in the intestine, thus the effect of protein restriction will vary greatly between cats with different intestinal microbiota.

While the clinical impact of different uremic toxins requires further investigation in cats, it has been shown that indoxyl sulfate is increased in cats with CKD when compared with healthy controls (17). Importantly, cats with IRIS stage 2 (and also stages 3 and 4) CKD have been found to have significantly higher-serum indoxyl sulfate concentrations, implying that some degree of protein restriction may be of benefit from IRIS stage 2 onwards. Human patients on very low-protein diets have been found to have a significant decrease in protein-derived uremic toxins – in one study, indoxyl sulfate was reduced by 69% (19). There is a lot more to learn about uremic toxins and their effects in cats with kidney disease; however, current research provides some compelling evidence for early and controlled reduction of non-essential protein.

What are the risks of protein restriction?

Despite the benefits of protein restriction detailed above, reasonable concern has been raised that low-protein renal diets may predispose feline patients to weight loss and loss of lean muscle mass. Protein-energy wasting, an under-appreciated condition in CKD, is undoubtedly the biggest fear surrounding dietary protein restriction (4). The International Society of Renal Nutrition and Metabolism expert panel has defined protein-energy wasting as "*a state of decreased body stores of protein and energy fuels (body protein and fat mass)*" (20). The proposed causes of protein-energy wasting are multifactorial, and include both nutritional and non-nutritional mechanisms.

In humans, concerns regarding protein-restricted diets and protein-energy wasting have been largely alleviated by a number of studies demonstrating that carefully planned low-protein diets (as followed by motivated and adherent patients) are effective and do not cause protein-energy wasting (21). It is well-established that protein restriction to the recommended minimum intake for a healthy human adult is very unlikely to promote protein-energy wasting, so long as the protein sources are highly digestible and have high biological value, and the patient is eating enough to meet their energy requirement (22).

Similarly, studies in cats with naturally occurring CKD that were fed therapeutic diets with restricted protein have found no detrimental effect on body weight or body condition score over a greater than two-year period (6). It is common for ageing cats and cats with CKD to experience a loss of body weight and lean body mass, but it is important to understand that increasing dietary protein is not necessarily the obvious solution, as some amino acid-derived uremic toxins are anorexigenic and, as noted previously, can also promote uremic sarcopenia and accelerate the kidney disease (23) **(Figure 2)**.

Another concern with protein restriction is that it can be challenging to objectively assess the protein status of a cat in clinical practice; muscle condition scoring is relatively subjective and careful nutritional assessment is often not performed regularly enough. Recommendations for humans with CKD involve a careful, monthly assessment of nutritional status, which includes appetite, dietary protein intake, energy intake, body weight and muscle mass, and urinary and serum biomarkers. Routinely monitoring nutritional status, particularly energy intake, in cats with CKD would be similarly beneficial, in order to allow any problems to be detected promptly. It is known that muscle-derived amino acids are used for gluconeogenesis if there is inadequate caloric intake, which decreases protein utilization for maintenance of lean muscle mass. When energy requirements are not met, catabolism occurs, leading to loss of lean mass and potentially resulting in clinical deterioration.

What degree of protein restriction is warranted?

Cats have a high requirement for dietary protein relative to omnivores in order to support both protein turnover and a relatively high rate of gluconeogenesis (24). When considering the degree of protein restriction that might be appropriate, it is important to understand what the protein requirement of a healthy adult cat is, and then how the requirement for cats with CKD might vary from this.

"It is common for cats with CKD to experience a loss of body weight and lean body mass, but it is important to understand that increasing dietary protein is not necessarily the obvious solution."

Meredith J. Wall

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Figure 2. This cat with advanced kidney disease has severe weight loss and loss of lean muscle mass.

The National Research Council (NRC) minimum requirements for protein and amino acids were established based on data from growing kittens, nitrogen balance studies, and other parameters. The NRC recommended intake of dietary protein for adult cats, 50 grams/1000 kcal ME (metabolizable energy), represents a 25% increase over the absolute physiological minimum requirement to account for variations in digestibility and bioavailability. In order to account for losses during processing and storage, and the low digestibility of some commercially available ingredients, the Association of American Feed Control Officials (AAFCO) Dog and Cat Food Nutrient Profiles were created. Therefore, the AAFCO minimum requirement adds a further "safety margin", and the minimum protein requirement for adult cats is 65 grams/1000 kcal ME. This margin helps ensure adequate intake of protein and amino acids for the majority of cats if calorie requirements are met.

"Current research is focused on uremic toxins, of which more than 130 exist; these are solutes normally excreted by the kidneys which accumulate in patients with CKD and can have a multitude of different detrimental effects."

Nick Cave

Unfortunately, there is insufficient clinical research to confidently establish the minimum protein requirement of cats with naturally occurring CKD, and certainly no studies that have compared different stages of CKD; however, it is believed to be similar to the minimum protein requirement of healthy cats (4). In one study, the dietary protein requirement of cats with spontaneous chronic kidney disease was found to be approximately 20% metabolizable energy (25). Commercial renal diets typically contain around 55-95 g protein/1000 kcal ME (26), or approximately 22-24% protein ME. This amount is above the NRC recommended allowance (50 g protein/1000 kcal ME) for adult cats, but is below that commonly employed in typical maintenance diets, which are around 80-120 g/1000 kcal ME.

Many owners do not realize that most commercial renal diets meet the AAFCO recommended minimum for protein, with a few exceptions. Furthermore, diligent manufacturers can optimize the digestibility and amino acid profile

of commercial renal diets to ensure high-protein quality and nutritional adequacy. More research on the protein requirement of cats in different stages of naturally occurring CKD would, of course, be desirable. However, there is no reason to currently believe that the degree of protein restriction used in commercial renal diets is inappropriate or excessive, or that it will increase the risk of protein-energy wasting, assuming that the cat's caloric intake is adequate.

When should dietary protein be restricted in a cat with CKD?

Severe protein restriction is unlikely to be necessary in the very early stages of non-proteinuric feline CKD (IRIS stage 1). However, this may be a good time to transition cats that are fed a very high-protein diet onto a diet with more moderate protein levels. It is also sensible to ensure that canned and/or dry diets will be accepted, if the cat is usually fed a dehydrated, raw or freeze-dried diet.

Delaying protein restriction until the cat begins to display clinical signs of uremia, typically during late IRIS CKD Stage 3 or IRIS CKD Stage 4, is likely too late and may result in harmful metabolic derangements due to undetected accumulation of uremic toxins or even development of an overt uremic crisis. Thus, the introduction of protein-restrition at the level of veterinary renal diets should begin in IRIS CKD Stage 2 (along with dietary phosphorus restriction), because it may slow the progression of CKD, delay the onset of uremic signs, and facilitate better acceptance of dietary adjustment. In addition, given that most commercial renal diets still exceed the minimum protein requirement for adult maintenance, there is no reason to avoid feeding them at the earliest stage, nor any compelling argument for gradually increasing restriction as the disease progresses.

Home-prepared or commercial renal diets?

One study evaluated the appropriateness of 28 home-prepared diets used in cats with CKD, and found that no single recipe that was utilized met all the NRC nutrient recommended allowances for adult animals (5). Importantly, with respect to the protein content of these diets, the authors reported that concentrations of either crude protein or at least one amino acid were low in 42.9% of the recipes evaluated. This is not to suggest that home-prepared diets cannot be the equal of commercial diets, but only that they need to be formulated with great care. Therefore, when considering use of a home-prepared diet, consultation with a board-certified veterinary nutritionist® for advice on formulation of an age- and disease-appropriate diet is strongly recommended **(Figure 3)**.

Raw meat-based diets for cats with CKD

With the rising popularity of raw feeding practices for both dogs and cats, there is increasing interest in feeding raw meat-based diets to cats with CKD. A willingness to acknowledge the benefits of phosphorus restriction is commonplace, but protein restriction of any kind is often regarded by

Figure 3. A home-prepared renal diet must be carefully formulated by a board-certified veterinary nutritionist®; it can be challenging to formulate suitable recipes and still maintain high palatability, given the protein restriction required.

Figure 4. Raw meat-based diets are typically rich in phosphorus and protein and often contain inadequate fiber and omega-3 fatty acids, making them inappropriate for cats with kidney disease.

proponents as unnecessary and potentially harmful. Many owners believe the only necessary change to their feeding practices to be the exchange of phosphorus-rich bone for ground eggshell. Most raw diets are quite palatable, which can certainly be advantageous, but they are often very high in protein (greater than 50% ME) and phosphorus. Providing a very high-protein diet, well in excess of the cat's requirement, is likely to increase production of uremic toxins, as previously discussed, and may advance disease progression. Moreover, meat-rich diets are acidifying, and some cats with CKD already have metabolic acidosis, which is why commercial renal diets are formulated to be alkalinizing. It is also challenging to adequately reduce phosphorus in meat-rich diets, especially if lean meats such as kangaroo, turkey or venison are being fed as a significant part of the diet **(Figure 4)**.

CONCLUSION

Despite the controversy, the well-researched benefits of dietary protein restriction in CKD include reducing the accumulation of nitrogenous wastes and harmful uremic toxins, improving proteinuria, decreasing renal oxidative stress, and limiting the metabolic disturbances characteristic of CKD. Although the ideal degree of protein restriction for cats with CKD is not yet known, commercial renal diets provide a moderate amount of high-quality dietary protein, which meets and slightly exceeds the established minimum requirement for an adult cat, to allow a reasonable margin of safety. No research suggests that protein-restricted renal diets increase the risk of protein-energy wasting, but careful attention to ensuring adequate energy intake is essential. Available evidence suggests that protein-restriction may be of value from IRIS CKD stage 2, or potentially earlier if proteinuria is documented in cats with IRIS CKD stage 1. As with the management of any chronic disease in cats, careful attention should also be given to monitoring appetite, body weight, body condition and muscle condition, in order to reduce the risk of catabolism and loss of lean mass.

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FRONT LINE ULTRASOUND IMAGING OF THE FELINE KIDNEY

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Most practices nowadays will have access to an ultrasound machine, using it for selected imaging of clinical cases; in this paper Greg Lisciandro discusses how a structured approach to abdominal scanning can be part of the clinician's first-line physical exam, and demonstrates how this can help rapid identification of renal abnormalities and related problems.

KEY POINTS

1. Point-of-care ultrasound is gaining more and more use in first opinion veterinary medicine, and can now be regarded as the clinician's first-choice imaging method.
2. A structured approach to abdominal scanning should minimize the risk of missing important pathologies.
3. Many renal abnormalities can be detected using a standardized approach.
4. Recording ultrasound findings using specific templates helps to emphasize the objectives whilst imaging, as well as chronicling patient data for future reference and comparison.

Introduction

Global FAST (an acronym for Focused Assessment with Sonography for Trauma) is a well-defined point of care ultrasound protocol that was first created as a triage and post-interventional screening test by human trauma surgeons in the 1990s, and then progressed into a non-trauma and monitoring imaging tool. The technique has now been developed for the veterinary field, and comprises abdominal FAST (AFAST), thoracic FAST (TFAST), and Vet BLUE (brief lung ultrasound examination) methods for assessing the small animal patient, although the latter two techniques will not be discussed in any detail in this paper.

The G-FAST approach includes target-organ interrogation (abdomen and thoracic organs including heart and lung) and involves 15 specific, standardized probe maneuvers **(Figure 1)**; when performed by a competent person the entire procedure can be accomplished in around six minutes. This article focuses on findings at the AFAST Spleno-Renal (SR) and Hepato-Renal (HR) views (as described below) which allow easy detection of soft tissue renal and adjacent ureteral abnormalities, as well as free fluid within the peritoneal cavity and

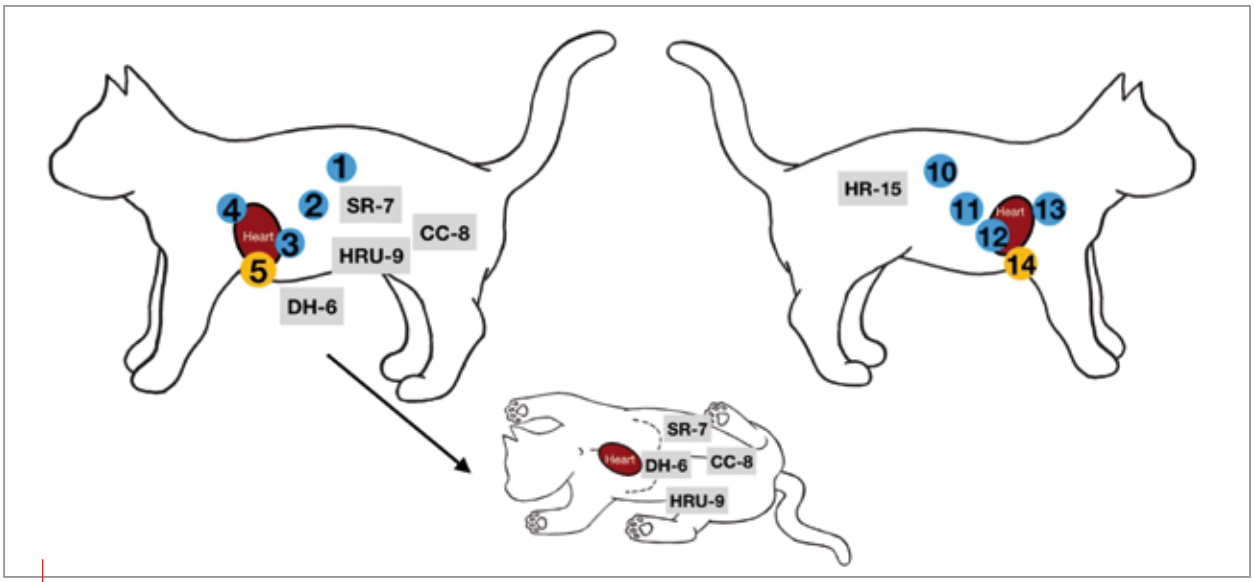

Figure 1. The 15 acoustic windows as used for Global FAST. In a standing cat the most efficient order is as follows: Left Vet Blue followed by TFAST left pericardial site and then AFAST – DH, SR, CC, and HRU (umbilical) Views. Once the sonographer has completed the left side of the patient he/she moves to the other side to perform the right Vet BLUE, TFAST echo views including short-axis and long-axis, followed by the HR 5th Bonus View. Lateral recumbency is generally only necessary if there is free fluid in the abdomen or if satisfactory images are not obtained when the cat is standing.

retroperitoneal space. The recording of findings on goal-directed templates gives value to the examinations and enables clear objectives to be achieved.

Importantly, a word of caution should be sounded. The veterinary point-of-care ultrasound (V-POCUS) movement lends itself to "satisfaction of search error" through selective imaging (picking and choosing) and will often fulfill a preconceived clinical bias, thus missing other important imaging information. This is potentially dangerous; a clinician would never selectively perform a physical examination, so without following a standardized global protocol whilst scanning, the clinician may not only miss pathology but will also fail to integrate other important G-FAST findings into the overall assessment of the patient (1-6). The mindset for those using ultrasound is that the G-FAST approach serves as an extension of the physical exam, as it is a standardized, achievable format that can be easily utilized by the non-specialist radiologist veterinarian and should be the first-line imaging modality; in other words, it is a new quick assessment test.

AFAST can be used for general abdominal evaluation, and includes a standardized fluid scoring system for assessment of free fluid; the target-organ approach involves visualization of the kidneys and adjacent ureters and retroperitoneal space. TFAST and Vet BLUE can be combined with this, and may be used for staging renal patients and assessing their overall volume status, as well as urine production and output.

How does the AFAST examination work?

The AFAST order for scanning is standardized, as shown in **Figure 2**. It begins with the Diaphragmatico-Hepatic view (DH), followed by the least gravity-dependent Spleno-Renal view (SR) in right lateral recumbency (or the Hepato-Renal View (HR) in left lateral recumbency) followed by the Cysto-Colic view (CC) and then ending at the most gravity dependent Hepato-Renal Umbilical view (HRU) (or the Spleno-Renal view (SRU) in left lateral recumbency). This standardized manner ensures that the patient's thorax is first screened at the DH view for any obvious intrathoracic problems, such as pleural and pericardial effusion, that could increase patient risk with restraint. The final AFAST view, which incorporates use of the abdominal fluid scoring system, ends at the *most* gravity-dependent region, the respective umbilical view, where abdominocentesis can be performed if effusion is detected; this should be done only after completing the AFAST exam.

The AFAST is performed by fanning (interrogating in longitudinal/sagittal planes) followed by rocking cranially and returning to the starting point at each of the respective AFAST views; this is because anatomy is more generally recognizable in the longitudinal planes, and the presence of ascites is independent of probe orientation (7). Therefore the SR (and HR) views interrogate the kidneys for obvious soft tissue abnormalities in longitudinal (sagittal) orientation while searching for free fluid in the adjacent retroperitoneal space and peritoneal cavity. The AFAST technique also allows imaging of the urinary bladder and the adjacent urethra. Generally, most experienced sonographers will image both kidneys via a single SR or HR view **(Figure 3)** depending on

Figure 2. AFAST views on a cat in A) right and B) left lateral recumbency. The patient has been sedated in readiness for endotracheal intubation for an elective ovariohysterectomy. The cat would generally be conscious and the abdomen not shaved, but this helps better illustrate the external landmarks for the respective AFAST views. Alternatively, imaging is often performed in the standing position, which has lower impact and is safer for the respiratory fragile, the hemodynamically questionable or unstable, and the stressed cat, as shown in **Figure 1**.

which side the animal is lying. If the kidneys are not readily visualized the HR 5th Bonus View (or SR 5th Bonus View) is used. These views are not part of the abdominal fluid scoring system, but provide soft tissue information on the respective kidney, its retroperitoneal space and adjacent liver and soft tissue. Transverse orientation is considered an add-on skill once image acquisition is mastered in longitudinal (sagittal) planes.

Although ultrasound imaging is typically undertaken with the patient in lateral recumbency, the G-FAST technique can also be performed with the animal in a standing or sternal posture, as image acquisition is independent of patient positioning. This approach has less impact and is safer for patients that are respiratory fragile, are potentially unstable in their

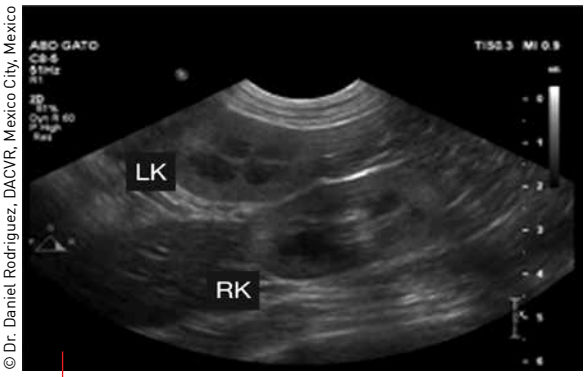

Figure 3. Both kidneys are usually imaged through the SR view in right lateral recumbency. Care must be taken to identify which is the left and right kidney when accurate identification is warranted, although this is often unnecessary when more advanced imaging is performed subsequently.

hemodynamics, or if the animal is stressed. Standing (or sternal recumbency) is actually preferred for most cats, and is better for evaluating pleural and pericardial effusion and pneumothorax; however, gravity-dependency, which affects where free fluid pools, and where sediment and intraluminal pathology settles, will differ depending on the chosen position, and must be acknowledged by the sonographer.

Since standing or sternal recumbency is often much less stressful for the cat; if no free fluid is detected, lateral recumbency is unnecessary. However this position is required for fluid scoring, so if a patient is fluid positive, it should be moved into either left or right lateral recumbency and a three-minute waiting period imposed (to allow for fluid redistribution) before rescanning to allow for fluid scoring (8).

What is the AFAST target-organ approach?

AFAST allows for sonographic assessment of easily recognized renal and other urinary tract-related conditions, since most are fluid-related, and a key strength of the ultrasound modality is in imaging fluid. The sonographer merely has to decide whether the kidneys are unremarkable or abnormal, and when abnormal, direct further imaging and a more streamlined diagnostic plan for definitive diagnosis. In other words, the non-expert sonographer should be able to identify cases that would otherwise be missed without expert ultrasound or computed tomography imaging. The AFAST (and indeed the entire G-FAST) approach should be of the mindset "do the kidneys – and other structures in the abdomen and thorax – deviate from what is expected in normalcy?" rather than "what is the diagnosis?" With point-of-care ultrasound it is important to understand the limitation that renal appearance does not always indicate normalcy, and that a radiologist evaluation is the gold standard for ultrasound. Clinical questions to be asked during the procedure are

shown in **Box 1**, and achievable abnormal AFAST findings are discussed below and summarized in **Table 1**. As a measure of how useful and effective this technique can be for renal problems, the reader is referred to the findings of a retrospective study that reviewed ultrasonographic findings in cats with acute kidney injury which identified various abnormalities and quantified them, as shown in **Table 2** (9).

What does the normal kidney look like?

A normal sagittal view of the kidney **(Figure 4)** should identify three areas:

1) A bright central echo complex (the renal sinus and peripelvic fat)

2) A hypoechoic medullary region surrounding the pelvis

3) A peripheral cortical zone of intermediate echogenicity

Importantly, a normal sonographic appearance does not necessarily indicate normal renal function; conversely, an abnormal sonographic appearance does not necessarily indicate abnormal function. The most commonly accepted normal range of dimensions for feline kidneys are:

- Length (L) 3.0-4.5 cm
- Width (W) 2.2-2.8 cm
- Height (H) 1.9-2.5 cm

Box 1. Questions to be asked, and comments, for the AFAST Spleno-Renal and Hepato-Renal Views.

Question	Comment
Is there any free fluid in the retroperitoneal space?	Yes or no
Is there any renal subcapsular fluid?	Yes or no
Is there any free fluid in the abdominal (peritoneal) cavity?	Yes or no
If there is free fluid in the abdominal cavity, how much fluid (using the AFS system)?	Score each view as 0, 1/2 (if fluid ⩽ 5 mm), 1 (if > 5 mm), total score is between 0 and 4.
What do the left and right kidney look like?	Unremarkable or abnormal
Is the patient intact reproductively?	Yes or no
Could I be misinterpreting an artifact or pitfall for pathology?	Know the pitfalls and artifacts

Table 1. Kidney AFAST ultrasound findings at the Spleno-Renal and Hepato-Renal views.

Finding	Easy to recognize during AFAST?
Normal kidney	Yes
Mineralization and renal calculi	Variable
Pyelectasia	Yes
Hydronephrosis	Yes
Cortical cysts	Yes
Polycystic disease	Yes
Perinephric pseudocysts	Yes
Nephromegaly	Yes
Renal & retroperitoneal masses	Yes
Perirenal fluid	Yes
Abnormal architecture	Variable
Infarction	Yes
Peritoneal fluid	Yes
Semi-quantitating peritoneal fluid	Yes

What abnormal kidney findings may be detected?

Mineralization and renal calculi

The ease with which mineralization and calculi are detected with ultrasound is variable **(Figure 5)**, and radiography is generally considered a better imaging modality for these cases. If large enough, nephroliths have clean shadowing. Note that the peripelvic fat can mimic mineralization, which may or may not shadow. The twinkle artifact may be helpful in such cases using color flow Doppler (10).

Table 2. Ultrasound findings from a study in cats with acute kidney injury (9). The classic appearance in B-mode imaging of these findings are as described in the text; most changes are easy to recognize during AFAST, with the exception of increased cortical or medullary echogenicity, which can be variable.

Finding	% of affected cats with the respective sonographic findings and comments
Normal kidney	< 10%, with no peritoneal/retroperitoneal effusion
Nephromegaly	69%, with 36% unilateral enlargement The median length was 4.5 cm (range 2.7-5.4); the maximum length should be < 4.5 cm in the sagittal plane
Increased cortical echogenicity	40%, with all having concurrent increased medullary echogenicity The cortex of the kidney is normally isoechoic to the spleen
Increased medullary echogenicity	51%, with some having unremarkable cortical echogenicity The medulla should normally be hypoechoic (darker) to the cortex
Significant pyelectasia	58%, with 12% affected unilaterally. The recorded range of the renal pelvis was 0.5-15 mm, with a median of 2.5 mm. 80% of affected cats were classed as mild (< 4 mm), 12% as moderate (5-10 mm) and 8% severe (> 10 mm). Normal is < 1-2 mm in diameter. 26% of cats had concurrent uroliths, with ureteroliths more common than nephroliths
Retroperitoneal fluid	33%
Peritoneal fluid	49%

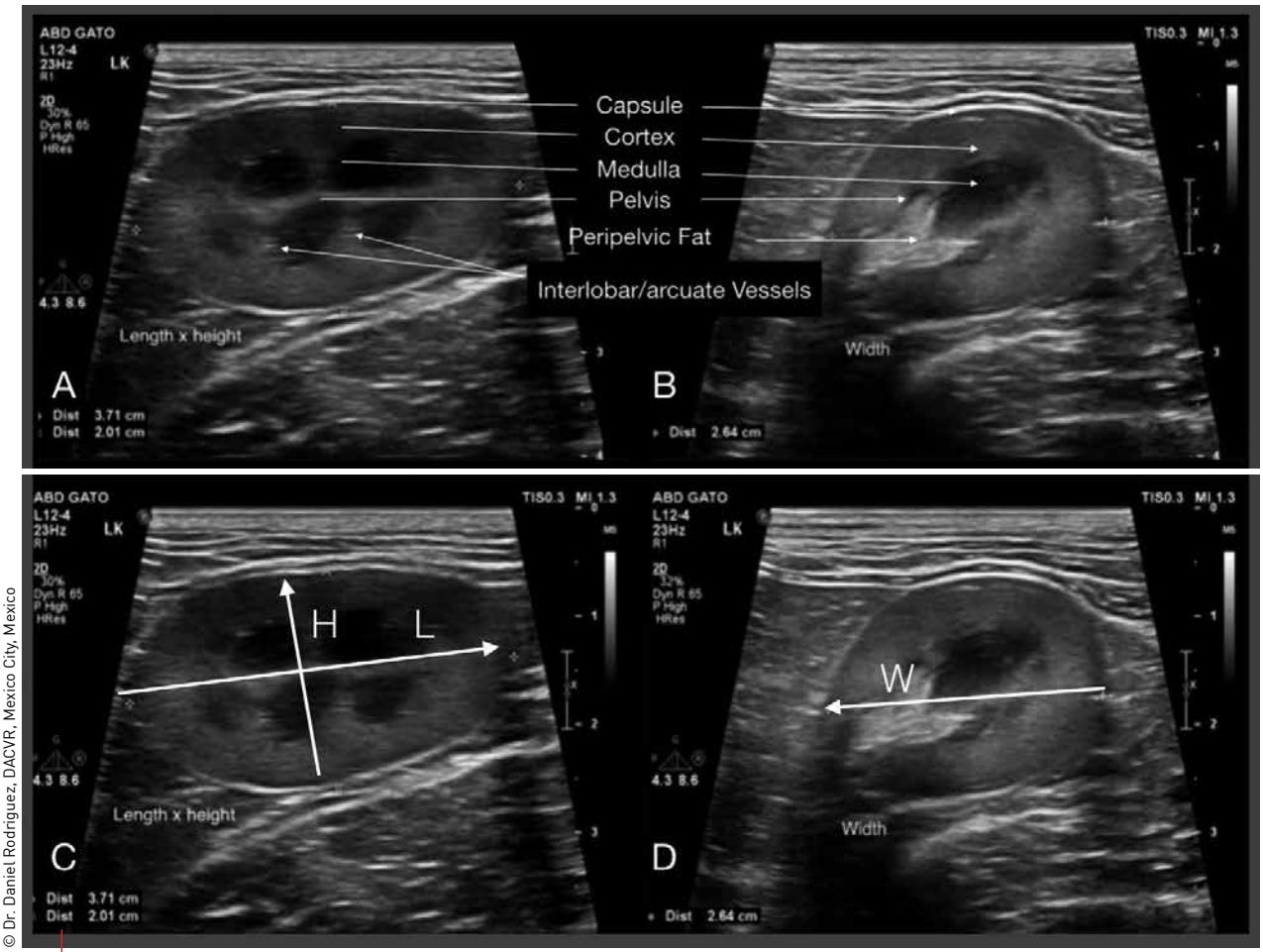

Figure 4. The expected normal anatomy of the feline kidney. **Figure 4a** shows the longitudinal/sagittal orientation and **Figure 4b** shows the transverse orientation, each with major structures labeled. **Figures 4c and 4d** show measurements of the length **(L)**, height **(H)**, and width **(W)**. Length is generally the most common dimension used to define the presence or absence of nephromegaly, as it is simple and is used independent of height and width.

Pyelectasia

Dilation of the renal pelvis is usually easily detected with AFAST **(Figure 6)**. The width of the feline renal pelvis can be measured and assessed as follows;

- Normal < 2 mm
- Mild dilation < 4 mm
- Moderate dilation 5-10 mm
- Severe dilation > 10 mm

Hydronephrosis

Hydronephrosis, or distension of the kidney, is severe pyelectasia with blunting of the renal papilla **(Figure 7)** and is usually easily identified on imaging.

Cysts

This term encompasses cortical cysts **(Figure 8)**, polycystic kidneys (usually seen in Persian cats **(Figure 9)**) and perinephric pseudocysts **(Figure 10)**, the latter being more common in older cats and cats with chronic renal failure. There may be a possible sex predilection, with males more commonly affected. AFAST should readily detect all types of renal cyst.

Nephromegaly

Kidney length should be assessed in all cases. The maximum length in the sagittal plane should be less than 4.5 cm; if kidney enlargement is detected **(Figure 11)** the rule-outs include lymphoma, acute kidney injury (AKI), and hepatic shunts.

Renal and retroperitoneal masses

If a retroperitoneal shadow is noted **(Figure 12)** it is essential to differentiate between a mass and a hematoma; this can be done using color flow Doppler to assess for the presence or absence of pulsatile flow in the mass, with the absence of flow indicating a hematoma. It may be appropriate to consider a coagulation profile if a hematoma is detected. If a renal or retroperitoneal mass is detected the animal should be staged using the G-FAST Approach, as discussed below.

Perirenal fluid

This is seen as fluid rounded within the renal capsule **(Figure 13)** and is not part of the abdominal fluid score. Again if fluid is detected the patient should be staged with the G-FAST

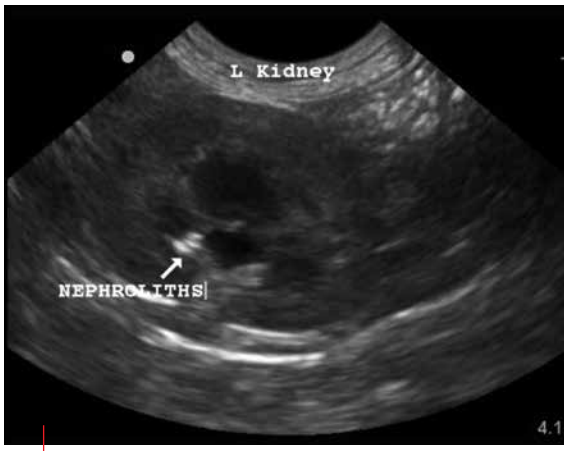

Figure 5. Nephroliths within the kidney may or may not be easy to identify on scan.

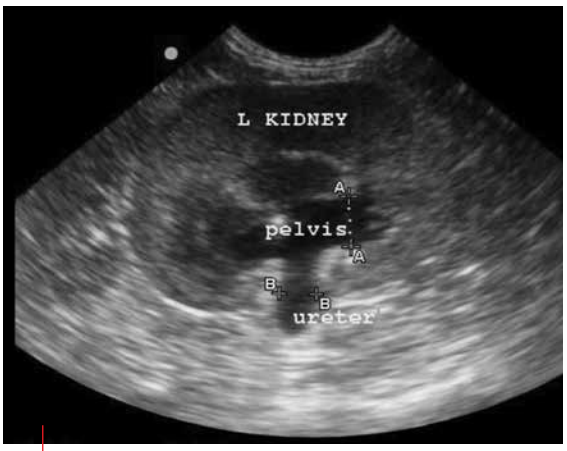

Figure 6. Dilation of the renal pelvis is usually obvious on ultrasound scan; the pelvis diameter should be measured to assess the degree of pyelectasia.

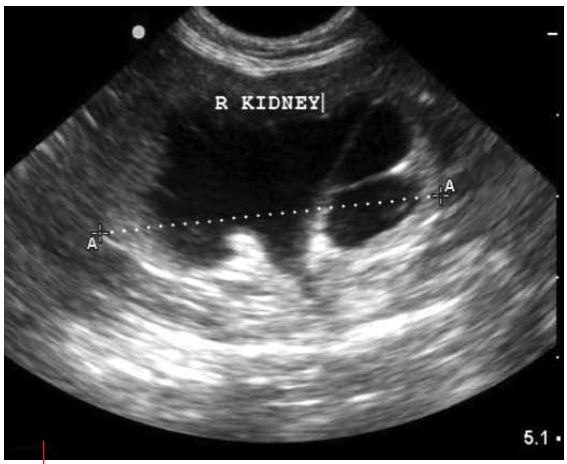

Figure 7. Hydronephrosis is defined as severe pyelectasia with blunting of the renal papilla.

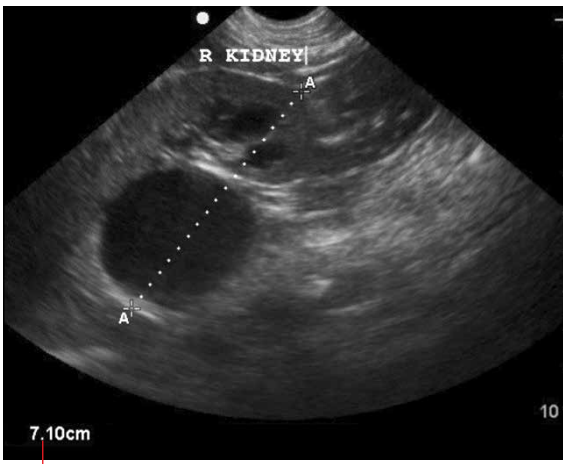

Figure 8. Renal cortical cysts are anechoic and intraparenchymal, and typically do not distort the renal capsule.

Approach, with the rule-outs including renal failure, especially AKI.

Abnormal architecture

If any abnormal renal architecture is found during imaging **(Figure 14)** it is essential to look for further obvious soft tissue abnormalities in the other abdominal organs during the AFAST process; the heart, pleural and pericardial effusion should also be reviewed via TFAST and the lung surfaces evaluated using the Vet BLUE technique.

Infarction

An infarct is usually easy to identify using AFAST **(Figure 15)**. When staging an affected animal the clinician should include TFAST echo views and Vet BLUE to look for any evidence of a "wedge" sign in the lungs, indicative of pulmonary thromboembolism (PTE).

Peritoneal fluid

Free fluid **(Figure 16)** is generally triangulated because the fluid is outside the renal capsule. If found the maximum dimension can be recorded. Peritoneal fluid can be semi-quantified using the AFAST-applied Abdominal Fluid Score (AFS) as described below. Note that cats with urinary obstruction commonly have ascites associated with the obstruction (11-13). In the most detailed study to date to the author's knowledge, ~ 60% of obstructed felines were positive for pericystic fluid (analogous to the AFAST CC View) and ~35% were positive for retroperitoneal effusion (13). It is important to be aware that the clinical course for the great majority of these cats is unaltered from standard care, and that the ascites and retroperitoneal effusion will usually resolve with time as the cat recovers, typically 24-36 hours after the obstruction is relieved and the patient successfully resuscitated (13). Sampling and testing the effusion may support a diagnosis of uroabdomen, however, the uroabdomen is most often treated medically. The author proposes that the cause for the effusion lies

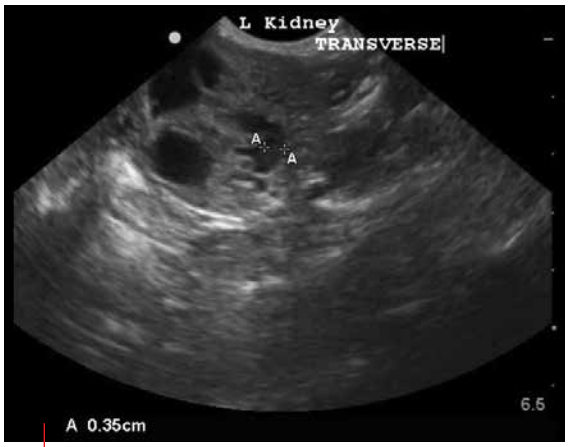

Figure 9. Polycystic kidney disease is a genetic disorder commonly seen in Persian cats; multiple cysts form within the kidneys and are readily detected on sonography.

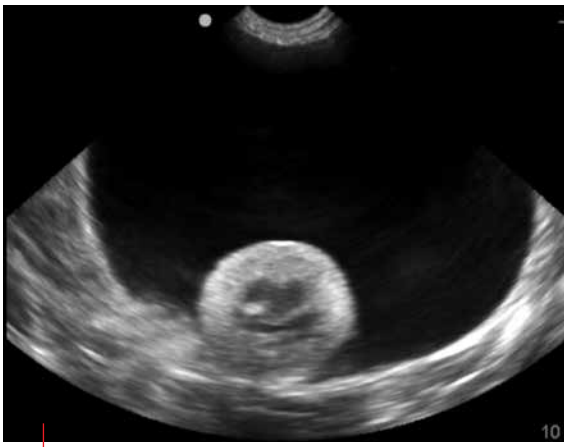

Figure 10. Perinephric pseudocysts are fluid-filled fibrous sacs that surround the kidney; in cats they are idiopathic in nature but usually occur in association with CKD.

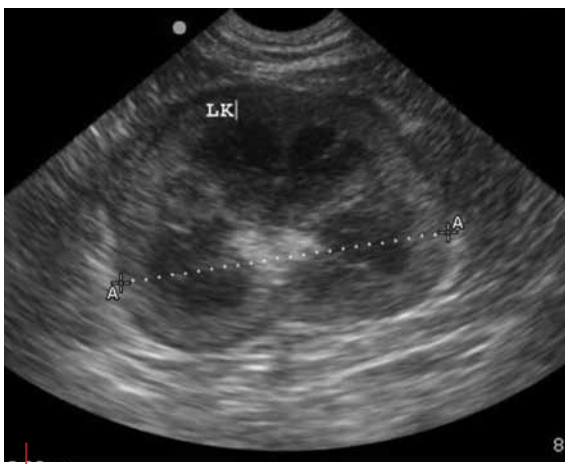

Figure 11. An enlarged kidney, measuring 6.26 cm in length – normal is less than 4.5 cm. Nephromegaly can be due to many different factors, including infection, obstruction, loss of function in the contralateral kidney, and infiltrative disease such as lymphoma.

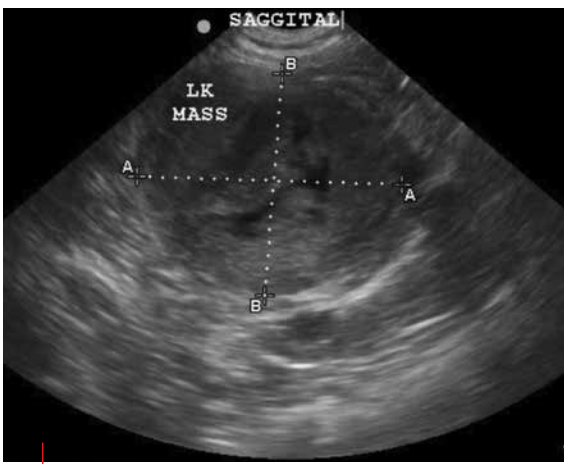

Figure 12. Any renal or retroperitoneal shadow should be investigated further; it is essential to differentiate between a mass and a hematoma, and if a mass is detected it should be staged to enable the clinician to advise the owner as to the next steps.

in inflammation and backpressure of urine against the urinary bladder wall and renal capsule over alternative speculation (14).

How is fluid assessed on imaging?

The abdominal fluid scoring (AFS) system has been developed as an objective semi-quantification method to evaluate the volume of free fluid detected within the abdominal cavity during AFAST, and can be used for hemorrhage, uroabdomen or ascites. Lack of space precludes an in-depth discussion of the system in this paper, but it essentially scores free fluid from 0 to 4, and also specifies positive and negative regions within the abdomen (1,8,15,16). If the abdomen is negative for free fluid at all four AFAST views a zero score is applied; a maximum score of 4 indicates positive free fluid at all four views. This method allows differentiation between small volumes of fluid (scoring 1 or 2) and large volumes of fluid (scoring 3 or 4) and the clinician can then act accordingly. The author recommends a modification of the system in cats; if the maximum fluid pocket dimensions are under 5 mm, or there are linear fluid stripes of < 5 mm, a score of "1/2" is applied; if over this a score of 1 is required (16,23).

This system provides distinct advantages over "trivial", "mild", "moderate" and "severe" volume characterization. Serial use of the AFS system is a means to regularly monitor the progress of cats with free peritoneal fluid, including during daily patient rounds and recheck evaluations.

When free fluid is safely accessible it must be sampled for accurate characterization, followed by fluid analysis and cytology to better direct care and diagnostics. When urinary tract rupture is suspected, comparative serum creatinine or potassium to the effusion should be performed. Importantly, ultrasound cannot accurately characterize free fluid; and in larger volume effusions, abdominocentesis is generally performed immediately after competing

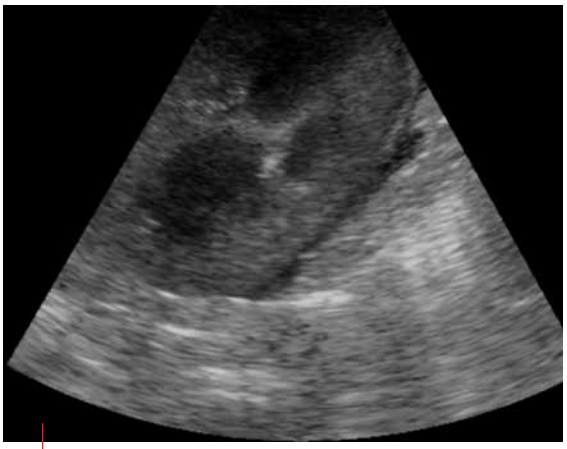

Figure 13. Perirenal fluid is visualized as fluid within the renal capsule; if found further investigation is warranted, as rule-outs include acute kidney injury.

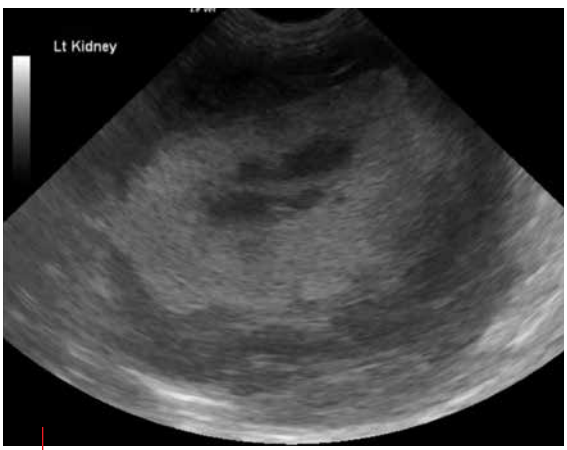

Figure 14. Detection of any abnormal renal architecture, such as alteration in the renal parenchyma, should be investigated further; this includes looking for obvious soft tissue abnormalities in other abdominal organs, assessment of the heart and lungs, and looking for evidence of pleural and pericardial effusion. Both kidneys in this cat showed abnormal architecture.

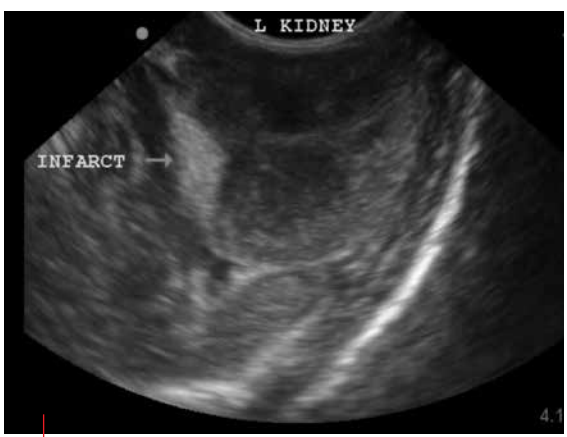

Figure 15. Chronic renal infarction can appear as a hyperechoic area within the kidney due to the formation of scar tissue.

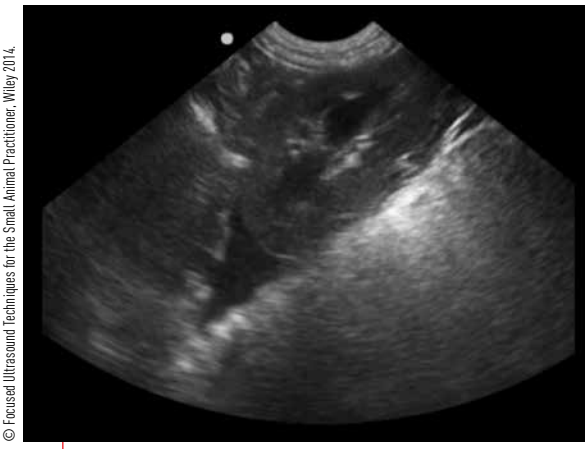

Figure 16. Free fluid in the peritoneal cavity is generally triangulated on ultrasound scan, because the fluid is outside the renal capsule, as evidenced here.

AFAST at its most gravity-dependent umbilical view, where free intra-abdominal fluid is pocketed. Safe sampling may be acquired in the retroperitoneal space as well as smaller volumes within the peritoneal cavity by sonographers with more advanced ultrasound-guided skills.

What about staging for renal masses and nephromegaly?

It is strongly advisable that any cat with a suspect renal mass should be staged with the G-FAST Approach to provide a better dialogue with the client. This avoids leaving an owner to make the decision as to whether or not they should proceed with further investigations. Remember that not all renal masses are neoplastic, and infectious, metabolic and other conditions must also be considered. A G-FAST sonographic examination may suggest that the renal mass or nephrogmegaly appears to be localized, and that there are no obvious other abdominal masses. If a Vet BLUE examination excludes lung masses and also confirms that there is no pleural or pericardial effusion, this is a positive step. If the cat allows TFAST echo views, (to confirm unremarkable cardiac chamber sizes), so much the better, and the clinician can discuss appropriate further diagnostics. Conversely, if serious findings are detected, such as lung nodules (17), then a different diagnostic plan is necessary. As with renal masses, do bear in mind that not all lung nodules are neoplastic – for example, they can be due to fungal disease, which still may be treatable. Using the G-FAST approach as a first line diagnostic tool will allow the veterinarian to help both client and pet as best as possible.

What about G-FAST for assessing patient volume status?

The cat as a species seems to be more susceptible to fluid volume overload (especially when receiving intravenous fluid therapy for urinary obstruction

and/or renal failure (18)) that may result in any combination of pulmonary edema, hepatic venous congestion, pleural effusion and pericardial effusion (19). Obtaining a baseline G-FAST on a patient is invaluable upon presentation, as integrating findings from TFAST and Vet BLUE are helpful in determining if left- versus right-side volume strain/overload/failure is occurring. Moreover, and importantly, echo views are not needed in many patients when using the so-called "G-FAST non-echo fallback views". Left-sided congestive heart failure results in cardiogenic lung edema and is readily ruled out or detected (96% sensitivity) and quantified using Vet BLUE (19-21). Right-sided congestive heart failure results in caudal vena cava distension and hepatic venous congestion, which is readily detected at the AFAST-TFAST Diaphragmatico-Hepatic View (DH). Pleural and pericardial effusion can occur concurrently with either left or right sided failure, and can be detected during TFAST (15,19,22-25). Therefore integration of echo findings from TFAST and characterization of the caudal vena cava and assessment of the lungs during Vet BLUE increase the probability for accurate assessment of the patient (3).

Recording results

Goal-directed templates are imperative to clearly convey objectives and for recording patient data that may be measured and compared initially and with future studies. Goal-directed template examples are published (1,25-27) and may be accessed through the website FASTVet.com.

CONCLUSION

In conclusion, if the question is "when should renal disease patients be scanned?" the answer is that the G-FAST approach should be part of the work-up for ALL cats with renal or urinary tract signs, including those with urinary obstruction. Using it as a first line-imaging test will also potentially detect incidental and unexpected findings, not only within the entire urinary tract but also the rest of the abdomen and the thorax, including the heart and lungs. Essentially the technique allows the clinician to rapidly assess a patient on initial presentation and make objective decisions as to the next steps in diagnostics and treatment, and can ultimately make the difference between life and death.

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DETECTION OF EARLY CHRONIC KIDNEY DISEASE IN CATS

Kidney disease is one of the most common causes of morbidity and mortality in older cats; Hannah Sargent and Jonathan Elliott review the best methods for early detection of the disease.

KEY POINTS

1. Chronic kidney disease (CKD) is a common condition of older cats and has been reported as the second most common cause of death in cats over 5 years of age.
2. Early diagnosis of feline CKD is important to allow timely appropriate therapeutic intervention as well as identification and treatment of underlying primary renal disease.
3. Early diagnosis of CKD requires the use of plasma or serum creatinine, SDMA concentrations and urinalysis, rather than considering one parameter in isolation.
4. Cats in early CKD may not present with clinical signs of disease, and physical examination findings can also be normal, highlighting the importance of screening, particularly in geriatric cats.

Introduction

Chronic kidney disease (CKD) is estimated to have a prevalence of up to 32% in cats over 12 years of age (1) and has been reported as the second most common cause of death in cats in the United Kingdom aged 5 years and older (2). In people CKD is recognized as a global public health problem, and the importance of intervention strategies focusing on early diagnosis is regarded as being key to tackling this global crisis. However, the major challenge for doctors is making a true diagnosis of early CKD, in particular due to the limitations of serum creatinine as a marker of glomerular filtration rate (GFR). This challenge is shared globally across disciplines; for the veterinarian, early diagnosis of CKD in cats would be a major advantage, as it prompts close monitoring for progression and the timely use of appropriate therapeutic interventions as well as early investigation for, identification and treatment of underlying primary renal disease. It is hoped that the recent availability of novel biomarkers – such as symmetric dimethylarginine (SDMA) – or other approaches using algorithms will help in identifying cats with early kidney disease, and that future research can aid our understanding of the appropriate therapeutic interventions these cats require to slow disease progression. This article briefly summarizes the current research on early diagnosis of feline CKD and how it can be applied in clinical practice.

Pathogenesis and etiology of feline CKD

CKD is simply defined as "the presence of persistent functional or structural abnormalities of one or both kidneys". Histopathologically, the most common changes are tubulointerstitial inflammation and fibrosis (3). However, the term CKD is non-specific and does not refer to one underlying disease process, but rather to a heterogeneous syndrome which can be defined as a sustained decrease in renal function over at least 3 months.

The widely accepted model of feline CKD development describes an initiation phase in which one or more factors initiates kidney damage, resulting in nephron loss, which leads to self-perpetuating injury to the kidney; this is termed intrinsic progression **(Figure 1)** (4). Knowledge of these initiating factors can help the veterinarian in identifying appropriate cats to screen for disease. Initiation factors include primary renal disease (including acute kidney injury, or AKI), aging, and environmental factors (4).

Primary renal disease can be categorized as acquired or congenital disease. The most common congenital disease is autosomal dominant polycystic kidney disease, which affects only Persian

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or Persian cross cats worldwide. Common acquired disease which may be suspected in CKD include renal lymphoma (3), bacterial pyelonephritis, uroliths of the upper urinary tract, chronic viral infection (FIV, FeLV, FIP and feline morbillivirus) (4) and chronic feeding of unbalanced diets (5).

AKI can be defined as a sudden reduction in kidney function resulting in a change in glomerular filtration, urine production and tubular function, and can be initiated by a variety of insults. Although AKI as an initiator of CKD has not been widely studied in cats, in humans it has been shown that an AKI episode increases the risk of subsequently developing CKD, and greater severity of AKI is associated with larger risk (6). In cats, insults to the kidney can be caused by nephrotoxins (*e.g.*, ethylene glycol), neoplasia, infection, sepsis or – perhaps most importantly in the context of CKD – through ischemia. It has been established that tubulointerstitial changes similar to those in feline CKD occur in the later recovery stage of experimentally induced ischemic AKI in cats (7), providing supportive evidence that AKI, and specifically ischemic AKI, leads to maladaptive repair mechanisms which can lead on to CKD. The possibility that other causes of AKI produce maladaptive repair and then CKD has not yet been explored.

In feline CKD a single primary renal disease is commonly not identified, and it is hypothesized that a combination of factors, including single or repeated AKIs, as well as animal-specific and environmental factors, act cumulatively to initiate CKD (4). Given the increasing prevalence of the disease in older cats (8) research has focused on establishing the link between CKD and aging. Estimates for the prevalence of CKD in cats aged over 12 years range from 32% (1) to 42% (8). The proportion of geriatric cats without CKD gives evidence that CKD is not an inevitability for aging cats, but it is hypothesized that aging compromises the protective mechanisms of the kidneys, making them less likely to recover from a renal insult. It is also speculated that some of the more common diseases of aged cats, such as hyperthyroidism (4), dental disease (9), hypertension (4) and inflammatory bowel disease (10), may adversely affect the kidneys. Finally, it has been suggested that the increased prevalence of CKD over the last few decades could be attributed to changes in the environment including food, vaccination and effects of environmental stress. For example, a recent epidemiological study noted a correlation between the severity of dental disease in cats and the development of azotemia (9). Although it has been established that dietary modification can slow progression of CKD in IRIS stages 2 and 3, evidence for the role of high levels of dietary phosphate as an initiating factor in CKD is lacking. However, recent studies have revealed a possible risk to renal function when healthy adult cats were fed high levels of phosphorus in an inorganic form (11). Further studies are required to better understand the relevance to feline husbandry, but understanding these possible initiating factors can be of use in clinical practice by allowing veterinarians to undertake targeted screening of cats that may be considered to be at greater risk of developing CKD.

Markers of GFR and CKD

GFR is the volume of ultra-filtrate formed in the nephrons of both kidneys per unit of time, and is correlated to the functioning renal mass.

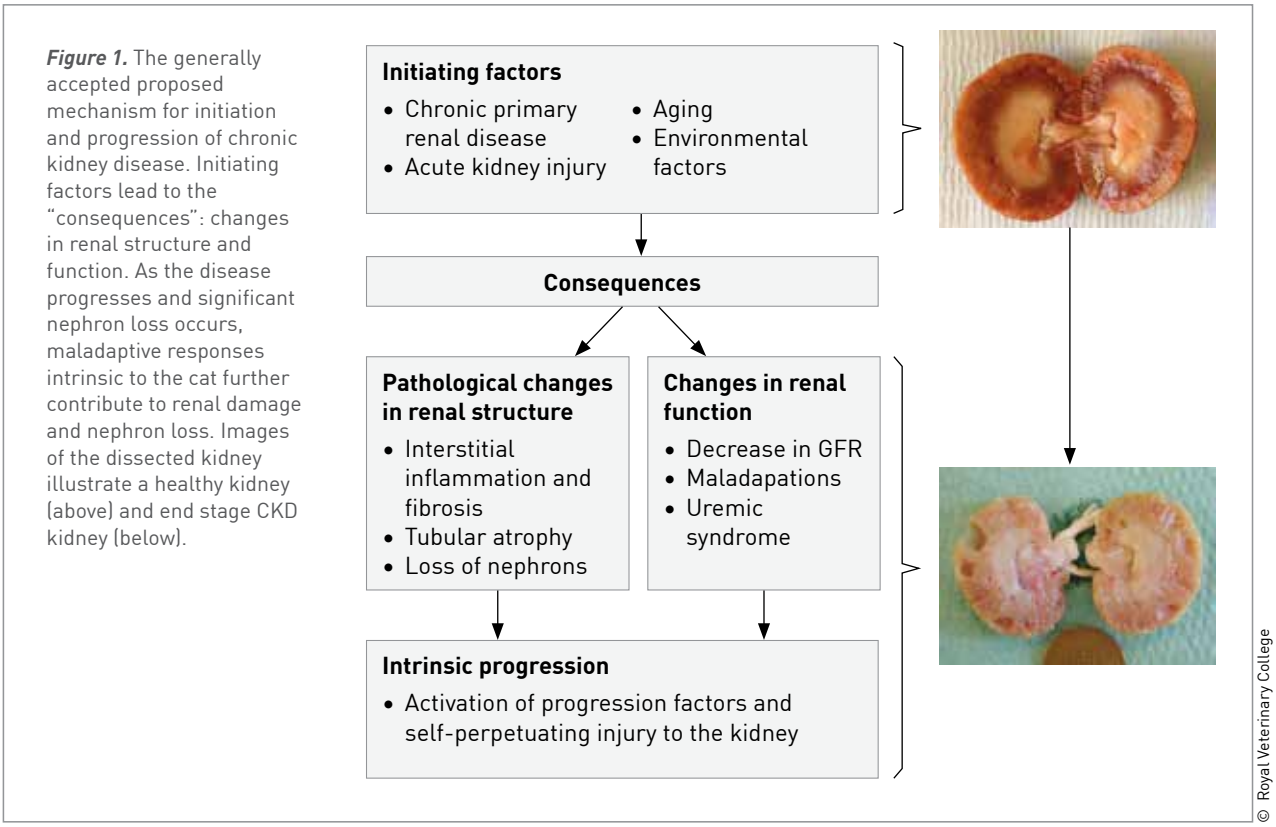

Figure 1. The generally accepted proposed mechanism for initiation and progression of chronic kidney disease. Initiating factors lead to the "consequences": changes in renal structure and function. As the disease progresses and significant nephron loss occurs, maladaptive responses intrinsic to the cat further contribute to renal damage and nephron loss. Images of the dissected kidney illustrate a healthy kidney (above) and end stage CKD kidney (below).

Measurement of the plasma clearance of an exogenous marker of filtration, such as iohexol, is the most accurate method of assessing the functional renal mass available to veterinarians. Typically, the estimation of GFR through measurement of a surrogate such as serum creatinine concentration remains the most useful assessment of kidney function in clinical practice.

The primary challenge for veterinarians using serum creatinine to diagnose early kidney disease in cats is the curvilinear relationship between serum creatinine concentration and GFR, as shown in **Figure 2**. A substantial decrease in GFR is required before a significant increase in serum creatinine concentration (and consequently azotemia) is found on clinical biochemistry, which is why it is an insensitive indicator of GFR.

"The identification of cats with IRIS stage 1 and stage 2, when creatinine may be within the laboratory reference interval, and where evaluation for other clinical evidence of chronic kidney disease is required, can be challenging."

Hannah J. Sargent

Increases in serum creatinine in early disease are small and often still within the laboratory reference interval. The IRIS CKD Staging system defines stage 1 CKD as a non-azotemia animal (serum creatinine concentration < 140 µmol/L, 1.6 mg/dL in cats) with some other renal abnormality present: *i.e.*, persistent inadequate urine concentrating ability with no identifiable non-renal cause, abnormal renal palpation or imaging, persistent proteinuria of renal origin, abnormal renal biopsy results, or an increase in blood creatinine concentration in serially collected samples[1]. However, the identification of cats with IRIS stage 1 and stage 2 (where creatinine is 140-250 µmol/L, 1.6-2.8 mg/dL), when creatinine may be within the laboratory reference interval (and documentation of the creatinine trend is unremarkable), and where evaluation for other clinical evidence of CKD is required, can be challenging.

This challenge is exacerbated by non-renal factors such as muscle mass (12), age and breed (*e.g.*, the Birman) (13) have all been shown to influence creatinine levels. To allow for these limitations, it is recommended that creatinine is always measured on a fasted blood sample and interpreted considering the breed, muscle mass and age of the cat.

[1] www.iris-kidney.com/pdf/IRIS_CAT_Treatment _Recommendations_2019

To tackle the limitations of serum creatinine concentration as a marker of early kidney disease, research in recent years has focused on other novel biomarkers of decreased GFR, tubular and glomerular damage that may detect changes earlier in the disease. The most readily available of these to veterinarians is symmetric dimethylargnine (SDMA).

SDMA – what do we know?

Symmetric dimethylarginine (SDMA) is a methylated form of arginine which is found in all intracellular proteins and released into the circulation during protein catabolism. Ninety percent is excreted by the kidneys, and SDMA has been shown to be a surrogate marker of GFR (14). Since 2015 a commercial quantification of SDMA has been available in many countries, whereby serum or plasma SDMA concentration is quantified through a patented immunoassay which has been shown to have good agreement with the gold standard liquid chromatography mass spectrometry (LC-MS) methodology (15).

Serum SDMA concentration has been reported to detect a decrease in GFR before serum creatinine concentration is elevated (as based on the established reference limits), and is now recognized as a useful screening tool for detection of early CKD. In a study of 21 geriatric colony cats with naturally occurring CKD, serum SDMA concentration was elevated above 14 µg/dL an average of 17 months prior to elevation of creatinine above the upper reference interval of 186 µmol/L (2.1 mg/dL) in 17 of the 21 cats (16).

Furthermore, SDMA is also reported to be a highly specific biomarker of reduced GFR, potentially having fewer non-renal influences than creatinine. Although it may be expected that there will be some small biological and individual day-to-day variability, there is evidence that SDMA is not significantly influenced by muscle mass (16,17) or recent protein ingestion (17). Age and breed have been shown to have some effect on SDMA concentrations, with research ongoing to establish age and breed specific reference intervals. Currently it is known that an SDMA concentration of up to 16 µg/dL may reflect normal renal function in juvenile cats (18) and it has been reported that SDMA concentrations are increased in Birman Cats; a breed-specific reference interval for these cats of 3.5-18.7 µg/dL has been suggested.

Given that SDMA is a relatively novel biomarker, understanding of possible non-renal influences on circulating concentrations is still developing; specifically it is important for the veterinarian to consider the influence of drug administration and concurrent disease. It has been reported that the presence or absence of myxomatous mitral valve disease (MVD) and the signs of (or pharmacological treatment for) congestive heart failure have no association with serum SDMA concentrations in dogs (19). Although MVD is specific to dogs, in cats the presence of hypertrophic cardiomyopathy has also been reported to have no effect on SDMA concentration (20), providing preliminary evidence that cardiac disease does not affect SDMA concentrations across species. One study in dogs has indicated that a large tumor burden without a reduction in renal function could result in elevated SDMA (21), and until further studies have been undertaken it should be assumed that this could be the case in cats as well. There is preliminary evidence that feline nephrolithiasis may increase SDMA above the reference interval, although this may be attributed to early alteration in renal function rather than a non-renal influence. Conversely, significantly lower SDMA concentrations have been reported in cats with diabetes mellitus undergoing insulin therapy (20) and in untreated hyperthyroid cats (22). Such findings should be kept in mind when evaluating renal function in cats with these endocrinopathies. In the study of hyperthyroid cats, SDMA had poor sensitivity (33.3%) for predicting development of azotemia following treatment for hyperthyroidism, although it was highly specific (97.7%). This suggests that an elevated SDMA prior to treatment for hyperthyroidism is a good indicator of post-treatment azotemia, but that normal SDMA does not rule out disease.

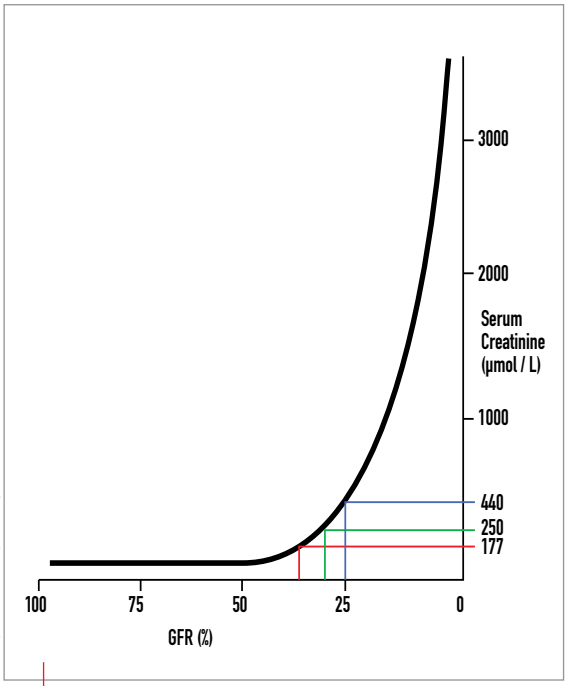

Figure 2. The curvilinear relationship between serum creatinine and glomerular filtration rate. 177 µmol/L represents a common upper reference interval in commercial laboratories and it can be seen clearly on the graph that a significant reduction in GFR occurs before creatinine is above this limit and azotemia is documented. 250 µmol/L is the upper limit for IRIS stage 2 CKD and 440 µmol/L is the upper limit for IRIS stage 3 CKD.

Markers of glomerular and tubular damage

Whereas serum creatinine concentration and SDMA are surrogate markers of renal function (*i.e.*, GFR), glomerular or tubular damage or dysfunction can be indicated by urinary markers. Several have been identified in veterinary medicine.

Proteinuria is a commonly used marker of glomerular or tubular damage or dysfunction. This is routinely identified in practice by the dipstick colorimetric test which detects urinary albumin **(Figure 3)**, however, it should be noted that both false negatives and, in particular, false positives are common in cats. Having detected proteinuria on a dipstick, pre- and post-renal causes such as hemoglobinuria or a urinary tract infection should be ruled out, and proteinuria should be quantified using the gold standard urine protein:creatinine ratio (UPC). Once persistent proteinuria is confirmed it should be staged according to IRIS guidelines. Even a low magnitude of proteinuria is associated with the development of azotemia, highlighting the importance of including urinalysis when screening cats for early CKD **(Figure 4)**.

Proteinuria may result either from the normal renal handling system of protein being overwhelmed (increased protein loss across the glomerulus) or malfunctioning (reduced ability of the tubular cells to reabsorb filtered proteins). In the healthy kidney, low molecular weight (MW) proteins (< 40 KDa) are able to pass freely through the glomerular filtration barrier; those of intermediate MW (40-69 kDa) have variable permeability depending on their charge, whilst high MW proteins (> 70 kDa) are generally restricted due to their size. Healthy proximal tubule cells reabsorb proteins that are filtered into the tubular space via receptor-mediated endocytosis. If the glomerulus is damaged, permeability of the filtration barrier is increased, resulting in marked proteinuria. Tubular damage will also result in proteinuria from a combination of leakage of proteins from damaged tubular cells, decreased reabsorption of proteins, and upregulation of proteins involved in injury and repair. Apart from albuminuria, other intermediate or low MW proteins may be developed as markers of early CKD in the future. Transferrin, which has a similar molecular weight to albumin but with a different isoelectric point, is reported to be found at very low concentrations in the urine of normal cats, but is increased in the urine of healthy or stage 1 CKD cats in which subsequent renal biopsy confirmed a chronic interstitial nephritis, suggesting it could be a very specific marker of early renal damage (23). Research into low molecular weight proteins such as retinol binding protein and neutrophil gelatinase-associated lipocalin is ongoing.

"Common acquired disease which may be suspected in CKD include renal lymphoma, bacterial pyelonephritis, uroliths of the upper urinary tract, chronic viral infection and long-term feeding of unbalanced diets."

Jonathan Elliott

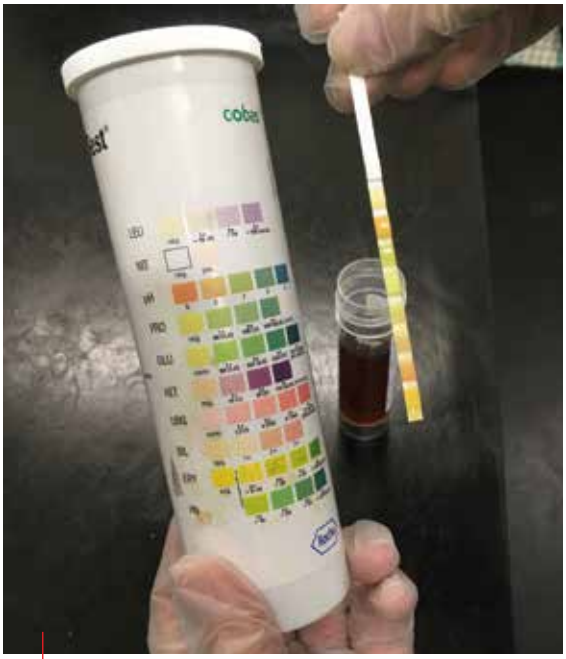

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Figure 3. A dipstick colorimetric test to detect urinary albumin is a quick and easy method for benchtop testing; however both false negatives and false positives are common in cats.

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Figure 4. Urine being collected by cystocentesis in a standing cat. This standing method is well tolerated by the majority of cats, involving minimal restraint or manipulation of the cat's position.

© Royal Veterinary College

Figure 5. A geriatric cat diagnosed with IRIS stage 1 CKD. Diagnosis in cats at this stage is not easy, as physical examination findings are often unremarkable and serum creatinine levels may be within normal limits.

Urinary proteomics has the potential to identify low molecular weight proteins which may facilitate early diagnosis of CKD in the cat (24). Prospective longitudinal studies to identify and validate urinary markers of early feline CKD are required before these tests are likely to be available in clinical practice.

Diagnosis of CKD and machine learning

Machine-learning models, whereby algorithms are used to analyze data, have been developed in human medicine to assess patient risk, predict individual outcomes and recommend personalized treatments, and it is likely that similar uses will be applied in veterinary medicine in the future. Machine learning has recently been used to develop an algorithm that combines age, urine specific gravity, serum creatinine and urea, collected on at least three occasions from cats undergoing routine health screening, to predict the risk of developing azotemic CKD within one year (25). Interestingly, this study reported that the algorithm performed with a specificity of over 99% and a sensitivity of 63% for predicting cats at risk of CKD a year before the condition was diagnosed by more conventional methods.

Practical diagnosis of early CKD

Clinical presentation

Cats in the later stages of CKD – *i.e.*, more advanced IRIS stage 2 and in IRIS stage 3 and 4 – will often present with polyuria and polydipsia as well as non-specific clinical signs, including weight loss, decreased appetite and lethargy. Physical examination findings may include small kidneys on palpation, which may be irregular in outline, or there may be one enlarged and one small kidney, for example in cases of renal lymphoma or acute ureteral obstruction with resulting hydronephrosis. Cats in early CKD may not present with clinical signs of disease and physical examination findings can also be within normal limits **(Figure 5)**; mild azotemia, an elevation in SDMA or proteinuria may be noted on routine pre-anesthetic screening or as part of a diagnostic work-up for a concurrent condition. Diagnostic testing for CKD, including a biochemistry profile, hematology and urinalysis, can be performed at wellness and vaccination visits of geriatric cats, as well as those cats where the veterinarian feels that the risk of CKD is increased through exposure to the initiating factors discussed above.

Box 1. Case study.

SIGNALMENT

"Minnie" Domestic Shorthair, female neutered, 13 years of age.

HISTORY

Over last 6 months owner noted worsening polyphagia, weight loss and generally poor coat condition.

CLINICAL SIGNS

Abnormal physical exam findings included tachycardia, a body condition score (BCS) of 3/9 **(Figure 6)**, weight loss (500 g in 6 months) and an anxious demeanor. Blood pressure via Doppler was 124 mmHg.

INITIAL DIAGNOSTICS

Significant biochemistry tests results (normal values are shown in **Box 3**) included thyroxine (T4) 150 nmol/L; creatinine 106 µmol/L; urea 7 mmol/L; SDMA 17 µg/dL. Urinalysis was unremarkable, but USG was 1.027.

TREATMENT

Treatment for hyperthyroidism was initiated with thiamazole 2.5 mg q12H PO. After 4 weeks on treatment, Minnie was no longer polyphagic. On clinical exam, the tachycardia had resolved and she had gained 250 g, with a BCS 5/9 **(Figure 7)**. Blood test results were; T4 36 nmol/L; creatinine 120 µmol/L; urea 8.4 mmol/L; SDMA 17 µg/dL. Urinalysis was unremarkable, but USG was 1.025.

FOLLOW-UP DIAGNOSTICS

To follow up on the elevated SDMA noted on the second test once the hyperthyroidism was controlled, a further blood test to check renal parameters was taken two weeks later and revealed creatinine 122 µmol/L; urea 8.8 mmol/L and SDMA 18 µg/dL. Urinalysis was unremarkable, but USG remained low at 1.025. A diagnosis of CKD stage 1 was made due to the persistent elevation in SDMA; this was supported by a USG persistently below 1.035. 8 weeks after confirming IRIS stage 1 CKD the renal parameters were checked again to monitor for progression of CKD and revealed creatinine 204 µmol/L; urea 6.8 mmol/L and SDMA 18 µg/dL. Urinalysis was unremarkable, but USG was 1.019.

CASE DISCUSSION

Minnie presented with the clinical signs of hyperthyroidism and diagnosis was confirmed by measuring total thyroxine levels. Prior to treatment for hyperthyroidism her creatinine was within normal limits and her urinalysis was unremarkable. However, her SDMA was mildly elevated and her USG was below 1.035, giving the veterinarian an indication that early CKD may be a possibility. However, regardless of pre-treatment values, renal parameters should always be monitored closely alongside treatment for hyperthyroidism, and routine blood and urine tests were repeated 4 weeks after commencing thiamazole treatment. These confirmed that Minnie's hyperthyroidism was controlled and that whilst the serum creatinine remained within the reference range, the SDMA continued to be elevated.

To confirm persistent elevation of SDMA with controlled hyperthyroidism, renal biochemistry was repeated 2 weeks later. With SDMA elevated on two consecutive occasions two weeks apart Minnie was diagnosed with early CKD and staged at IRIS stage 1; this diagnosis was supported by a USG persistently below 1.035. It was advised that further investigations, including a repeat urinalysis and renal imaging to check for underlying renal disease, should be carried out.

Staging Minnie at stage 1 CKD prompted the veterinarian to monitor her closely for progression of CKD, and 8 weeks after the initial CKD diagnosis her renal parameters revealed azotemia with a USG of 1.019. Stage 2 CKD was diagnosed, and appropriate management according to IRIS guidelines was commenced.

Figure 6. Minnie at initial presentation with body condition score 3/9 and unkempt coat.

Figure 7. Minnie at follow-up consultation after treatment of hyperthyroidism with thiamazole. Body condition score is now 5/9 and she has a smooth hair coat.

Box 2. Case study.

SIGNALMENT

"Jeremy"; Norwegian Forest cat, male neutered, 12 years of age **(Figure 8)**.

HISTORY

Been in owner's possession since a kitten, fully vaccinated, seen for routine booster vaccination. Owner has no concerns.

CLINICAL SIGNS

Physical examination normal.

Systolic BP via Doppler 130 mmHg.

Figure 8. Jeremy on initial presentation.

INITIAL DIAGNOSTICS

Annual hematology and biochemistry tests (including T4) were performed according to guidelines for geriatric cats. Biochemistry revealed creatinine 135 µmol/L; urea 8 mmol/L; SDMA 18 µg/dL (normal values as shown in **Box 3**) whilst hematology was unremarkable. Urinalysis was also unremarkable, with USG 1.040. With SDMA elevated above the RI a repeat biochemistry was indicated.

FOLLOW-UP DIAGNOSTICS

Jeremy was seen again 4 weeks later to check his renal parameters, although urinalysis was not obtained at this visit. Biochemistry revealed creatinine 130 µmol/L; urea 8.7 mmol/L; SDMA 13 µg/dL. SDMA was not elevated on this occasion and no further action was required.

CASE DISCUSSION

Elevated SDMA on one occasion in a non-azotemic cat should not be considered diagnostic; SDMA must be persistently elevated on a follow-up testing to allow a diagnosis of early CKD. In Jeremy's case the USG of 1.040 was also less indicative of early CKD. USG below 1.035 is sometimes taken to indicate reduced urine concentrating ability, but on a spot sample such a finding has poor specificity for renal dysfunction unless combined with other indicators. However, a USG that is > 1.035 on a spot sample makes a diagnosis of early stage CKD less likely, as it indicates urine concentrating ability is adequate. For Jeremy, no further action was required after the follow-up test, and annual monitoring should continue at the next vaccination appointment.

Diagnostic testing

Early diagnosis of CKD in cats requires the combined use of plasma or serum creatinine, SDMA concentrations and urinalysis, rather than considering one parameter in isolation, as no single test is 100% specific and sensitive. Upward trends in creatinine, elevation in SDMA above the reference interval, a decline in USG and identification of proteinuria can all be used to aid diagnosis, and should be interpreted according to IRIS guidelines. Renal imaging should also be undertaken following abnormalities noted on palpation or where identified on blood and urine testing. Two clinical scenarios **(Boxes 1 and 2)** give practical examples of early CKD diagnosis.

Box 3. Reference intervals* for feline biochemical tests.

Parameter	Reference interval (RI)
Thyroxine (T4)	10-55 nmol/L
Creatinine	80-203 µmol/L
Urea	2.5-9.9 mmol/L
SDMA	1-14 µg/dL

* normal reference values will vary from one laboratory to another.

What to do following diagnosis – interventions in early CKD

IRIS guidelines outline the introduction of a renal diet in stage 2 CKD[2] and feeding a phosphate and protein-restricted diet to cats with azotemic CKD has been shown to improve survival and slow progression of disease (26). There is currently less research into the potential benefits of a similar diet in early or stage 1 CKD. Dietary intervention studies in geriatric cats with IRIS stage 1 CKD fed a test diet containing functional lipids, antioxidants and high-quality protein have demonstrated that such a diet resulted in significant decreases in variable combinations of renal function markers, including SDMA and creatinine, when compared to the normal diets (*i.e.*, those chosen by owners) (27). The study authors speculate that improvement in renal function secondary to the effect of the test diet may explain the stability of, or decrease

[2] www.iris-kidney.com/pdf/IRIS_CAT_Treatment _Recommendations_2019

in, circulating SDMA concentrations. However, no clearance technique was performed to confirm this or to evaluate the significance of changes in serum creatinine concentration in the face of stable serum SDMA or vice versa. It is also worth noting that although creatinine and SDMA can aid in early diagnosis of CKD, both are surrogate markers of GFR only and do not inform on the metabolic status of an animal.

Chronic kidney disease-mineral and bone disorder (CKD-MBD), resulting in derangements of parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23), 25-dihydroxyvitamin D, serum calcium and phosphate, with accompanying renal osteodystrophy and vascular/soft tissue calcification is recognized in cats. Neither creatinine nor SDMA alone are able to inform about the presence of CKD-MBD, and further research is therefore required to establish the derangements in phosphate homeostasis that can be identified with stage 1 CKD and the role of measuring markers of bone mineral disturbance (such as FGF23), in determining which cats require clinical intervention in the form of dietary modification. Currently, FGF23 assessment is not commercially available.

CONCLUSION

Chronic kidney disease has a significant prevalence in the feline population and is a major cause of death in older cats. Early diagnosis of CKD is clearly advantageous, as it prompts close monitoring for progression and the timely use of appropriate therapeutic interventions. Using serum creatinine concentration remains the most common assessment of kidney function in practice, but the recently developed SDMA test may detect early signs of CKD some months prior to elevation of creatinine above the upper reference interval. However, accurate early diagnosis requires the combined use of plasma or serum creatinine, SDMA concentrations and urinalysis, rather than considering one parameter in isolation, as no single test is 100% specific and sensitive.

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UPPER URINARY TRACT UROLITHIASIS

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After completing veterinary school and an internship at the University of Pennsylvania, Dr. Aronson undertook a small animal surgical residency at the University of California, Davis (UCD). She then joined the faculty at the University of Pennsylvania – where she is currently Professor of Surgery – and started their renal transplantation program. Her clinical interests include all areas of soft tissue surgery, but in particular microvascular surgery, complex urinary tract surgery, and treatment of urolithiasis.

Renal and ureteral surgery in small animals can be challenging, even for the most experienced surgeon; Lilly Aronson gives an overview of the best options currently available for treating upper urinary tract obstructions.

KEY POINTS

1. Calcium oxalate (CaOx) uroliths are commonly identified in the upper urinary tract of both cats and dogs.
2. Owners should be made aware that the majority of cats presenting with CaOx urolithiasis have pre-existing chronic kidney disease.
3. Traditional surgical techniques may be successfully performed with appropriate surgical training and can avoid complications associated with the use of long-term implants.
4. In some situations a combination of traditional and interventional techniques are necessary to relieve an obstruction; at other times interventional techniques alone may be indicated.

Introduction

Surgical intervention of the upper urinary tract is most commonly indicated when urolithiasis develops, resulting in partial or complete obstruction of urinary outflow. In cats, > 90% of upper urinary tract uroliths are composed of calcium oxalate (CaOx) although other urolith types, including struvite and dried solidified blood calculi, also occur (1,2). In dogs, CaOx and struvite uroliths are seen with a more equal frequency, with a reported incidence of struvite uroliths in the upper urinary tract between 20-60% (3). When an obstruction is not present, less invasive treatment using medical dissolution is recommended for certain urolith types (struvite and possibly cysteine and purine), but CaOx uroliths will not dissolve with medical management and surgical intervention is often necessary to relieve the obstruction and prevent further renal injury.

Renal and ureteral surgery in cats and dogs can be challenging for even the most experienced surgeon, mainly due to the sheer size of the ureter, particularly in cats. Meticulous surgical technique and appropriate magnification are essential in preventing both short and long-term complications. The choice of surgical treatment often depends on patient presentation, which can vary with regard to the number and location of ureteroliths and whether the disease is unilateral or bilateral, the presence or absence of concurrent nephrolithiasis, and any underlying kidney infection or dysfunction. Additionally, the duration of obstruction

likely impacts the recovery of renal function; unfortunately in many cases, and particularly in patients with unilateral disease, this information is unknown. Depending on the type of urolith and location within the urinary tract, treatment may involve a combination of medical, interventional and/or surgical management.

Diagnosis

History and clinical exam

Historical information (including the onset and progression of clinical signs) and physical examination findings, as well as biochemical testing and imaging studies, help guide the clinician as to the best treatment approach for any given animal. A thorough evaluation is critical since many affected patients are older and may have concurrent disease. Animals with non-obstructive nephroliths are often asymptomatic. Cats with ureteroliths may be asymptomatic or display non-specific signs including lethargy, depression, weight loss, fever, anorexia, vomiting, polydipsia and polyuria. Oral uremic ulcers may be observed and hematuria may or may not be present. Dogs more often present with signs of dysuria (*e.g.*, pollakiuria, stranguria, hematuria, polyuria and incontinence) and are frequently systemically ill, since pyelonephritis is commonly seen with obstruction. Abdominal palpation may reveal pain, splinting or renomegaly. A fundic examination should be performed to evaluate the retinas for detachment or hemorrhage which may be an indication of hypertension.

Biochemical testing

Most cats with ureteroliths are azotemic, even with unilateral obstruction, and studies confirm that many affected cats have pre-existing chronic kidney disease (CKD) (2,4,5). In addition cats often have a small, marginally functional, non-obstructed kidney in conjunction with an enlarged, hydronephrotic obstructed contralateral kidney (Big Kidney Little Kidney (BKLK) syndrome) (6). Anemia is often present and may suggest chronicity. An elevated white blood cell count may be seen in cases of ureteritis or to support a diagnosis of pyelonephritis secondary to obstructive urolithiasis.

Routine urinalysis, including culture and evaluation of the urine sediment, should be performed. Assessment of urine pH may help differentiate between CaOx and struvite uroliths and guide medical management during the postoperative period. In dogs, a history of urinary tract infection or evidence of bacteria, pyuria and/or hematuria on sediment evaluation should raise suspicion for struvite urolithiasis. Urease-producing bacteria, including *Staphylococcus*, *Klebsiella* and *Proteus spp.* are most commonly identified in dogs. Urinary tract infections have been identified in up to 32% of cats on presentation, with *Escherichia coli* identified as the most common isolate (4,7).

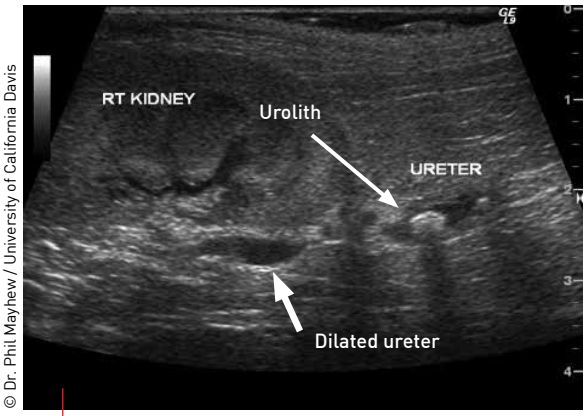

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Figure 1. An ultrasound scan of a cat presented with a unilateral ureteral obstruction of unknown duration. The urolith can be identified in the proximal ureter causing a partial obstruction; dilation is identified distal to the obstruction. Note that the ureteral dilation proximal to the urolith does not extend to the level of the obstruction and that pelvic dilation is minimal; this is uncommon but may be seen in some cases if obstruction is subacute.

Imaging

Uroliths are often visualized on plain survey radiographs, although small or radiolucent ureteroliths, or those overlying vertebral bodies or colonic contents, are occasionally missed; the sensitivity of survey radiography for identifying feline ureteral uroliths is around 81% (7). The use of a compression paddle (*e.g.*, a wooden spoon) during radiography to isolate the ureter from other abdominal viscera may help identification of a ureterolith.

Ultrasonography should be performed in all cases of suspected ureteral obstruction and can have excellent sensitivity and specificity (8). This also provides information as to the degree of hydronephrosis and/or hydroureter, and allows assessment of the renal parenchyma and the retroperitoneal space for any evidence of peri-renal inflammation or effusion. Note that renal pelvic dilation can be seen with other conditions including CKD, pyelonephritis, diuresis and ectopic ureters, and if the obstruction is subacute, pelvic or ureteral dilation may be minimal. In both dogs and cats, a renal pelvic height > 13 mm is consistent with obstruction and in cats, a ureteral diameter > 6 mm is consistent with obstruction (9). In some cases, ureteral dilation may not extend to the level of the obstruction **(Figure 1)**. Ultrasound is also a useful monitoring tool to identify worsening dilation and the need for surgical intervention.

Antegrade pyelography may be indicated in some cases and can facilitate identification of both radiopaque and non-radiopaque causes of obstructions such as dried solidified blood calculi, ureteritis and strictures. The technique can be performed under ultrasonographic and/or fluoroscopic guidance; urine should be collected from the renal pelvis for analysis and culture at the same time.

Computed tomography and magnetic resonance imaging are rarely used for cases of upper urinary tract obstruction.

Nephrolithiasis

If nephroliths are identified as incidental findings, patient monitoring without intervention is generally recommended. If urolith composition can be predicted based on signalment, urinalysis and radiographic appearance, medical dissolution should be attempted for amenable urolith types and preventative measures instituted whenever possible. One study in cats diagnosed with concurrent mild or moderate CKD found that surgical removal was not necessarily indicated, since the presence of nephrolithiasis was not associated with disease progression or increased mortality rate (10). Removal is considered when complications such as progressive renal injury, intractable pyelonephritis, obstruction of urine outflow, chronic pain or hematuria develop.

In humans, minimally invasive techniques are employed for treating nephrolithiasis, including extracorporeal shockwave lithotripsy (ESWL) and percutaneous nephrolithotomy. Although these techniques have been performed successfully in dogs, availability is often limited to specialist centers, and ESWL is not an effective treatment for nephrolithiasis in cats. If advanced equipment is not available for minimally invasive treatment, surgical removal is recommended for problematic nephroliths, and there are two options available.

Nephrotomy

The kidney is partially dissected from its retroperitoneal location and the renal artery and vein isolated and temporarily occluded **(Figure 2a)**. A longitudinal incision is made through the convex surface of the kidney on midline **(Figure 2b)** and the parenchyma incised. Uroliths are removed from the renal pelvis and collecting ducts, and the area flushed with sterile saline. If a small urolith is present, a stab incision may be adequate to place retrieval forceps into the pelvis. Closure is accomplished by approximating the two "halves" of the kidney with the capsule sewn together with monofilament absorbable material in a simple continuous pattern. Vascular occlusion is removed and the two halves of the kidney are held firmly opposed for another five minutes **(Figure 2c)**.

Pyelolithotomy

Pyelolithotomy is rarely performed in dogs and cats but may be warranted for smaller uroliths if dilation of the renal pelvis is present. The kidney is dissected free of its peritoneal attachments and folded medially (occlusion of the renal vasculature is not required) and an incision made over the proximal ureter and pelvis. The stones are removed, and ureteral patency is evaluated by passing a suture distally into the urinary bladder before the proximal ureter and pelvis are closed with a standard suture pattern.

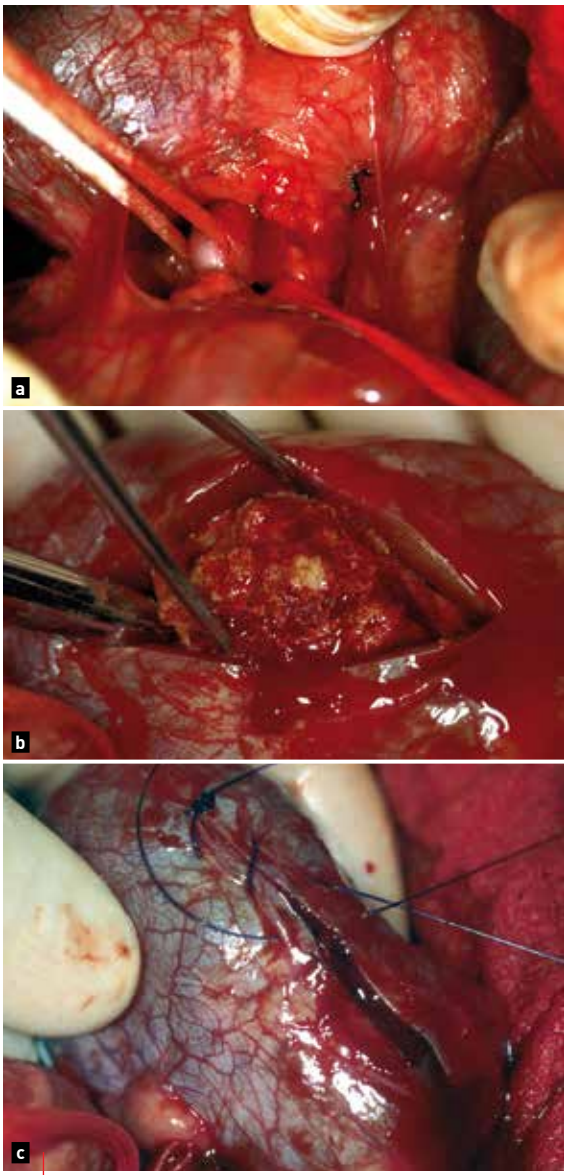

Figure 2. **(a)** Nephrotomy; the renal artery and vein are isolated and temporarily occluded with Rummel tourniquets using umbilical tape. **(b)** A longitudinal incision is made with a scalpel through the convex surface of the kidney on midline and the urolith removed. **(c)** The incision is closed by approximating the two "halves" of the kidney and the renal capsule is sewn together with monofilament absorbable material in a simple continuous pattern.

Ureterolithiasis

The human ureter is described as having 3 anatomic sites of narrowing where uroliths typically become lodged, including the ureteropelvic junction (UPJ) where the ureter crosses the iliac vessels, and the ureterovesicular junction (UVJ) where the ureter courses through the bladder wall

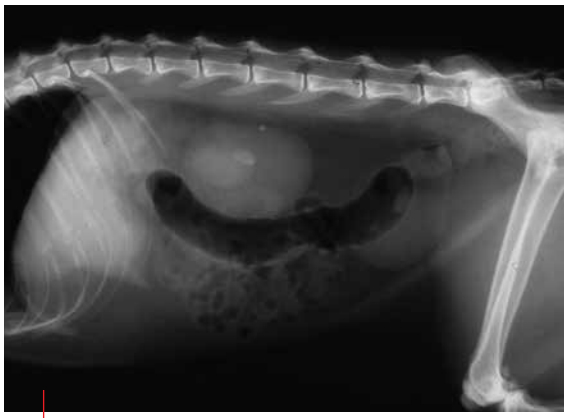

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Figure 3. A radiograph of a cat with Big Kidney Little Kidney (BKLK) syndrome. Note the small, non-obstructed right kidney and the enlarged left kidney with evidence of nephroliths and a proximal ureterolith at the level of the L4 vertebral body, likely causing an obstruction.

to the ureteric orifice (11). Males more commonly have uroliths lodged at the UVJ compared to females. In a study evaluating the radiographic distribution of feline ureteral uroliths, the proximal ureter was the most common site for obstruction, and the L4 vertebral body was the most frequently marked urolith location (which may correlate to the UPJ) **(Figure 3)**. As in humans, uroliths located at the UVJ were more common in males and larger uroliths had a more proximal location (12).

If patients are stable on presentation, medical management (including the administration of intravenous fluid therapy alone or with the diuretic mannitol) may be attempted for 24-48 hours to determine if spontaneous passage of uroliths into the bladder will occur. Smooth muscle relaxants (*e.g.*, prazosin), the tricyclic antidepressant amitryptiline and other alpha antagonists (*e.g.*, tamsulosin) have also shown anecdotal efficacy with ureteral relaxation and stone passage (13), but note that aggressive medical therapy can also result in complications, including fluid overload, electrolyte abnormalities, migration of a nephrolith into the ureter or migration of a ureterolith that was causing only a partial obstruction to a location where complete obstruction occurs. In the author's experience, successful passage of stones with medical management is uncommon and often only identified in patients presenting initially with a distal ureteral obstruction (6,7). Because the incidence of urinary tract infections in dogs is > 50% with ureteral obstructions, broad-spectrum antimicrobial therapy is also indicated (14).

"If ureteroliths necessitate surgical intervention, the decision as to the preferred technique should be based on the patient's clinical presentation, imaging studies and surgical findings."

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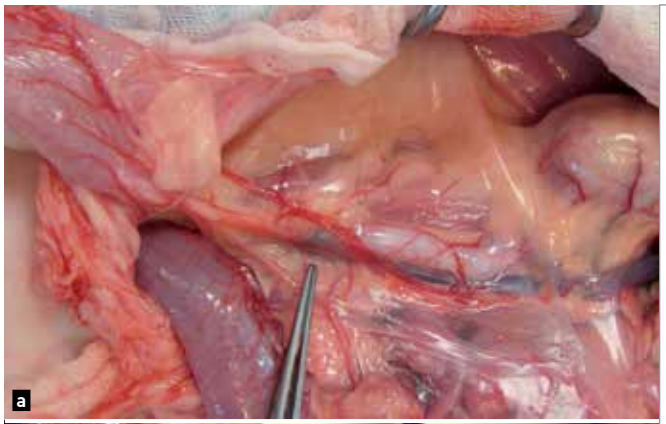
When surgical intervention is necessary, the preferred option (*i.e.*, a traditional surgical procedure, stenting or subcutaneous ureteral bypass (SUB)) is made based on clinical presentation, imaging studies and surgical findings. In certain cases a combination of techniques may be warranted, but the availability and cost of equipment can be a major factor; substantial (*e.g.*, 8-10X) magnification via an operating microscope is usually necessary, although in larger dogs surgical loupes (2.5-4.5X magnification) may be adequate. Placement of ureteral stents also requires a considerable array of specialist equipment including a fluoroscopic C-arm. For cystoscopic stent placement, which is not possible in male cats, a rigid endoscope or flexible ureteroscope may also be necessary. Human ureteral stents can be used for most dogs, but special commercial stents are required for cats.

Ureterotomy and ureteral reimplantation

For urolith removal the author prefers traditional surgical techniques, including ureterotomy and ureteral reimplantation, over the use of long-term implants in order to avoid complications often associated with these devices (15).

A ureterotomy is suitable for patients presenting with one or two stones in the proximal ureter. Once the location of the stone(s) is/are identified **(Figure 4a)** the affected segment of ureter is isolated using silastic material proximally and distally **(Figure 4b)**; this decreases urine flow into the surgical field and prevents spontaneous retrograde movement of ureteroliths back into the kidney. If the ureter is dilated proximal to the obstruction, a longitudinal incision can be made in this location and the stone gently manipulated out of the ureterotomy site **(Figure 5)**; occasionally, more than one urolith can be removed via the same incision. More commonly, the urolith is embedded within the wall of the ureter and the incision needs to be made directly over the urolith. Care is taken when manipulating the ureter so as not to disrupt the blood supply or inadvertently traumatize the ureter. Following urolith removal, the proximal silastic can be loosened temporarily to verify urine flow from the kidney, and a suture can be passed distally from the ureterotomy site to confirm patency of the distal ureter. Closure of the ureterotomy site is routine, but absorbable material is preferred so that the suture does not act as a nidus for new urolith formation.



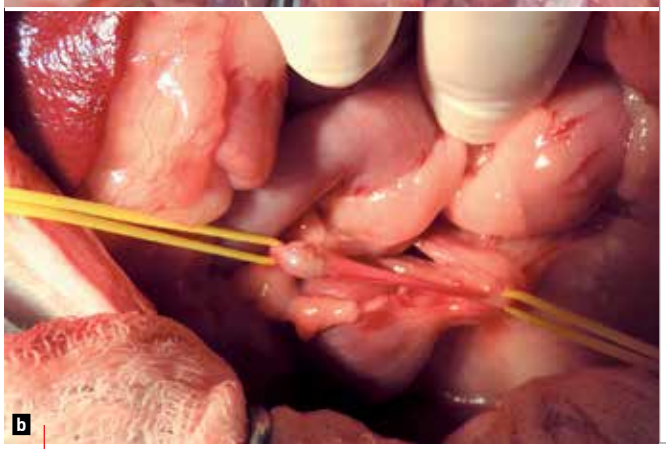


***Figure 4* (a)**. A urolith (cranial to the forceps) in the mid ureter causing a complete obstruction. Note the thickened ureter (chronic ureteritis) proximal to the obstruction and the normal segment of ureter distal to the obstruction. **(b)** The affected segment of ureter is isolated using silastic material proximally and distally before the ureter is incised.

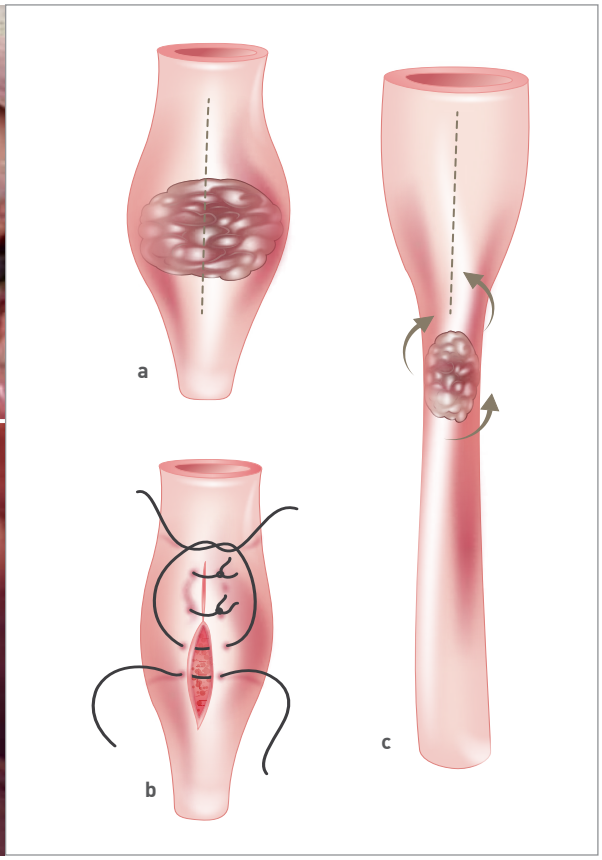


***Figure 5.* (a)** The urolith is often embedded within the wall of the ureter and an incision needs to be made directly over the urolith in order to remove it. **(b)** Following removal of the urolith closure of the ureterotomy site is routine. **(c)** If the ureter is dilated proximal to the obstruction, a longitudinal incision can be made in this location and the stone gently manipulated out of the ureterotomy site.

Stones lodged in the mid to distal ureter may be removed by ureterotomy, or the ureter can be transected adjacent to the most proximal urolith, the distal portion of the ureter removed, and the ureter reimplanted into the bladder (ureteroneocystostomy) using either an intravesicular or an extravesicular technique **(Figure 6)**; the reader is referred to specialist texts for full details. Although uncommon, ureteroneocystostomy can also be performed when only the proximal third of the ureter is available for anastomosis, using one or more specialist techniques to avoid tension on the tissues postoperatively **(Figure 7)** (15). These include;

- Renal descensus, where the kidney is mobilized from its retroperitoneal attachments and shifted caudally so that the renal capsule can be sutured to the adjacent body wall.
- Cystopexy, where the bladder is fixed cranially to the body wall or the tendon of the psoas muscle (psoas hitch).
- Nephrocystopexy, where sutures are placed between the caudal pole of the kidney and the apex of the bladder.

Ureteral stenting

In humans with urolithiasis, ureteral stents are often used in conjunction with ureteroscopy and ESWL, usually as a short-term measure to maintain drainage of the kidney until swelling resolves. The stents are often removed within a few days following the procedure, although longer-term placement is possible. If stents do need to be left long term, they are exchanged every few months to prevent complications. In contrast, both temporary and long-term use of ureteral stents are described for dogs and cats (4,16-20). Although cystoscopic placement is common in dogs, the vast majority of cats require laparotomy for ureteral stent placement because of the small size of the feline ureter.

Following ureterotomy, if concerns exist regarding healing of the ureteral incision, a temporary stent can be placed to divert urine during healing; this may also be useful when an obstructive stone has been associated with a pyonephrosis, and again a stent allows urinary diversion and continued drainage of purulent material post-surgery. In these cases, stents are removed approximately one month later. Note that if using a stent in conjunction with a ureterotomy, closure of the incision is aided by

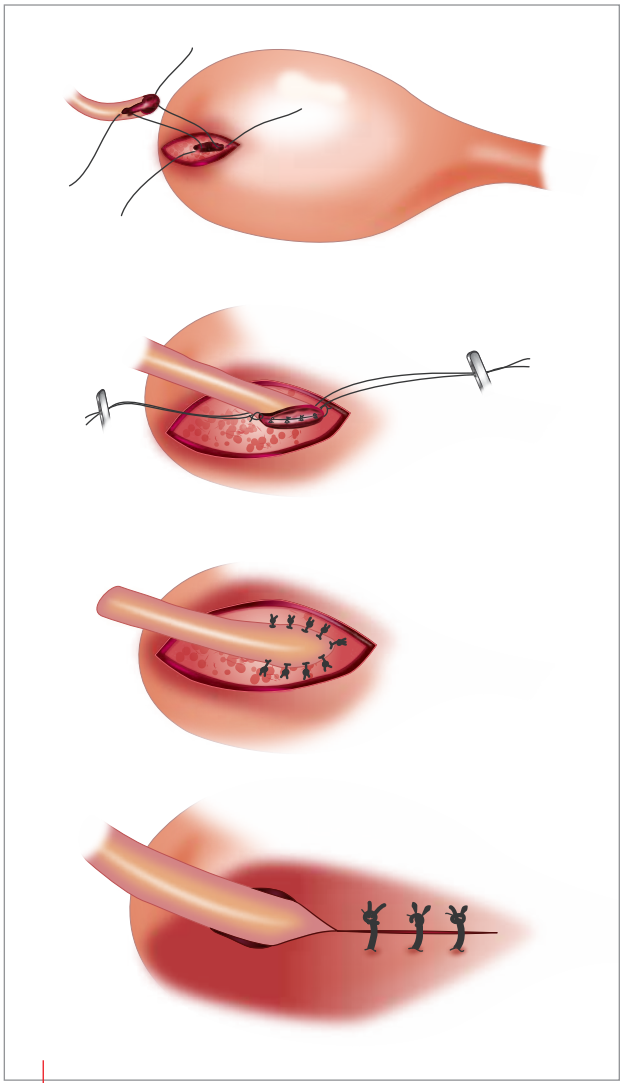


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Figure 6. The extravesicular technique for ureteral reimplantation. A 1 cm incision is made on the ventral surface of the bladder through the seromuscular layer allowing the mucosa to bulge through the incision. A smaller incision (3 to 4 mm) is made through the mucosal layer at the caudal aspect of the seromuscular incision and the ureteral mucosa sutured to bladder mucosa. The seromuscular layer is apposed in a simple interrupted pattern over the ureter.

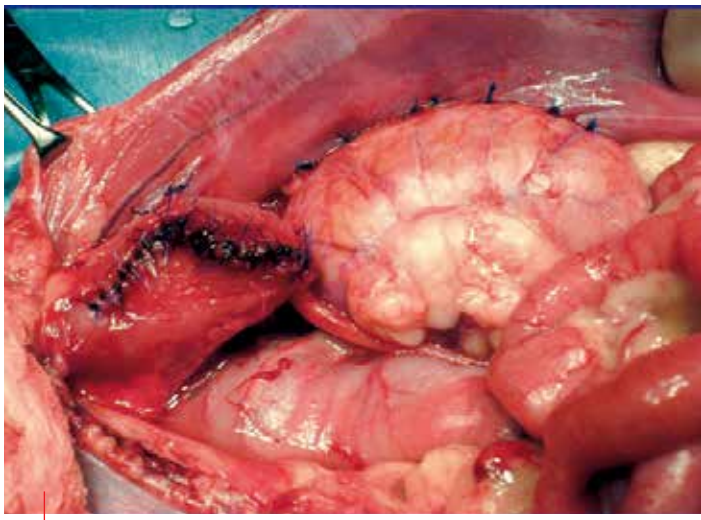

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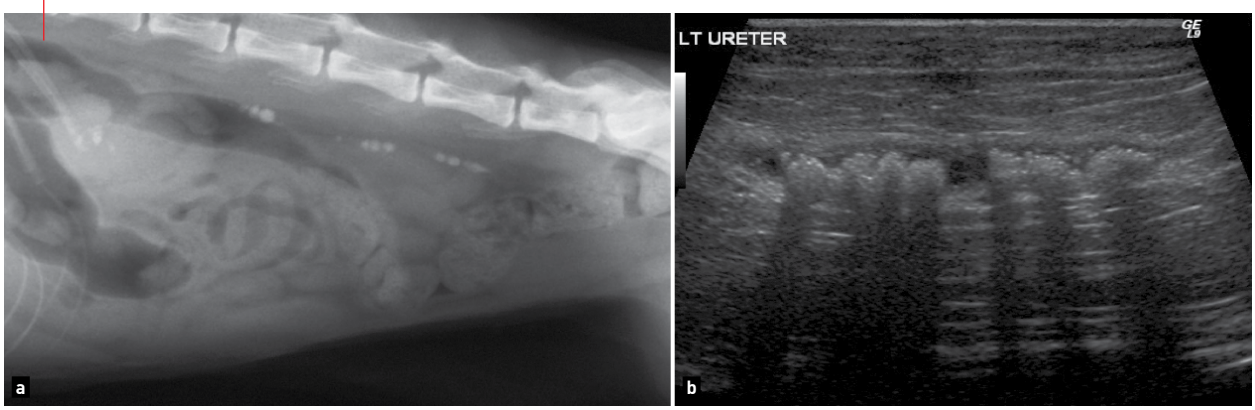
Figure 7. A dog that had a renal descensus, cystopexy and cystonephropexy performed to relieve tension following ureteral resection and reimplantation. A cystotomy was also performed. Note the proximity of the apex of the bladder to the caudal pole of the kidney.

placing the stent first. Ureteral stenting has also been used for patients with multiple ureteroliths (unilaterally or bilaterally) with or without the presence of nephroliths **(Figure 8)**. In this situation, stent exchange may be done every few months, but permanent removal is rarely possible.

Ureteral stents can be placed via an anterograde or retrograde approach, although in dogs with ureterolithiasis, cystoscopic placement in a retrograde manner is usual (16,17), whilst anterograde surgical placement is preferred for cats. For both techniques, surgical dissection and digital manipulation of the ureter may be necessary to remove tortuosity and to straighten the ureter prior to guide wire passage. Ureterotomy may also be necessary to facilitate wire and stent passage. Both techniques require fluoroscopy and a high level of surgical expertise.

Potential complications following a traditional surgical intervention include urine leakage and obstruction, but are relatively uncommon.

Figure 8. **(a)** An abdominal radiograph of a 7-year-old Himalayan cat with multiple bilateral ureteroliths and nephroliths. **(b)** An ultrasound scan of the left ureter of the same cat, showing multiple ureteroliths along the entire length of ureter.



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Complications following stenting are more common and include urine leakage and uroabdomen, persistence of the ureteral obstruction or re-obstruction, sterile cystitis, urinary tract infection, and stent migration. Potentially in patients that have concurrent nephrolithiasis and ureterolithiasis, nephroliths can pass into a ureter that was recently unobstructed (6). Various studies have evaluated success rates and long-term outcomes (16,18-21), with at least one study reporting a 21% incidence of perioperative mortality in cats, although the cause of death was frequently associated with progression of CKD and not related to surgical complications (22). Careful counseling of owners before undertaking such procedures is therefore essential.

Subcutaneous ureteral bypass

The initial indication for using a SUB device was for patients in which stent placement had been unsuccessful or was contraindicated, but in the author's facility the device has been used most commonly for presumptive strictures in the proximal ureter. The device consists of 2 locking loop pigtail catheters (one placed within the renal pelvis and the other within the urinary bladder) and a shunting port (23). Placement of the device requires fluoroscopic assistance and the renal pelvis should be at least 5 mm in size to allow accurate placement of the renal portion of the system. If the pelvis is small, the catheter can be placed in the proximal ureter without locking the loop. Cyanoacrylate glue is used to help secure the system in place to the kidney and bladder and prevent urine leakage. The access port allows urine samples to be collected for bacterial culture. It is recommended that the port be flushed one month post-surgery and then every three months to help maintain patency. However, as above, potential complications are considerable and include fluid overload, dysuria, persistently high-creatinine levels, catheter malfunction (kinking, obstruction or mineralization), urine leakage, infection, inappetence, and the need for revision surgery (23,24).

New developments

Brief mention should be made of a novel technique recently developed at the author's facility to treat a proximal ureteral obstruction in a cat. The method is based on a modification of a tubularized bladder flap that relies on the surrounding natural tissues for treatment, and in future may potentially avoid complications with long-term implant use (25).

CONCLUSION

Surgery of the upper urinary tract in cats and dogs can be challenging, even for the experienced clinician. Regardless of technique chosen, thorough diagnostic evaluation and follow-up for each patient, the availability of equipment, and appropriate surgical training, are all critical to prevent or limit complications with these techniques.

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FELINE RENAL PROTEINURIA

Proteinuria is a common and clinically relevant finding when performing a urinalysis, but is not always followed up in a consistent manner by the clinician; Stacie Summers explains the significance of proteinuria in cats and how best to approach the problem.

KEY POINTS

1. Proteinuria is associated with the development of azotemia in geriatric cats and is an independent risk factor for survival in cats with chronic kidney disease.
2. Renal proteinuria is often caused by chronic kidney disease in cats, and can occur early in the disease process.
3. Immune-complex glomerulonephritis is found in cats, but diagnosis requires renal biopsy for transmission electron microscopy with immunofluorescence.
4. Treatment of proteinuria depends on the underlying etiology and may involve a combination of drugs, modified-protein diets and (where appropriate) immunosuppressive therapy.

Introduction

The etiology of proteinuria in cats is multifactorial and can be due to pre-renal, renal, or post-renal disease, or it can occur as an outcome of transient altered renal physiology (functional proteinuria). Proteinuria is a concern for both veterinarians and cat owners as it is associated with the development of azotemia in geriatric cats, and is an independent risk factor for survival in cats with chronic kidney disease (CKD) (1,2). Persistent renal proteinuria is of particular clinical importance and is defined as abnormal quantities of proteins in the urine that occur secondary to disease in the renal tubules, glomeruli and/or interstitial space. Because proteinuria is associated with negative outcomes in cats, it is important for veterinarians to diagnose and treat proteinuria in a strategic manner. This paper offers an update on the current understanding of the etiology of renal proteinuria in cats, outlines the clinical approach to diagnosis, and presents the current management strategies available.

Documentation of proteinuria

Two urine samples taken at different time points should be used to confirm persistent proteinuria; for accuracy, it is essential that the samples have an inactive urine sediment and that the patient is stable at the time of collection. In some instances, proteinuria may be noted alongside clinical signs for hypoalbuminemia (peripheral edema, cavitary effusion) and in this scenario immediate evaluation and treatment may be necessary. In most cases, once the persistence of proteinuria is confirmed by urine dipstick or the sulfosalicyclic turbidimetric test, then the magnitude of the proteinuria should be determined using the urine protein to creatinine ratio (UPC), a quantitative test that measures total urine protein. Based on the International Renal Interest Society (IRIS) guidelines, cats are identified as either non-proteinuric (UPC < 0.2), borderline proteinuric (UPC 0.2-0.4), or proteinuric (UPC > 0.4), again ideally based on two or more urine samples (3). Cats with persistent proteinuria (UPC > 0.4) should always be investigated.

Diagnosis of proteinuria

After determining the degree of proteinuria, the clinician should evaluate for the different causes of pre-renal, post-renal, and functional proteinuria **(Table 1)**. Pre-renal proteinuria occurs when there are increased amounts of small proteins in the systemic circulation that overload the glomeruli and are unable to be completely resorbed in the renal tubules. Post-renal proteinuria occurs when the tissue barrier of the ureters, bladder, urethra, or genital tract is disrupted, allowing plasma proteins to leak into the urine. Functional proteinuria is due to altered renal physiology, with the most well-documented cause in cats being systemic hypertension, either secondary to disease or idiopathic in senior cats (4).

If pre-renal, post-renal, and functional proteinuria causes have been excluded, then this should point clinicians towards pathologic renal proteinuria. Renal proteinuria is described as either tubular or glomerular in origin, or it can be a mixture of both. Glomerular proteinuria is the most common form in proteinuric cats (5) and should be suspected in animals with UPC > 1.0, although a lower UPC value

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does not exclude glomerular disease (6). Glomerular proteinuria can be further classified as immune-complex glomerulonephritis (ICGN) or non-immune-complex glomerulonephritis (non-ICGN) based on the presence or absence of immune-complex deposits in the glomeruli; these can be identified by submitting renal biopsies for immunofluorescence and transmission electron microscopy.

CKD is the most common cause of non-ICGN renal proteinuria. Based on gel electrophoresis, glomerular proteinuria is most common in CKD cats, followed by mixed proteinuria and tubular proteinuria (7). These findings are consistent with non-specific changes that affect both the tubules and glomeruli found on renal histopathology in cats with CKD (8). Importantly, tubular proteinuria can occur in cats with non-azotemic (IRIS stage 1) CKD, which is consistent with tubular damage that occurs early in the disease process. Other causes of renal proteinuria include renal neoplasia, dysplasia, glomerulosclerosis or atrophy, and acute kidney injury (AKI) secondary to hypoxic injury, toxin ingestion (*e.g.*, ethylene glycol, lilies), or pyelonephritis. Inherited renal disorders such as amyloidosis or polycystic kidney disease should be considered differentials for renal proteinuria based on signalment and clinical suspicion.

Table 1. Classification and causes of proteinuria and diagnostic testing to consider in the evaluation of cats with proteinuria.

Causes	Diagnostic tests
Pre-renal proteinuria	
• Hemoglobinuria • Myoglobinuria • Immunoglobulin light chains	• Complete blood count • Biochemistry panel • Visualization of the urine supernatant color • Urine protein electrophoresis
Functional proteinuria	
• Hypertension • Seizures • Fever • Strenuous exercise	• Indirect blood pressure measurement • Body temperature
Renal proteinuria	
ICGN: • Infectious (FeLV, FIV, FIP) • Idiopathic **Non-ICGN:** • Chronic kidney disease (IRIS stages 1-4) • Acute kidney injury • Glomerular sclerosis or atrophy • Amyloidosis • Polycystic kidney disease • Renal dysplasia • Renal lymphoma or other neoplasia	• Serum creatinine and/or symmetric dimethylarginine (SDMA) with urine specific gravity • Screening test for FeLV and FIV • Abdominal ultrasound • Renal histology with transmission electron microscopy and immunofluorescence
Post-renal proteinuria	
• Urolithiasis • Neoplasia • Sterile cystitis • Urinary tract infection	• Urinalysis • Urine culture • Abdominal radiographs and/or ultrasound • Urolith analysis

FeLV = Feline Leukemia Virus; FIV = Feline Immunodeficiency Virus; FIP = Feline Infectious Peritonitis; ICGN = Immune-complex glomerulonephritis; IRIS; International Renal Interest Society

ICGN is an immune-mediated disease where immune complexes are deposited within the kidney glomeruli. The location of the deposition varies and can occur in the glomerular basement membrane (membranous glomerulonephropathy), in the luminal surfaces of capillary walls (membranoproliferative glomerulonephritis), and the mesangium (mesangioproliferative glomerulonephritis) **(Figure 1)**. Cats with ICGN should be tested for infectious disease, and especially retroviral infections. In a recent retrospective study, cats with ICGN were found to have high UPC ratios (> 2) and to be younger compared to cats with non-ICGN. In addition, a UPC ratio > 3.8 is both sensitive (91.9%) and specific (93.5%) for ICGN in cats (9). In contrast to cats with CKD, cats with ICGN often suffer from hypoalbuminemia and can subsequently develop cavitary effusions or pitting edema (5).

Table 1 summarizes diagnostic tests to consider during the evaluation of feline proteinuria. The diagnostic approach to cases will depend on history, signalment, physical examination, and clinical suspicion. In particular, a renal biopsy with transmission electron microscopy and immunofluorescence (as well as traditional light microscopy) is required for diagnosis of ICGN, and should be considered in cats with rapidly progressive and/or marked proteinuria. Contraindications to renal biopsy include uncontrolled hypertension, hydronephrosis, anemia, coagulopathy, renal cystic disease, and end-stage CKD with creatinine > 5 mg/dL (442 µmol/L).

Treatment

For pre-renal, post-renal, and functional proteinuria, the underlying condition should be addressed. In cases of renal proteinuria, treatment may include a

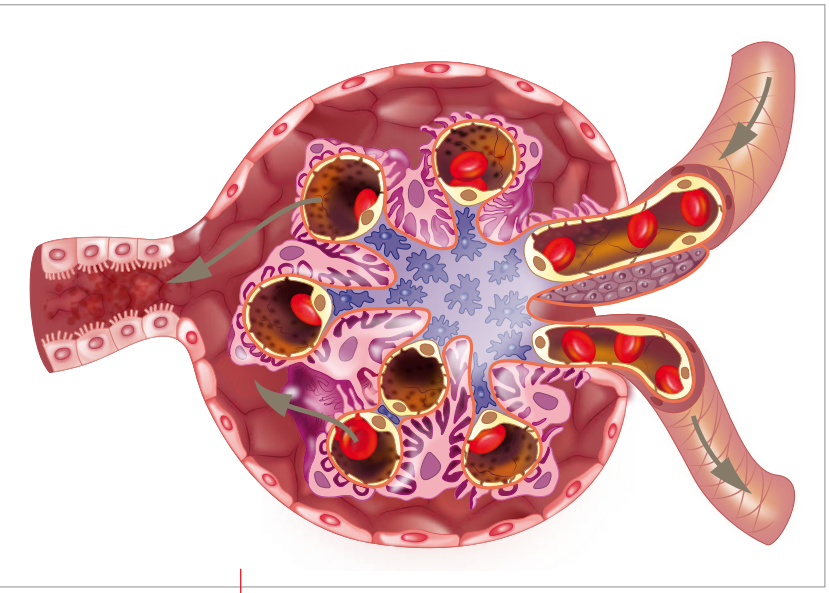

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Figure 1. Schematic diagram of a normal glomerulus. Glomerular basement membrane = orange; capillary walls = yellow; mesangium = blue.

combination of inhibition of the renin-angiotensin-aldosterone system (RAAS), dietary management, and (when appropriate) immunosuppressive medications.

Inhibition of RAAS

The renin-angiotensin-aldosterone hormone system regulates vascular resistance, blood pressure, and fluid and electrolyte balance in the body **(Figure 2)**. The two drug classes that are most commonly used to inhibit RAAS in cats are angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), and while both drugs inhibit RAAS and improve proteinuria, their specific mechanism of action differs.

As the name suggests, ACE inhibitors inhibit the angiotensin converting enzyme in the RAAS cascade. Drugs most commonly used in cats within this class include enalapril and benazepril, but note enalapril may accumulate where there is severe kidney disease and should be used cautiously in cats with end-stage CKD. ARBs inhibit the action of angiotensin II by blocking its binding to tissue receptors; telmisartan is the most common ARB used in cats and selectively binds and blocks the angiotensin II type 1 receptor whilst sparing the renoprotective benefits provided by the angiotensin II type 2 receptor. The renoprotective benefits of telmisartan makes it an attractive treatment option in cats with renal proteinuria; in some countries it is also licensed for the treatment of hypertension in cats and is formulated as an oral liquid. In addition, telmisartan may be more efficacious for the treatment of proteinuria in cats compared to ACE inhibitors, especially when used long term (10).

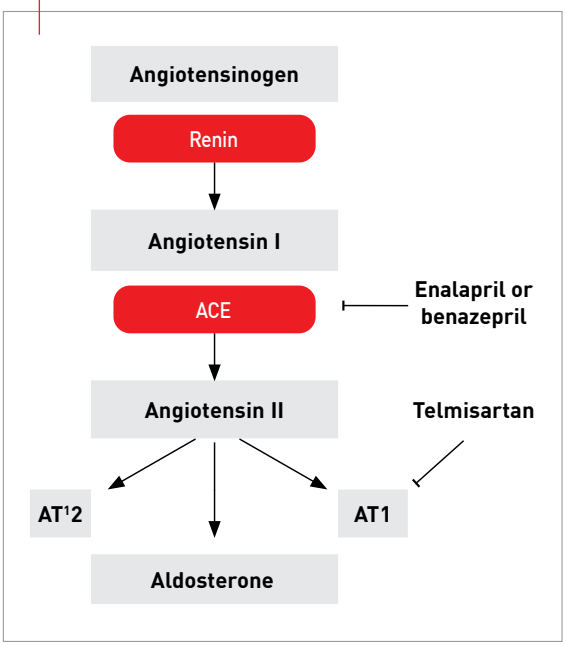
Both ACE inhibitors and ARBs should be started at the recommended dose which is then increased over time until the treatment goal has been achieved **(Table 2)**. Side effects of RAAS inhibition include hyperkalemia, and at high doses hypotension can occur. In addition, AKI is a reported side effect, although the incidence of this in both azotemic and non-azotemic cats treated with telmisartan was rare in a recent study (11). Because both drug classes can reduce glomerular filtration rate, they should only be used in patients with stable azotemia and euvolemia.

Dietary management

There is limited information as to the efficacy of dietary management in cats with proteinuria (12), although a study showed that a moderate-protein (27.6% dry matter basis) wet diet fed for one year to cats limited proteinuria and glomerular injury in comparison to those fed a high-protein (51.7% dry matter basis) wet diet (13). A modified-protein diet is generally recommended in cats with proteinuria, but they should be monitored for signs of protein malnutrition (anemia, hypoalbuminemia, weight loss, muscle wasting), especially where appetite is reduced.

Daily caloric intake should also be monitored closely to prevent muscle wasting and weight loss, which can develop if energy malnutrition is present. An esophagostomy feeding tube should

Figure 2. The renin-angiotensin-aldosterone system and the sites of action for the most commonly used inhibitors in cats.



[1] AT = Angiotensin

Table 2. Inhibitors of RAAS most commonly used in cats with proteinuria.

Drug	Initial dose	Dose increase strategy
Benazepril/ Enalapril	0.25-0.5 mg/kg PO per day; can be given q12H	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 2 mg/kg
Telmisartan	1 mg/kg PO q24H	Increase by 0.5 mg/kg to a maximum daily dose of 3 mg/kg

be considered early on in the disease process if a cat is unable to consume sufficient calories on its own. If necessary it may also be pertinent to review an animal's hydration status, and address this as necessary, either by using canned diets (> 70% moisture), subcutaneous or intravenous fluid therapy, or an esophagostomy tube.

Immunosuppressive drugs

Based on the benefit in dogs, immunosuppressive therapy is recommended in cases of ICGN confirmed on renal biopsy with severe, persistent, or progressive proteinuria and no contraindication to immunosuppression (14). In one study, there was a statistical trend showing ICGN cats that received immunosuppression lived longer, with a median survival time of 204 days compared to 34 days (5). Mycophenolate mofetil monotherapy (8-10 mg/kg PO q12H) is the preferred drug of choice, and can be used in combination with a short tapering course of prednisolone in severe cases. Mycophenolate mofetil is well tolerated in cats, although animals should be closely monitored for side effects, which may include gastrointestinal signs (in particular, diarrhea), bone marrow suppression, and infection (15). Treatment effect may take up to 8-12 weeks.

Monitoring proteinuria

After initiating RAAS inhibition, or after a dose change, indirect blood pressure, serum creatinine and potassium levels should be measured within 7 days. A urinalysis and UPC should be checked 4-6 weeks later to monitor treatment efficacy. After establishing the maintenance dose, routine monitoring every 3-6 months in a stable patient is encouraged.

Although the biological variation of the UPC ratio in cats is unknown, based on studies in dogs it can vary over time by 35-80%, depending on the severity of the proteinuria. UPC values tend to be higher in samples collected in the hospital compared to samples collected at home (16). Additionally, the UPC can be falsely increased by macroscopic red blood cell contamination, which can occur during cystocentesis in cats. UPC should therefore be performed on a urine sample with an inactive sediment collected using a consistent method (free catch or cystocentesis). Because of the significant day-to-day variations, trends in the UPC may be necessary to determine efficacy of treatment, but the treatment goal for proteinuria is a consistent reduction in UPC by at least 50%.

CONCLUSION

Proteinuria is a clinically relevant finding and the origin of the proteinuria should be explored prior to treatment. Chronic kidney disease is the most common cause of renal proteinuria in cats and can occur in early stage disease. Immune-complex glomerulonephritis is commonly seen in proteinuric cats, especially in younger cats and those with significant proteinuria or retroviral infections. Monitoring the UPC with a consistent urine sample collection method repeatedly over time is necessary to determine treatment efficacy.

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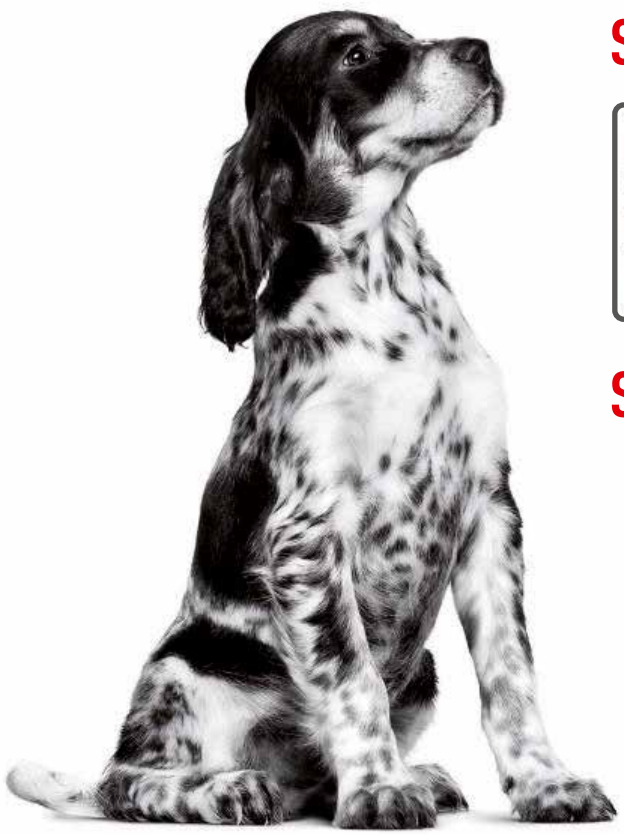

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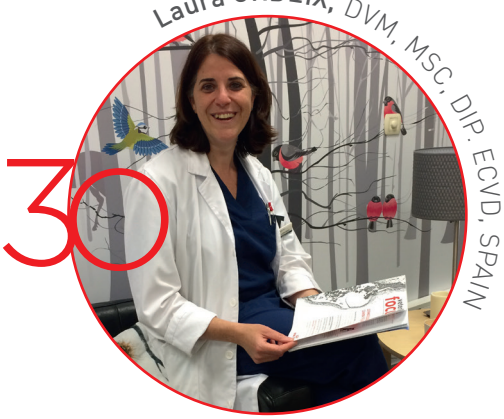

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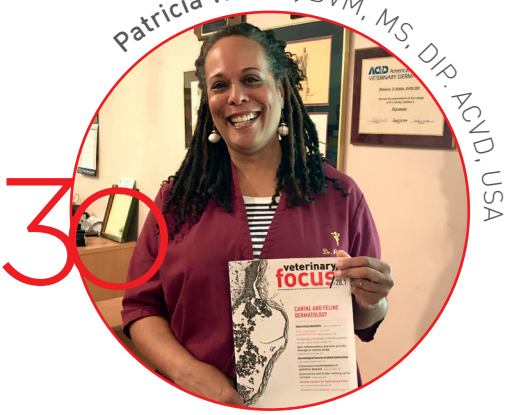

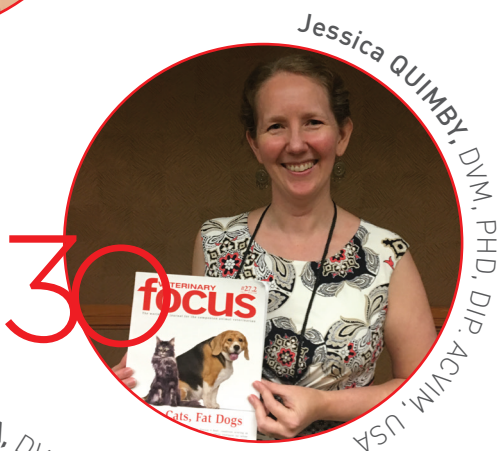

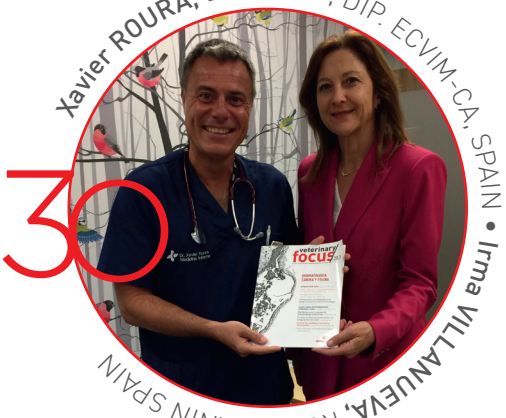

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