Ace Inhibitors and CKD: The Good, Bad, and Ugly
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By altering pre-glomerular resistance, healthy kidneys can maintain relatively stable glomerular capillary pressures despite variations in systemic blood pressure. This pressure regulatory process is termed “renal autoregulation”. Autoregulation can be reduced when renal disease results in loss of nephrons. Compromised autoregulation allows high systemic blood pressure to be transmitted to glomerular capillaries. This glomerular hypertension has been documented by micropuncture studies in dogs and cats with surgically reduced renal mass. In these models, glomerular hypertension was associated with glomerular hypertrophy and sclerosis and proteinuria. Systemic hypertension is relatively common in dogs and cats with renal disease. In a recent study of dogs with spontaneous chronic kidney disease (CKD), 29/45 (64%) had systolic blood pressure ≥ 144 mm Hg and 14/45 (31%) had systolic blood pressure ≥ 161 mm Hg. In cats with naturally-occurring CKD, systemic hypertension has been observed in 19-65% of cases depending on the definition of hypertension.

Renal proteinuria can result from glomerular and/or tubular abnormalities in dogs and cats with CKD. Glomerular proteinuria may arise from immune complex disease or structural abnormalities involving the glomerular capillary wall (more common in dogs e.g., amyloidosis and x-linked hereditary nephropathy). Protein-losing nephropathy caused by glomerular capillary wall lesions is often accompanied by systemic hypertension and glomerular proteinuria can be exacerbated by intraglomerular glomerular hypertension that can result from systemic hypertension. Tubular proteinuria occurs when tubular reabsorption of protein from the glomerular filtrate is compromised. Whether caused by capillary wall lesions, tubular lesions, or intraglomerular hypertension, excessive quantities of protein in the glomerular filtrate may contribute to additional glomerular and tubulointerstitial lesions leading to loss of more nephrons. Indirect systolic blood pressure greater than 160 mmHg is often listed as the threshold for systemic hypertension in dogs and cats.

Hypertension
Systemic hypertension in animals has largely been thought to be secondary to another disease (e.g., renal disease and endocrinopathies), as opposed to idiopathic (primary or essential). This has recently been called into question. For example, in a report of 69 hypertensive cats, seen at North Carolina State University for ocular disease, revealed that at least 17%, and possibly as many as 50%, of cats had no identifiable cause for their systemic hypertension. Elliott and associates at the Royal Veterinary College in London have documented that approximately 20% of hypertensive cats, diagnosed in primary-care practices, were idiopathic. Another retrospective study, which used very strict criteria for the diagnosis of primary (essential, idiopathic) hypertension, revealed a prevalence of 11% in cats.

Described and potential etiologies of secondary hypertension include acute and chronic renal disease, hyperthyroidism, hypothyroidism, hyperadrenocorticism, hyperaldosteronism, pheochromocytoma, diabetes mellitus, and obesity. Chronic kidney disease has the greatest association with hypertension and may often be causal. A recent report suggested approximately 29% of elderly cats with CKD were hypertensive, with the range reported in 4 studies being 19-65%. In dogs with CKD, approximately one-third will be normotensive, one-third will have borderline hypertension, and one-third will be hypertensive.

Systemic hypertension may contribute to progressive nephron loss by causing irreversible glomerular damage via increased intraglomerular pressures and glomerulosclerosis. By altering pre-glomerular resistance, healthy kidneys can maintain relatively static glomerular capillary pressures despite variations in systemic blood pressure via autoregulation. Inappropriate dilation of the afferent glomerular arteriole occurs in dogs and cats with CKD and diminishes the ability of the afferent arteriole to protect the glomerulus from variations in systemic blood pressure. Although the exact mechanism of the CKD-associated hypertension is not known, a combination of glomerular capillary and arteriolar scarring, decreased production of renal vasodilatory prostaglandins, increased responsiveness to normal pressor mechanisms, and activation of the renin-angiotensin-aldosterone system (RAAS) may be involved. The increased renin secretion leads to increased production of angiotensin II and aldosterone. In addition to its direct pressor effects, angiotensin II also has a stimulatory effect on the sympathetic nervous system, increasing vascular tone, and, in CKD, constrictor effect of the efferent arteriole which further contributes to the intraglomerular hypertension. Finally, angiotensin and aldosterone may also stimulate renal tissue remodeling via increased matrix production and fibrosis.

The consequences of systemic hypertension are usually dependent on the magnitude and duration of the blood pressure elevations. Acute ocular and central nervous system abnormalities can occur associated with hemorrhage or edema formation. Renal damage associated with hypertension tends to be more chronic and characterized by glomerular lesions (e.g., glomerulosclerosis) and proteinuria. Finally, functional/adaptive changes like ventricular hypertrophy can occur due to increased after-load in patients with
hypertension. Diagnosis and treatment of hypertension in dogs and cats with CKD may prevent development of retinal and CNS lesions or may limit or slow progression of renal and cardiac lesions.

Proteinuria
Renal proteinuria is a diagnostic marker of the severity of renal disease and potentially a mediator of glomerular and tubular injury. Recent findings have demonstrated that proteinuria is associated with increased risk of developing azotemia in aged cats and progression of renal disease in both dogs and cats with azotemic CKD. In addition, studies have shown that therapies that reduce the magnitude of proteinuria may be renoprotective. Proteinuric renal disease is often associated with systemic hypertension, which can conversely exacerbate renal proteinuria and therefore, it is difficult at times to separate the effects of high systemic and intraglomerular pressures and proteinuria.

Management
Indications for the use of ACEI in dogs and cats with CKD include hypertension and/or proteinuria. The initial recommended dose for ACEI is: 0.5 mg/kg PO once daily. Treatment goals are an indirect blood pressure < 160 mm Hg and/or ≥ 50% reduction in baseline UP/C. The initial ACEI dose can be doubled if the desired outcome is not achieved. Doses greater than 0.5 mg/kg twice daily may result in further reductions in proteinuria; however there are no controlled studies proving these higher doses are beneficial. Questions often arise regarding the use of Benazepril vs. Enalapril. Most of the canine studies have been accomplished with enalapril whereas most of the feline studies have used benazepril. There are differences in excretion; enalaprilat (the active metabolite of enalapril) is excreted via the kidney whereas there is hepatic metabolism of benazeprilat. Use of ACEI is likely associated with reduced efficacy and increased risk of adverse drug events as azotemia increases. Increased monitoring should be employed in dogs and cats with serum creatinine concentrations greater than 3.0 mg/dl. Use of ACEI in dogs and cats with serum creatinine concentrations greater than 5.0 mg/dl is usually not recommended. In addition, use of renal diets with reduced quantity/high quality protein may have an additive effect on proteinuria when used with ACEI (Burkholder WJ, et al, J Vet Intern Med 2004; 18:165 and Cortadellas O, et al, ACVIM Proceedings 2012).

Gradual reduction of dietary salt is often recommended as the first line of treatment for hypertension; however there are no studies that document the efficacy of this treatment. The calcium channel antagonist (CCA), amlodipine is often recommended as the first choice anti-hypertensive treatment for cats. Recent studies have shown that treatment with a CCA alone reduces proteinuria in cats with CKD suggesting that intraglomerular pressures were also reduced by this treatment (see # 8 above). In those cases where systemic hypertension persists after initiation of ACEI treatment, or is initially greater than 180 mm Hg, a CCA can be added. The overall risk of target organ damage to the eyes, brain, heart, and kidneys is thought to be minimal if systolic blood pressure is maintained at ≤ 150 mm Hg.

What evidence exists that ACEI are beneficial in dogs and cats with CKD (the good)?

ACEI are not always effective in modulating proteinuria and hypertension (the bad)
Unfortunately, ACEI treatment is not always effective in reducing hypertension and/or proteinuria. It’s well known that CCA (vs. ACEI) are usually more effective in reducing systemic hypertension in cats compared with dogs. In some cases renal proteinuria may initially respond to treatment with an ACEI and then “escape”. This escape may be associated with up-regulation of alternative pathways for production of angiotensin II. For example, elastase and cathepsin G may directly convert angiotensinogen to angiotensin II. In other cases, renal proteinuria may fail to respond to even the initial ACEI treatment. Potential reasons for this lack of efficacy may involve dosing (i.e., suboptimal doses) or advanced renal disease. Very few of our patients with proteinuric CKD undergo a
thorough histologic evaluation. Dogs and cats with advanced histologic disease may be less likely to be responsive to any pharmacologic influence. Similarly, there may be certain structural pathologies that are more likely to be responsive than others. Histologic correlation with response to ACEI treatment has not been evaluated.

In those cases where there is a poor response to treatment (i.e., less than 50% reduction in baseline UP/C), the use of angiotensin receptor blockers (ARB) (either alone or in combination with ACEI) has been recommended. A recent meta-analysis on the effects of mono-therapy and combination therapy with inhibitors of the renin–angiotensin system compared the efficacy of ARB and ACEI in people with proteinuric renal disease. Forty-nine studies involving 6181 participants reviewed randomized trials of ARB versus placebo, ACEI, or the combination of ARB and ACEI in patients with microalbuminuria or proteinuria for whom data were available on urinary protein excretion at baseline and at 1 to 12 months. The conclusions were the reduction in proteinuria from ARB and ACEI is similar, but their combination is more effective than either drug alone. However, the authors stated that the uncertainty about adverse effects and outcomes that are important to patients limits applicability of these findings to clinical practice (Kunz R, et al, Ann Intern Med. 2008; 148:30). There are no studies in veterinary medicine evaluating the safety and efficacy of ARB (alone or in combination with ACEI) for the treatment of proteinuric renal disease.

**ACEI treatment may be associated with worsened azotemia in CKD (the ugly)**
In some cases treatment of proteinuric renal disease with ACEI is associated with worsening azotemia. Fortunately, this adverse event is relatively rare. Most adverse effects occur in dogs with congestive heart failure (CHF) and the relative contributions of the ACEI vs. decreased cardiac output and Lasix therapy on renal function are unknown. It should be noted however that ACEI treatment of CHF have relatively few adverse effects on kidney function (The COVE study, J Vet Intern Med 1995; 9:243 and Atkins CE, et al, J Am Vet Med Assoc 2002; 221:1149). Adverse effects on renal excretory function would be expected to be more commonplace as azotemia increases. Increased monitoring for worsening of azotemia is recommended in patients with baseline serum creatinine concentrations greater than 3.0 mg/dl; use of ACEI in dogs and cats with serum creatinine concentrations greater than 5.0 mg/dl is not recommended.
Chronic kidney disease (CKD) is a common problem that adversely affects both quality of life and survival time. Although the prevalence of CKD in the general small animal population is ill defined, CKD may affect up to 10% of dogs and 35% of cats in referral hospital populations (Polzin and Osborne 1986; Krawiec and Gelberg, 1989). Nephron damage associated with CKD is usually irreversible and can be progressive. Renal failure results when three-quarters or more of the nephrons of both kidneys are not functioning. Whether the underlying CKD primarily affects glomeruli, tubules, interstitial tissue, or renal vasculature, irreversible damage to any portion of the nephron renders the entire nephron nonfunctional. Healing of irreversibly damaged nephrons occurs by replacement fibrosis and therefore a specific etiology is often not determined. Chronic kidney disease occurs over a period of weeks, months, or years and since it is often not possible to improve renal function in CKD, treatment is aimed at stabilizing renal function. In addition to dietary therapy, there is increasing evidence that treatment with ACE inhibitors can decrease the progressive nature of CKD by attenuating systemic hypertension, intraglomerular hypertension, and proteinuria.

By altering pre-glomerular resistance, healthy kidneys can maintain relatively stable glomerular capillary pressures despite variations in systemic blood pressure. This pressure regulatory process is termed “renal autoregulation”. Autoregulation can be reduced when renal disease results in loss of nephrons. Compromised autoregulation allows high systemic blood pressure to be transmitted to glomerular capillaries. This glomerular hypertension has been documented by micropuncture studies in dogs and cats with surgically reduced renal mass. In these models, glomerular hypertension was associated with glomerular hypertrophy, sclerosis, and proteinuria. Systemic hypertension is relatively common in dogs with renal disease. In a recent study of dogs with spontaneous chronic kidney disease (CKD), 29/45 (64%) had systolic blood pressure $\geq$ 144 mm Hg and 14/45 (31%) had systolic blood pressure $\geq$ 161 mm Hg. In cats with naturally-occurring CKD, systemic hypertension has been observed in 19-65% of cases depending on the definition of hypertension.

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Diagnosis of hypertension and proteinuria

Current recommendations are that blood pressure be measured in a quiet area prior to examining the patient, typically in the presence of the owner and after a 5-10 minute period of acclimation. The ACVIM Panel on Hypertension suggests discarding the first measurement, then obtaining a minimum of 3, preferably 5-7, consecutive measurements with less than 10-20% variability in systolic blood pressure. The animal’s disposition, body position, and heart rate, the cuff size and measurement site as well as all measurable variables should be recorded in the medical record. Many clinicians suggest that hypertension be documented on more than one occasion before accepting the diagnosis (unless ocular lesions compatible with systemic hypertension already exist).

Diagnosis and management of proteinuria in cats and dogs with CKD should be accomplished in a step-wise fashion. The specificity of the dipstick screening test for proteinuria is poor and therefore confirmation of traditional dipstick positive proteinuria should be accomplished with a more specific follow-up test such as the sulfosalicylic acid (SSA) turbidimetric test, UP/C, or species specific albuminuria assay. The second step is assessment of proteinuria is to determine its origin. Renal proteinuria can adversely affect the prognosis of dogs and cats with CKD and therefore, physiologic or benign proteinuria and pre- and post-renal proteinuria should be ruled out. Subsequently, via serial monitoring, it should be determined if the proteinuria is persistent or transient and if persistent – is the magnitude stable or increasing or decreasing over time? Persistent proteinuria is defined as at least two positive tests at two week intervals. Relatively mild proteinuria in dogs and cats with spontaneous/naturally-occurring CKD appears to be a negative predictor of survival. In dogs and cats with the remnant kidney model of CKD, proteinuria is associated with nephron hypertrophy and increased intraglomerular pressures. Persistent proteinuria of renal origin of a magnitude $\geq$ UP/C of 0.4 in cats and $\geq$ 0.5 in dogs with azotemic CKD should be treated with an ACEI and/or dietary protein reduction. Borderline proteinuria is defined as a UP/C between 0.2 and 0.5 in dogs and 0.2 and 0.4 in cats.
What evidence exists that systemic hypertension and/or proteinuria are detrimental to canine and feline kidneys?


In dogs with naturally occurring CKD, the relative risk of uremic crises and mortality was approximately three time greater in dogs with UP/C's > 1.0 (n=25) compared with dogs with UP/C's < 1.0 (n=20). In this study the risk of an adverse outcome was approximately 1.5 times greater for every 1 unit increase in UP/C and the decline in renal function was greater in dogs with higher UP/C's. Jacob F, et al. Am J Vet Res 2005;226:393.

In cats with naturally occurring CKD, relatively mild proteinuria (UP/C's > 0.4) appear to be negative predictors of survival. Increasing proteinuria was associated with increasing serum creatinine concentrations and increasing systolic blood pressure (presumably related to glomerular hyperfiltration). UP/C, age, and serum creatinine concentration (but not blood pressure) were independently associated with mortality. Syme HM, et al. J Vet Intern Med 2006;20:528.

Proteinuria has been associated with increased risk of mortality due to all causes in cats that have normal renal function when their proteinuria is first detected. Walker D, et al. J Vet Intern Med 2004;18:417.

In 141 client-owned cats with naturally-occurring systemic hypertension, amlodipine treatment decreased both blood pressure and proteinuria. Proteinuria (UP/C) (before and after treatment as well as the change in UP/C) was the only variable related to survival in these cats. Jepson RE, et al. J Vet Intern Med 2007;21:402.


In a prospective, longitudinal cohort study of non-azotemic cats ≥ 9 years, 95 cats (median age = 13) were followed for 12 months or until death or azotemia developed. 29/95 (30.5%) developed azotemia (Sr Cr > 2.0 mg/dl). Proteinuria at presentation (median UP/C of 0.19 vs. 0.14) was significantly associated with development of azotemia. Jepson RE, et al. JVIM 2009; 23:806-813.

In cats with the remnant kidney model of CKD, hypertension was associated with more severe glomerular histologic lesions. Mathur, et al, AJVR 2004;65:1006-1013.

In 59 cats with CKD (serum creatinine concentrations > 2.0 mg/dl, USG < 1.035, and history and clinical signs compatible with CKD vs. AKI) with postmortem data and biochemistry and urine protein data (obtained during the last 2 months of life) the UP/C was positively correlated with both renal interstitial fibrosis score and maximal glomerular volume. 34 of the 59 cats (58%) were classified as proteinuric. Chakrabarti, et al. Diagnostic Pathol 2013;50:147-155.

When cats with CKD surviving for more than one month (surviving group, n = 34) were compared with cats with CKD surviving less than one month (non-surviving group, n = 16), UP/C was significantly higher in the non-surviving group. In the surviving group, UP/C was the only clinicopathologic variable that exhibited a consistent alteration (increase) in relation to first visit data and was most likely to be associated with mortality. Kuwahara, et al. J Small Anim Pract 2006;47:446-450.

When client-owned cats with stable CKD (n=112) were compared with client-owned cats with progressive CKD (n=101), median UP/Cs in the progressive group were higher than the stable group (0.27 vs. 0.14). A 0.1 increase in UP/C was associated with a 24% increase in risk of progression of CKD. Chakrabarti, et al. J Vet Intern Med 2012; 26:275-281.
In 69 cats with CKD (serum creatinine concentrations > 2.0 mg/dl, USG < 1.035, and history and clinical signs compatible with CKD vs. AKI) with postmortem data and time-averaged systolic blood pressure (SBPOT) (obtained over a mean of 284 days) the SBPOT was positively correlated with maximal glomerular volume, hyperplastic arteriolosclerosis, and glomerulosclerosis. 34 of the 69 cats (49%) were classified as hypertensive (SBPOT of 159 mm Hg vs 136 mm Hg in normotensive cats). Chakrabarti, et al. *Diagnostic Pathol* 2013;50:147-155.

Hyperthyroidism is one of the most commonly diagnosed diseases of the older cat. Geriatric cats with hyperthyroidism may also have concurrent chronic kidney disease (CKD). Systemic hypertension, proteinuria, and urinary tract infection (UTI) can be consequences of either hyperthyroidism or CKD. Hyperthyroidism can increase glomerular filtration rate (GFR) in cats with CKD which can attenuate or resolve mild to moderate azotemia. In addition, serum creatinine may be decreased in cats with weight loss and decreased muscle mass. In both cases, reductions in BUN and serum creatinine concentrations make it more difficult to detect concurrent CKD. Conversely, the CKD may depress thyroid hormone concentrations (euthyroid sick syndrome) making it more difficult to diagnose hyperthyroidism. Initial treatment of hyperthyroid cats with azotemic CKD should ideally be accomplished with a reversible anti-thyroid medication in order to assess any adverse effects on renal function. Systolic blood pressure and urine protein creatinine ratio (UP/C) should be evaluated prior to and after treatment. Urine cultures should be obtained as part of the workup of both hyperthyroidism and CKD. In either case, a concurrent UTI should be managed as a complicated UTI with long-term antibiotic treatment based on culture and sensitivity results.

Clinical signs/physical examination

Classic clinical signs of hyperthyroidism include weight loss, polyuria/polydipsia (PU/PD), and polyphagia in an older cat. Fewer than 5% of cats with hyperthyroidism are less than 8 years of age; the average age at diagnosis is 12-13 years. A thyroid enlargement (thyroid slip) can often be palpated in hyperthyroid cats, although some euthyroid cats will also have enlargement of one or both glands. In cats with concurrent CKD, kidneys may be small and/or irregular. Approximately 50% of cats with hyperthyroidism will exhibit PU/PD. A primary polyuria may occur as a result of thyrotoxicosis increasing cardiac output and GFR as well as increased renal medullary blood flow which has the potential to decrease renal medullary hypertonicity and urine concentrating ability. Some cats with hyperthyroidism may also have a primary polydipsia secondary to the effects of high thyroid hormone concentrations on the thirst center. Regardless of the mechanism, decreased urine specific gravity makes interpretation of azotemia problematic (is it pre-renal azotemia superimposed on decreased concentrating ability or renal azotemia?). Systemic hypertension is another common finding in hyperthyroid cats. High blood pressure may be caused by increased cardiac output, sympathetic tone, and arteriolar resistance and if sustained, can lead to intraglomerular hypertension, glomerulosclerosis, and proteinuria. No matter what the underlying cause, hypertension can damage the eyes, brain, heart, and kidney of affected cats. For example, tachycardia murmurs, and gallop rhythms may be associated with hypertrophic cardiomyopathy. Similarly, whether proteinuria arises from hypertension or CKD, progressive renal disease is a potential consequence.

Increased practitioner awareness of hyperthyroidism, an increasing population of geriatric cats, and increased diagnostic testing of older cats (wellness exams) has resulted in earlier diagnosis of hyperthyroidism in many cases. Clinical signs in these cases may be more subtle compared with an advanced case of hyperthyroidism. With earlier diagnosis, weight loss may be present but emaciation will be less likely and body condition scores will be higher. Similarly, PU/PD is less likely to be observed by owners and appetite and activity levels may be only slightly increased in cats with early hyperthyroidism.

Clinicopathologic findings associated with hyperthyroidism may include a slight erythrocytosis; perhaps secondary to increased tissue oxygen consumption. Serum ALT is increased in approximately 75-90% of cats with hyperthyroidism and is thought to be associated with malnutrition, hepatic hypoxia, and/or toxic effects for thyroid hormone on hepatocytes. Azotemia is observed in approximately 25% of hyperthyroid cats and may be due to dehydration, increased protein turnover (BUN), and/or CKD. Concurrently, urine specific gravity is often decreased as discussed previously.

Diagnosis

The best screening test for the diagnosis of hyperthyroidism is the total T₄ (TT₄) concentration. An increased TT₄ is specific for hyperthyroidism however false negative results may occur with non-thyroidal illness (e.g., CKD). In cats with compatible clinical signs of hyperthyroidism that have a TT₄ in the normal range, repeating the test in two weeks is usually the first recommendation. If results are still in the normal range on the second test, a free T₄ (fT₄) (measured by equilibrium dialysis) may be assessed. In comparison to the TT₄, the fT₄ is more sensitive but may result in more false positive results. A low normal TT₄ with a high fT₄ is more suggestive of non-thyroidal illness, whereas and high normal TT₄ with an increased fT₄ suggest hyperthyroidism (especially with compatible clinical signs). Rarely a T₃ suppression test may be employed to help confirm a diagnosis. Nuclear scintigraphy compares
the uptake of technetium-99m by the thyroid to the salivary glands (a normal thyroid to salivary gland ratio is approximately 1:1). Nuclear scintigraphy is both sensitive and specific and it is considered the gold standard diagnostic test.

**Pre-treatment evaluation**

Several studies have demonstrated that GFR declines with treatment for hyperthyroidism; this decline is independent of the treatment modality (medical, surgical, radioactive iodine). This decrease in GFR should be considered a consequence of the resolution of the hyperthyroid state and not a side effect of the treatment itself. The potential for a decrease in GFR to adversely affect the patient’s quality of life suggests that a thorough pre-treatment evaluation of the heart (potential pre-renal effects) and kidneys is important. The goal is to identify patients that may be harmed by permanent treatment of their hyperthyroidism.

Thoracic radiographs to assess the cardiac silhouette should be performed to rule out cardiomyopathy (especially in cases with a murmur or gallop rhythm). Any changes in the cardiac silhouette should be further evaluated with echocardiography. A baseline blood pressure should be determined and a complete minimum database (CBC, serum biochemistry profile, UA) obtained. Although it is thought to be a better positive prognostic indicator than minimally concentrated urine, hypersthenuric urine specific gravity (>1.035-1.040) prior to treatment does not guarantee adequate renal function post-treatment. Combining urine specific gravity and TT4 concentration was helpful in predicting post-treatment azotemia in one study (USG < 1.035 and TT4 > 7.8 µg/dL together were poor prognostic indicators). The urine dipstick and sulfosalicylic acid assays are unreliable screening tests for proteinuria in cats and therefore a feline specific albuminuria assay and/or a urine protein/creatinine ratio (UP/C) should be utilized to quantitate proteinuria/albinuricuria. Persistent proteinuria of renal origin is a poor prognostic indicator for progression of CKD in cats; however pre-treatment proteinuria does not appear to be predictive of post-treatment azotemia in hyperthyroid cats. Urinary excretion of NAG was also not predictive of post-treatment azotemia in hyperthyroid cats. Urine cultures are recommended in all cases but are required in cats with pyuria and/or hematuria; UTI occurs in 12-22% of hyperthyroid cats and 13-30% of CKD cats and with both underlying diseases, the infection is often clinically silent. Pre-treatment GFR measurement may be a useful predictor of post-treatment renal function. Although exceptions exist, pre-treatment GFR values > 2.25-2.5 ml/min/kg body weight are thought to predict adequate post-treatment renal function. Finally in cats with suspected CKD, renal imaging with ultrasound and/or radiographs is recommended to further assess kidney tissue architecture and help rule out ascending infections, uroliths, and renal infiltrative disease. In cats that have obvious CKD and/or severe hypertension (> 180 mmHg), these issues should be addressed prior to treatment of the hyperthyroidism.

**Effects of treatment of hyperthyroidism on renal function**

Regardless of the modality utilized (thyroidectomy, methimazole, 131I), successful treatment of hyperthyroidism decreases renal excretory function, resulting in an increase in the serum creatinine concentration and a decrease in the GFR. The major changes in serum creatinine concentration and GFR occur within the first month post-treatment and then renal function tends to stabilize. Although renal function tends to stabilize after 30 days, it is advisable for clinicians to monitor serum creatinine concentration for at least 6 months after the cat has become euthyroid. Importantly, it has been shown that cats that develop post-treatment azotemia do not have decreased survival times compared with hyperthyroid-treated cats that remain nonazotemic. However, cats with azotemia prior to initiation of treatment for hyperthyroidism appear to have decreased survival compared with cats that become azotemic following treatment.

**Effects of hypothyroidism on renal function**

Just as hyperthyroidism tends to increase renal function, hypothyroidism tends to decrease renal function. Diminished GFR could have significant consequences for hyperthyroid cats with preexisting renal disease that become hypothyroid as a result of treatment. Cats with iatrogenic hypothyroidism are not only more likely to develop azotemia, but hypothyroid cats with azotemia also have decreased survival. Supplementing cats with iatrogenic hypothyroidism secondary to 131I with thyroid hormone, or reducing the dosage of anti-thyroid medication, to achieve a euthyroid state, may improve renal function. Identifying and treating cats with iatrogenic hypothyroidism therefore is important. Inasmuch as hypothyroidism may not occur for as long as 3-6 months after radiiodine treatment, monitoring total T4 for at least 6 months post-treatment should be accomplished. A low total T4 concentration alone is not sufficient for diagnosis of iatrogenic hypothyroidism because euthyroid sick syndrome may be present. The combination of reduced total T4 concentration and elevated TSH concentration is consistent with iatrogenic hypothyroidism and thyroxine supplementation or adjustment of antithyroid medication should be considered.

**Summary**

Successful treatment of hyperthyroidism has the potential to unmask pre-existing CKD, but the associated changes in renal function are usually mild and renal function largely stabilizes within 1-2 months of the hyperthyroid treatment. Overall survival of those cats
that do become azotemic does not differ from non-azotemic cats. Therefore, treatment of hyperthyroidism is recommended with the target total T4 in the lower half of the reference interval, without creating hypothyroidism. Increases in serum creatinine concentrations may occur over several months post-treatment (due to decreases in GFR and increases in muscle mass), so monitoring renal function for 6 months following restoration of euthyroidism is recommended. When treating cats with evidence of CKD prior to treatment, the decreased survival times associated with pre-therapy CKD should be discussed with owners, and continued monitoring of renal function for months following return euthyroidism is necessary. Due to the increased risk of azotemia and poor prognosis in cats with iatrogenic hypothyroidism, total T4 (and TSH when appropriate) concentrations should be monitored for at least 6 months after euthyroidism is achieved, and iatrogenic hypothyroidism should be corrected via adjustment of anti-thyroid medication or thyroid supplementation if necessary.
Chronic kidney disease (CKD) is a common problem that affects an estimated 0.5 to 7% of dogs. Radiographic signs of osteoarthritis (OA) occur in 20% of dogs. The majority of OA and CKD are acquired and both conditions are more prevalent in older dogs. Use of non-steroidal anti-inflammatory drugs (NSAIDs) has dramatically improved the quality of life for many dogs with OA. The potential nephrotoxicity of NSAIDs however make their use problematic in dogs with CKD. Thorough evaluation of renal function prior to the use of NSAIDs and follow-up monitoring for any adverse effects on renal function is extremely important in the older dog. Newer evidence suggests that the cyclooxygenase (COX) II enzyme is important in maintaining renal blood flow (RBF) in dogs and therefore, COX II selective/specific NSAIDs at least have the potential to adversely affect renal function in dogs. In contrast, the hepatotoxicity associated with NSAIDs in dogs appears to idiosyncratic and unrelated the COX selectivity of the drug.

Potential nephrotoxicity of NSAIDs
Renal damage and disease can be caused by acute or chronic insults to the kidney. The terms renal disease and renal damage are used to denote the presence of renal lesions; these terms however imply nothing about renal function or the cause, distribution, or severity of the renal lesions. Acute kidney injury (AKI) often results from ischemic or toxic insults and usually affects the tubular portion of the nephron. Early detection of AKI facilitates appropriate intervention that can arrest or at least attenuate tubular cell damage and the development of established acute renal failure (ARF). In contrast, nephron damage associated with CKD is usually irreversible and can be progressive. Pre-existing CKD increases the risk of AKI associated with the use of potentially nephrotoxic drugs.

Renal prostaglandins help regulate RBF and glomerular filtration rate (GFR), renin release, and sodium excretion. Potential adverse effects of renal prostaglandin inhibition with NSAIDs can include decreased RBF and GFR, hypertension, salt retention and edema. Since both COX-1 and COX-2 enzymes are present/expressed in the canine kidney, any NSAID, regardless of its COX specificity or sparing properties, has the potential to produce adverse renal effects. In particular, dogs express higher basal levels of COX-2 in the kidney than some other species and may be uniquely sensitive to the nephrotoxic effects of COX-2 selective drugs. Although a number of studies have shown no adverse effects of the commonly used NSAIDs in dogs with normal kidneys, increased BUN and creatinine are common adverse events listed for NSAIDs at the FDA Adverse Drug Event website. Dogs in field trials of deracoxib and firocoxib had increased BUN at the end of the trials, while dogs treated with etodolac did not. In cases where RBF is decreased (e.g., dehydration and decreased cardiac output), the vasodilatory effects of renal prostaglandins are critical in the maintenance of renal perfusion and the potential for adverse effects associated with NSAID use is increased. There is also concern that patients treated with drugs that can decrease GFR (such as angiotension-converting enzyme (ACE) inhibitors) may have increased renal toxicity when treated with NSAIDs. Studies of elderly human patients have confirmed this effect, but in a study of normal dogs treated with enalapril and tepoxalin no alteration of GFR was noted.

Risk factors for acute kidney injury
Dehydration and volume depletion are perhaps the most common and most important risk factors for development of AKI/ARF. Hypovolemia not only decreases renal perfusion which can enhance ischemic damage, but also decreases the volume of distribution of potentially nephrotoxic drugs. In addition to hypovolemia, renal hypoperfusion may be caused by decreased cardiac output, decreased plasma oncotic pressure, increased blood viscosity, systemic hypotension, and decreased renal prostaglandin synthesis. Any of these conditions can increase the risk of AKI associated with the use of NSAIDs.

Pre-existing renal disease can increase the potential for nephrotoxicity and ischemic damage by several mechanisms. The pharmacokinetics of potentially nephrotoxic drugs can be altered in the face of decreased renal function. Animals with renal insufficiency also have reduced urine concentrating ability and, therefore, decreased ability to compensate for prerenal influences. Renal disease may also compromise the local production of prostaglandins that help maintain renal vasodilatation and blood flow. Age has been identified as a risk factor because many geriatric dogs have pre-existing renal lesions and sub-clinical loss of renal function.

Use of NSAIDs in dogs with chronic kidney disease
In dogs with pre-existing renal disease, the use of NSAIDs has the potential to exacerbate the renal disease and further decrease renal function and therefore NSAIDs should be avoided whenever possible in such animals. Hypertension and proteinuria associated with NSAID adverse effects may be increased in dogs with these complications. Certainly, the more advanced the stage of CKD, the greater the relative contraindication for the use of NSAIDs. It is
important to remember that as early as stage II, > than 75% of the patient’s nephrons are no longer functional and the patient’s ability to auto-regulate RBF is compromised.

Recommendations surrounding the use of NSAIDs in CKD patients are largely speculative, but practical suggestions include:
- Maintain good hydration in these patients at all times
- Increase the monitoring of these patients for early signs of AKI
- Increase the monitoring of these patients for hypertension.
- Use the lowest efficacious dose of a NSAID
- Use analgesic drugs with less renal toxicity in place of NSAIDs
- Monitor quality of life indices on a regular basis. In people, small stable increases in BUN and creatinine are often tolerated in rheumatoid and osteoarthritis patients on NSAIDs, because no other drugs maintain adequate quality of life.

**Early recognition of acute kidney injury**

Numerous urine parameters can herald the development of AKI in patients with initially normal renal function. The value of monitoring these parameters in CKD patients receiving NSAIDs has not been assessed. Increased urine turbidity or changes in urine sediment (increasing numbers of renal epithelial cells or cellular or granular casts) may be indications of AKI. The acute onset of tubular glucosuria (normoglycemic glucosuria) or the acute onset or increases in proteinuria may also be indicative of AKI. The interpretation of these urine parameters is enhanced by knowledge of baseline values.

Detection of enzymes in the urine such as gamma-glutamyl transpeptidase (GGT) and N-acetyl-beta-D-glucosaminidase (NAG) has proven to be a sensitive indicator of early AKI. These enzymes are too large to be normally filtered by the glomerulus, and, therefore, enzymuria indicates cell leakage, usually associated with tubular epithelial damage or necrosis. Urinary GGT originates from the proximal tubule brush border and NAG is present in proximal tubule lysosomes. In studies of gentamicin-treated dogs, increased urinary GGT and NAG activity was one of the earliest markers of renal damage/dysfunction. Interpretation of enzymuria is aided by baseline values obtained prior to a potential renal insult; 2 to 3-fold increases over baseline suggest significant tubular damage. Urine enzyme/creatinine ratios have been shown to be accurate in dogs prior to the onset of azotemia obviating the need for time urine collections.

**Potential hepatotoxicity of NSAIDs**

Hepatocellular toxicosis associated with administration of carprofen has been reported in a retrospective study of 21 dogs. The most common clinical signs were anorexia, vomiting, lethargy, and diarrhea. All of the dogs had elevations in serum ALT, 20 had elevations in serum ALP, and 18 were hyperbilirubinemic. The elevations in serum ALT were greater than the elevations in serum ALP in 16 dogs. Eighteen of the dogs had histologic evidence of hepatic necrosis characterized by multifocal to extensive vacuolar change, lytic necrosis, and apoptosis. It’s interesting to note that 7 of 9 dogs evaluated by urinalysis had changes ranging from mild to severe proteinuria, normoglycemic glucosuria, and/or renal epithelial cells and casts in the urine sediment. Four of the affected dogs died or were euthanized within 3-5 days of presentation. The authors speculated that an idiosyncratic hepatopathy that may have been caused by the interaction of glucuronide metabolites of the acidic NSAID with plasma and hepatocellular proteins; resulting in the formation of antigenic NSAID-altered proteins causing immune-mediated damage to the liver.

**Early recognition of hepatic damage**

NSAID-associated hepatotoxicity appears to be a sub-acute toxicity (within 2-3 weeks of initiation of treatment) and unrelated to the type (COX selectivity) of the NSAID. Baseline liver enzyme values should be established prior to treatment. Post-treatment, any anorexia, vomiting, lethargy, or diarrhea should prompt NSAID discontinuation and re-assessment of liver enzymes compared to baseline values. In dogs that remain clinically normal, reassessment of liver enzymes should be performed between 2-3 weeks after the NSAID treatment is started. If pre-treatment assessment reveals mild to moderate elevations in liver enzymes, pre- and post-prandial bile acid concentrations should be measured. Mild to moderate pre-treatment elevation in liver enzyme in the absence of liver dysfunction is probably not a risk factor for NSAID-associated hepatotoxicity. In dogs with reduced liver function (e.g., abnormal bile acids or hyperbilirubinemia), NSAIDs should be avoided, if at all possible.

Recommendations surrounding the use of NSAIDs in patients with decreased liver function are largely speculative, but practical suggestions include:
- Maintain good hydration in these patients at all times
- Increase the monitoring of these patients for early signs of hepatotoxicity
- Use the lowest efficacious dose of a NSAID/increasing the interval between doses
- Use alternative analgesic drugs in place of NSAIDs

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Almost all (99%) of the body’s calcium (Ca) is stored in crystalline form in bone along with phosphate (hydroxyapatite). Less than 1% of the body’s calcium is typically present in the extracellular fluid and this circulating Ca exists in three forms: 1) that which is bound to serum proteins; principally albumin (~ 40%), that which is complexed with anions like citrate, bicarbonate, phosphate, lactate, and sulfate (~ 10%), and that which is ionized or active (iCa) (~ 50%). The ionized and complexed forms of Ca are diffusible, whereas the protein bound fraction is not. The Ca values reported on standard laboratory serum biochemistry profiles reflect the total Ca concentration (tCa). Most of the day to day Ca homeostasis is balanced by dietary intake and loss through the gastrointestinal tract with the kidneys having a relatively minor role. For example, 90% of ingested Ca is usually excreted via the GI tract but if necessary, greater than 100% of dietary intake can be excreted via GI secretory fluids. Within the kidneys, normally Ca in the glomerular filtrate is highly conserved via tubular reabsorption by the proximal convoluted tubule cells. The ionized form of Ca accounts for most of the biologic activity of calcium (e.g., muscle contraction, neuromuscular transmission, vascular tone, and cellular membrane and transport functions) and this active form is highly regulated by parathyroid hormone, calcitriol, and calcitonin. When this homeostatic control is impaired, serum Ca concentrations may increase above the normal range resulting in hypercalcemia. Although the term “hypercalcemia” is often used in reference to increases in tCa, its use is best reserved for those instances when the iCa is increased.

**Parathyroid hormone (PTH)**

Minute to minute control of serum iCa is influenced primarily by PTH and its essential role is to increase plasma Ca concentrations. The major stimulus for production and release of PTH is a decrease in plasma Ca concentrations. PTH exerts direct effects on bone and kidney and indirect effect on the gastrointestinal tract through calcitriol. PTH stimulates osteoclast activated release of Ca from bone (phosphorus is released as well). At the kidney, PTH increases renal reabsorption of Ca in the loop of Henle and distal convoluted tubule, increases activation of 25-hydroxycholecalciferol to the calcitriol (1,25 hydroxycholecalciferol), and increases excretion of phosphorus by decreasing its tubular reabsorption.

**Calcitriol (1,25-dihydroxycholecalciferol)**

Calcitriol is the active form of vitamin D and its production is stimulated by PTH as well as decreased concentrations of phosphorus, Ca, and calcitriol itself. Calcitriol promotes absorption of Ca and phosphorus from the gut and resorption of Ca and phosphorus from bone. Cats ingest cholecalciferol from food (but it has limited biologic activity – it must be hydroxylated). Hepatic hydroxylation produces 25-hydroxycholecalciferol and then renal hydroxylation, which requires α 1-hydroxylase, produces calcitriol.

**Calcitonin**

Calcitonin’s primary role is limiting the degree of postprandial hypercalcemia. Together with PTH, calcitonin maintains iCa within its normal narrow physiologic range. At physiologic concentrations, calcitonin has limited biologic potency and even maximal secretion will not correct a sustained hypercalcemic state. At high doses, calcitonin may promote urinary Ca excretion.

**Fibroblast growth factor-23**

Fibroblast growth factor-23 (FGF-23) is a recently characterized “phosphatonin” hormone whose primary action appears to be regulation of phosphate. FGF-23 is secreted primarily from bone in response to increased plasma phosphate and calcitriol concentrations. Within the kidney FGF-23 causes down-regulation of phosphate transporters and vitamin D synthesis. These actions result in increased renal phosphate excretion and reduced renal calcitriol formation. In the parathyroid gland, FGF-23 decreases PTH production and secretion. FGF-23 concentrations are increased in cats with early stage chronic kidney disease and via the actions described above, help maintain normophosphatemia.

**Effects of hypercalcemia in cats**

Gastrointestinal signs are common and may include anorexia, vomiting, constipation (perhaps associated with decreased gut motility). Pancreatitis has also been observed in cats with experimentally induced hypercalcemia. Hypercalcemia will result in a calciuresis which can predispose towards the formation of calcium oxalate (CaOx) urolithiasis (iCa concentrations should always be assessed in cats with CaOx uroliths). Renal damage may occur if the Ca X phosphorus product is > 60-70 mg/dl. Increases in iCa concentration may also have adverse effects on renal tubules independent of soft tissue mineralization. Severe increases iCa concentration may result in neuromuscular/CNS dysfunction and cardiac arrhythmias.
Differential diagnosis: “gosh darn it” eponym
G: Granulomatous disease (granulomatous disease: 1 case in literature – SQ Nocardia pyogranulomatous mass in 6 year old CM DSH; O: Osteolytic; S: Spurious, supplements, schistosomiasis; H: Hyperparathyroidism, humoral hypercalcemia of malignancy, houseplants (calcitriol glycosides e.g., Cestrum, Solanum, Triestum), hyperthyroidism; D: Vit D toxicosis, drugs, dehydration, diet; A: Addison’s, aluminum toxicity, Vit A, milk-alkali (excessive calcium carbonate ingestion); R: Renal disease, raisin/grapes (dogs); N: Neoplasia, nutritional; I: Idiopathic, infectious, inflammatory; T: Temperature, hyper- and hypothermia

Feline differential diagnosis for hypercalcemia: “shirt” eponym
S: Spurious laboratory results
H: Hyperparathyroidism
I: Idiopathic
R: Renal
T: Tumors – usually related to the releases of a fetal protein (PTH-related protein) which mimics the effects of PTH

Diagnostic approach
Mild hypercalcemia in an asymptomatic patient should be confirmed with a subsequent biochemistry profile after a 12 hour fast. If the hypercalcemia is persistent or in cases with moderate/severe hypercalcemia, an iCa concentration should be assessed to confirm true hypercalcemia. Any other abnormalities on the minimum data base (e.g., azotemia, lymphocytosis) should be appropriately pursued. A “PTH panel” that includes tCa, iCa, PTH, and PTH-rp should be assessed. Finally careful cervical palpation may reveal a thyroid/parathyroid nodule and radiographs, ultrasound, bone marrow or mass aspirate cytology, and bone marrow or mass biopsy may also be indicated.

Primary hyperparathyroidism
Benign adenoma of one of the 4 parathyroid glands (Siamese cats may be over-represented) is the usual cause of primary hyperparathyroidism. A cervical mass may be palpable and PTH concentrations should be above reference range ([PTH] in normal range is still inappropriate in face of ↑ iCa). Surgical removal of adenoma is the treatment of choice.

Idiopathic hypercalcemia in cats
Most common cause of hypercalcemia in cats in US over the last 10 years is idiopathic hypercalcemia. Diagnosis is made by exclusion; hypercalcemia is usually mild to moderate ([tCa] < 15 mg/dl) and [PTH] is low, [Vitamin D] is normal, and [PTH-rp] is not detected. Serum phosphorus concentrations are usually normal unless there is impaired renal function. Many cats with idiopathic hypercalcemia appear clinically normal; some have non-specific signs (e.g., wt loss, vomiting, and constipation) but all affected cats are predisposed to CaOx urolithiasis.

Cats with [tCa] > 13 mg/dl, [iCa++] > 1.0 mg/dl above normal, Ca X phosphorus > 60 mg/dl, urolithiasis, or evidence of renal disease should probably be treated; however there is no consensus on treatment.

Diet
Initially acidifying diets were implicated as a potential cause of the hypercalcemia. Alkalinizing diets may help; generally they contain less Ca and phosphorus than do maintenance diets and they decrease calciuresis and therefore CaOx formation. High fiber diets may decrease gut transit to decrease Ca absorption but these diets generally contain more Ca. Vitamin D content of diets is difficult to determine and the same wet vs. dry diet may have different Ca/Vitamin D content.

Glucocorticoids may reduce iCa in some cases, but high doses may be necessary (> 10 mg/cat/day). The mechanism is probably decreased gut absorption of Ca. In one short term study glucocorticoids had no effect on calciuresis.

Bisphosphonates block enzyme pathways in osteoclasts to decrease bone resorption but may be associated with adverse reactions (e.g., esophageal damage, nephrotoxicity).

Primary chronic kidney disease (CKD) and hypercalcemia
In many cats with CKD and concurrent hypercalcemia the increase in Ca is caused by high complexed Ca rather than increases in iCa (i.e., not true hypercalcemia). Some cats with Stage 3/4 CKD (10-30%) have increased iCa with increased PTH = (tertiary hyperparathyroidism). The cause of increased PTH is unclear; an altered set point for release has been hypothesized. Calcitriol treatment had no effect on [PTH] in one short-term study.

Control of hyperphosphatemia is the most important aspect of management. Up to 20% of cats with Stage 2/3 CKD develop mild increases in [tCa] when eating a renal diet (perhaps caused by decreased dietary phosphorus increasing gut absorption of Ca due to decreased chelation in the gut). This hypercalcemia often resolves when the cat is taken off the phosphorus restricted diet; first try a 50/50 mix of the renal diet with a senior diet and then if the hypercalcemia persists try a straight senior diet.
Tumors
Lymphoma and squamous cell carcinoma in the cat are the tumors most commonly associated with hypercalcemia. Typically the serum phosphorus is decreased and the PTH-rp is increased (although undetectable [PTH-rp] does not rule out neoplasia).
Most bacterial infections of the lower urinary tract respond quickly to antimicrobial treatment; however, urinary tract infections (UTI) associated with defects in the host immune system (complicated UTI) often fail to respond or recur after antibiotic withdrawal and can be a therapeutic challenge.

Etiology
The most common bacterial pathogens associated with UTI in the dog include Escherichia coli, Klebsiella, Staphylococcus, Enterococcus, Proteus, Pseudomonas, Enterobacter, and Streptococcus. These are dermal or intestinal floras that ascend the urethra and then adhere to the mucosa of the bladder and multiply. Although many enteric organisms are anaerobes, the oxygen tension in urine probably inhibits growth of strict anaerobic bacteria and therefore, anaerobic UTI is rare. A recent study of recurrent and persistent UTI in dogs showed that 25% of culture positive urine specimens had two or more bacterial species isolated. Mycoplasmal infections are relatively rare but have been associated with recurrent or persistent UTI in dogs. Mycoplasma should be considered in dogs with persistent pyuria and negative urine culture, dogs with persistently alkaline urine and negative urine cultures, and dogs with persistent or recurrent UTI that don’t respond to appropriate conventional antibiotic treatment.

Normal host defense mechanisms
The status of host defense mechanisms appears to be the most important factor influencing the pathogenesis of UTI. Normal voiding is an efficient natural defense mechanism against UTI. Mechanical washout as a result of complete voiding is responsible for removing greater than 95% of non-adherent bacteria that gain entrance into the urinary bladder. Increased urine production and frequency of voiding enhance washout of bacteria. Disorders that decrease the frequency and/or volume of voided urine, or that result in an increased urine residual volume may predispose animals to UTI. Normal urine residual volume for dogs is less than 0.2 to 0.4 ml/kg body weight.

Bacteria are normally present in increasing numbers from the mid to distal urethra, but seldom do these organisms cause UTI in normal dogs. The high-pressure zone in the mid urethra and spontaneous urethral contractions help prevent ascension of bacteria. Differences in epithelial morphology (decreased epithelial receptor sites) also help decrease bacterial colonization in the proximal and mid urethra. The length of the urethra and bactericidal prostatic secretions in male dogs are thought to decrease the incidence of UTI compared with female dogs, however, nearly equal gender distribution in recurrent/persistent UTI has recently been reported. In both sexes, the valve-like nature of the vesicoureteral junction helps protect against bacterial ascension to the upper urinary tract.

Colonization of vulval and preputial luminal mucous membranes by nonpathogenic flora serves to decrease colonization by uropathogens. Normal flora occupy most of the epithelial receptor sites, produce bacteriocins that interfere with uropathogen metabolism, and have a high affinity but low requirement for essential nutrients required by uropathogens. Mucosal secretions also help prevent adherence of uropathogens to epithelium; immunoglobulins coat pathogenic bacteria and glycosaminoglycans form a protective barrier over the mucosal surface.

The antibacterial property of urine is an additional important host defense mechanism against UTI. Urine is frequently bacteriostatic and sometimes can be bactericidal depending on its composition. Low pH and high concentrations of urea and weak organic acids in concentrated urine inhibit bacterial growth. Although polyuric disorders may increase washout of non-adhered bacteria from the bladder, UTI may occur due to decreased antibacterial properties of urine.

Complicated vs. uncomplicated UTI
Uncomplicated UTI are infections without detectable underlying structural or functional abnormalities in the host's defense mechanisms. This form of infection is easier to treat and is usually cleared soon after appropriate antibiotic treatment is initiated. Complicated UTI are associated with a defect in the host's defense mechanisms; i.e., interference with normal micturition, anatomic defects, damage to mucosal barriers, alterations in urine volume or composition, or systemic immunocompromise. In almost all cases, the underlying defect must be corrected in order to eliminate the UTI.

Abnormal micturition often results in incomplete voiding and retention of urine, which allows for multiplication of bacteria within the urinary tract. Damage to mucosal barriers may result in UTI depending on the extent of the lesion and concurrent introduction of uropathogens. It is interesting to note that pathogenic bacterial inoculation of the urinary bladder in experimental animals usually fails to establish a UTI unless the uroepithelium is first damaged by a chemical or mechanical insult. Any time the urinary bladder is
catheterized; bacteria are carried up the urethra to the bladder. If the catheter is inserted too far and damages the bladder mucosa, the chance of infection increases. Anatomic defects may allow ascending migration of bacteria (e.g., indwelling urinary catheters or an ectopic ureter) or may damage mucosal barriers (e.g., urolithiasis, neoplasia, urachal remnant, thickened bladder wall due to chronic inflammation). Altered urine composition (glucosuria or excretion of irritating drugs like cyclophosphamide) can enhance the environment for bacterial growth. In addition to the above local factors, systemic disorders such as renal failure, hyperadrenocorticism, prolonged steroid administration, neoplasia, and diabetes mellitus can result in complicated UTI. In a recent retrospective study, aerobic urine cultures from 159 dogs with diabetes mellitus yielded bacterial growth in 34 cases (21%).

Elimination of clinical and laboratory signs of complicated UTI with antibiotic treatment is usually not possible; signs either persist during antibiotic treatment or recur shortly after antibiotic withdrawal. Although antibiotic treatment is the cornerstone of management, the status of host defense mechanisms is thought to be the single most important determinant of the outcome of UTI treatment. In complicated UTI, antibiotic treatment should control the pathogenic bacterial growth for a period sufficient to allow host defense mechanisms to prevent colonization of the urinary tract without further antibiotic administration.

Recurrent UTI

Recurrence of clinical and laboratory signs of UTI can be classified into two groups: relapses and reinfections. Relapses are infections caused by the same species of bacteria usually within several days of cessation of treatment. In this case the previous antimicrobial treatment failed to eliminate the infection. Relapses may be due to use of improper antibiotic, or dose, emergence of drug-resistant pathogens, or failure to eliminate predisposing causes that alter normal host defense mechanisms and allow the persistence of the bacteria. Urinary tract infections that relapse are frequently associated with a higher degree of antimicrobial resistance compared to the original infection. Relapses in male dogs may be caused by chronic prostatic infections.

On the other hand, recurrent UTI may be reinfections. In this case, the previous antibacterial treatment cleared the first infection and the urinary tract has subsequently become infected with another bacteria. In most cases the time between reinfections is greater than the time between relapses. Reinfections often indicate failure to eliminate predisposing causes that alter normal host defense mechanisms. Alternatively, reinfections may be iatrogenic (follow-up catheterization) or spontaneous. Reinfections with less invasive bacteria (e.g., *Pseudomonas aeruginosa*) generally suggest the host’s immune system is compromised.

Treatment

It is important to try to identify those patients with immune system defects; therefore a complete physical examination should be performed on all animals that present with signs of UTI. If a simple UTI is suspected, bacterial sensitivity results are not available, antibiotic treatment choice should be based on bacterial identification or the gram-staining characteristics of the bacteria. Clinical experience at several different veterinary teaching hospitals indicates that intelligent choices may be made about bacterial susceptibility to antibiotics. Without benefit of bacterial sensitivity testing, the following are the drugs of choice for the bacteria listed: *E. coli* - enrofloxacin; *Proteus* - amoxicillin-clavulanic acid; *Staph* - amoxicillin-clavulanic acid; *Strep* - amoxicillin-clavulanic acid; *Enterobacter* - tetracyclines; *Klebsiella* - enrofloxacin; *Pseudomonas* - tetracycline. If bacterial identification is unknown, treatment is best based on the gram-staining characteristics, i.e., ampicillin/amoxicillin or amoxicillin-clavulanic acid for gram-positive bacteria and trimethoprim-sulfur or enrofloxacin for gram-negative bacteria. In cases of suspected or known complicated UTI or in cases of recurrent UTI, bacterial culture and sensitivity of the urine is necessary.

Cystocentesis is the preferred method of collection for urine culture and sensitivity. The urine sample should be submitted in a sealed container for culture as quickly as possible. Refrigeration is recommended if a delay in culturing is anticipated. Many practices inoculate a blood agar plate with urine and then submit the plate for identification and sensitivity if there is bacterial growth after incubation. Minimum inhibitory concentrations (MIC) and Kirby-Bauer agar diffusion tests can be used to determine bacterial sensitivity. The Kirby-Bauer method is acceptable for most UTI; however the MIC technique is often advantageous with apparently resistant UTI.

Steps to follow for management of a UTI are given in Table 1. The duration of therapy of lower UTI must be individualized and should be based on the cessation of clinical signs and elimination of abnormal urine sediment as well as a negative urine culture. In general uncomplicated lower UTI should be treated for 2 to 3 weeks, while complicated UTI should be treated for a minimum of 4 weeks. Verification of proper selection of antibiotic therapy can be made after three to five days of therapy, by assuring that the urine is sterile. The urine sediment, however, may be still abnormal at this time.

Recurrent UTI should always be evaluated by urine culture and sensitivity. Additionally, attempts should be intensified to identify defects in the host immune system. Double contrast cystography and ultrasonography may be used to rule out anatomic abnormalities and mucosal lesions of the bladder. In male dogs, semen and prostatic wash cytology and culture as well as ultrasonographic examination should be employed to rule out bacterial prostatitis. Excretory urography, ultrasonography, and renal biopsy may confirm the presence of pyelonephritis; however these parameters may be normal in chronic pyelonephritis. Finally, consideration
should be given to the possibility of otherwise asymptomatic hyperadrenocorticism causing recurrent UTI, especially infections associated with low numbers of WBCs and RBCs in the urine sediment.

The prognosis for complicated UTI is always guarded in comparison to uncomplicated UTI. The single most important treatment for a complicated UTI is correction of the underlying defect in the host defense mechanisms. If predisposing factors cannot be identified or corrected, relapses and reinfections are common. For animals with frequent infections, which cannot be cured, low dose (1/3 to 1/2 of the conventional daily dose) antimicrobial administration at bedtime may be recommended after the urinary tract has been sterilized with standard dose antibiotic treatment. This allows the drug to be present in the bladder overnight supplementing the animal's defense mechanisms. Low (sub therapeutic) dosages of antibiotic may reduce infections by interfering with bacterial fimbria production and therefore uroepithelial attachment. For recurrences due to gram-positive bacteria, penicillins are recommended; while for recurrences caused by gram-negative bacteria, trimethoprim-sulfa or enrofloxacin is recommended. It should be noted however, that long-term, sub therapeutic antibiotic treatment could predispose the animal to a resistant UTI. Any “break-through” UTI should be treated with therapeutic antibiotic dosages on the basis of bacterial culture and sensitivity.

Table 1. Steps to follow for management of urinary tract infections

- Diagnosis based on history, urine sediment, and ideally urine culture and sensitivity.
- Selection of an antimicrobial agent.
- Reculturing of urine in 3-5 days to ascertain effectiveness of selected antimicrobial agent.
- Examine urine sediment 3-4 days before discontinuing antibiotic treatment.
- Recheck urine 10 or more days following cessation of therapy.
- Recurrent urinary tract infections should be evaluated for underlying predisposing factors (e.g., contrast radiography, CBC, serum biochemistry profile, ACTH stimulation test).
- Frequent reinfections may need to be treated with prophylactic doses of antibiotics after initial inflammation has been cleared up with standard dose antibiotic treatment.