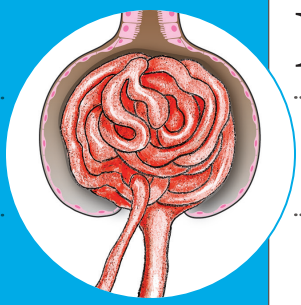
Feline Friendly Article



# Feline Chronic Kidney Disease

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Chronic kidney disease (CKD) affects an estimated 1% to 3% of all cats.[1] This important cause of mortality in cats develops over a period of months or years. The associated nephron damage is progressive and irreversible even though some cats with CKD have stable serum creatinine concentrations for months to years.

Diagnosis of early CKD, followed by appropriate treatment, may result in improved survival. There is solid evidence that dietary treatments, and increasing evidence that antiproteinuric treatments, can slow the progression of CKD.

## PROFILE

Prevalence of feline CKD increases with age; as many as 30% to 50% of cats older than 15 years of age have CKD.[2–4] Frequency of CKD in male and female cats is similar, but male cats are often diagnosed at a younger age than female cats.[5] Certain breeds appear to be overrepresented, including Maine Coon, Abyssinian, Siamese, Burmese, and Russian blue.[4]

## ETIOLOGY

The cause of feline CKD is usually difficult to determine. Due to the interdependence of the nephron's vascular and tubular components, the end point of irreversible glomerular or tubular damage is the same: fibrous scar tissue replacement of nephrons (**Figure 1**).

Morphologic heterogeneity between nephrons exists in the chronically diseased kidney, with changes ranging from severe atrophy to marked hypertrophy. Histologic changes are not process specific and, therefore, an etiologic diagnosis is frequently not established. The most common histologic diagnosis is chronic tubulointerstitial nephritis.[6]

Renal diseases associated with development of feline CKD are listed in **Table 1**.[6] Progressive diseases that slowly destroy nephrons allow intact nephrons to undergo compensatory hypertrophy, which can delay onset of renal failure. Therefore, when renal failure occurs (< 25% of the original nephrons functional), nephron hypertrophy can no longer maintain adequate renal function. For example, 80% nephron loss may result in a serum creatinine concentration of 2 mg/dL. With progression, serum creatinine concentration should be approximately 4 mg/dL when 90% nephron loss has occurred.

At the onset of International Renal Interest Society (IRIS) Stage 4 CKD (serum creatinine

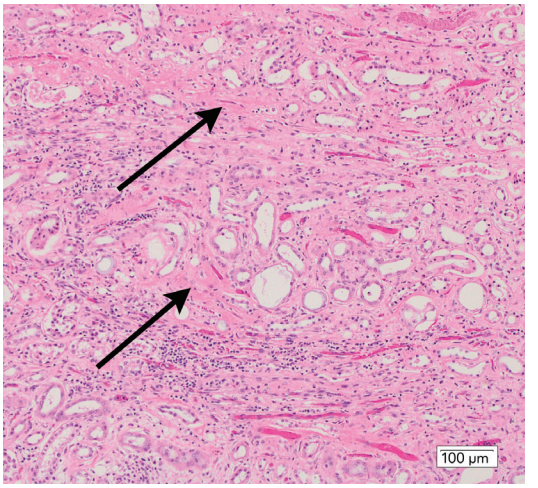


FIGURE 1. **Histopathologic image from a feline kidney with CKD. Note the fibrous scar tissue replacement** (arrows)**; and mononuclear cell infiltrates.**

TABLE 1.
**Renal Diseases Associated with Feline CKD Development**

- Amyloidosis
- Feline infectious peritonitis
- Glomerulonephritis
- Neoplasia
- Nephrolithiasis
- Polycystic kidney disease
- Pyelonephritis
- Tubulointerstitial disease
- Acute kidney injury that results in permanent loss of nephrons

## Kidney Disease or Renal Failure: Which Term to Use?

The term ***chronic kidney disease*** is preferred to ***chronic renal failure*** because CKD can exist *without* renal failure and clients often feel discouraged when a diagnosis includes the term "failure." Renal failure—defined by persistent renal azotemia superimposed on the inability to concentrate urine—results when 75% or more of the nephrons of both kidneys are not functioning.

concentration > 5 mg/dL; **Table 2**), it is likely cats have < 10% of their original nephron population. These figures emphasize the need for early diagnosis and intervention.

## PATHOPHYSIOLOGY

Pathophysiology of CKD can be considered at both the organ and systemic level.

### Decreased Glomerular Filtration

At the level of the kidney, the fundamental abnormality is loss of nephrons and decreased glomerular filtration. Reduced glomerular filtration results in increased plasma concentrations of substances that are normally eliminated from the body by renal excretion.

### Hormonal Disturbances

In addition to excreting metabolic wastes and maintaining fluid and electrolyte balance, the kidneys function as endocrine organs and catabolize several peptide hormones. Therefore, hormonal disturbances are part of the pathogenesis of multisystem disorders associated with CKD. For example, decreased production of erythropoietin contributes to the nonregenerative anemia of CKD, and decreased metabolism and excretion of parathyroid hormone contributes to osteodystrophy.

### Compensatory Mechanisms

Finally, part of the pathophysiology of CKD is brought about by compensatory mechanisms. The individual glomerular filtration rate (GFR) of intact nephrons increases in an attempt to maintain adequate renal function; however, proteinuria and glomerulosclerosis may be consequences or "trade-offs" of this hyperfiltration (**Figure 2**). In CKD autoregulation of renal blood flow is lost, and single nephron GFR increases in proportion to the number of nephrons lost. The resulting increased intraglomerular pressure damages the glomerular capillary wall and increases plasma protein filtration, leading to subsequent glomerular and tubulointerstitial damage.

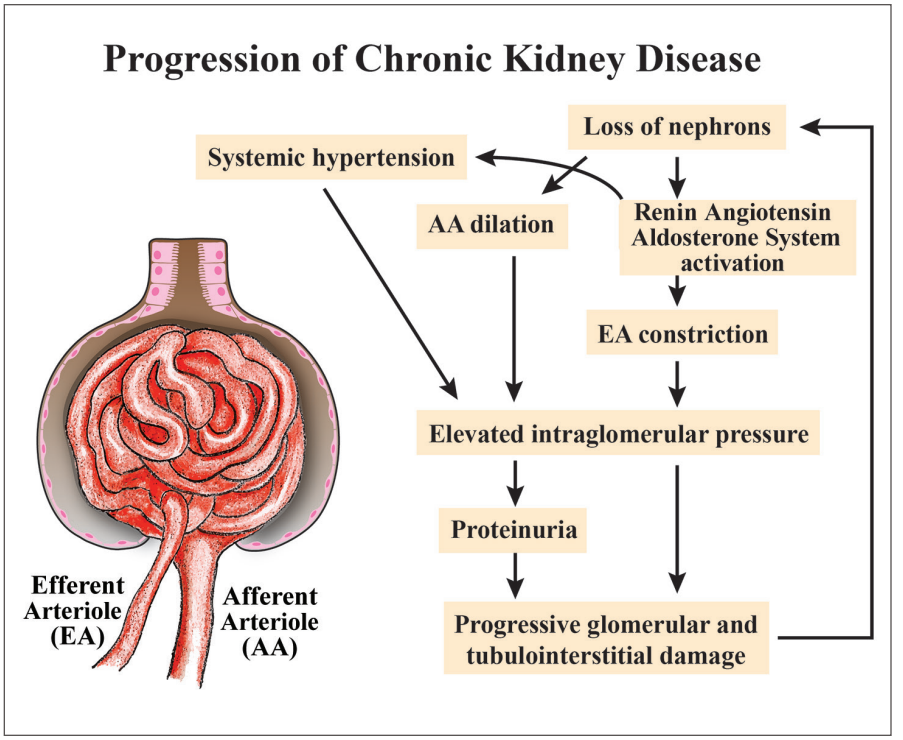


FIGURE 2. **Potential mechanisms of progressive loss of nephrons in CKD.**
*Courtesy Mal Hoover Rooks, CMI, Kansas State University*

## STAGING FELINE CKD

Many different terms have been used to describe renal disease and decreased renal function, and unfortunately, these terms can be confusing due to lack of standard definitions and application.

The IRIS (iris-kidney.com) was created to advance the scientific understanding of kidney disease in small animals and, specifically, to help practitioners better diagnose, understand, and treat canine and feline renal disease.

IRIS developed guidelines (**Table 2** and **Tables 3–4**, page 38)—adopted by the American and European Societies of Veterinary Nephrology and Urology—for staging stable feline CKD in order to:

1. Improve communication about CKD

TABLE 2.
**IRIS Guidelines: Staging Feline CKD by Serum Creatinine Concentration**

| STAGE & DESCRIPTION | SERUM CREATININE CONCENTRATION | |
|---|---|---|
| | mg/dL | mcmol/L |
| **Stage 1** Nonazotemic CKD | < 1.6 | < 140 |
| **Stage 2** Mild Renal Azotemia | 1.6 to 2.8 | 140 to 250 |
| **Stage 3** Moderate Renal Azotemia | 2.9 to 5 | 251 to 440 |
| **Stage 4** Severe Renal Azotemia | > 5 | > 440 |

TABLE 3.
**IRIS Guidelines: Classifying Feline CKD by Urine Protein-to-Creatinine Ratio**

| CLASSIFICATION | UPC RATIO |
|---|---|
| **Nonproteinuric** | < 0.2 |
| **Borderline Proteinuric** | 0.2 to 0.4 |
| **Proteinuric** | > 0.4 |

2. Link appropriate diagnostic and therapeutic efforts to patients with varying degrees of CKD.

### Serum Creatinine Concentration

The staging system outlined in **Table 2** is not used until the presence of CKD has been confirmed. This system, which categorizes kidney disease into one of 4 stages, is based on serum creatinine concentrations in well-hydrated cats with stable CKD; stability is documented by < 20% variation in serum creatinine concentrations over a minimum 2-week period.

Note that this staging system suggests that azotemia in cats begins with serum creatinine concentrations of 1.6 mg/dL or greater. However, serum creatinine concentrations must always be interpreted in light of the patient's muscle mass, urine specific gravity (USG), and physical examination findings in order to rule out pre- and postrenal causes of azotemia.

This staging system cannot be applied to patients with pre- or postrenal azotemia or those with acute or acute-on-chronic kidney disease.

### Proteinuria

The stages in **Table 2** are further substaged by the presence or absence of proteinuria (**Table 3**). Renal proteinuria is:

- Persistent (at least 2 positive test results separated by 10–14 days)
- Associated with inactive urine sediments
- Glomerular or tubular in origin (ie, excessive filtration, decreased tubular reabsorption, or both).

Urinary protein-to-creatinine ratios > 2 suggest glomerular-range proteinuria, which is rare in cats compared with dogs.[7] It is important to recognize that this ratio does *not* differentiate renal proteinuria from proteinuria associated with lower urinary tract inflammation; the clinician needs to differentiate proteinuria by assessing urine sediment.

### Systolic Blood Pressure

Systolic blood pressure is typically measured by the Doppler method in cats. IRIS blood pressure substaging is based on risk for target organ damage (eyes, brain, heart, and kidneys). Most clinicians consider systolic hypertension to be systolic blood pressure > 160 mm Hg, and initiate treatment at that point.

## CLINICAL SIGNS & DIAGNOSIS

### Clinical Signs

Clinical signs of CKD may not be present in early stages and, when present in later stages, are usually nonspecific, such as lethargy, weakness, anorexia, vomiting, and dehydration. Occasionally, uremic breath or oral ulcers may be observed.

Unique signs of CKD (versus acute kidney injury) include a long standing history of weight loss and polydipsia/polyuria, poor body condition, small and irregular kidneys, and renal secondary hyperparathyroidism.

### Diagnostic Findings

The classic diagnosis of renal failure based on renal azotemia (persistent azotemia superimposed on the inability to concentrate urine) pertains to CKD stages 2 through 4. Some cats with renal azotemia retain the ability to produce hypersthenuric urine (USG > 1.035) and, in these cases, response to fluid therapy helps diagnose prerenal versus renal azotemia.

Stage 1 CKD can be diagnosed based on:

- Abnormal renal palpation or ultrasonographic/radiologic findings
- Persistent renal proteinuria

TABLE 4.
**IRIS Guidelines: Classifying Feline CKD by Systolic Blood Pressure**

| ARTERIAL PRESSURE CATEGORY | SYSTOLIC BLOOD PRESSURE (mm Hg) | RISK FOR TARGET ORGAN DAMAGE |
|---|---|---|
| **AP0** | < 150 | Minimal |
| **AP1** | 150 to 159 | Low |
| **AP2** | 160 to 179 | Moderate |
| **AP3** | ≥ 180 | High |

- Urine concentrating deficits due to renal disease
- Increases in serum creatinine over time, even if the values remain in the normal range.

For example, a serum creatinine concentration that increases from 0.6 to 1.2 mg/dL over several years could indicate at least a 50% reduction in GFR (at least 50% loss of nephrons because compensatory hypertrophy of remaining nephrons increases their functional capacity).

### Serum Symmetric Dimethylarginine

Serum symmetric dimethylarginine (SDMA) is a new renal function marker that may aid in the early diagnosis of CKD in cats. In a recent longitudinal study of cats that developed CKD, SDMA concentrations increased above normal approximately 17 months before serum creatinine concentrations increased above the reference range (> 2.1 mg/dL).[8] Of note, if a serum creatinine concentration of ≥ 1.6 mg/dL had been considered abnormal in this study, both serum creatinine and SDMA would have identified renal azotemia at nearly the same time.

## THERAPEUTIC APPROACH

Similar to the diagnostic approach to CKD (see **Diagnostic Approach to Feline CKD**),

## Diagnostic Approach to Feline CKD

In general, the diagnostic approach to patients once CKD has been identified and staged focuses on 3 areas (**Table 5**):

1. Characterizing the primary renal disease and/or complicating disease processes
2. Characterizing the stability of renal disease and function
3. Assessing patient problems associated with decreased renal function

**Further definition of renal disease** (beyond a complete blood count, serum biochemistry profile, and complete urinalysis) includes:

- Quantitation of proteinuria
- Measurement of blood pressure
- Urine culture
- Urinary tract imaging with radiographs and ultrasound

**Stability of renal function** is assessed by serial monitoring of abnormalities identified during the initial characterization of renal disease. This monitoring should always include:

- Serum biochemical profile
- Urinalysis
- Quantitation of proteinuria
- Measurement of blood pressure

Monitoring may also include follow-up urine cultures and ultrasonography.

**Further definition of renal disease** is most important in earlier stages of CKD when correction of the underlying disease or disease complication has the greatest potential to improve or stabilize renal function.

**Characterization of the disease stability** is most important in earlier stages of CKD, when appropriate treatment has the greatest potential to stabilize renal function.

**Characterization of patient problems** becomes more important in later stages of CKD, when clinical signs tend to be more severe. In this case, diagnostic (and subsequent therapeutic) efforts should be directed at patient problems, including anorexia, vomiting, dehydration, acidosis, potassium depletion, and anemia.

TABLE 5.
**IRIS Chronic CKD Stages Correlated to Diagnostic & Treatment Considerations**

| IRIS STAGES | DIAGNOSTIC/ TREATMENT FOCUS | CONSIDERATIONS |
|---|---|---|
| **Stages 1 & 2 Early Stage 3** | Assess primary disease and complicating disorders | **Specific diagnostics/therapies:**<br>• Ultrasonography/urine culture to rule out ascending UTI; antibiotics for pyelonephritis<br>• Radiography and ultrasonography (with or without FNA) to rule out renal infiltrative disease and obstructive uropathy; chemotherapy (renal LSA) or subcutaneous ureteral bypass (ureteral obstruction)<br>• Assessment of serum calcium/ionized calcium to rule out hypercalcemic nephropathy |
| **Stages 2 & 3 Early Stage 4** | Assess CKD stability/ progression | **Renoprotective therapy to slow CKD progression:**<br>• Hyperphosphatemia: Renal diets with or without intestinal phosphorous binders to control serum phosphorus (Stage 2, < 4.5; Stage 3, < 5; Stage 4, < 6)<br>• Hypertension: Calcium-channel blockers and/or ACE inhibitors<br>• Proteinuria: ACE inhibitors and/or calcium-channel blockers |
| **Late Stage 3 Stage 4** | Assess patient problems | **Symptomatic problems and treatments:**<br>• Metabolic acidosis: Dietary alkalization<br>• Potassium depletion: Potassium supplementation<br>• Dehydration: Oral rehydration/parenteral fluid therapy<br>• Anemia: Recombinant erythropoietin<br>• Calorie malnutrition: Appetite stimulants, dietary variety, feeding tube placement |

*ACE = angiotensin-converting enzyme; FNA = fine-needle aspiration; LSA = lymphosarcoma; UTI = urinary tract infection*

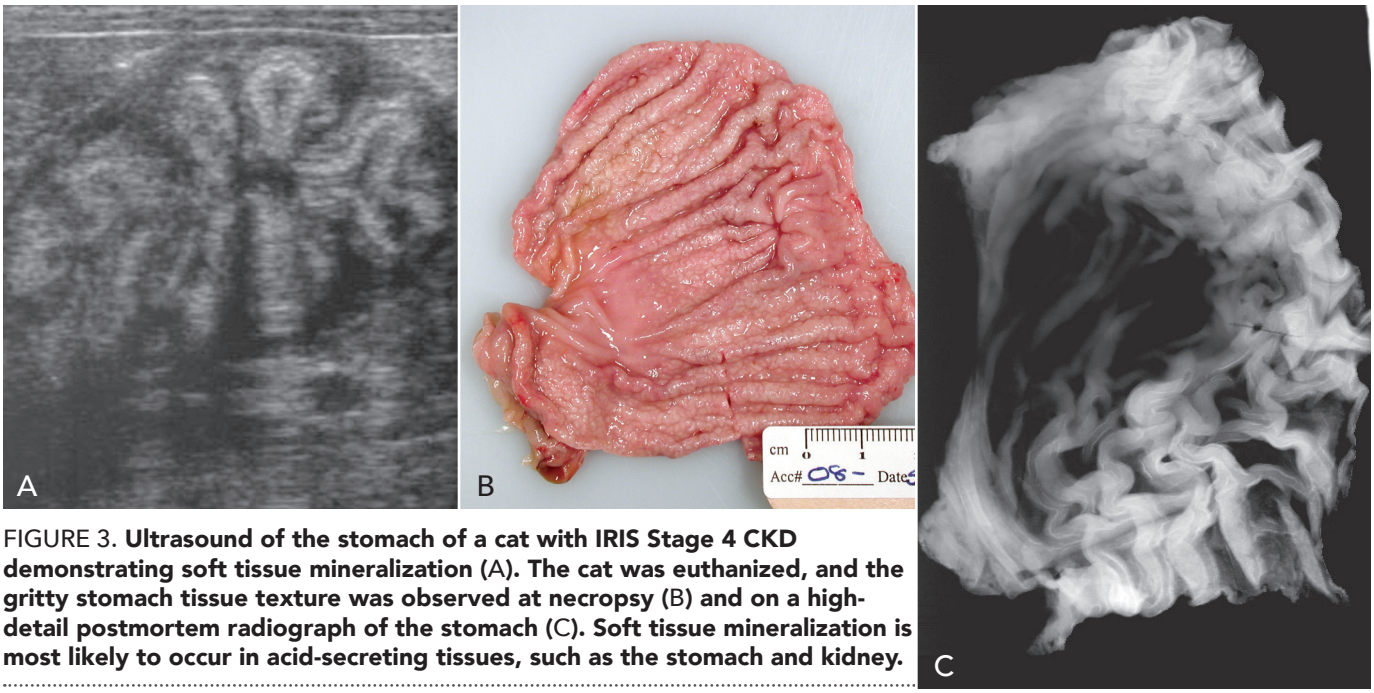


FIGURE 3. **Ultrasound of the stomach of a cat with IRIS Stage 4 CKD demonstrating soft tissue mineralization (A). The cat was euthanized, and the gritty stomach tissue texture was observed at necropsy (B) and on a high-detail postmortem radiograph of the stomach (C). Soft tissue mineralization is most likely to occur in acid-secreting tissues, such as the stomach and kidney.**

the therapeutic approach should be tailored to the patient's disease stage (**Table 5**, page 39).

For example, in the earlier stages of CKD, disease-specific treatments for nephroliths and bacterial pyelonephritis, as well as treatments designed to slow the progression of renal disease (*renoprotective treatments*), provide the most value. Renoprotective treatments include dietary change that reduces serum phosphorous concentrations[9] and decreases soft tissue mineralization (**Figure 3**).

Proteinuria is an important risk factor for the development and progression of azotemia and for decreased survival in cats.[10-13] Angiotensin-converting enzyme inhibitors and calcium-channel blockers are used to reduce proteinuria and normalize systemic and intraglomerular blood pressure.[14-16]

In later stages of CKD, treatment tends to focus on limiting clinical signs associated with decreased renal function.

## ACUTE DECOMPENSATION OF CKD

The cause of acute-on-chronic decompensation usually falls into 1 of 3 categories (**Table 6**):

1. **Prerenal:** Most common prerenal causes are dehydration/hypovolemia and decreased renal perfusion; decreased renal perfusion can also be associated with decreased cardiac output and thromboembolic disorders
2. **Renal:** Renal causes include ascending urinary tract infections (ie, pyelonephritis that may or may not be associated with nephroliths), renal neoplasia, and precipitous progression of underlying renal disease (rare)
3. **Postrenal:** Postrenal causes include obstructive uropathies—most commonly a nephrolith that migrates into a ureter (less commonly inflammatory debris or stricture), resulting in partial or complete obstruction

## PROGNOSIS

In a recent retrospective study, survival times were linked to the IRIS CKD staging system (**Table 7**).[17] In Table 7, IRIS CKD Stage 2 was modified to Stage 2b, which included only cats with stable serum creatinine concentrations between 2.3 and 2.8 mg/dL. This change was made because the high end of the normal reference range for serum creatinine at the study center was 2.3 mg/dL; in other

TABLE 6.
**Common Causes of Acute Uremic Crisis in Cats with Previously Stable CKD**

| CAUSE OF ACUTE UREMIC CRISIS | DIAGNOSTIC APPROACH |
|---|---|
| **Ascending infection resulting in pyelonephritis** | Urine cultures, pyelocentesis |
| **Hypertensive crisis** | Indirect measurement of systolic blood pressure |
| **Primary disease progression** | Diagnosis of exclusion |
| **Obstructive uropathy** | Imaging with/without contrast studies |
| **Prerenal dehydration/hypovolemia** | Response to fluid therapy |
| **Renal neoplasia** | Ultrasonography with/without fine-needle aspiration with cytology |

TABLE 7.
**Survival Data From 211 Cats Based on IRIS CKD Stages[17]**

| STAGE AT BASELINE[a] | NUMBER OF PATIENTS | MEDIAN SURVIVAL (range of days)[b] |
|---|---|---|
| **Stage 2b** (2.3–2.8 mg/dL) | 82 (39.4%) | 1151 (1014–1565) |
| **Stage 3** (2.9–5 mg/dL) | 84 (40.3%) | 679 (445–910) |
| **Stage 4** (> 5 mg/dL) | 42 (20.2%) | 35 (21–99) |

*a. Serum creatinine concentration in parentheses*
*b. 95% confidence interval*

words, the investigators had no way to retrospectively identify cats with serum creatinine concentrations between 1.6 and 2.3 mg/dL. The remainder of the staging system used in this study correlated with standard IRIS stages.

Notice the stepwise decline in survival as CKD stage increases: 1151 days for Stage 2b cats (which would be higher if all stage 2 cats had been included) versus 679 days for Stage 3 cats and 35 days for Stage 4 cats. This trend is not surprising, but the actual numbers facilitate better prognostication and emphasize early diagnosis.

CKD = chronic kidney disease; GFR = glomerular filtration rate; IRIS = International Renal Interest Society; SDMA = serum symmetric dimethylarginine; USG = urine specific gravity

## References


1. Brown SA. Linking treatment to staging in chronic kidney disease. In August JR (ed): *Consultations in Feline Internal Medicine*. St. Louis: Elsevier Saunders, 2010, pp 475-482.
2. Polzin DJ, Osborne CA, Adams LG, Lulich JP. Medical management of feline chronic renal failure. In Kirk RW, Bonagura JD (eds): *Kirk's Current Veterinary Therapy XI*. Philadelphia: Saunders, 1992, pp 848-853.
3. Ross SJ, Polzin DJ, Osborne CA. Clinical progression of early chronic renal failure and implications for management. In August JR (ed): *Consultations in Feline Internal Medicine*. St Louis: Elsevier Saunders, 2005, pp 389-398.
4. Lulich JP, Osborne CA, O'Brien TD, et al. Feline renal failure: Questions, answers, questions. *Compend Cont Educ Pract Vet* 1992; 14:127-153.
5. White JD, Norris JM, Baral RM, et al. Naturally-occurring chronic renal disease in Australian cats: A prospective study of 184 cases. *Aust Vet J* 2006; 84:188-194.
6. DiBartola SP, Rutgers HC, Zack PM, Tarr MJ. Clinicopathologic findings associated with chronic renal disease in cats: 74 cases (1973-1984). *JAVMA* 1987; 190:1196-1202.
7. Lees GE, Brown SA, Elliott J, et al. Assessment and management of proteinuria in dogs and cats; 2004 ACVIM forum consensus statement (small animal). *J Vet Intern Med* 2005; 19:377-385.
8. Hall JE, Yerramilli M, Obare E, et al. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Intern Med* 2014; 28:1676-1683.
9. Polzin DJ, Osborne CA, Ross S, et al. Dietary management of feline chronic renal failure. Where are we now? In what direction are we headed? *J Feline Med Surg* 2000; 2:75-82.
10. Chakrabarti S, Syme HM, Elliott J. Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. *J Vet Intern Med* 2012; 26:275-281.
11. Jepson R, Brodbelt D, Vallance C, et al. Evaluation of predictors of the development of azotemia in cats. *J Vet Intern Med* 2009; 23:806-813.
12. Syme HM, Markwell PJ, Pfeiffer D, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. *J Vet Intern Med* 2006; 20:528-535.
13. King JN, Tasker S, Gunn-Moore DA, Strehlau G. Prognostic factors in cats with chronic kidney disease. *J Vet Intern Med* 2007; 21:906-916.
14. King JN, Gunn-Moore DA, Tasker S, et al. Tolerability and efficacy of benazepril in cats with chronic kidney disease. *J Vet Intern Med* 2006; 20:1054-1064.
15. Mizutani H, Koyama H, Watanabe T, et al. Evaluation of the clinical efficacy of benazepril in the treatment of chronic renal insufficiency in cats. *J Vet Intern Med* 2006; 20:1074-1079.
16. Jepson RE, Elliott J, Brodbelt D, Syme HM. Effect of control of systolic blood pressure on survival in cats with systemic hypertension. *J Vet Intern Med* 2007; 21:402-409.
17. Boyd LM, Langston C, Thompson K, et al. Survival in cats with naturally occurring chronic kidney disease (2000-2002). *J Vet Intern Med* 2008; 22:1111-1117.



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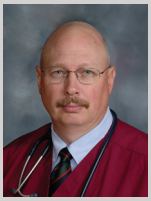

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