CHRONIC KIDNEY DISEASE UPDATE

Has SDMA become the preferred means of diagnosing CKD?

The measurement of serum creatinine has long been a widely used marker to estimate glomerular filtration rate (GFR) as it is freely filtered by the glomerulus. Creatinine has an inverse but nonlinear relationship to GFR; as GFR declines serum creatinine rises. But the relationship between creatinine and GFR has limited sensitivity for detection of early renal dysfunction due to a steep curvilinear relationship. Initially there is only a modest increase in creatinine associated with a significant decline in GFR. Conversely, in advanced renal disease small changes in GFR have a large impact on the creatinine level. Currently, a loss of 75% of renal functional must be lost before creatinine rises above the laboratory reference interval.

SDMA is a blood-based renal biomarker that identifies kidney dysfunction earlier when compared to traditional tests such serum creatinine. SDMA is stable molecule originating from intercellular proteins during cellular metabolism. The small size and positive charge of the SDMA molecule allows it to be freely filtered at the glomerulus. SDMA is correlated to glomerular filtration rate (GFR), increases earlier in the course of acute or chronic renal dysfunction and is not affected by loss of lean muscle mass often present in association with advanced CKD which falsely lowers serum creatinine value. Significant increases in SDMA occur prior to increases in serum creatinine and are proposed to identify changes in International Renal Interest Society (IRIS) classification for CKD earlier compared to using serum creatinine. These guidelines are suggested to guide decision making as to when to start or change treatments that may slow CKD progression and/or improve patient life quality. The IRIS guidelines classify patients into Stage 1-4 CKD. CKD sub-staging based on systemic blood pressure and proteinuria is also provided. IRIS grading of acute kidney injury (AKI) has not included SDMA to date. While it is now well-established that chronic renal disease can be identified earlier via SDMA testing in dogs and cats, the impact of early treatment remains undetermined on the progression of CKD and quality of life of the patient.

Should quantitative urine protein values be determined in routinely in patients?

Evaluating for protein loss (albumin) as a biomarker of chronic renal disease is recommended as part of a standard diagnostic screening evaluation in healthy geriatric patients and all sick patients. A patient identified with consistent proteinuria should undergo further diagnostic evaluation to determine the origin and cause of the renal protein loss. The detection of persistent proteinuria serves as a warning that renal damage is present and both specific and general supportive treatments to reduce ongoing renal damage should be implemented. Timely identification and treatment of any secondary underlying disease could make a huge impact on a patient’s future prognosis. Underscoring its importance as a routine screening test, multiple studies conducted in humans, dogs and cats demonstrate an increased mortality in patients with chronic proteinuria. Once it has been determined that the proteinuria is of true renal origin, each individual should be evaluated to determine whether a primary renal disease (chronic interstitial
renal disease, glomerulonephropathy) is ongoing vs. some secondary disease process located in another organ system (not of primary renal origin). Findings of elevated serum BUN, creatinine, SDMA; renal imaging abnormalities and possibly more detailed renal function testing (iohexel clearance) can be used as supportive criteria for a primary kidney disease. Identification of extra-renal disorders, such as underlying chronic inflammation (teeth, skin, ears, immune-mediated); infection (HWD, tick-borne, other regional); endocrine (adrenal, diabetes, thyroid) or neoplastic disease, that cause glomerular entrapment of circulating immune complexes and subsequent renal damage should be undertaken. This diagnostic evaluation may be comprehensive depending on the potential infectious diseases present in the geographic region the patients resides.

Several methods are available to screen for the presence of urine protein. The urine dipstick is a semiquantitative colorimetric test which is interpreted by examining a color change and comparing it to a colored standard – thus a subjective interpretation. The lower limit of urinary protein is 30mg/dl. False positives occur if the urine is concentrated, alkaline, has been contaminated with quaternary ammonium compounds or if urine is allowed to contact the dipstick for an extended period of time. False negative results can occur with dilute or acidic urine. A sulfosalicylic acid test is often used to confirm dipstick positive results. False positive results can be seen following treatment with penicillins, cephalosporins, sulfonamides, and radiocontrast agents. Thus this simple, inexpensive and universally performed test lacks sensitivity and specificity and its ability to accurately detect proteinuria in our patients is questionable. Urine protein-creatinine determination is a quantitative test that measures total urine protein. Urine creatinine is used to correct for normal variations in urine specific gravity among patients. However, variations in urine creatinine values exist between individuals which can confound interpretation of a single UPC determination; lower urine creatinine values will result in increased UPC ratios. Also individual analyzers may underestimate urine creatinine concentrations (VetTest). The normal cut-off UPC value (<0.5) has been reduced over time to help identify patients with lower levels of protein loss. The UPC test appears to be best used to monitor urine protein loss in an individual patient as their urine creatinine excretion tends to remains constant over time. Tests that evaluate for microalbuminuria are best suited as screening tests for abnormal levels of urine protein. Microalbuminuria is defined as albumin excretion above the normal range but below the level of detection by other standard tests. These tests are able to detect 1 mg/dl of urinary albumin and are extremely sensitive and specific. A quantitative species-specific microalbuminuria test that provides a mg/dl value is available. This test can provide a sensitive screening test for early urine protein loss. Regardless of the method used, abnormal proteinuria should be confirmed prior to extensive testing and treatment as transient proteinuria and false positive results do occur.

**How important is blood pressure determination in chronic renal patients?**

Renal disease is the most common recognized cause of systemic arterial hypertension in dogs and cats. Hypertension is linked to renal, ocular, neurologic, and cardiac complications. Higher blood pressure is a risk factor for uremic crisis and mortality. When indicated antihypertensive treatment may be considered to reduce hypertension and the risk of multi-organ damage. It is appropriate to institute antihypertensive therapy in patients if the arterial BP is > 160mmHg (systole) or 120mmHg (diastole). Which type of apparatus provides the most accurate blood pressure reading is debatable. - oscillometric monitor and the doppler method (Parks) continue to be useful in individual patients. Careful attention should be paid to obtaining a blood pressure in the least stressful means possible and with use of appropriate cuff size. The wide spread accepted use of drugs to reduce angiotensin, aldosterone and renin will aid in management of glomerular and systemic hypertension in all CKD patients regardless of the
limitations of obtaining precise and accurate readings in our patients.

When should renal biopsy be considered?

Renal biopsy allows for histologic diagnosis and should only be considered when the information obtained is likely to alter patient management. Examples of such clinical situations might include evaluation of diffuse uniform renomegaly in dogs (lymphoma, fungal) and cats (lymphoma, FIP, fungal) and discreet nodular infiltrates and masses (tumors). While ideal, using tissue evaluation to differentiate type of protein-losing glomerular diseases, ARF etiology, determination of the tubular basement membranes in ARF, and determination of the patient's response to therapy or the progression of previously documented renal disease is rarely performed in clinical practice.

In my practice we rarely biopsy kidneys in chronic renal disease as my experience has been that the information obtained is usually academic (see The Ohio State University Renal Lab) and as of this time rarely alters patient treatment approach. The complication rate even with an experienced operator is real and should not be underestimated. Renal biopsy can result in severe hemorrhage in up to 10% of dogs and 15% of cats that have normal coagulation profile results; hemorrhage contributed to death in 1% of dogs and 3% of cats. (J Vet Int Med 2005 Renal Biopsy: A Retrospective Study of Methods and Complications in 283 Dogs and 65 Cats. Vaden SL, et al.).

If you still feel it is necessary to obtain a renal biopsy then consider the blind percutaneous needle, ultrasound-guided needle, laparoscopic needle, and surgical keyhole or open (laparotomy) techniques. The choice of technique depends largely on the experience and technical skill of the veterinarian. If the operator is relatively inexperienced with renal biopsy or if a larger sample is required, wedge biopsy by means of laparotomy is recommended. Laparotomy offers the surgeon the advantages of being able to inspect the kidneys, choose a biopsy site and provide excellent hemostasis. Needle biopsy specimens of the kidney can be obtained from dogs and cats under ultrasound guidance using one of several sedation protocols. Ultrasound-guided technique is most appropriate for larger patients in which you cannot palpate and immobilize the kidney. The biopsy needle should be directed along the long axis of the kidney as the goal is to biopsy the cortex and avoid the renal hilus and major vessels within the medulla to avoid iatrogenic infarction and fibrosis within the biopsy region. The blind percutaneous technique is often advocated in cats and small dog when the kidney can be readily palpated and immobilized; however needle guidance is impossible with this technique. The most common complication of renal biopsy is hemorrhage. Subcapsular hemorrhage commonly occurs at the site of biopsy, and many patients experience microscopic hematuria during the first 48 hours after biopsy. Severe hemorrhage into the retroperitoneal cavity can occur associated with improper technique. Such hemorrhage must be treated aggressively by compression bandage of the abdomen, fresh whole blood transfusion, and exploratory surgery if necessary.

Which treatments reduce urine protein loss and improve blood pressure in patients with non-azotemic CKD?
Reduction of proteinuria is often provided with medications that block the production of angiotensin II which in turn lessens efferent glomerular arteriolar resistance leading to a reduction in glomerular transcapillary pressure and decreased proteinuria. Angiotensin converting enzyme inhibitors (ACEI) are commonly used for this purpose. ACE inhibitors generally produce a relatively small reduction in systemic blood pressure, but have renoprotective effects even in absence achieving adequate blood pressure control by altering intraglomerular hemodynamics, proteinuria, and fibrotic effects of the renin, angiotensin and aldosterone. ACE inhibitors are generally well tolerated. Although the serum creatinine concentration should be monitored, it is uncommon for dogs to have worsening of azotemia due ACE-I administration alone. A potential drawback to ACEI therapy is the fact that over time some patients will experience loss of efficacy over time (often referred to as aldosterone escape) which is associated with increasing levels of angiotensin and aldosterone and a loss of the renoprotective effects of ACEI. This phenomenon likely occurs secondary to ACE up-regulation, other active kinases cleaving AT1 to AT2 or increased metabolism and excretion of ACEI drugs.

**Canine - Enalapril 0.5 - 1.0 mg/kg PO BID.** **Benazepril 0.5 - 1.0 mg/kg PO BID.**  
**Feline - Enalapril 0.5 - 1.0 mg/kg PO QD.** **Benazepril 0.5 - 1.0 mg/kg PO QD.**

Angiotensin Receptor Blockers (ARB) are becoming a more popular and possibly more effective way to favorably alter glomerular hemodynamics in veterinary patients. This drug type may provide a more effective reduction in both angiotensin and aldosterone levels by directly binding with the AT-1 receptor in tissues resulting in vasodilation, reduces vasopressin release and reduced aldosterone release. Aldosterone escape is blunted by direct ARB action on the end receptor. Temisartan is an ARB drug that has been studied for use in dogs and cats and can effectively reduce proteinuria and alter glomerular hemodynamics.

**Telmisartan (dogs) 1.0 mg/kg PO QD.**

**Semintra® (cats) 1.5 mg/kg PO BID X 14 d, then 2.0 mg/kg PO QD**

Calcium channel blockers antagonize preglomerular vasoconstriction so may not directly reduce glomerular hypertension. But they may reduce renal injury by other metabolic effects and clinically appear to be beneficial in the management of systemic hypertension related to CKD. The addition of a calcium channel blocker is often necessary to reduce systemic hypertension to an acceptable level (< 160 mmHG) when angiotensin blocking agents are not effective.

**Canine - Amlodipine 0.1 - 0.5 mg/kg PO QD, titrate to effect.**  
**Feline - Amlodipine 0.625 mg < 4 kg; 1.25 mg > 4 kg, titrate to effect.**

**What are the realistic goals in treating chronic kidney disease?**

Maintenance of good quality life in CKD requires prevention of clinical uremic symptoms, minimize disturbances associated with electrolyte, vitamin and mineral imbalances, support adequate nutrition and modify the progression of renal disease.

Avoidance of risk factors that promote progression of renal failure are critically important to reduce progressive renal damage. Risk factors associated with decline in renal function include: volume depletion, urinary obstruction, and nephrotoxic drugs (select antibiotics, NSAIDs, ACE inhibitors and angiotensin-2 receptor blockers, IV contrast agents), urinary tract infection, nephrolithiasis, ureterolithiasis, systemic hypertension, proteinuria, inappropriate diets and other
co-morbid conditions (diabetes, hyperadrenocorticism, heart failure).

**When should a therapeutic renal diet be started in CKD patients?**

Diet therapy is the most commonly recommended treatment for CRF. Protein content has always been stressed but there are other diet modifications that are important and should be considered. Reduced protein, phosphorus and sodium, increased B vitamins and caloric density, neutral effect on acid-base, potassium supplementation, increased omega-3/omega-6 ratio and added fiber to enhance GI excretion of nitrogenous wastes are the basis of what makes renal formulated diet different from typical maintenance diets.

Diet therapy is recognized as an important factor in reducing progression of CRF but the timing for initiating restrictions are undetermined – studies demonstrate that renal-formulated diet treatment significantly reduces the risk of uremic crisis and death in dogs with serum creatinine concentration over 2.0mg/dl. Initiating early protein restriction in cats (IRIS stage 1) must be done carefully due to their dependence on protein metabolism - prolonged protein restriction could lead to protein malnutrition and physical debilitation. Reducing the dietary intake of phosphorus once chronic kidney disease is recognized may play a vital role in reducing progression. Newly released feline early stage renal prescription diets are available which provide for modest protein restriction with severe phosphorus restriction. The phosphorus content of feline diets are available (catinfo.org) and this information can be very helpful in determining alternate diets appropriate for feline CKD.

Renal diets are potassium supplemented to restore potassium that is washed out through hyperfiltration and polyuria. Additional potassium supplementation may be necessary especially in cats. However, serum potassium should be monitored as some patients develop consistent hyperkalemia on these supplemented diets. Home-made or personalized renal diet may have to be considered in these patients to better control potassium content.

Omega-3-fatty acids are renoprotective and included in prescription renal diets. Oral supplementation should be encouraged in patients not receiving these Rx diets.

**Oral phosphorus binders - Yuck. How important is this drug?**

Phosphorus binding agents are mandatory to maintain normal serum phosphorus levels for as long as possible as high phosphorus is a promoter of progressive CKD and is a strong contributor to uremic signs. A previous study has determined that phosphorus restriction plays a more significant role in reducing CKD progression versus dietary protein restriction. Serum phosphorus should be maintained < 4 mg/dl in IRIS 1-2 CKD and this may be accomplished with a phosphorus restricted diet therapy alone. However as GFR decreases in more advanced IRIS 3-4 CKD the addition of oral phosphorus binding agents is usually necessary to maintain serum phosphorus < 6 mg/dl.

Orally administered aluminum hydroxide is used to reduce phosphorus levels in patients with renal failure when dietary phosphorus restriction fails to maintain serum phosphorus concentrations in the normal range. Adverse reactions – constipation; aluminum neurotoxicity unlikely in domestic animals. Dose - 50 to 100 mg/kg PO divided daily, titrate to effect

*Aluminum Hydroxide Concentrated Gel Liquid: 600 mg/5 mL; AlternaGEL®, generic; (OTC)*
Aluminum Hydroxide Gel, Dried Powder, tasteless bulk powder to mix in food is available from a variety of sources including many veterinary distributors.

Lanthanum carbonate (Fosrenal). Lanthanum has a potential advantage over calcium or aluminum containing phosphate binders in that it does not appear to be absorbed, even at high dosages or with continued use, though palatability can be an issue. Lanthanum ions bind to dietary phosphate and form highly insoluble lanthanum phosphate complexes that are then eliminated in the feces. Vomiting has been reported in some cats and food avoidance can occur when lanthanum carbonate is mixed into food.

Lanthanum carbonate - initially, 30 mg/kg/day PO divided 2-3 times a day on or in food and titrated to maintain the desired serum phosphorus level. A proprietary product (Renalzin® — Bayer-UK) for cats has been discontinued in Europe. The standard recommended dosage is 2 mLs (400 mg) applied in the cat’s food, once or twice daily depending on the cat’s feeding regimen.

Sevelamer HCL or Carbonate (Renagel, Renvela) directly binds phosphorus in the gut but is not absorbed systemically; when combined with decreased phosphorus in the diet it can substantially reduce serum phosphorus levels. It also reduces serum low-density lipoproteins and total cholesterol. There are no pharmacologic studies in small animals - when used cats and small dogs receive 200 – 400 mg per dose q8-12h with meals; medium to large dogs receive 400 – 1600 mg per dose q8-12h with meals. It is available in 400 & 800mg tablets and 0.8gm & 2.4gm packets for oral suspension.

Calcium-based agents (Epakin) can also be used but cautious must be exercised regarding the possibility of promoting hypercalcemia, especially when using concurrent calcitriol therapy.

“Go Buckeyes - Is this just an Ohio State things”?
Vitamin D, calcium and PTH in CKD. Is calcitriol treatment necessary in CKD?

Calcitriol (1,25-dihydroxyvitamin D) is a vitamin D analog may be useful in dogs and cats for treatment of renal secondary hyperparathyroidism and in the management of chronic renal disease. This specific vitamin formulation replaces the production loss of naturally occurring vitamin D in CRF patients. Unlike other forms of vitamin D, calcitriol does not require renal activation to be effective. Vitamin D has multiple actions including enhancing calcium absorption from the GI tract, promoting reabsorption of calcium by the renal tubules, and regulating calcium metabolism in bone. Vitamin D levels and ionized claim levels are gradually reduced in CRF patients and effects are documented as early as IRIS-2 disease stage during which increasing levels of compensatory parathyroid hormone (PTH) is noted. PTH is a potent uremic toxin and has detrimental effects in the well-being of CRF patients. Oral calcitriol provides for a rapid onset of increased vitamin D activities but has a short duration of action. This is an advantage in CRF patients as its use has a mild impact on blood calcium but a potent and longer acting effect in reducing serum PTH production. Surveys and clinical impressions suggest use of this drug in CKD dogs results in clinically improved mentation, activity, appetite and longer survival times in CRF patients. A positive effect in cats is postulated but has not been proven to date. The possible development of hypercalcemia and hyperphosphatemia is a concern, however, hypercalcemia is unlikely unless a concurrent calcium-containing phosphorus binder is being used. Hyperphosphatemia is best avoided by normalizing serum phosphate levels before therapy is begun. Periodic monitoring of serum calcium and phosphorus levels is mandatory when using this drug.
A formulated daily dose of 2.5 to 3.5 ng/kg PO q 24 hr is recommended in dogs and cats. A pulse dosing strategy (giving 3x dose every 72 hours) is suggested as this approach will minimize acute GI calcium absorption and maintain prolonged PTH suppression. This drug is best obtained via a formulating pharmacy to ensure proper dosing as the human capsules and solution are at much higher dosages then required by most veterinary patients.

**Appropriate use of erythropoietin analog drugs in anemic CKD patients.**

*Erythropoietin* (EPO) is a naturally hormone produced in the kidney that regulates bone marrow erythropoiesis. Various uremic toxins and renal tissue damage result in decreased production of EPO by the kidney. Progressive non-regenerative anemia is a common complication of chronic renal disease. Restoration of normal red blood cell numbers may be important in improving appetite, appetite and stamina in CRF patient. Erythropoietin-stimulating drug therapies are available in the human medical field and have been used in CRF patients. Recombinant Human epoetin alfa (r-HuEPO-alpha) has been used as a substitute for endogenous EPO in dogs and cats with renal disease. Autoantibodies development results in resistance to treatment or destruction of bone marrow RBC precursor cells may be encountered with this drug thus limiting its usefulness. Other side effects including vomiting, hypertension, seizures, local reactions at injection sites, fever, arthralgia, & mucocutaneous ulcers have been reported. *Darbepoetin* (Aranesp®) is a recombinant DNA-produced protein related to erythropoietin. It stimulates erythropoiesis via the same mechanism as endogenous erythropoietin by interacting with progenitor stem cells to increase RBC production. Compared to recombinant DNA-epoetin, darbepoetin appears less immunogenic because of its formulation utilizing carbohydrates as part of its structure which "shield" the sites on the drug of greatest antigenic potential from immune cell detection. Another advantage is that darbepoetin is administered less often to maintain PCV following induction treatment. Darbepoetin is now the drug of choice in cats and dogs and has been found to be effective in increasing marrow red blood cell production. Significant adverse effects have not been reported in cats. However, dogs may develop elevated blood pressure, seizures, vomiting and diarrhea and uncommonly pure red blood cell aplasia in a recent retrospective study. An initial weekly SQ dose of 0.5 to 1.0 micrograms/kg of darbepoetin in dogs and cats has been reported. The dose and frequency are then adjusted using clinical judgment and careful monitoring of RBC values. Once a suitable increase in RBC is achieved the administration frequency can be reduced to q 2 weeks. If the hematocrit continues to rise then administration frequency may be reduced to q 3 weeks in some patients. A reduction in dose may also be possible in some patients with continued use.

*Darbepoetin* 25, 40, 60, 100, 150, 200, 300 micrograms/mL preservative free single-dose vials.

**Appropriate use of fluid therapy and appetite stimulants in hyporexic CKD patients.**

The use of gastroprotectant drugs and fluid therapy is not necessary in the non-uremic CKD patient. Chronic fluid therapy may lead to hypervolemia, increased blood pressure and increased solute excretion which all can contribute to CKD progression.

The use of gastrointestinal medications for uremic CRF patients is extremely important. Antiemetic (maropitant) and/or antinausea (ondansetron, dolesetron) drugs may can be crucial in improving appetite/water intake by reducing nausea and vomiting. Antacid therapy is controversial in CKD as uremic gastritis has not been documented in dogs and cats. Appetite stimulation therapy (mirtazapine, capromorelin) is also of great benefit in many advanced CKD
patients. Subcutaneous fluid therapy may also be of significant importance in uremic patients that are not achieving adequate oral hydration.
“RECOGNITION AND TREATMENT OF ACUTE KIDNEY DISEASE (AKI)”

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INTRODUCTION

Acute kidney injury (AKI) is associated with a rapid decline in renal function over hours to days, and the development of acute clinical signs in affected dogs and cats. Providing prompt diagnosis and treatment can prevent or minimize permanent renal damage. If renal tissue is not irreversibly damaged, patients may regain sufficient renal function to sustain normal life following initial supportive care.

CAUSES AND RISK FACTORS

There are numerous causes of AKI in dogs and cats. AKI causes can be categorized as prerenal, primary renal, or postrenal in origin.

Prerenal causes and disorders that effectively reduce blood volume include: dehydration, hemorrhage, hypoadrenocorticism, hypoalbuminemia, prolonged anesthesia, congestive heart failure, diuretics, ACE-inhibitors, antihypertensives, NSAIDs, epinephrine and sepsis.


Postrenal causes include: urethral stones and plugs (mucoïd/cellular/crystalline), urethral stricture (neoplasia, granulomatous inflammation, fibrosis, or trauma, urinary bladder neoplasia with trigonal outflow obstruction.

Risk factors that have been reported include: increasing age, preexisting chronic kidney disease (CKD), adverse drug combinations (gentamicin/furosemide; amphotericin/furosemide), sepsis, prolonged anesthesia (especially with concurrent NSAIDs), dehydration, hypovolemia, hypotension.

AKI PHASES

Two distinct phases of AKI are recognized: oliguric and polyuric.

Oliguric AKI is the sudden onset and rapid development of azotemia with reduced urine flow (measured production <0.25 mL/kg/h). In oliguric AKI, renal blood flow, glomerular filtration rate (GFR), and urine production are all typically diminished, and affected dogs and cats demonstrate sudden onset of depression, vomiting, anorexia, and polydipsia; seizures and muscle fasciculations may be observed, and terminal patients can become comatose. Laboratory studies may show hyperkalemia and severe metabolic acidosis with a wide anion
gap. Blood glucose concentrations may be mildly increased. Urine specific gravity (USG) is usually low (ie, <1.020) despite dehydration. Proteinuria, hematuria, and glucosuria in the absence of severe hyperglycemia are commonly findings.

Polyuric AKI patients also present with sudden onset and rapid development of azotemia but with increased urine flow (dogs: >45 mL/kg/d; cats: >40 mL/kg/d). Renal damage is generally less severe than with oliguric AKI. GFR is reduced, but glomerular and tubular damage are insufficient to cause oliguria.

During recovery from the oliguric phase of AKI, patients may develop transient polyuria, typically lasting 24 to 72 hours. Electrolyte depletion especially hypokalemia can develop. Proposed causes of polyuria following oliguria include excretion of accumulated solutes, excretion of fluid volume overload from overzealous treatment, and poor modification of the glomerular filtrate by damaged tubular cells.

**CLINICAL SIGNS**

Clinical findings, such as dehydration and uremic breath odor, are common to all causes of AKI. Many other clinical signs are shared with a variety of AKI causes whereas others signs are specific to the origin of the injury. Common clinical signs include: increased kidney size, painful palpation (except when AKI is superimposed on CKD); fluid within the peritoneal cavity, retroperitoneal space, or subcutaneous perineal tissues; and lingual, palatine, and gingival necrosis. Hypothermia is common, with the exception of infectious causes which may present with a fever.

**DIAGNOSTIC FINDINGS**

Hypertension (systolic pressure >160 mm Hg) is common in AKI patients. Rapid increases in serum creatinine, blood urea nitrogen, and phosphate concentrations occur early in the disease process. Electrolyte disturbances are common with hyperphosphatemia and hyperkalemia commonly present; hypocalcemia is also a frequent finding, hypokalemia is possible especially in Leptospiral infections. Severe metabolic acidosis with a wide anion gap is present especially in ethylene glycol poisoning. An active urine sediment is expected often with varying numbers of epithelial cells, erythrocytes, neutrophils, lymphocytes, and hyaline, granular, and cellular casts.

**Differentiating Acute Kidney Injury vs Chronic Kidney Disease**

There are numerous historical, clinical and diagnostic findings that should be considered when differentiating patients with AKI from patients with CKD.

Patients with AKI: Sudden onset clinical signs, no previous problems, toxin and risk factor exposure. Depression, anorexia, vomiting. Normal or large kidney size, lingual palatine and gingival necrosis, hypothermia (except in the presence of infections), large, distended bladder. PCV normal, hyperkalemia, active urine sediment with many granular casts & many inflammatory cells. Normal or large kidney size on radiography or ultrasonography.

Patients with CKD: Chronic weight loss and reduced appetite, chronic intermittent vomiting, chronic polyuria/polydipsia. Poor body condition score, poor hair coat, small or irregular kidneys, pale mucous membranes. PCV often low, hypokalemia (in cats), urine sediment
inactive with few casts and cells. Small irregular kidneys on radiography and ultrasonography; increased cortical echogenicity and loss of corticomedullary distinction, cortical infarcts, irregular kidney borders on ultrasonography.

**TREATMENT**

Recognition and prompt correction of potential initiating causes of AKI can minimize or prevent renal damage, however, AKI often is recognized well after renal damage has occurred. Once established, life-threatening aberrations in ECF volume and composition must be corrected for a sufficient period to allow return of adequate renal function. Adequate time must be allowed for tubular regeneration, nephron compensation, and restoration of renal function. AKI recovery can take at least 2 to 4 weeks of supportive care before renal function improves. Patients must be given time to convalesce.

At the first signs of AKI, initiating causes should be identified and addressed and then treated and managed by:

- Correct prerenal influences that negatively affect renal blood flow (hypovolemia, hypotension)
- Avoid overhydration during the oliguric phase
- Avoid dehydration during the polyuric phase
- Regularly monitoring and addressing electrolyte and acid-base disturbances

**Fluid & Electrolyte Correction**

Any prerenal factors that negatively affect renal blood flow should be corrected with appropriate IV fluid administration or other appropriate measures. Balanced isotonic electrolyte solutions (sodium 130-154 mEq/L [mmol/L]) typically are chosen unless their is a unique needed based on the hematologic, colloidal, electrolyte, and acid-base status of the patient.

Anemia should be corrected with whole blood or packed red blood cells to achieve a PCV at least at the low end of the normal range (dogs: 30%-35%; cats: 20%-24%).

Hypoalbuminemia should be treated with replacement plasma or alternative albumin solutions but hydroxystarches should be avoided as they can result in further kidney insult.

Hyperkalemia (potassium >7.5 mEq/L [mmol/L]) should be corrected with specific treatment, including calcium gluconate, which counteracts the cardiotoxic effects of hyperkalemia but does not reduce plasma potassium, and sodium bicarbonate, which decreases plasma potassium. These treatments reduce or ameliorate the effects of hyperkalemia only transiently, and more aggressive therapy (dialysis) may be necessary if hyperkalemia persists.

Most dogs and cats with AKI develop metabolic acidosis with a wide anion gap but patients may be acidemic or alkalemic depending on respiratory compensation and vomiting extent. Replacement bicarbonate can be given if the deficit is known. Frequent reevaluation of bicarbonate deficit may be necessary in patients with severe azotemia.

Once dehydration is corrected, patients may demonstrate oliguria or polyuria. If oliguria persists, rapid fluid and electrolyte administration must be curtailed to avoid excessive volume
overload with pulmonary edema, respiratory distress, and respiratory failure. In persistent oliguria, IV fluid administration rate should be calculated as follows: Daily fluid volume = insensible losses (10-15 mL/kg/d) + measured urine loss + extraordinary losses (eg, vomiting, diarrhea, fever). Body weight should be measured twice daily to assess fluid volume administration adequacy. Insensible losses during oliguria must be replaced by fluids lower in sodium (65.5-77 mEq/L [mmol/L]) or 5% dextrose in water.

Careful attention to fluid and electrolyte status is essential during the polyuric phase because patients can become dehydrated and develop hypokalemia. Frequent assessment of clinical fluid status and measurement of both urine output and body weight are essential, and regular measurement of serum sodium and potassium concentrations may be necessary. The rate of fluid administration should be based on and match urine volume (“ins and outs”), with careful attention to the patient’s body weight and clinical signs indicating the level of hydration. Balanced electrolyte solutions are appropriate for the polyuric phase of AKI. Potassium supplementation may be necessary, but the IV administration rate should not exceed 0.5 mEq/kg/h (mmol/kg/h). To avoid unnecessary prolongation of diuresis with excessive IV fluid administration, replacement volume should be judiciously reduced with careful monitoring of hydration status.

**Diuretic therapy**

After appropriate rehydration and correction of renal underperfusion, diuretics have been recommended to induce increased urine production because establishing adequate urine output simplifies fluid management of AKI patients. Furosemide can be administered IV, and treatment can be repeated if diuresis is not induced in 30 minutes. If a brisk diuresis is established, diuresis can be maintained with furosemide CRI at an appropriate dosage. Furosemide may be contraindicated if the AKI is associated with aminoglycoside administration.

Mannitol should not be given to patients who are already hyperosmolar (ethylene glycol intoxication) because patients with a high risk for congestive heart failure can develop volume overload, pulmonary edema, and respiratory failure. Renal function and prognosis are not improved when osmotic diuretics, loop diuretics, calcium channel blockers, and dopamine agonists are given after oliguric AKI is established.

**Hypertension Reduction**

Systemic arterial hypertension is reported in 50% of canine AKI patients, and amlodipine is effective in reducing systolic blood pressure. Treatment with amlodipine, however, was not associated with increased survival in studies.

**RENNAL REPLACEMENT THERAPIES**

Hemodialysis, both continuous and intermittent, is the most reliable treatment for eliminating nephrotoxins, reducing azotemia, and correcting life-threatening disturbances of ECF volume and composition, which include hyperkalemia, acidemia, and volume overload. Renal replacement therapy (RRT) is a developing field and is now available at an increasing number of hospitals at this time. If an oliguric AKI patient does not demonstrate an adequate response to initial supportive treatments within 24 to 48 hours then consultation is recommended. Unfortunately, advanced renal treatment is not affordable for all patients and is not a guarantee that restoration of renal function will occur.
Treatment Considerations and Prevention Strategies for Simple and Complex Bacterial Urinary Tract Infections
“Stopping the Repeat Offender”

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INTRODUCTION
Bacterial urinary tract infection (UTI) is a leading cause of urinary disease in dogs. Antibiotic therapy is routinely prescribed for dogs diagnosed with UTI. UTI treatment is a leading contributor to overall antibiotic use in companion animals. There is genuine concern about use, misuse and overuse of antibiotic therapy in veterinary patients especially in regard to development of antibiotic resistance. There have been numerous individual commentaries, studies and reviews regarding the diagnosis, treatment and prevention of bacterial UTI. In 2011 the International Society for Companion Animal Infection Diseases (ISCAID) published comprehensive guidelines to provide consensus guidelines to assist in the diagnosis and management of upper and lower urinary tract infections in dogs and cats. These guidelines were recently updated in 2016. The purpose of these publications is to improve antibiotic prescribing practices in UTI patients as part of a broader antibiotic stewardship program.

DIAGNOSIS AND TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTION.
An uncomplicated UTI is an occasional bacterial infection of the urinary bladder in an otherwise healthy individual with normal urinary tract anatomy and function. Clinical signs of a lower UTI are present and are typically characterized by dysuria, pollakiuria, and/or increased urgency of urination. Whenever possible a urine sample should be collected via cystocentesis. Urinalysis generally reveals the presence of pyuria and bacteriuria which supports evidence of a UTI; hematuria and proteinuria are also often present. Bacteria can be present in the urine in the absence of clinical signs (covert bacteriuria/subclinical bacteriuria) and is not always associated with an active UTI. Therefore, the clinician must interpret the clinical evaluation, gross and cytological appearance of the urine in parallel to determine the likelihood of a clinically significant UTI. Urine culture should be considered to confirm the presence of bacterial infection, identify the presence of resistant bacteria that may not respond to initial antibiotic therapy, and to help differentiate reinfection from relapse should a UTI return following initial therapy.

Antimicrobial therapy is recommended for confirmed UTI and initial therapy with amoxicillin (11–15 mg/kg PO q 8hr) or trimethoprim-sulfonamide (15 mg/kg PO q12 hr) is recommended to provide a narrow antibiotic spectrum while maintaining optimal efficacy. Uncomplicated UTIs are generally treated for 7–14 days. Providing the full course of an appropriate antibiotic has been administered correctly by the owner, then there is no strong indication that measures beyond monitoring of clinical signs is necessary to determine the efficacy of treatment. If culture and susceptibility testing is performed and demonstrates an isolate that is resistant in vitro to initial antibiotic therapy but there has been a positive clinical response, then maintaining the current antibiotic is acceptable and follow-up urinalysis, including culture, is indicated after treatment has been completed to verify resolution of infection. If culture and susceptibility results indicate that an isolate is not susceptible to the chosen antimicrobial and there is a lack of clinical response, then therapy with the original antibiotic should be discontinued and treatment with an alternative drug begun based on the culture and susceptibility result.
DIAGNOSIS AND TREATMENT OF COMPLICATED URINARY TRACT INFECTION.

A complicated UTI is a bacterial infection that occurs in association with an anatomic or functional urinary tract abnormality or a comorbidity that predisposes the patient to persistent infection, recurrent infection, or treatment failure. An identifiable abnormality is not always confirmed because of the difficulty diagnosing some anatomical, functional, metabolic, or other abnormalities. Comorbid medical conditions such as urinary calculi, urinary neoplasia, prostatitis, neurogenic bladder, diabetes mellitus and immunocompromising disorders (hyperadrenocorticism, immunosuppressive drug therapies) often are associated with recurrent UTIs. Recurring use of antibiotics can also predispose to complicated UTI development. Recurrent UTIs often occur 3 or more times during a 12-month period.

Recurrent UTIs can be defined as bacterial reinfection or relapse. Reinfection is recurrence of a UTI within 6 months of completing apparently successful antibiotic treatment and isolation of a different bacterial microorganism. Relapse is recurrence of a UTI within 6 months of completing apparently successful treatment and isolation of an indistinguishable bacterial organism from the one that was present previously; presumably relapse occurs due to failure to completely eliminate the pathogen with prior treatment. Relapses tend to occur earlier than reinfections (i.e., within weeks rather than months). Refractory infection is similar to a relapse except that it is characterized by persistently positive culture result during treatment (despite in vitro susceptibility to the antimicrobial), with no period of eliminated bacteriuria during or after treatment.

A thorough investigation is necessary in most cases to determine the presence of underlying factors that could be associated with recurrence or relapse. All drugs or supplements that are administered should be documented. A thorough physical examination, including prostatic examination via rectal palpation and examination of the vulva, vagina and urethra, is required. A complete blood cell count, serum biochemical profile, urinalysis, urine culture, radiographic and ultrasound imaging and, if appropriate, endocrine testing should be performed. Lower urinary endoscopic exam (vaginoscopy, urethrocystoscopy), advanced imaging (contrast-enhanced CT) and urethral pressure profile exam, particularly in females, should be considered to further investigate underlying causes. Any underlying concurrent causes identified on physical examination or diagnostic testing should be managed appropriately, whenever possible. If an underlying cause cannot be found and corrected, it is possible therapy will ultimately be unsuccessful. Client compliance with previous antibiotic treatment should be determined; this is particularly important in cases where relapse is suspected.

Consideration should be given to waiting on culture results before starting antibiotic therapy. If treatment must be initiated immediately, a narrow antibiotic spectrum drug should be selected as recommended for initial treatment of uncomplicated UTI. The drug class used should be different from that used to treat prior UTI(s) (i.e., if amoxicillin was used initially, start treatment with trimethoprim-sulfa drug). Continued antibiotic treatment should be amended as indicated based on the results of culture and susceptibility testing. Preference should be given to drugs that are excreted in urine predominantly in an active form (individual drug descriptions and doses are presented in lecture; see drug table).

There is no supporting evidence for administration of additional drugs for the purpose of breaking down bacterial biofilm. There is no supporting evidence that direct instillation of antimicrobials, antiseptics, DMSO or glycosaminoglycans directly into the bladder via a urinary catheter is effective for treatment of recurrent UTIs; these compounds are quickly flushed out of the bladder when the animal urinates and may be locally irritating.

Antimicrobial therapy should be directed against all identified pathogenic organisms when possible. If more than one bacterial species is identified on culture, the relevance of each organism should be considered, based on the bacterial counts and the pathogenicity of the
organisms. Certain bacterial species, such as Enterococcus, generally do not require specific treatment in mixed infections. A single effective antibiotic may not be available. Reasonable combination therapy that would be potentially effective against all organisms based on susceptibility testing should be employed when available.

Evidence supporting the duration of therapy for complicated UTI does not exist, but typically 4 weeks of appropriate antibiotic treatment is a reasonable recommendation. In patients with a non-recurrent but complicated UTI (e.g., first instance of UTI in a diabetic or cushinoid patient), a shorter term treatment course may be considered.

A urine culture can be considered 5–7 days after initiation of antibiotic therapy to access the efficacy of the particular antibiotic especially in patients with previous relapsing or refractory infection, those at higher risk for ascending or systemic infection or if clinical signs are not improving. Bacterial growth during treatment indicates treatment failure and should prompt immediate re-evaluation. A second urine culture can be considered 14 days after completing antibiotic treatment. If a positive urine culture is obtained after treatment, more in-depth investigation of predisposing factors for relapse or reinfection should be performed. Unless there is clear evidence for the reason for failure, retreatment without any other investigation is not recommended. If no clinical signs of lower urinary tract disease are present, then the patient should be managed as described for subclinical bacteriuria.

MULTIDRUG RESISTANT INFECTIONS

There are individual patient and public health concerns with regard to resistant pathogens. Multi-drug resistant bacterial pathogens, including various Enterobacteriaceae, staphylococci, and enterococci, are increasingly problematic. These pathogens are often harder to treat because of limited drug choices. Because of the high incidence of antimicrobial use in UTIs of dogs and cats, veterinarians must be aware of the role of inappropriate treatment in the emergence and dissemination of multi-drug resistant pathogens. Use of antibiotics in the treatment of canine and feline UTIs can be justified as long as their use is prudent and proper, based on culture and susceptibility data. Virulent infection must be documented based on clinical, cytological and culture abnormalities. Antibiotic use in subclinical multi-drug resistant organisms is not recommended as organisms may be replaced with susceptible organisms which can allow for self resolution or practical treatment at a later time.

SUBCLINICAL BACTERURIA

Subclinical bacteriuria is the presence of bacteria in the urine as determined by urinalysis and confirmed positive by bacterial culture in the absence of clinical and cytological evidence of UTI. In this circumstance the bacteria identified is likely avirulent. Quantitative culture result cannot differentiate subclinical bacteriuria vs UTI. Subclinical bacteriuria may be present in healthy dogs and cats but is more commonly identified in patients with obesity, diabetes mellitus, Cushing’s disease and immunosuppressive drug treatment. In humans and initial veterinary studies subclinical bacteriuria has no association with subsequent UTI development. Antibiotic treatment may not be necessary in patients with no clinical signs of UTI even when pyuria is present on urine sediment exam. In fact a higher bacterium recurrence rate may be seen following antibiotic therapy.

Antibiotic treatment of subclinical bacteriuria may be considered if there is concern that there is a particularly high risk of ascending or systemic infection (e.g., immunocompromised patients, patients with underlying renal disease) or in patients that are unable to display clinical signs of UTI (e.g., spinal injury). The presence of multidrug-resistant bacterium does not represent an absolute indication for treatment. Multidrug-resistant organisms may be replaced with
susceptible organisms if treatment is withheld, and subsequent treatment with routine antimicrobials may be more practical if bacterial decolonization is desired or if clinical disease develops. Treatment of subclinical Corynebacterium urealyticum should be considered because of its association with encrusting cystitis.

**UPPER URINARY TRACT INFECTION (PYELONEPHRITIS)**

Urine culture and susceptibility testing should always be performed; urine sampling should be performed by cystocentesis (or ultrasound-guided pyelocentesis). Treatment should be initiated immediately, while awaiting culture and susceptibility results. Initial treatment should involve antimicrobial drugs known to have efficacy against gram-negative Enterobacteriaceae, based on the predominance of those organisms in canine and feline pyelonephritis. Treatment with a fluoroquinolone is an acceptable first choice. The initial antibiotic selection should be reviewed when culture results are received. If resistance is reported and clinical evidence of improvement is not evident, the antibiotic selection should be changed to a drug to which the offending organism is susceptible. Antibiotic treatment for at least 4–6 weeks is generally recommended. Treatment efficacy and monitoring is generally the same as for a complicated UTI (i.e., multiple cultures).

**PREVENTION OF RECURRENT URINARY TRACT INFECTIONS**

Patients that are predisposed to UTI or have experienced recurrent infection may benefit from prevention strategies to reduce the likelihood of future infection. A variety of non-antibiotic drug treatment, supplement (nutraceutical) treatments and elective surgery can be considered in individual patients.

A thorough examination of the vulva should be completed in all female dogs. Particular attention should be directed to determining if a “hooded” (juvenile, inverted) vulvar confirmation or excessive vulvar folds are present. Superficial fold pyoderma or abnormal waxy exudate may be present. All of these issues can promote superficial bacterial colonization with easier access to the lower urinary tract. Weight loss, corrective surgery (i.e., vulvoplasty) and superficial cleansing of the perivulvar area are all critical considerations in recurrent UTI prevention. The client should be questioned and the perivulvar hair and skin should be examined for evidence of moisture that might suggest mild involuntary urinary incontinence. Mild urethral hypotonus is associated with incontinence but also allows bacterial translocation and an opportunity to for bacteria to gain easier access to the urinary bladder.

Castration should be considered in intact male dogs to reduce the likelihood of recurrent bacterial prostatitis development and subsequent UTI.

**Phenylpropanolamine (PPA)** is approved for the control of urinary incontinence due to urethral sphincter hypotonus. This drug acts via sympathomimetic agonist activity which results in an increase in urethral sphincter tone and closure of the bladder neck. PPA treatment trial (1.25 mg/kg PO q 8-12 hr) should be considered in any individual that has recurrent UTI and clinical evidence of even subtle involuntary urinary incontinence. Promoting enhanced urethral tone helps restore an effective urethral defense mechanism to prevent ascending bacterial translocation. Long term therapy is generally safe so if a decreased incidence of UTI results with PPA treatment then continued indefinite use should be considered. PPA stimulation of alpha and beta-adrenergic receptors can result in increased vasoconstriction, heart rate, coronary blood flow, blood pressure, mild CNS stimulation, and decreased nasal congestion and appetite. Oral estrogen replacement therapy can also be considered in younger females that develop recurrent UTI following ovariectomy.
**Cranberry extract** supplementation has been suggested for UTI prevention. Initially it was thought that this extract produced an inhospitable acidic urine environment. However, it has now been shown that the American cranberry (Vaccinium marcoarpon) contains a natural bioactive tannin (proanthocyanidin, PAC-A) which inhibits E. coli fimbriae adhesion to the uroepithelium. This activity results in reduced bacterial numbers via bacterial elimination through urinary wash-out and reduced pathogenic colonization and infection. A similar activity has been shown against Enterococcus faecalis. Pharmaceutical cranberry extract with PAC-A is available in concentrated formulation in veterinary medicine. Recent in vitro and in vivo studies in dogs have demonstrated efficacy and safety.

**D-mannose** is a sugar moiety with antibacterial properties. Its presence in urine causes inhibition of bacterial adherence to urothelial cells. In vitro experiments have shown that D-mannose binds and blocks FimH adhesin, which is positioned at the tip of the type 1 fimbria of enteric bacteria. During bacterial colonization, FimH binds to carbohydrate-containing glycoprotein receptors on the epithelium of the urinary tract. D-mannose is similar in structure to the binding site of urothelial glycoprotein receptors, and acts as a competitive inhibitor of bacterial adherence; in sufficient concentration in urine D-mannose saturates FimH adhesins and prevents the bacteria from binding to urothelial receptors. Escherichia coli, Pseudomonas aeruginosa and Streptococcus zooepidemicus bacterial species have been shown to be affected by D-mannose.

**Methenamine Mandelate** | **Methenamine Hippurate** is used as an antimicrobial agent for prophylaxis of recurrent urinary tract infection. Following oral administration, plasma concentrations of methenamine are very low and have negligible systemic antibacterial activity. 70-90% of each dose is excreted unchanged into the urine. In an acidic urinary environment (pH <6.5), methenamine is converted to formaldehyde. Formaldehyde is a non-specific antibacterial agent that exerts a bactericidal effect. Some urea-splitting bacteria (e.g., Proteus and some strains of staphylococci, Enterobacter and Pseudomonas) may increase urine pH. The addition of a urinary acidifier may be required using dietary modification and acidifying drugs. Hippuric acid is added primarily to acidify urine, but it also has some non-specific antibacterial activity. Bacterial resistance to formaldehyde or hippuric acid does not usually occur. Methenamine also has reported activity against fungal urinary tract infections. It is not commonly used in veterinary medicine and little good evidence is available to confirm its efficacy in dogs or cats. Adverse effects are related to gastrointestinal upset, with nausea, vomiting, and anorexia noted; the drug can be given with food to prevent stomach upset. Tablets are very large, but can be split. Recommended anecdotal doses: Methenamine hippurate 500mg PO q 12 hr; Methenamine mandelate usually range from 10 – 20 mg/kg PO q 8-12hr (practically, this is rounded off to the nearest 250 mg as only available in 1 gram tablets).

**Probiotics** (oral, vaginal suppository) have been postulated to prevent recurrent UTI by increasing the number of lactic acid commensal bacterial flora present in the vagina (or presumably the prepuce) of affected dogs. Humans studies are mixed as to the ability of probiotics to prevent recurrent infections. There are currently no evidence-based veterinary studies that provide data as to whether this therapy is effective. Probiotic treatment is not associated with any significant side effects so an empirical trial may be considered.
Antibiotic considerations for urinary tract infections in the dog and cat


**Amoxicillin** 11–15 mg/kg PO q 8h

Optimal first-line option for UTIs as excreted in urine predominantly in active form and effective against most common urinary tract pathogens. Ineffective against beta-lactamase producing bacteria. Development of multi-drug resistance unlikely.

**Amoxicillin/clavulanate** 12.5–25 mg/kg PO q8h (dose based on combination of amoxi + clavulanate).

Not established whether there is any advantage over amoxicillin alone against common urinary tract pathogens. Use in complicated infection based on culture result.

**Amikacin** Dogs: 15–30 mg/kg IV/IM/SC q24h. Cats: 10–14 mg/kg IV/IM/SC q24h.


**Ampicillin**

Not recommended because of poor oral bioavailability. Amoxicillin is preferred.

**Cephalexin, Cefadroxil** 12–25 mg/kg PO q 8-12 h

May be effective against common urinary tract pathogens but widespread use results in frequent resistance. Use may encourage multi-drug resistance. Enterococci are resistant. Enterobacteriaceae resistance in some regions.

**Cefovecin** 8 mg/kg single SC injection.

Should only be used in situations where oral treatment is problematic. Pharmacokinetic data is available to support use in dogs and cats, with a duration of 14 days (dogs) and 21 days (cats) but may not be able to maintain an effective Cmax against bacteria with higher MIC. May be effective against common urinary tract pathogens but extended release may promote resistance. Use may encourage multi-drug resistance. Enterococci are resistant.

**Cefpodoxime proxetil** 10 mg/kg PO q24h

May be effective against common urinary tract pathogens but widespread use results in frequent resistance. Use may encourage multi-drug resistance. Enterococci are resistant.

**Ceftiofur sodium** 2 mg/kg q12-24h SC
Approved for treatment of UTIs in dogs in some regions. May be effective against organisms that exhibit resistance to other cephalosporins. Enterococci are resistant.

**Chloramphenicol** Dogs: 40–50 mg/kg PO q8h Cats: 12.5–20 mg/kg PO q12h

Reserved for multi-drug resistant infections with few other options. May reduce hepatic elimination of other drugs (i.e. NSAIDs). Myelosuppression can occur, particularly with long-term therapy. Avoid contact by humans due to potential for rare idiosyncratic aplastic anemia.

**Ciprofloxacin** 30 mg/kg PO q24h (consider 40-50 mg/kg PO q 24h or 25 mg/kg PO q 12h)

Used because of lower cost compared to veterinary fluoroquinolones. Lower and more variable oral bioavailability than enrofloxacin, marbofloxacin, and orbifloxacin. Difficult to justify use over approved fluoroquinolones.

**Doxycycline** 5 mg/kg PO q12h

Highly metabolized and excreted through intestinal tract, so urine levels may be low. Not recommended for routine uses. Consider based on culture results against methicillin resistance Staph infection.

**Enrofloxacin** 5 mg/kg PO q24h (maximum dose cats); 10–20 mg/kg q24h (dogs)

Excreted in urine in active form. HDSD use in canine uncomplicated cases. Reserve for documented sensitive organisms in recurrent UTIs. Good first-line choice for pyelonephritis. Limited efficacy against enterococci. Associated with risk of retinopathy in cats. Do not exceed 5 mg/kg per day dose in cats. High dose use in juvenile dogs could result in cartilage abnormality.

**Imipenem-cilastatin** 5 mg/kg IV/IM q6-8h

Reserve for treatment of multidrug-resistant infections, particularly those caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*. Recommend consultation with a urinary or infectious disease veterinary specialist or veterinary pharmacologist prior to use.

**Marbofloxacin** 2.7–5.5 mg/kg PO q24h

Excreted in urine in active form. Reserve for documented sensitive chronic UTIs. Good first-line choice for pyelonephritis. Limited efficacy against enterococci. No reported cases of retinal damage in cats.

**Meropenem** 8.5 mg/kg SC/IV q 12hr (SC) or 8hr (IV)

Reserve for treatment of sensitive multi-drug resistant infections, particularly those caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*.

**Orbifloxacin** Tablets: 2.5–7.5 mg/kg PO q24h; Oral suspension: 7.5 mg/kg PO q24h (c) or 2.5-7.5 mg/kg PO q24h (dogs)

Excreted in urine predominantly in active form. Reserve for documented sensitive chronic UTIs. Good first-line choice for pyelonephritis. Limited efficacy against enterococci. Retinal damage has been reported in cats.

**Pradofloxacin** 7.5 mg/kg susp PO q 24hr (cats); 3 - 5 mg/kg tab PO q 24hr (dogs)
Excreted in urine predominantly in active form. Reserve for documented sensitive chronic UTIs. Good first-line choice for pyelonephritis. Expanded anaerobic spectrum not likely to be beneficial in UTI. Limited efficacy against enterococci. Retinal damage has not been reported in cats. Bone marrow suppression has been reported in dogs.

**Trimethoprim-sulfadiazine** 15 - 30 mg/kg PO q12h
Note: dosing is based on total trimethoprim + sulfadiazine concentration

Good first-line option in complicated UTI. Concern regarding idiosyncratic adverse effects in some patients, especially with prolonged therapy. If prolonged (>7d) therapy is anticipated, baseline Schirmer’s tear testing is recommended, with periodic re-evaluation and owner monitoring for ocular discharge. Avoid in dogs breeds that have known documented adverse effects such as KCS, hepatopathy, blood dyscrasias, and skin eruptions.
Urinary Tract Infection: Treatment & Prevention

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May be effective against common urinary tract pathogens but wide spread use results in frequent resistance. Use may encourage multi-drug resistance. Enterococci are resistant. Enterobacteriaceae resistance in some regions.

Cefovecin

8 mg/kg single SC injection. Can be repeated once after 7–14 days. Should only be used in situations where oral treatment is problematic. Pharmacokinetic data is available to support use in dogs and cats, with a duration of 14 days (dogs) and 21 days (cats) but may not be able to maintain an effective Cmax against resistance bacterium. May be effective against common urinary tract pathogens but extended release may promote resistance. Use may encourage multi-drug resistance. Enterococci are resistant.

Cefpodoxime proxetil

10 mg/kg PO q24h

May be effective against common urinary tract pathogens but wide spread use results in frequent resistance. Use may encourage multi-drug resistance. Enterococci are resistant.

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2 mg/kg q12-24h SC

Approved for treatment of UTIs in dogs in some regions. Enterococci are resistant.

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Dogs: 40–50 mg/kg PO q8h Cats: 12.5–20 mg/kg PO q12h

Reserved for multi-drug resistant infections with few other options. May reduce hepatic elimination of other drugs (i.e. NSAIDs). Myelosuppression can occur, particularly with long-term therapy. Avoid contact by humans due to potential for rare idiosyncratic aplastic anemia.

Ciprofloxacin

30 mg/kg PO q24h (consider 40-50 mg/kg PO q 24h or 25 mg/kg PO q 12h)

Used because of lower cost compared to veterinary fluoroquinolones. Lower and more variable oral bioavailability than enrofloxacin, marbofloxacin, and orbifloxacin. Difficult to justify use over approved fluoroquinolones. Dosing recommendations are empirical.

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5 mg/kg PO q12h

Highly metabolized and excreted through intestinal tract, so urine levels may be low. Not recommended for routine uses. Consider based on culture results against methicillin resistant Staph infection.

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Excreted in urine in active form. HDSD use in canine uncomplicated cases. Reserve for documented sensitive organisms in recurrent UTIs. Good first-line choice for pyelonephritis. Limited efficacy against enterococci. Associated risk of retinopathy in cats. Do not exceed 5 mg/kg per day dose in cats. High dose use in juvenile dogs can result in cartilage abnormality.

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5 mg/kg IV/IM q6-8h

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**Meropenem**

8.5 mg/kg SC/IV q 12hr (SC) or 8hr (IV)

Reserve for treatment of sensitive multi-drug resistant infections, particularly those caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*.

**Nitrofurantoin**

4.4–5 mg/kg PO q8h

Consider second-line option for uncomplicated UTI, particularly when multi-drug resistant pathogens are involved. May reduce clinical signs but often fails to eliminate infection. GI toxicity limits use. Peripheral neuropathy has been reported.

**Orbifloxacin**
Tablets: 2.5–7.5 mg/kg PO q24h;

Oral suspension: 7.5 mg/kg PO q24h (c) or 2.5-7.5 mg/kg PO q24h (dogs)

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INTRODUCTION

*Feline lower urinary tract disease* (FLUTD) is a general term used to describe conditions affecting the urinary bladder and urethra of cats. Between 5% to 10% of cats present to veterinary practices for FLUTD. The term FLUTD does not indicate a specific diagnosis. Various causes of FLUTD may be identified including physical conditions and behavioral disorders resulting in inappropriate urination. Because FLUTD encompasses a set of diseases manifesting similar clinical signs, an individualized, thorough diagnostic approach is required to determine the cause and optimize therapy. Specific causes for FLUTD include:

- Idiopathic cystitis (FIC)
- Urolithiasis
- Urethral plugs
- Urinary tract infection
- Neoplasia
- Congenital anatomical defects (e.g., urethral stricture, urachal remnant)
- Trauma
- Neurologic disorders (e.g., reflex dyssynergia)
- Behavioral disorders

SIGNALMENT

Most FLUTD cats are between 1 and 10 years of age. In cats younger than 10 years, feline idiopathic cystitis (FIC) is the most common cause, followed by urolithiasis and urethral plugs. Bacterial urinary tract infection (UTI) is uncommon in younger cats, although cats aged 10 years or older are reported to have a slightly higher risk for UTI. Additionally, cats with certain metabolic disorders, urolithiasis and prior urinary tract procedures (e.g., urethral catheterization, perineal urethrostomy) have an increased incidence of UTI. Lower urinary neoplasia is rare in cats but is more common in cats older than 10 years. Certain breeds may have an increased risk of specific etiologies of FLUTD; for example, in some studies, Russian Blue, Himalayan, and Persian breeds have had an increased risk of urolithiasis.
Clinical signs will help localize the problem to the lower urinary tract. Common clinical signs include pollakiuria, stranguria, periuria, hematuria and licking at the vulva or prepuce. FLUTD can be nonobstructive or obstructive; because of urethral diameter, obstruction is more common in male cats. Clinical signs of urethral obstruction vary with the duration of obstruction but may also include generalized lethargy, depressed mentation, inappetence and vomiting; stranguria with dribbling or complete anuria may be recognized.

**PHYSICAL EXAMINATION**

A complete physical examination should be performed, including measurement of vital parameters, as urethral obstruction can result in severe metabolic derangements including hypothermia and bradycardia. A distended, painful bladder that cannot be expressed is the classic finding with urethral obstruction; the penis may be reddened from self-trauma. Patients with nonobstructive FLUTD often have a small or minimally distended bladder that may have a palpably thickened wall.

**DIAGNOSITICS**

A complete urinalysis and survey abdominal radiography should be performed for all cats with signs of FLUTD. For an adult cat younger than 10 years with acute signs, FIC and urolithiasis are the primary differentials, so urinalysis and radiography are typically adequate. Geriatric cats may have UTI or neoplasia, so urine culture is indicated and abdominal ultrasonography should be considered.

Urine should be analyzed within 60 minutes of collection for the most reliable results as crystals may form in vitro as urine cools following collection. The leukocyte esterase test pad on the dipstick has a high false-positive rate in cats and, therefore, is not useful.

Common findings with any inflammatory diseases of the lower urinary tract include gross or microscopic hematuria, proteinuria, and possibly pyuria. Bacteriuria should prompt submission of a sample for quantitative urine culture, as debris can be easily mistaken for bacteria. In general, struvite (i.e., magnesium ammonium phosphate) stones are associated with an alkaline to neutral urine pH and calcium oxalate stones are associated with an acidic to neutral pH. Struvite crystals and calcium oxalate crystals may be present with or without urolithiasis. Struvite or calcium oxalate crystalluria does not predict which cats will form stones, can occur in apparently healthy cats, and does not require treatment if the cat has never formed stones previously.

Survey abdominal radiographs should be evaluated as uroliths are the cause of lower urinary tract signs in approximately 15% to 20% of feline patients. Uroliths must be ruled out before FIC can be diagnosed (by exclusion). Struvite and calcium oxalate stones are radiopaque, and radiographs allow assessment of their presence, location, number, and size.

Urinary ultrasonography can be performed at the time of urine collection and may be helpful to assess for radio-opaque uroliths and anatomic abnormalities such as a thickened bladder wall, urachal remnant, or bladder mass. Ultrasound does not allow evaluation of the distal urethra.

**What causes idiopathic cystitis in cats?**

The most common age at initial presentation is 2 to 7 years. There is no single diagnostic test to confirm FIC, and diagnosis is based on exclusion of other etiologies for FLUTD. Spontaneous
resolution of clinical signs may be mistaken for response to empirical therapy (e.g., treatment with antibiotics).

Results of studies over the past 20 years suggest that idiopathic/interstitial cystitis in cats is the result of complex interactions between the bladder, nervous system, adrenal glands, husbandry practices and the environment in which the cat lives. Many cats with a diagnosis of feline idiopathic (interstitial) cystitis (FIC) have lower urinary tract (LUT)-predominant clinical signs that are part of a larger systemic disorder that has been referred to as ‘Pandora syndrome’. Additional medical problems not involving the lower urinary tract are common in FIC cats and may include signs related to the gastrointestinal tract, respiratory system, skin, central nervous system, cardiovascular system and the immune system. It has been traditional to refer to cats that have obvious LUT signs of undetermined cause as those having “feline urological syndrome”, “feline lower urinary tract disease”, “feline idiopathic hematuria” and “feline interstitial cystitis”, but this method of naming the disease focuses on an organ (urinary bladder) with the predominant clinical sign rather than a thoughtful evaluation of the entire cat and all of its organ systems. “Pandora syndrome” would apply to those cats that exhibit clinical signs in other organ systems (in addition to the LUT), waxing and waning of clinical signs associated with stressful events that presumably activate the stress response system, and undergo resolution or improvement in severity of clinical signs following effective environmental enrichment.

There are four possible urinary presentations associated with FIC.

1. An acute self-limiting episode of non-obstructive LUT signs is thought to be the most common presenting condition; recurrence may occur if stressful situations become severe enough in the future.

2. Frequently recurrent episodes of clinical signs related to non-obstructive FIC is next in occurrence.

   Clinical signs associated with an initial or recurrent episode of non-obstructive idiopathic cystitis often resolve within about 7 days, with or without treatment. Over 50% of cats with idiopathic cystitis will have recurrent signs within 1 year based on recent studies.

3. Persistent forms of non-obstructive FIC in which the clinical signs never abate.

4. The fourth possibility is urethral obstruction development in male cats suffering from FIC.

**What is the best treatment for symptomatic idiopathic cystitis?**

The goals of managing FIC are to decrease the severity of clinical signs and increase the interval between episodes. It is important to help owners understand known predisposing factors and develop strategies to alleviate them. Multiple modalities are commonly used to manage FIC, including medications to provide analgesia and to decrease urethral spasm, dietary management, and environmental management to meet the individual cat’s needs.

There is no single best treatment! Since the cause is still undetermined in most cases it is likely that a multifactorial condition is present. An important treatment consideration is to maintain hydration status and increase water consumption if possible. This will help dilute the urine, increase bladder flushing via more frequent micturition and potentially reduce bladder mucosal exposure to noxious urine substances and less likelihood of obstruction in males.
Urethral obstruction is often due to urethral plugs or classified as idiopathic. Urethral plugs consist of a matrix (mucoprotein and inflammatory debris) and aggregates of crystals (predominantly struvite). Urinary prescription diets should be used in any cases with struvite crystals or urethral plug matrix. Change to a canned food diet is usually recommended as part of MEMO if this is not too stressful for the cat or the owners. The effects of feeding canned foods may be due to elaboration of more dilute urine due to increased moisture - this could prove less noxious when gaining access to the highly permeable bladder wall of the FIC cat. Alternatively, the oral feel of moist food may change the neurobiology of the cat. A third mechanism that could explain this benefit is the ritual of feeding canned foods is substantially different than that of feeding dry foods and could favorably alter the owner's interaction with the cat.

Anti-inflammatory and pain management treatment may be a very beneficial to reduce clinical signs. I frequently use oral meloxicam (0.05 mg/kg daily) and buprenorphine for 3-5 days; there is minimal risk for renal dysfunction or GI disease in otherwise healthy hydrated cats. Oxybutynin can also be used to lessen straining.

What other treatments might work to reduce idiopathic cystitis flare-ups?

Methods to reduce environmental stressors has also been effective in some cases. A review of the indoor cat lifestyle with appropriate relaxation modifications may be of great help in reducing the occurrence of this condition (The Ohio State University Indoor Pet Initiative). Information regarding the cat's environment, including diet, litterbox management, access to the outdoors, other pets in the household and potential stressors, may be helpful when modifying environmental conditions as part of chronic management of FIC. Available online surveys, such as the one included in the 2014 AAFP and ISFM Guidelines for Diagnosing and Solving House-Soiling Behavior in Cats (catvets.com/guidelines/practice-guidelines/house-soiling), can be helpful in obtaining a detailed environmental history.

The overarching premise of multimodal environmental modification (MEMO) is that some cats suffer adverse consequences of indoor housing, especially when cats are forced to spend nearly all of their time indoors in association with people and other animals. Behavioral studies demonstrate that captivity may elicit a stress response in some cats. The indoor environment of some house cats may be monotonous and predictable, which could be stressful. If we are to continue to recommend indoor housing to reduce the risks of exposure to accidents and infectious agents, recommendations to improve the indoor environment from the cat's point of view should be considered. Many indoor-housed cats appear to survive adequately by accommodating to less than perfect surroundings. The neuroendocrine abnormalities in cats with recurrent idiopathic cystitis suggest a sensitized response to stress indicating that these cats may have greater needs for enriched surroundings than do healthy cats. Extensive indoor housing in un-enriched environments does not create idiopathic cystitis, but it can contribute to its development and maintenance by unmasking the tendency of a particular cat to develop idiopathic cystitis in response to external risk factors. Successful MEMO may obviate the need for drug therapy in many instances. It has been estimated that 80% of cats with recurrent idiopathic cystitis will have clinically significant reductions in signs during the year following successful implementation of the first level of MEMO. Stressors in an individual cat can emanate from another cat, people, other aspects of environment or combinations of these. MEMO is a package of recommendations designed to reduce environmental or social stressors. A tailored treatment plan for
each cat is created, since individual cats and environments vary widely. These include general recommendations for all cats with FIC and then specific recommendations for some cats.

The American Association of Feline Practitioners and the International Society of Feline Medicine have described the 5 pillars of a healthy feline environment that support a cat’s physical health, emotional wellbeing, and interactions with humans and other animals in its environment:

1. Provide a safe place
2. Provide multiple, separated key environmental resources (food, water, toileting areas, scratching areas, play areas, rest areas)
3. Provide opportunities for prey and predatory behavior
4. Provide positive, consistent, and predictable human-cat social interaction
5. Provide an environment that respects the importance of the cat’s sense of smell

Litter box hygiene and management may be suboptimal for some sensitive cats, a situation that provides a source of stress for some cats with FIC. Optimal litter box management is often not discussed adequately with cat owners before problems with FIC develop. There are many nuances as to the suitability of the litterbox and substrate to any particular cat, such as adequate number and location, size, depth, shape, hooding and automatic cleaning devices. The goal is to make the litter box a pristine place for the cat to comfortably eliminate and not hesitate to do so willingly.

Increased interaction between cats and their owners may increase the quality of life for some cats. This may be accomplished depending on the particular cat during grooming and petting, playing games with laser pointers and simulating hunting of prey activities (feathered or tailed devices). Cats often enjoy playing with toys, particularly those that are small, move and that mimic prey characteristics. Use of containers or toys that intermittently release food during play may provide actions to simulate hunting behavior. Timing of these activities at dawn or dusk may be helpful since cats are generally more active at these times. It is essential to implement a system of follow-up consultation and encouragement that is often best executed by animal technicians with special interest and training in this area (under the supervision of a veterinarian).

Feline facial pheromones may be considered for cats with signs of stress or if signs persist after implementation of multimodal environmental modification (MEMO).

A cat that has been properly diagnosed with FIC will have the propensity to develop recurrent LUT signs for all of its life depending on the magnitude of exposure to external stressors. It is preferred to prevent future episodes of FIC with MEMO than to treat active flares.

Recent diets (Hill’s Prescription CD Multicare Stress formula) have become available that promote a “calming” effect to help reduce FLUTD.

**What is the best way to treat FLUTD cats with suspected urethrospasm?**
Both the smooth and striated muscle of the urethra can be hypertonic. To lessen smooth muscle tone, the alpha-antagonist *Phenoxybenzamine* has often been prescribed. The dose used most frequently is 2.5mg to 5.0mg PO daily. If needed, the dose can be increased up to a maximum 10mg/day in the cat. Administration of the drug divided BID may be more effective than using it once daily. Since this drug is an alpha-antagonist, the primary side-effect is hypotension. This drug should therefore never be used when a patient is clinically ill. If used in cats following relief of urethral obstruction it should not be started until azotemia is resolved. The efficacy of the drug has been questioned, particularly after urethral obstruction in cats. For the treatment of reflex dysnergia in dogs, phenoxybenzamine can be combined with striated muscle relaxant and a cholinergic drug for bladder atony.

*Prazosin HCl* is also an alpha-1 adrenergic antagonist used to reduce sympathetic tone and treat functional urethral spasticity in dogs & cats. While it may also cause hypotension at higher dosages it has proven to be safer and has superior efficacy compared to phenoxybenzamine in reliably reducing urethral tone. Feline dosage is 0.25 – 1.0 mg/cat PO q 8-24hr.

*Diazepam and Alprazolam* are striated smooth muscle relaxants, and may be used in combination with an alpha antagonist in FLUTD cats. Diazepam is dosed at 1.25 to 2.5mg per cat PO q 8hr. Alprazolam is dosed at 0.125 – 0.25 mg per cat 1-3 times a day. The potential for sedation as a side effect is minimal. Increased appetite may occur in some animals. Diazepam should be used with caution in cats as rare reports of hepatocellular necrosis have been reported.

Are there other drugs or supplements that may be helpful in reducing FLUTD?

There is insufficient evidence to support the chronic use of glucosamine products in cats with FIC. *Pentosan* is a glycosaminoglycan used to treat interstitial cystitis in women. It may improve bladder wall health and may lessen adherence of crystals and bacteria to the bladder mucosa. Cosequin for Cats can be tried and it is less expensive.

*Amitriptyline* can also be administered at 2.5 to 5.0 mg/cat po at night in an attempt to reduce interstitial bladder inflammation. This drug may relax the bladder wall (anticholinergic effect) and decrease mast-cell histamine release. If it is going to help it should do so within a 2 to 6 week period. Many cats in my experience may improve but relapse while still receiving this drug. Studies documented no consistent benefit with short-term treatment with amitriptyline, although long-term treatment has not been evaluated. Transdermal preparations are variably absorbed and not recommended.

*Oxybutynin* (Ditropan) is frequently prescribed for stress incontinence in women. It has anticholinergic and antispasmodic effects. The dose is 1.25 to 10mg po q 8-12hr. Side effects are as for other anticholinergics. This drug has been used successfully to decrease urgency and discomfort in patients with idiopathic FLUTD.

Other suggested therapies for FIC have been shown to be ineffective or have been inadequately evaluated. *Antibiotics* should not be administered unless a urine culture by cystocentesis is positive. In cats with FIC, an anti-inflammatory dose of prednisolone given for 10 days did not reduce clinical signs compared with placebo.

Cats with FIC that were given a single treatment of lactated Ringer’s solution subcutaneously did not show improvement, but other subcutaneous fluid protocols have not been evaluated.
"Written in Stone"

Management of Canine and Feline Uroliths

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Introduction

Urolithiasis is a common medical disorder in both cats and dogs. Urolith formation occurs under specific circumstances that occur during sustained urine supersaturation with one or more substances allowing for precipitation, organization and growth. Most uroliths (> 95%) occur in the lower urinary tract of dogs and cats; a lesser percentage occur within the kidney or ureter. Management of uroliths varies depending on the mineral type and location. The presence of a stone does not always necessitate removal, however, when discomfort, infection or urine blockage occurs related to the stone then treatment is necessary. Treatment may involve dissolution, lithotripsy, removal via voiding (hydromassage), endoscopic removal or surgical removal depending on the stone composition and location.

What are the most likely urinary stones seen in dogs and cats?

Ongoing analysis of stones from dogs reveals approximately 80% are composed of struvite or calcium oxalate; in cats 90% of stones are composed of struvite or calcium oxalate. Currently struvite and calcium oxalate stones occur at almost an equal frequency in both species although calcium oxalate stones have been increasing over the past decade. Urate stones are the third most frequent mineral composition in both species. Other mineral compositions occur less frequently in both species.

Uroliths are usually diagnosed on survey radiography either as an incidental finding or in patients with symptoms of urinary tract disease. Occasionally, an astute owner may observe a naturally voided urolith in which case it should be submitted for analysis. When a urolith(s) is detected, the entire urinary tract (upper and lower) should be imaged to determine if additional uroliths are present in other locations. The most common uroliths (struvite and calcium oxalate) are radiopaque and readily visible on abdominal radiographs, however some uroliths have the same radiopacity as the surrounding soft tissues (radiolucent) and are difficult to detect on radiographs. If urolithiasis is suspected but not confirmed on survey radiography then (failure rate can be up to 25% depending on the size and composition of the stone) then ultrasound imaging should be performed as this modality will allow visualization of both radiopaque and radiolucent stones and has a false-negative result of 5%.

Once the number and location of uroliths is determined, the next step is to determine the type of urolith present and formulate a treatment plan. If a urolith is not voided for instant analysis, then the mineral composition can often be correctly predicted ("guesstimeted") based on the patient signalment, urinalysis and radiographic density.

Breeds: Miniature schnauzers - calcium oxalate, struvite and urate (due to portosystemic shunts). Dalmatians - urate (metabolism of uric acid). English bulldogs - urate and cystine. Dachshunds,

**Sex predisposition**: Struvite stones occur more frequently in female dogs. Metabolic stones tend occur more frequently in male dogs.

**Cats**: Longhaired cats (e.g., Burmese and Himalayans) - calcium oxalate formation. Struvite stones (not associated with bacterial urinary tract infection) typically form in cats less than 10 years of age.

**Urine pH**: > 7.0 - struvite, calcium phosphate/carbonate. < 7.0: Calcium oxalate, urate, cystine, silica.

**Cystalluria**: crystal type often associated with mineral composition of urolith.

**Radiographic features**: (see table below).

**Bacterial Infection**: bacteria producing urease (Staphylococcus spp, Proteus spp; rarely mycoplasma/Ureaplasma) result in struvite formation. Secondary bacterial infections can occur due to breakdown of local defense and may not be associated with a specific stone type.

**Metabolic issues**: Hypercalcemia - risk factor for calcium oxalate stones.

Hyperadrenocorticism - increased risk of calcium oxalate urolith formation (due to hypercalciuria) and struvite formation (due to bacterial urinary tract infection).

Immunosuppressive disease / Immunosuppressant drug therapy - increased risk for infection-induced struvite uroliths.

Liver disease - urate uroliths may form in animals with liver disease (e.g., portosystemic shunts).

### Characteristics of Common Canine Uroliths

<table>
<thead>
<tr>
<th>COMPOSITION</th>
<th>RADIOGRAPHIC DENSITY</th>
<th>SURFACE CHARACTER</th>
<th>URINE pH</th>
<th>CRYSTAL S</th>
<th>URINARY TRACT INFECTION</th>
<th>COMMONLY AFFECTED BREEDS*</th>
<th>OTHER</th>
</tr>
</thead>
</table>

(See table below for further details.)
<table>
<thead>
<tr>
<th>Calcium oxalate monohydrate (COM) and/or calcium oxalate dihydrate (COD)</th>
<th>Moderately to markedly radiopaque</th>
<th>Sharp projection, mulberry shaped or smooth round uroliths; COD may appear jackstone shaped</th>
<th>Acidic to neutral</th>
<th>Calcium oxalate dihydrate crystals (square envelope) or calcium oxalate monohydrate crystals (dumbbell or picket-fence shapes)</th>
<th>None or secondary urinary tract infection (UTI) with common uropathogens</th>
<th>Miniature schnauzer, Lhasa Apso, Yorkshire terrier, Bichon frise, Pomeranian, Shih Tzu, Cairn terrier, Maltese, miniature poodle, Chihuahua</th>
<th>Often multiple small uroliths in bladder; multiple nephroliths if present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struvite (magnesium ammonium phosphate hexahydrate)</td>
<td>Moderately to markedly radiopaque; larger uroliths appear more radiopaque</td>
<td>Single may be smooth or speculated; Multiple smooth surfaces where uroliths contact each other, often pyramidal shape</td>
<td>Alkaline</td>
<td>Struvite or “triple phosphate” crystals (&quot;coffin lid&quot; appearance)</td>
<td>Urease-producing organisms <em>Staphylococcus</em>, (Proteus, mycoplasm a); sterile struvite uroliths in cocker spaniels</td>
<td>Miniature schnauzer, Shih Tzu, Bichon frise, miniature poodle, cocker spaniel, Lhasa Apso</td>
<td>Uroliths &gt;10 cm diameter are likely to be struvite; nephroliths are often staghorn shaped</td>
</tr>
<tr>
<td>Urate/xanthine</td>
<td>Radiolucent to faintly radiopaque</td>
<td>Multiple smooth uroliths</td>
<td>Acidic</td>
<td>Ammonium urate crystals (yellow-brown &quot;thorn apple&quot; or spherical shapes) or amorphous urate crystals</td>
<td>None or secondary UTI with common uropathogens; rarely, urease-producing organisms</td>
<td>Dalmatian, English bulldog, miniature schnauzer, Shih Tzu, Yorkshire terrier</td>
<td>PSS or other liver dysfunction; yellow-green urolith color</td>
</tr>
<tr>
<td>Cystine</td>
<td>Faintly to moderately radiopaque</td>
<td>Multiple smooth round uroliths in bladder and/or urethra; nephroliths may be staghorn shaped if present</td>
<td>Acidic</td>
<td>Cystine crystals (hexagonal shape) Cystine crystalluria always abnormal</td>
<td>None or secondary UTI with common uropathogens</td>
<td>Mastiff, Australian cattle dog, English bulldog, Staffordshire bull terriers, Newfoundland, dachshund</td>
<td>Positive urine cyanide-nitroprusside test; metabolic screening of urine available; males &gt;&gt; females</td>
</tr>
</tbody>
</table>
Calcium phosphate | Moderately to markedly radiopaque | Hydroxyapatite - multiple small uroliths with variable shape; brushite - multiple smooth round or pyramidal uroliths | Alkaline to neutral pH for hydroxyapatite, acidic for brushite | Amorphous phosphates or calcium phosphate crystals (thin prisms) | None or secondary UTI with common uropathogens | Yorkshire terrier, miniature schnauzer, Bichon friese, Shih Tzu, springer spaniel, Pomeranian, miniature poodle, cocker spaniel | Hypercalce mia is a predisposing factor

Silica | Moderately radiopaque | Classic jackstone appearance | Acidic to neutral | None | None or secondary UTI with common uropathogens | German shepherd, OESD, Labrador retriever, golden retriever, miniature schnauzer, cocker spaniels, Shih Tzus, Bichon frises | Males >> females

**There are crystals in the urine – should I change the diet?**

Therapy per se for crystalluria is usually not necessary however the findings of crystals may warrant additional diagnostic investigations.

Microscopic mineral precipitates in urine are crystals and their solubility depends on the urine pH, temperature, and specific gravity. Crystals commonly are present in the urine of dogs and cats and often are of little diagnostic significance. The presence of crystalluria is not synonymous with disease. This is particularly true of struvite and calcium oxalate crystals in all breeds and urate crystals in dalmatians. > 50% of urine samples in healthy dogs will contain struvite crystals without a bacterial urinary tract infection and without subsequent urolith formation. Bilirubin crystals may be found in concentrated samples of normal dog urine.

Conversely, some crystal types are not a normal finding and warrant further investigation even in the absence of uroliths. These include cystine, xanthine, and (in breeds other than dalmatians) urate crystals.

Likewise, some animals with active stone disease will not have crystals; however, most animals with active struvite stone disease will be crystalluric.

**Do all stones need to be removed?**
While it is desirable to obtain a valid stone analysis to determine appropriate dietary and supportive treatments, not all stones need to be removed from a practical sense. Fortunately, struvite stones can be medically dissolved. Non-dissolving stones that are not causing abnormal clinical signs do not necessarily have to be removed especially when associated with patients that have high anesthetic risk, compromised renal function, when stones are located in areas of high surgical risk (kidneys, ureters). Patients that have repeated stone reoccurrences may not need removal if they remain silent.

**Management of Struvite Uroliths**

Struvite uroliths may develop in any dog with urease-producing bacterial urinary tract infection. They are more common in female dogs because of the higher risk for bacterial urinary tract infection. They may also occur in dogs with immunosuppressive diseases or receiving immunosuppressive therapy. They occur at any age, but are more common in younger adult dogs and are the most common type of urolith in puppies (dogs <1 year of age). Infection-induced struvite urolith formation are occasionally seen in older cats (>10 years) and in kittens (<1 year) because of their increased risk for development of a bacterial urinary tract infection.

Sterile struvite uroliths occur typically in young adult cats. Sterile struvite uroliths have been documented in dogs, but it is very rare. Sterile struvite uroliths are typically composed of 100% struvite and do not contain "contaminant" minerals. The mechanism(s) for sterile struvite formation is not clear, although an alkaline urine pH is necessary. Persistent or recurrent alkaluria is a predisposing risk factor for sterile struvite formation. Other factors that have a role include: highly concentrated urine resulting in retention of urine and concentration of calculogenic minerals and high levels of magnesium and phosphorous in feline urine.

The goal of struvite urolith therapy is to eliminate existing uroliths, eliminate bacterial urinary tract infection, and prevent recurrence of uroliths. Existing struvite uroliths may be dissolved medically by changing the state of urine saturation to undersaturated which "pulls" minerals from the stone causing gradual progressive shrinking. Other methods of stone removal may be performed when necessary.

**Infection-induced struvite:** A change in diet to a prescription selection that is reduced in protein content (reduced urea and ammonia), lower in magnesium, lower in phosphorous, acidifying, and induces diuresis will produce stone dissolution. It is important to also eradicate the UTI that caused the infection-induced struvite uroliths to form; therefore, an appropriate antimicrobial agent (based on urine culture) must be administered during the entire treatment time of stone dissolution. As the stone dissolves, trapped bacteria are released justifying the prolonged antibiotic therapy. Clinical signs often improve or resolve within 2 to 4 days of treatment initiation. Average dissolution time is 8 weeks but depends on urolith size. Urinalysis and a lateral abdominal radiograph should be monitored every 4 weeks. Uroliths usually decrease in size and/or number by approximately 50% in the first 4 weeks of beginning dissolution. Dissolution therapy should continue for 4 weeks beyond radiographic evidence of dissolution of uroliths to ensure all stones are dissolved. An alternative dissolution protocol was reported to be effective in >80% of dogs. In this protocol, the diet was not changed; but instead a urinary acidifier (d,l-methionine) was administered in combination with an appropriate antibiotic. The potential advantage is that the diet does not require changing and the acidifier is safe. However, a possible disadvantage in that study is 2 dogs had stones that did not dissolve and had a shell of calcium phosphate on analysis that may have developed from "over" acidification.
**Sterile struvite:** A change in diet to a prescription selection that is reduced in protein content (reduced urea and ammonia), lower in magnesium, lower in phosphorous, acidifying, and induces diuresis will produce stone dissolution. Antibiotic therapy is not necessary (unless a secondary UTI is documented). Sterile struvite uroliths typically dissolve more rapidly in 2–4 weeks; therefore, at 4 week recheck, uroliths may no longer be visible on survey abdominal radiographs. The diet should be continued for 2 to 4 weeks beyond medical dissolution.

**Prevention of struvite uroliths:** Prevention of repeat struvite urolith formation involves modifying the risk factors that caused the stone to form initially. For infection-induced struvite stones, the most important component is preventing bacterial urinary tract infection. Long term dietary modification for prevention of infection-induced struvite uroliths is not warranted, and often not successful. For sterile struvite stones, long term dietary modification is often required to decrease risk of recurrent sterile struvite urolith formation. Specific struvite preventative diets are modified to decrease risk.

Commercial calculolytic diets are available for dissolution of struvite uroliths in dogs and cats: (1) Hill's Prescription Diet s/d® and c/d® Multicare, (2) Royal Canin Canine S/O Lower Urinary Tract Support Diet, (3) Purina St/Ox Feline.

**Why does struvite dissolution diet therapy not always work for me?**

Medical dissolution of infection-induced struvite stones requires a combination of appropriate antimicrobial and calculolytic dietary therapy. Antibiotic selection should be based on urine culture and antibiotic-susceptibility testing from urine obtained by cystocentesis. Antimicrobial therapy must be given throughout the entire dissolution period because viable bacteria are contained within each layer of struvite uroliths. Antimicrobial and dietary therapy should continue approximately 4 weeks beyond radiographic resolution of struvite urolithiasis because uroliths too small for radiographic detection may still be present. Average time for dissolution of canine infection-induced struvite stones is often 2 months.

A common cause of failure to effectively dissolve struvite uroliths is inadequate control of the UTI. Therefore if therapeutic attempts fail or cease, urinalysis and urine culture should be repeated. Another common cause of dissolution failure is poor diet compliance by the patient (or the owner). Also if the urolith contains layers of calcium apatite, carbonate apatite, or calcium oxalate, this may prevent dissolution of the struvite component of the urolith. If the suspected struvite urolith is composed of another mineral obviously dissolution will fail as well.

**Calcium Oxalate Urolithiasis**

Calcium oxalate uroliths are common and account for 40–50% of all uroliths and >85% of nephroureteroliths. Increased urinary calcium excretion (hypercalciuria) may result from hypercalcemia, excessive GI absorption of calcium, bone resorption or reduced calcium reabsorption form the renal distal tubules. Increased urinary oxalate excretion (hyperoxaluria), may result from excessive absorption from the GI tract, excessive absorption from the GI tract
due to reduction of certain enteric bacteria that metabolizes oxalate in the GI tract (Oxalobacter formigenes), and possibly due to vitamin B6 deficiency.

Medical protocols that promote dissolution of calcium oxalate uroliths have not been identified; therefore, if necessary uroliths must be removed physically. Removal of calcium oxalate uroliths may involve minimally invasive or invasive procedures. Cystotomy and/or urethrotomy/urethrostomy may be required for larger stones or if a stone becomes lodged in the urethra. Voiding urohydropropulsion is indicated for removal of smaller stones.

Calcium oxalate uroliths are generally recurrent; therefore, preventative measures are warranted. There is an 8% recurrence at 6 months, a 35% recurrence at 1 year and increasing percentages in subsequent years. "Pseudorecurrence" refers to leaving uroliths behind after a procedure is performed and occurs in 15–20% of cystotomies. If hypercalcemia is documented then the potential cause should be investigated and treated (i.e., primary hyperparathyroidism in dogs), idiopathic hypercalcemia in 20–35% of cats with CaOx uroliths. Prevention is best achieved by decreasing urinary levels of calcium and oxalate and by increasing urine volume in order to dilute the minerals.

**What is the best means of preventing Calcium Oxalate urolith reoccurrence?**

Great question but difficult answer!

The most important feature of CaOx stone prevention may be the addition of water to the diet or changing to a canned diet formulation. A larger volume more dilute urine can effectively dilute calculogenic substances and increase voiding to flush/remove free crystals in the urinary tract. The client can obtain a refractometer and monitor urine specific gravity at home with a goal of maintaining Usg < 1.020.

**Diet Management for CaOx uroliths**

Cats with normal serum calcium levels should be fed a diet that induces diuresis, is mineral restricted, and induces a neutral to alkaline urine pH. There are several "multiple use" feline diets formulated to prevent struvite and calcium oxalate. Data from controlled clinical studies in cats with CaOx uroliths is lacking but data from healthy, non-urolith-forming cats have demonstrated decreased urinary saturation with calcium oxalate when cats consumed oxalate preventative diets. Cats with idiopathic hypercalcemia should be fed a high fiber, mineral restricted diet.

Dogs should be fed a diet that is mineral restricted, alkalinizing and induces diuresis. These diets are generally higher in fat compared to maintenance foods and may cause unwanted weight gain or predispose certain breeds to pancreatitis (i.e., Miniature Schnauzers). Patients in which dietary fat is a concern can be fed a higher fiber diet and an oral alkalinizing agent (potassium citrate).

**Pharmacologic Management for CaOx uroliths**
Oral potassium citrate may be beneficial in managing calcium oxalate uroliths because it is a calcium oxalate inhibitor and because it is alkalinizing in nature. Citrate forms a soluble salt with calcium in the urine and may inhibit calcium oxalate crystal formation. Calcium oxalate preventative diets often contain supplemental potassium citrate. Oral supplementation has been recommended at a dose of 50 to 75 mg/kg orally every 12 hours if the urine pH is acidic or if calcium oxalate crystals are still present despite dietary therapy. Dosage is titrated to achieve a urine pH of approximately 7.5.

Vitamin B6 increases metabolism of glyoxylate, a precursor of oxalic acid, to glycine. Whether vitamin B6 deficiency occurs in adult animals with calcium oxalate uroliths is unknown, but unlikely. Vitamin B6 supplementation is however inexpensive and safe and should be considered in pets that have difficult to control recurrent CaOx uroliths.

Thiazide diuretics: induce diuresis and decrease urinary calcium excretions they may be beneficial in patients with difficult to control CaOx uroliths. Diuretic administration may be associated with dehydration and electrolyte imbalances and should be used cautiously in patient with renal dysfunction.

Supplementation of vitamin C or vitamin D should be avoided in dogs with calcium oxalate urolithiasis. Because vitamin C is converted to oxalate, excessive vitamin C may contribute to hyperoxaluria and increased risk of calcium oxalate urolithiasis. Vitamin D supplementation increases intestinal absorption of calcium, thereby promoting hypercalciuria and increased risk of calcium oxalate urolithiasis.

How do I manage ammonium urate stones?

Urate comprises 5–8% of uroliths retrieved from dogs and cats. Ammonium urate is the primary salt. It is the second most common mineral found in uroliths from dogs and cats <1 year of age behind infection-induced struvite.

For urate uroliths to form, urine must be oversaturated with ammonia and uric acid, which can occur in genetic predisposed breeds (Dalmation, English Bulldog) or in associated with liver dysfunction particularly small-breed dogs, often <1 year of age with portovascular anomalies. Uric acid is a metabolic product of purine metabolism. Purines originate endogenously from cell turnover (nucleic acids) and exogenously from diet. In most dogs and cats, the final endpoint of purine metabolism is allantoin. For urate urolith formation, uric acid is the metabolic endpoint. Uric acid is converted to allantoin by hepatic uricase. With liver disease, this conversion does not occur and without liver disease, there is a transport defect where this conversion does not occur. Dalmatians have adequate hepatic uricase; however, they lack a necessary transporter encoded by the SLC2A9 gene. This results in slightly higher serum uric acid concentrations when compared to most non-Dalmatian breeds of dogs and high urine uric acid concentrations. Urine uric acid concentrations are typically 20–30 mg/dl/24h in non-Dalmatian dogs and 600–1200 mg/dl/24h in Dalmatians. High uric acid excreting (HUA) Dalmatians are homozygous recessive for the SLC2A9 gene; therefore, all excrete higher levels of urinary uric acid; however, incidence of urate urolithiasis is 10–30%.

Treatment of urate uroliths in dogs involves combining dietary modification and urine alkalinization to promote stone dissolution. Several commercial prescription "ultra-low protein" alkalinizing diets are available (Royal Canin Urinary UC, Purina HA, Royal Canin Hydrolyzed Protein HP or Royal Canin Vegetarian). Potassium citrate (initial dose 40–90 mg/kg PO q12hr) may be used
to alkalinize the urine if necessary. Urine pH values over 7.5 may predispose to the formation of calcium phosphate uroliths.

Allopurinol (15 mg/kg PO BID) is a drug that blocks conversion of xanthine to uric acid. This results in decreased concentrations of uric acid and ammonia in urine and alkaluria. Dissolution usually occurs in 4–8 weeks; if it does not occur by then, it won’t. Dissolution is successful in approximately 1 out of 3 dogs; in 1 out of 3 dogs, stones decrease in size but do not dissolve and most can be retrieved non-surgically; and in 1 out of 3 dogs, stones increase in size or number associated with xanthine formation. Allopurinol should be discontinued for 1 to 2 months and dietary therapy continued to allow for xanthine dissolution.

No published protocol for medical dissolution exists in cats. There is no "ultra-low protein" diet available in cats. Urate uroliths have been dissolved using "renal failure" diets and administering allopurinol at 50% of the dog dose.

Dissolution therapy is not typically successful in patients with liver dysfunction therefore, minimally invasive or invasive removal may be required. Surgical removal may be performed at time of correction of a portovascular anomaly or medical treatment of underlying liver disease helps with prevention.

Longer term measures to reduce reoccurrence include feeding an "ultra-low protein" or "vegetarian" diet on a long term basis - this is successful in >80% of dogs. Occasionally, a low dose of allopurinol is also required.

**What is the significance of ammonium urate stones in non-Dalmation breeds?**

Urate-containing calculi confirmed in non-Dalmatian dogs is usually an indicator of hepatic dysfunction. Diagnostic testing to evaluate for an underlying portovascular anomaly (i.e., shunt) or other hepatic disorder should be performed.

**Cystine Urolithiasis**

Cystine urolithiasis occurs due to abnormally high levels of cystine in urine. This occurs as a heritable disorder in dogs due to a proximal renal tubular defect in cystine reabsorption. Urinary loss of other amino acids is often documented in these dogs - COLA (cystine, ornithine, lysine, arginine). The most common affected breeds include English bulldogs, Newfoundlands, and Dachshunds with an increased prevalence in young adults, males > females. Typical urinalysis findings include aciduria and cystine crystalluria. Radiography reveals multiple, small, round, smooth, marginally radiodense stones. UTI is not present unless caused by a secondary infection. General laboratory evaluation is usually normal.

Cystine uroliths can be dissolved. by feeding an ultra-low protein or vegetarian diet in dogs (or a renal diet in cats). Low protein diets are typically alkalinizing. Cystine is more soluble in alkaline pH >7.2. An alkalinizing agent may also be necessary as well (e.g., oral potassium citrate). Administration of a thiol-containing drug (2-mercapto- propionylglycine (2-MPG) and D-penicillamine). These drugs bind to the individual cysteine molecules at the sulfur groups preventing cystine formation. Do not use these drugs in cats as it causes hemolysis. Inducing a diuresis decreases concentration of urinary cystine and therefore urinary saturation for cystine.

Long term prevention is accomplished by continuing a low protein or vegetarian-based diet and is effective in >90% of dogs. Urine pH should be maintained >7.5. If necessary, administer a thiol containing drug.
Can I perform voiding urohydropropulsion to remove cystic calculi in my practice?

Voiding urohydropropulsion is a non-surgical technique used to remove smaller urocystoliths in dogs and cats. This technique uses a forced urine void in a sedated/anesthetized patient that is positioned vertically to encourage urocystoliths to pass with the voided urine stream. Heavy sedation or general anesthesia facilitates urethral relaxation and makes the procedure easier and safer to perform. As a general guideline, females may pass stones in the 5-10mm range; males may pass stones in the 1-5mm range.

To perform this technique the patient is heavily sedated or anesthetized and the urinary bladder is distended (based on abdominal palpation) with sterile saline via urethral catheterization. The patient is positioned so that the spine is roughly vertical to the ground surface; smaller patients can be held up by the axilla, larger dogs may require a tilt table (or very strong technicians). The bladder is palpably agitated to remove stones from the bladder mucosal surface and settle in the bladder neck. The urinary catheter is removed and steady pressure is applied to the bladder via palpation to initiate detrusor contraction and induce a strong urine flow. Once voiding begins, the bladder is compressed firmly to maintain maximum urine flow rates, dilate the urethra, and flush out the urocystoliths. Place a collection container under the urethral orifice or vulva to collect voided stones. The procedure is repeated until all stones are removed. Postprocedural radiographs are performed to confirm complete removal of the urocystoliths.

This technique is ideal for patients that develop recurrent stones; however, to be successful the stones must be small enough to pass through the urethra so the timing of follow-up imaging is needed for early detection.

Do not perform in animals that have had a cystotomy in the previous 14 days as incision strength is reduced. Use caution when applying pressure on the bladder in patients with bacterial cystitis as this may cause reflux of infected urine up the ureters into the kidneys. Hematuria occurs commonly and generally subsides in a couple of hours. This procedure will not work if urethral obstruction is already present. Urethral obstruction may occur if one or more stones are larger than the smallest diameter of the urethra. Bacterial urinary tract infection occurs uncommonly, but may occur secondary to poor technique and urethral catheterization; an appropriate antibiotic can be prescribed if there is concern that infection may have been induced. Bladder and/or urethral rupture could occur, but is very rare.

Is lithotripsy an effective treatment for stones in dogs and cats?

I am commonly asked why we don’t recommend lithotripsy in dogs and cats as is often performed in people for stone fragmentation. The answer is expensive, more time consuming compared to surgery, does not always work well for cystic calculi and is not widely available. There are 3 basic types of lithotripsy.

Extracorporeal shock wave lithotripsy (ESWL) is fragmentation of uroliths using shock waves that are generated outside the body. ESWL is better for fragmentation of uroliths fixed in one location such as nephroliths or ureteroliths but cystic calculi have been fragmented with this technique. It is another
minimally invasive alternative for the removal of upper tract calculi in the renal pelvis, or ureters. ESWL uses external shockwaves that is passes through a water medium directed under fluoroscopic guidance in 2 planes. The stone is shocked at different energy levels to allow for implosion and powdering of a stone. The debris is then left to pass down the ureter into the urinary bladder over a 1-2 week period. This procedure can be performed safely in nephroliths smaller than 5 mm, and ureteroliths smaller than 3 mm.

Electrohydraulic lithotripsy (EHL) was the first form of contact lithotripsy developed. EHL can fragment urinary calculi of all compositions but it has the narrowest margin of safety. Injuries to structures surrounding a stone occur when the probe discharges too close to the tissues. the generator creates hydraulic shock waves that can successfully fragment and remove urocystoliths and nephroliths. The procedure requires cystoscopy and specialized EHL generator and takes from 1 to several hours to complete.

Laser lithotripsy using the holmium laser can be performed through a cystoscope. Cystoscopy is performed and a Ho:YAG laser fiber is inserted through the operating channel. The laser energy is used to fragment the stone into small fragments that can be retrieved.

What other minimally invasive techniques might be used vs open cystotomy?

Cystoscopy can be performed using rigid cystoscope (in female dogs and cats) or flexible cystoscope (in male dogs). Direct visualization of the lower urogenital tract may allow retrieval of uroliths with baskets and/or graspers that are inserted through the operating channel of the cystoscope. Uroliths must be small enough to be extracted through the narrowest portion of the urethra.

Cystoscopic-assisted cystotomy: A cystoscopic-assisted cystotomy is similar to laparoscopic removal. A small incision is made on ventral midline. In male dogs, the incision is made just cranial to the preputial reflection. The urinary bladder is grasped and brought to the incision edge of the linea. It is sutured to the edges of the linea. A stab incision is made and a rigid cystoscope is inserted into the urinary bladder. Stones are retrieved using instruments passed through the cystoscope.

Upper Urinary Tract Considerations - How to manage Nephroliths and Ureteroliths.

Nephroliths contributing to pelvic outflow obstruction, recurrent infection, pain, and those enlarging to the point of causing renal parenchymal compression should be considered for removal. Nephroliths traditionally have been removed by pyelolithotomy or bisection nephrotomy but is associated with substantial loss of renal function. The development of interventional urinary procedures allows for stone removal and drainage of the renal pelvis, (i.e., retrograde ureteroscopy with lithotripsy, percutaneous nephrolithotomy (PCNL) and Percutaneous Nephrostomy Tube Placement).

Ureteroliths can also be present, especially in cats, and may cause urinary blockage resulting in hydrourereter and hydronephrosis. If ureteral obstruction is present causing hydrourereter and hydronephrosis then placement of a ureteral stent or subcutaneous ureteral bypass device
(SUB) should be performed. If hydroureter and hydronephrosis are not present associated with a ureterolith, then medical expulsion therapy may be attempted and if unsuccessful then additional procedures as described should be considered.
DIAGNOSIS, TREATMENT AND PREVENTION OF CANINE URINARY INCONTINENCE

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INTRODUCTION

Micturition refers to the normal physiologic process of storing and periodically voiding urine. It is a complex process involving central, sympathetic, parasympathetic, and somatic nervous integration and regulation of muscular activity affecting the urinary bladder and the urethra. The urinary bladder and the proximal urethra are composed of smooth muscle under autonomic nervous system control and the distal urethra is composed of skeletal muscle under somatic nervous system control.

Urinary incontinence (UI) is the involuntary leakage of urine. In other words, a dog urinates when it does not intend to do so due to loss or weakening of the normal micturition process. There are numerous disorders of the lower urinary tract that can result in urinary incontinence; broadly classified into lower urinary tract inflammation, urethral sphincter incompetence, congenital anatomic anomalies (ectopic ureter, vaginal stricture) and abnormal urine retention and overflow. Partial urethral obstruction due to luminal stone presence can result in paradoxical incontinence in male dogs. Functional urethral obstruction, also known as detrusor urethral dys-synergia (DUD) can also result in paradoxical incontinence in male dogs.

History, Physical Exam and Diagnostics

A focused and thorough history is essential when speaking with an owner complaining of an abnormal urinary issue. There are many disorders, including behavioral conditions, polyuria, pollakiuria, etc…, that may be confused with or promote incontinence. It is critical to establish that a pet is unaware of the passage of urine. The timing of the incontinence episodes and the observed ability of a dog to initiate and maintain urination while emptying the bladder are important in determining the probable cause.

Congenital anomalies such as ectopic ureter should be suspected in very young dogs that have never been continent or have been “difficult to house train”. Patients with UI and concurrent increase in water intake should be evaluated for disorders causing polyuria and polydipsia. Patients whose UI and concurrent pollakiuria or stranguria should be evaluated for bacterial UTI, urolithiasis or infiltrative LUTD disease.

Physical examination should focus on the caudal abdomen and lower urinary tract; exam should include a digital rectal examination with careful palpation of the urethra and prostate. Urethral infiltrative/obstructive disease, including urethral/prostatic neoplasia and prostatic hyperplasia, may be best detected on this exam. Always make it a priority to observe the dog while it is actively urinating. Dogs with urethral sphincter incompetence will urinate normally. Male dogs often have overflow incontinence associated with structural or functional urethral obstruction as a common cause of UI. Residual urinary bladder volume should be determined when incomplete or disrupted urination is observed. Neurologic and orthopedic examination are conducted if a dog has difficulty posturing normally to urinate, as this can lead to interrupted urination, incomplete emptying of the bladder and overflow UI.
Complete urinalysis is performed in all patients with UI or any time UI relapse occurs in a previously continent dog. Urine leakage may be exacerbated by a bacterial urinary tract infection (UTI) and incontinence itself may predispose a patient to the development of UTI.

Additional diagnostics should be performed in older dogs that develop UI or in cases in which other findings suggest that USMI is not the primary consideration. Survey radiographs and/or ultrasound exam are performed to evaluate for urethral calculi in male dogs and to evaluate the urinary bladder in patients with dysuria, inflammatory urine sediment and lack of response to antibiotics. Some dogs may have mild USMI and are rarely incontinent until increased urine volume develops as a result of polydipsia or a lack of urinary concentrating ability (PU/PD).

**DISORDERS OF URETHRAL MUSCLE COMPETENCE**

**Urethral Sphincter Mechanism Incompetency (USMI)** The most frequent disorder resulting in canine urinary incontinence is urethral sphincter mechanism incompetence (USMI); occurring in up to 20% of neutered females with increasing prevalence in neutered female dogs weighing more than 20kg. It is characterized by intermittent involuntary leakage of urine, usually when the patient is resting or sleeping; awake voiding is normal. USMI is less commonly seen in intact females, intact and neutered males and cats. Onset of incontinence is usually observed 1-4 years following ovariectiony. As previously mentioned, some females may not develop obvious clinical incontinence until later in life when other disorders cause increased urine production or lower urinary tract inflammation associated with bacterial UTI.

Breed predisposition has been reported in Boxer, Doberman Pinscher, German Shepherd, Weimeraner and Old English Sheepdog. Larger breed dogs (>15 kg adult weight) that are neutered early are reported to be at increased risk for developing USMI.

Risk factors associated with USMI have been identified but the exact mechanism for development remains unclear. Multiple factors including the pituitary-gonadal axis, the anatomic structure of the lower urinary tract, and the integrity and tissue characteristics of the lower urinary tract supporting structures all likely play an integral role in USMI development. Urethral muscle tone, the strength of supporting pelvic structures, and the position of the urinary bladder contribute to bladder neck and urethral closing pressure. Following ovariectiony, the subsequent decline in estrogen levels is associated with an increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in females. These hormones may affect and decrease smooth muscle tone in the lower urinary tract. Estrogen also has trophic effects on the vasculature and tissue matrix of the lower urinary tract and its supporting structures; a decline in post-neutering estrogen level may reduce blood flow to the urethra and its supporting tissues which reduces urethral closing pressure.

Bladder position within the caudal abdomen also plays a supporting role in maintaining closing pressure to the bladder neck and urethra. Intra-abdominal pressure normally transmits equal pressure to both the urinary bladder and the proximal urethra favoring normal urinary continence. A caudally malpositioned urinary bladder (“pelvic bladder”) still is effected by abdominal pressure but pressure is relieved on the pelvic urethra; an increase in abdominal pressure occurring with movement, barking, and coughing may create enough of a pressure gradient between the bladder to urethra resulting in urine leakage.
Adrenergic alpha-receptors within the urethra muscle can be targeted to effectively increase urethral muscular tone in a post-neuter female dogs with UI. These receptors reduce in number and have diminished sensitivity following decrease in estrogen exposure. Pharmacologic alpha-receptors agonists can increase contractile tone of the urethral smooth muscle. This effect can be promoted by either increasing the number of receptors (with estrogen supplementation) or increasing stimulation (with α-agonist drugs) and forms the basis for medical therapy of acquired USMI in dogs.

Orally administered **estrogen replacement therapy** has been used for many decades in the treatment of USMI in dogs. Estrogen increases alpha-receptors and improves urethral vascularity as well as other urogenital mucosal characteristics. **Diethylstilbestrol (DES)** is available at veterinary compounding pharmacies as it is no longer manufactured for humans. Oral DES treatment is safe and reasonably effective (40–65%). Estriol (Incurin™, Merck Animal Health) is an FDA approved estrogen replacement product for dogs; estriol is reported to have a 93% response rate. The human drug Premarin administered at 20 mcg/kg po q 4 days is a potential alternative to DES, however, the drug does not seem to be as effective for most patients. Multiple treatment schedules are described for DES treatment. I prescribe DES at 0.5 – 1.0 mg dose (0.5mg for dogs <15kg and 1mg for dogs > 15kg) PO q 24hr x 7 days, then q 48hr x 7 days, then q 72hr for 7 days with the dosing frequency then tapered to q 5-7 day dosage. Incurin is started at 2 mg PO q24h initially and subsequently reduced to 0.5–2 mg PO q 2–3d based on clinical response.

Once urine continence has been maintained estrogen treatment may discontinued; subsequent UI relapse would require reinitiating and continuing drug therapy. Off-label injectable estrogens should never be used as they pose a much greater risk for bone marrow toxicity. Potential side-effects include estrus signs, gynecomastia and attractiveness to male dogs; these effects generally resolve when the medication dose is decreased or stopped. The risk of bone marrow suppression is extremely minimal when oral DES is used appropriately; a 1940s experimental study in Beagles required a 1mg dose every day for > 200 days to cause pancytopenia.

Gonadotropin releasing hormone (GnRH) analogs have also been used to treat USMI. Administration of GnRH analogs paradoxically reduces FSH and LH over time. It has been found to be effective in some studies.

**Phenylpropanolamine HCl (Proin™, PRN Pharmacal)** is an alpha-adrenergic agonist useful in increasing internal urethral sphincter tone via its effect on smooth muscle. Reported success rate associated with PPA ranges from 85% to 97%. The maximal alpha-receptor effect of this drug likely occurs 2-6 hours following oral administration. The FDA label dose is 2 mg/kg PO BID, however some dogs may be adequately controlled on once daily treatment while others may require TID dosing. An extended release formulation (Proin-ERTM) received FDA approval fin April 2019 for use in dogs with urinary incontinence due to urethral sphincter hypotonus. The new extended release formulation will allow for once daily administration at 2 to 4 mg/kg, thereby providing for owner ease of use, increased client compliance and in addition importantly reducing side effect potential due to the maintenance of a steady state blood level over an extended period of the day.

It has been reported that some dogs will regain continence but later relapse while still receiving the drug; alpha-receptor down regulation with continued drug use has been proposed; in this event temporarily discontinuing the medication followed by reinitiating may be effective by allow-
ing for receptor upregulation. Hypertension is a potential adverse effect of α-adrenergic therapy. Systolic blood pressure should be determined prior to and monitored initially after starting treatment especially in older or high-risk patients. Other side effects are uncommon but can include restlessness, insomnia, decreased appetite and aggression.

With refractory, PPA and an estrogen supplement can be given together and may provide for a synergistic effect on the alpha receptor and clinical improvement. If incontinence cannot be controlled with either an estrogen drug or PPA then the diagnosis should be re-evaluated. Abdominal ultrasund exam, CT contrast imaging and urethrocystoscopy should be considered; urethral dynamic testing can be considered if available. In cases in which USMI is still likely adjunctive treatment such as urethral collagen injection or surgical treatments to increase urethral pressure (colposuspension, cystopecty, urethropexy, cystourethrolepasty) may also be effective. Colposuspension, which attaches the uterine remnant to the pelvic ligament and drawing the bladder neck and proximal urethra farther into the abdomen, has variable success. More recently surgical treatments have centered on placement of urethral hydraulic constrictors to increase urethral luminal pressure.

Injectable urethral bulking agents, such as bovine cross-linked collagen, increases resting urethral pressure in dogs with UI. Collagen material is injected submucosally into the proximal urethra via cystoscopy which stretches sphincter muscle fibers enhancing closure pressure in the urethra and narrowing the diameter of the urethral lumen. Reported results of post-procedure continence is ~ 66% in affected female; continued medical therapy may improve efficacy. Injectable bulking agents have also been used with success in select male dogs. The drawback of this procedure is the variability in duration of effect due to collagen resorption; duration of continence ranges from 8 months to 2 years.

Surgical placement of a silicon hydraulic cuff urethral sphincter is a novel approach to increasing urethral pressure. It is attached to a subcutaneous port with an injection membrane. Fluid inside the cuff can be adjusted to achieve a level of pressure that will maintain continence during bladder filling but does not lead to obstruction when the bladder and abdomen contract. Initial published cases document significantly improved continence, with few dogs having complications involving partial urethral flow obstruction.

Continued medical therapy with PPA and/or estrogen is usually necessary following adjunctive urethral collagen or surgical treatments to improve the number of patients that will achieve acceptable results per client satisfaction.

**Male dogs with urinary incontinence issues**

Male dogs with UI pose a diagnostic and therapeutic challenge. Less than 50% of male dogs respond to medical therapy as described above; phenylpropanolamine has been the most successful treatment. Androgen replacement therapy with testosterone cypionate may result in clinical improvement in some dogs. Alternative treatment in males that fail medical therapy can also include placement of a hydraulic urethral sphincter and urethral collagen injections.

The poor treatment response of male dogs may relate to the fact that USMI may not be the cause of their UI. Large breed male dogs often develop spontaneous overflow incontinence secondary to an inability to empty their bladder during micturition due to spontaneous urethral hyperreflexia. Although the bladder can contract (intact detrusor function), failure of urethral relaxation results in a functional obstruction and urine retention. The exact cause of this condition (detrusor urethral dyssynergia /DUD) is unknown. Diagnosis is suspected after observing an
impaired urine stream following initiation of micturition leading to diminished bladder evacuation and increased residual urine volume. Other causes of obstruction, such as strictures, uroliths, and extramural compressive lesions, must be ruled out before a diagnosis of DUD can be made. Cystourethrography examination is suggested to rule out other causes of urethral obstruction and aid in confirming urethral luminal narrowing at the location of highest urethral resistance.

Medical treatment for DUD generally consists of urethral muscle relaxation and, occasionally, anxiolytic therapy. The prostatic urethra contains primarily smooth muscle, and the penile urethra contains primarily skeletal muscle. It is often necessary to use both smooth and skeletal muscle relaxants in these patients to achieve urethral relaxation and improved urine flow. Alpha α-adrenergic antagonists (prazosin, tamsulosin) can provide smooth muscle relaxation. Diazepam or alprazolam administered several times daily prior to urination provides skeletal muscle relaxation. Some dogs exhibit clinical signs only when stressed or anxious; these patients may benefit from trazadone, fluoxetine, or other anxiolytic medication. Clients can be taught to perform urethral catheterization in their male dog at home as needed when medications are not effective as this will provide immediate relief and prevent emergency visits. Some male dogs require significant initial medication dose adjustments to achieve optimal therapy and restore normal urethral flow. Some dogs will achieve spontaneous remission over time and no longer require drug therapy. Castration of intact males may also be of benefit. Dogs that do not respond to medical treatment could require a urethral stent implant.

**Conclusion**

Urinary incontinence is a frequent occurrence in dogs and is an anticipated medical issue in veterinary medical practice. There are multiple potential causes and thorough investigation is warranted. Treatment is based on the underlying cause which generally involves either an inability to hold/store urine or an inability to empty the bladder during active urination. Medical therapy is most often directed at altering urethral muscle function to either improve muscular tone or enhance muscular relaxation. Select cystoscopic and surgical treatments can be considered to improve outcome if medical therapy fails.
TRANSITIONAL CELL CARCINOMA

A new and better way to make the diagnosis.
The treatments that really can make a clinical difference.

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INTRODUCTION
Transitional cell carcinoma (TCC) is the most common urinary bladder tumor in both dogs (73% TCC, 9% undifferentiated carcinoma) and cats (60% TCC, 12% undifferentiated carcinoma). It is a commonly encountered neoplasm in dogs but is much less commonly seen in cats. TCC involves malignant proliferation of the transitional uroepithelium, the mucosal lining of the urogenital tract. It can affect any part of the urinary tract including the renal pelvis, ureters, urinary bladder, prostatic urethra (males), and the distal urethra. The urinary bladder is the most common site of involvement. In dogs, the trigone region of the urinary bladder is unfortunately the most common site of involvement.

RISK FACTORS
Thirteen purebred canine breeds represent 85% of the TCC patients that are diagnosed (American Eskimo, Australian Cattle Dog, Australian Shepherd, Beagle, Bichon Frise, order Collie, Jack/Parson Russel Terrier, Lhasa Apso, Rat Terrier, Scottish terrier, Shetland Sheepdog, West Highland White Terrier, Wire Fox Terrier). Beagles, Scottish Terriers, Shetland Sheepdogs, and West Highland White Terriers compromise over one-third of the these cases.

Almost all cases (95%) occur in dogs greater than 6 years of age. Females are more predisposed than males; male dogs generally urinate more frequently than female dogs so in theory urinary carcinogens are in contact with the uroepithelium for a longer period of time in females.

Some of the older studies look at animals that live close to mosquito sprayed areas and urban industrial areas. Insecticides and herbicides exposure has been implicated as a higher risk. Obesity is also a reported risk factor but the exact link is unknown - possibly obese individuals retain a higher insecticides level. A study that looked at Scottish Terriers found eating a diet that high in leafy green vegetables had a decreased incidence in the development of transitional cell carcinoma.

BIOLOGIC BEHAVIOR
While TCC can involve any area of the urinary tract or urinary bladder, the most common location for TCC development is the trigonal (neck) region of the urinary bladder. Over time the tumor spread can involve a larger area of the urinary bladder. Approximately one-third (1/3) of affected male dogs will have prostatic tubular involvement. As early clinical signs are identical to other lower urinary tract diseases the diagnosis may be delayed and it is estimated that about 15% of patient have metastasis at diagnosis. Metastasis may be either to the draining local lymph nodes
(sublumbar or iliac nodes), or can be to distant sites including pelvic bones, the lungs or other organs.

TCC is much less commonly seen in cats compared to dogs and there is very limited data (*Clinical signs, treatments, and outcome in cats with transitional cell carcinoma of the urinary bladder: 20 cases* (1990–2004). JAVMA July 1, 2007, Vol. 231. Wilson HM, et al.). Cats have been reported to have more apical location than trigonal. Progression of disease appears similar to what is seen in dogs.

**CLINICAL SIGNS**

TCC is often misdiagnosed or confirmed with advanced involvement because clinical signs are identical to those patients with urinary tract infection or cystic calculi. These patients often respond to antibiotics or other treatments, clinically improve, then relapse and undergo further diagnostic investigation delaying TCC diagnosis for several months. The most common clinical signs include hematuria, dysuria, pollakiuria and stranguria. A small number of patients can present with involuntary incontinence as there is involvement of the proximal urethra. Tenesmus may be described but usually it is because of straining to urinate.

Occasional patients may present with a partial or complete urethral obstruction. Lameness is a rare presenting clinical sign relating to either bone metastasis or paraneoplastic hypertrophic osteopathy (HO).

**PHYSICAL EXAMINATION**

Physical examination of often unremarkable. A far caudal abdominal mass may be palpable in small dogs or cats. Urethral or prostatic mass effect may be detected via digital rectal palpation in both males and females.

**GENERAL DIAGNOSTICS**

Bloodwork is generally unremarkable. Abnormalities including hematuria, pyuria, proteinuria, +/- bacteriuria are usually present to varying degrees on urinalysis (identical to urinary tract infection). Transitional cells may be present in the urine sample; they can vary in number and cytologic appearance; a clinical pathologist often has difficulty in determining reactive versus neoplastic cytology especially when there is concurrent inflammation which can make normal uroepithelial cells look more atypical.

**IMAGING STUDIES**

Survey abdominal radiographs are an important test to rule-out radio dense uroliths but are often normal in most TCC patients; although a caudal abdominal mass effect or dystrophic soft tissue calcification of tumor tissue may be detected. Pelvic bone metastatic involvement is present in some patients. Thoracic radiography may reveal pulmonary metastatic involvement so if TCC is considered likely thoracic views should be evaluated.

Ultrasound examination is an excellent means of evaluating for TCC involvement, usually allowing easy identification of abnormal mural tissue infiltrate/mass, localizing
location, determining proximal urethral and/or prostatic involvement, determining ureteral involvement, evaluating for local nodal metastasis and determining whether secondary hydronephrotic renal changes are present. While ultrasound does provide pre-treatment assessment, it may not be as good at determining response to treatment due to intra-and inter-operator variability and considering the fact that the bladder volume affects tumor measurements. CT imaging is also very good at detecting abnormal tissue but a study did show that when calculating tumor volume, CT and ultrasound are fairly comparable.

**DEFINITIVE DIAGNOSIS**
Traditionally TCC diagnosis is based on tissue histopathology (gold standard). Tissue samples can be obtained either through surgery, cystoscopy, or via traumatic catheterization. Urine cytology may be helpful but can be misleading as inflammatory urine sediments often contain atypical “angry” uroepithelial cells; however if large rafts of atypical epithelial cells with mitotic figures or multiple nucleoli are present then neoplastic TCC is certainly likely. Ultrasound-guided fine needle aspiration cytology of abnormal tissue can be considered and may also reveal rafts of large atypical epithelial cells but there are some limitations including allowing cancer spread along the needle tract line within the abdomen and into the subcutaneous tissues and skin.

Could we find these tumors without invasive tissue sampling? If we could find them easier and earlier, would treatment results be better? Identifying an “actionable” molecular anomaly in a free catch urine sample could allow for a simpler non-invasive test for TCC. The single BRAF mutation has been identified in TCC cells and this mutation is involved in sustained activation of a very specific pathway, that plays a role in cancer development. The BRAF mutation can be routinely tested in genetically predisposed dog breeds or can be used in patients with recurrent urinary tract signs. Blood in the urine, protein in the urine, and bacteria in the urine do not influence the test result.

The basic BRAF mutation is detected in 85% of confirmed TCCs (85% sensitive, 15% false negative, zero false positives). This test can detect down to 0.03% of mutated alleles so it requires very few cells to be able to determine a positive result. This test can also provide the level (or amount) of current disease. Higher level of mutated cells is generally associated with symptoms and has visible disease. Lower level means that earlier (or less) disease. 15% TCC dogs may not have the specific BRAF mutation. However, a second test can be performed which detects an additional 10% of these TCC dogs increasing sensitivity to 95%.

The BRAF test can be used to monitor disease status as well. Initial tests demonstrate that BRAF levels go down following chemotherapy and when the disease starts to return again the value increases.

**TREATMENT**
Traditionally, TCC is a difficult cancer to treat and usually only palliative measures are provided because this tumor is usually located in trigonal region of the bladder. If it is
identified in an apical location then traditional surgical excision should be considered as early complete resection could result in a potential cure; however local reoccurrence may still occur due to a local "field effect.” Some studies suggest that local excision followed by chemotherapy or piroxicam treatment may result in longer remission times so early surgery before extensive disease has developed should be a consideration.

Laser ablation has also been studied as a local palliative treatment to debulk tumor mass. However, cancer cells will be left behind and will start to grow again. Multiple treatments may be performed to maintain clinical remission for as long as possible. This procedure can be difficult to perform in very small breed and male dogs.

Many medical treatments to reduce tumor mass and delay progression have been investigated but a preferred protocol remains undetermined. Treatment with a COX-2 inhibiting nonsteroidal anti-inflammatory drug is popular due to simplicity, availability and low side effect potential. Piroxicam is the drug that has been studied the most; a dose of 0.3 mg/kg PO QD will generally provide a partial response, or at least stable disease with an average survival in most studies of six months. Deracoxib and Firocoxib can also be considered at traditional daily dosages. Renal and gastrointestinal side effects may be seen with continuous use.

Multiple chemotherapy agents have been used individually or in some combination protocols. Currently the most commonly used protocol uses Mitoxantrone (IV q 3 weeks x up to 6 cycles) with piroxicam; this provided an overall 33% response rate and the average survival was close to one year. Cisplatin and carboplatinin with piroxicam provides a similar response and survival time but patients may develop significant renal disease.

Advances in radiation therapy now allow this to be a mainstream option for TCC treatment. Intensity modulated radiation therapy (IMRT) allows a high radiation dose to be delivered directly to the tumor with minimal effect outside the desired radiation field. A recent study demonstrated 90% clinical response with 20 daily treatments; side effects were relatively mild; first event reoccurrence was over 300 days with overall survival close to two years.

**ALTERNATE TREATMENTS**
The development of interventional radiology techniques will allow for placement of a urethral stent in dogs with urethral tumor obstruction. While this technique is basically a salvage procedure it is a viable technique when an owner is faced with the reality of potentially euthanizing the dog. Urinary incontinence is expected in up to 25% of the cases.

Urinary bladder removal and bilateral subcutaneous ureteral bypass (SUB) placement. SUBs can be placed into each kidney which then drain urine to the subcutaneous hub port. Frequent urinary evacuation is necessary. Pyelonephritis development is a concern.
Artificial neobladder placement for dogs with resectable lower urinary tract tumors. Recruiting cases at AMC-NY.

PROGNOSIS
TCC prognosis is also based on location and tumor grade. High grade tumors grow faster, have more blood vessels, and have a greater chance to spread so naturally are associated with a poorer prognosis. Location within the urethra or prostate gland is associated with a less favorable prognosis compared to a tumor growing in the bladder that can grow to a larger size before it causes an obstruction. Ureteral involvement and obstruction is generally associated with a poorer prognosis. Metastasis generally carries a poor response and a poor prognosis.

For urinary bladder involvement only, the general outlook with a COX-2 nonsteroidal drug alone is about a six month survival. A COX-2 nonsteroidal plus chemotherapy extends survival to about a year. Early experience with IMRT suggests an 18-24 month survival. The role of surgery, chemotherapy and radiation therapy are still evolving. In the near future, earlier detection and monitoring with the BRAF test may allow for improved survival with this tumor.
Leptospirosis - Emergence, Testing, Treatment & Vaccination

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Introduction
Leptospirosis is a zoonotic bacterial disease with a worldwide distribution, and is an emerging infectious disease in humans and in dogs. It has been reported in more than 150 mammalian species. Leptospira spp. are thin, motile spirochetes with a hook-shaped end. Both saprophytic and pathogenic species exist in nature. Saprophytic species, such as Leptospira biflexa, live in water and soil and do not infect animals. There are over 250 pathogenic serovars based on differences in the carbohydrate component of the bacterial lipopolysaccharide. Different serovars are adapted to different wild or domestic animal reservoir hosts, and thus serovar recognition has epidemiologic importance. Serovars are further grouped into antigenically related serogroups. Immunity to leptospires is serogroup specific, and knowledge of serogroups that commonly cause disease within a particular geographic region is important for vaccine development.

Disease in dogs is caused primarily by serogroups Leptospira interrogans and Leptospira kirschneri. The most common serovars thought to infect dogs before the introduction of leptospirosis vaccines 30 years ago were icterohaemorrhagiae and canicola. Since the introduction of bivalent icterohaemorrhagiae and canicola vaccines, more widespread involvement of additional serovars has been suspected, including grippotyphosa, pomona, bratislava, and autumnalis. Increased recognition of leptospirosis associated with these serovars may have resulted partly from increased testing, because a broader range of serovars has been included in microscopic agglutination test (MAT) serology for canine leptospirosis. It also may have resulted from increased contact between dogs and the reservoir hosts for these serovars.

Although serologic evidence of exposure of cats to leptospires exists, clinical disease in cats is rarely reported. Serovars canicola, grippotyphosa, and pomona have been isolated from cats. Experimental infection of cats results in leptospiremia and leptospirosis, but disease is generally mild, although histopathologic evidence of renal and hepatic inflammation can be present. Cats may be exposed as a result of rodent contact. The extent to which cats contaminate the environment with leptospires is unknown.

The ACVIM Infectious Disease Study Group (IDSG) published an evidence-based justification for recommendations and a consensus manuscript was published in the Journal of Veterinary Internal Medicine in 2011 (J Vet Intern Med 2011;25:1–13).
Clinical Syndromes associated with Leptospira infection

Infection of dogs with leptospires results in illness of varying severity, depending on the infecting strain, geographical location, and host immune response. Some dogs display mild or no signs of disease, whereas others develop severe illness or death, often as a result of renal injury. In general, veterinarians should suspect leptospirosis in dogs with signs of renal or hepatic failure, uveitis, pulmonary hemorrhage, acute febrile illness, or abortion.

Fever occurs early in the course of illness, and may be accompanied by shivering, generalized muscle tenderness, and reluctance to move. Dogs presenting with acute renal failure may show polyuria, polydipsia, dehydration, vomiting, diarrhea, inappetence, lethargy, or abdominal pain or some combination of these signs. Oliguria or anuria also may occur. Dogs may present with signs of hepatic failure, including icterus. Other reported manifestations of infection include conjunctivitis, uveitis, and tachypnea or dyspnea because of acute respiratory distress syndrome or leptospiral pulmonary hemorrhage syndrome (LPHS), which has been reported most frequently in dogs from some parts of Europe. LPHS is increasingly recognized in human patients, appears to have an immune-mediated basis, and is associated with high mortality. Changes suggestive of pancreatitis have been detected in some dogs by abdominal ultrasonography. Hematuria can occur after natural infection. Bleeding tendencies also may be manifested as hematemesis, hematochezia, hemoptyisis, melena, epistaxis, and petechial hemorrhages. Hepatic failure, disseminated intravascular coagulation (DIC), and direct vascular damage by spirochetes may play variable roles in causing clinical hemorrhage. Vasculitis also may be manifested as peripheral edema and mild pleural or peritoneal effusion. Cardiac damage occurs in human patients and ECG alterations suggesting myocardial damage can occur in dogs. Abortion has occurred in dogs after transplacental spread of serovar Buenos Aires and 1 report suggested abortion associated with serovar Bratislava infection.

Polyuria and polydipsia can develop in dogs with leptospirosis in the absence of azotemia. In some cases, this may result from a decreased glomerular filtration rate sufficient to cause impaired renal concentrating ability. However, these patients also may be hyposthenuric. Experimentally, leptospiral infection causes decreased vasopressin responsiveness of the inner medullary collecting ducts suggesting polyuria may result from acquired nephrogenic diabetes insipidus.

Chronic active hepatitis was reported in 1 kennel in association with development of antibodies to serovar grippotyphosa and in another to serovar australis. Attempts to detect leptospiral DNA in liver samples from dogs with chronic hepatitis were unrewarding. Leptospirosis should be considered as a differential diagnosis in dogs with hepatitis or hepatic fibrosis. Similarly, dogs surviving acute renal tubulointerstitial injury may have residual chronic kidney injury that progresses over months to years, culminating in signs of decompensated chronic kidney disease.
Attempts have been made to correlate the infecting serovar with clinical presentation. Evidence for a correlation has been weak because of the poor ability of antibody tests to predict the infecting serovar, and lateral transfer of virulence attributes may occur between serovars. Thus at this time, no clear correlation has been made between the suspected infecting serovar based on antibody testing and clinical manifestations of disease in naturally occurring canine leptospirosis. Future attempts to correlate clinical presentation and infecting leptospiral strain should be based on a combination of isolation, serotyping, and genetic studies.

**Geographic Distribution of Leptospirosis**

Leptospirosis is especially prevalent in geographic regions with higher annual rainfall and warm climates, but factors such as host exposure and the presence of wild and domestic animal reservoir hosts also influence geographic distribution of the disease. For humans, the Caribbean and Latin America, the Indian subcontinent, Southeast Asia, Oceania, and to a lesser extent Eastern Europe are major disease foci. Hawaii accounts for most human cases in North America. Within the United States, regions of high antibody prevalence among dogs include Hawaii, southeastern United States, the west coast (esp northern California, Oregon, and Washington), the upper Midwest and Midwest parts of Texas, Colorado, and the northeast and mid-Atlantic coastal regions.

**Risk Factors for Infection**

Pathogenic leptospires infect and are shed from the renal tubules of a wide range of domestic and wild animals. Naïve animals become infected by contact of intact mucous membranes or abraded skin with infected urine or urine contaminated soil, water, food, or bedding. Leptospires do not replicate outside of the host but may remain viable for weeks to months in soil saturated with urine. Transmission also has occurred after bite wound inoculation, ingestion of infected tissues, and venereal and placental transfer. Ingestion of raw meat by dogs was associated with leptospirosis.

The organism prefers temperatures around 30C (86F). Freezing and UV radiation inactivate leptospires. Contact with slow-moving or stagnant warm water is a risk factor in humans. Outbreaks of disease in dogs have followed periods of higher rainfall with overall peak seasonal distribution occurring in the late fall in the United States. The time of year for peak leptospirosis incidence varies geographically depending on local rainfall patterns and periods of freezing temperatures. In some geographic regions, disease generally occurs in dogs that are exposed to or drink from rivers, lakes, or streams, or dogs roaming on rural properties. In others, suburban backyard dogs may be exposed after contact with urbanized wild animal populations. In developing countries, access to sewage increases risk of the disease in dogs. Outdoor, intact male working dogs have been shown to be at risk, although dogs of any age, breed, and sex may become infected. In areas where wild animal species access suburban backyards, small breed dogs with minimal contact with water sources may be at risk. Contact with rodents also may pose a risk to these dogs, as well as dogs residing within cities.
Incubation period after exposure

The incubation period for leptospirosis can be as short as a few days, the organisms replicating rapidly within the blood as early as 1 day after infection before invading tissues. The incubation period in experimental studies has been 7 days, but varies depending on the infecting dose, strain, and host immune response. Shorter incubation periods can occur with large inocula, and longer incubation periods may occur after low-grade, chronic infections of the renal tubules or hepatocytes, with clinical illness not being detected until some time after renal or hepatic injury.

Which serovars cause clinical disease in dogs

Infected serovars vary geographically among dog populations depending on exposure to infected wild or domestic animal reservoir hosts. A complete understanding of infecting serovars in the dog population has been limited because published studies usually have not included isolation efforts. Furthermore, the MAT has poor ability to predict the infecting serogroup. Although dogs are considered maintenance hosts for leptospires in serogroup Canicola, the prevalence of seroreactivity to this serogroup in dogs from the United States and Europe currently is low. Infection with serogroup Canicola serovars was reported in dogs from the United States in the 1950s and 1960s. Chronic canine infection with leptospires may be an ongoing public health problem in developing countries. Serovar Icterohaemorrhagiae, the major serovar infecting humans worldwide, is often found in rodent populations and was isolated from dogs in the United States before 1980. Based on antibody testing, evidence of canine infection by this serovar is less common now, possibly because of improved rodent control and other public health measures in cities and on farms in the United States. A high prevalence of seroreactivity to serogroup Icterohaemorrhagiae sometimes has been documented in nonrodent periurban wildlife (eg, raccoons), and the role of transmission of serovar Icterohaemorrhagiae by these hosts is unclear. Given that the MAT is not effective for predicting the infecting serovar, more studies by isolation are required to confirm the importance of various wildlife hosts as reservoirs of serogroup Icterohaemorrhagiae. Serovars from serogroups Icterohaemorrhagiae and Canicola cause disease in dogs after experimental inoculation. A study from India reported disease in dogs experimentally infected with serovars Autumnalis and Canicola. An Autumnalis serovar was isolated from sick dogs in France. A Pomona serovar caused disease after experimental inoculation of dogs. In the same study, inoculation of dogs with a serovar Bratislava isolate did not result in disease or seroconversion. However, another Bratislava serovar was isolated from a dog with leptospirosis. Antibody titers to serovar Bratislava (serogroup Australis) often increase with titers to Grippotyphosa and Pomona, and thus in some cases serologic evidence of serovar Bratislava exposure may represent cross-reactivity. Serovar Grippotyphosa also causes disease in dogs and other studies have reported disease in association with serogroups Sejroe and Ballum. Although an Autumnalis serovar was isolated from raccoons in Georgia in the 1950s, but there have been no documented cases of serovar Autumnalis isolates from dogs in
North America. Antibody titers to serovar Autumnalis often increase together with antibody titers to serovars Grippotyphosa, Pomona, and Bratislava. Nonspecific increases in titers to serogroup Autumnalis have been observed in dogs with diseases other than leptospirosis, and in dogs vaccinated for or infected with serogroup Pomona or Grippotyphosa and caution is advised when interpreting titers to this serovar.

Clinicopathologic Abnormalities in Dogs with Leptospirosis

Renal tubular infection by leptospires is associated with acute interstitial nephritis and tubular dysfunction, although acute tubular necrosis can occur in naturally infected dogs. Mesangial proliferative glomerulonephritis and interstitial nephritis may also be present. Histopathologic changes in the liver often are mild and can include mild to moderate scattered hepatic necrosis and mild neutrophilic periportal hepatitis.

Findings on CBC may include neutrophilia, sometimes with a left shift, lymphopenia, and mild to moderate, nonregenerative anemia. Uncommonly, severe anemia occurs, which may follow gastrointestinal or pulmonary hemorrhage. Hemolysis does not appear to be a feature of canine leptospirosis. Thrombocytopenia is present in up to 58% of affected dogs, and when accompanied by evidence of acute kidney damage with or without hepatic injury, can help increase suspicion for a diagnosis of leptospirosis.

Increased serum urea and creatinine concentrations may be present in 80–90% of dogs. Hepatic dysfunction may be manifested by increases in serum ALT, AST, and ALP activities and total bilirubin concentration, almost always in conjunction with azotemia. Increases in serum ALP activity and total bilirubin concentration are more common than increases in the activity of serum ALT. A combination of azotemia and increased liver enzyme activities should markedly increase suspicion for leptospirosis. Electrolyte abnormalities may be a consequence of gastrointestinal or renal fluid losses. Inhibition of Na1-K1 ATPase activity within the nephron by leptospiral endotoxin may contribute to renal losses. Hyponatremia, hypochloridemia, marked hypokalemia, and hyperphosphatemia occur in many cases, but dogs with oliguric or anuric renal failure may become hyperkalemic. Increased serum creatine kinase activity also may be present, presumably because of myositis. Increased serum troponin concentrations in some dogs suggest myocardial damage.

Urinalysis from dogs with leptospirosis may show isosthenuria, occasionally hyposthenuria. Glucosuria and proteinuria are common, and bilirubinuria, hematuria, pyuria, and cylindruria also may be present. Although high-molecular weight proteins have been detected in urine from some dogs with leptospirosis, it is suggested that urinary proteins were primarily tubular, rather than glomerular, in origin. Leptospires are not visible in the urine sediment by routine light microscopic evaluation.

Clotting function assays show variable increases in fibrinogen, D-Dimer and fibrinogen degradation product concentrations, and decreases in antithrombin activity, in addition to thrombocytopenia. Prolongations of PT or PTT have been detected 6–50% of tested dogs. Prolongations were most prevalent in western European dogs. A shortened PT also may be present, possibly because of DIC.
Thoracic radiographs from dogs with leptospirosis may show diffuse interstitial patterns or more severe nodular interstitial to alveolar patterns. Abdominal sonography can disclose nonspecific findings including renomegaly, increased cortical echogenicity, perirenal fluid accumulation, mild pyelectasia, and a medullary band of increased echogenicity. Enlargement and hypoechogeticity of the pancreas, thickening of the gastric and (less commonly) intestinal wall, splenomegaly with a mottled splenic echotexture, and mild abdominal lymphadenomegaly also may be found.

**Antibody Testing to Diagnose Canine Leptospirosis**

Use of antibody testing for diagnosis of leptospirosis generally is based on the MAT, which involves reacting serial dilutions of patient sera with an array of live leptospiral serovars, and assessment of organism agglutination by darkfield microscopy. The highest serum dilution causing agglutination of 50% of the leptospires in the reaction is reported to the veterinarian. The MAT is widely available and inexpensive, and there is a large body of data regarding its use; as such, it is the current diagnostic test of choice for canine leptospirosis in patients with consistent clinical signs. Unfortunately, the test is hazardous to perform because of the need to maintain live cultures of pathogenic serovars, and is difficult to standardize. Test interpretation is somewhat subjective and requires considerable expertise, and serovar identity must be verified regularly to ensure accurate results. Serovar cultures may become cross-contaminated over time. Considerable variation in results has been noted among laboratories performing the MAT for diagnosis of canine leptospirosis, possibly as a result of variable quality control and standardization. There is a lack of consensus over what titer should be used as a cut-off for a negative result. The International Leptospirosis Society offers an inexpensive leptospirosis testing proficiency scheme that enables laboratories to maintain quality assurance for the MAT on a regular basis. Laboratory participation in the scheme is encouraged and it is recommended that practitioners use laboratories that participate in this program. Molecular methods also have been advocated to ensure quality control within leptospiral reference laboratories.

In the 1st week of illness, dogs frequently have negative MAT results, and consequently acute and convalescent phase antibody testing is recommended. Traditionally, convalescent titers for acute infectious disease diagnosis are performed 2–4 weeks after the acute titer, although seroconversion can occur as early as 3–5 days after dogs are brought to a veterinarian. Practitioners should wait 7–14 days between successive titers to demonstrate seroconversion. A 4-fold change in titer supports recent infection, although an increase in titer may be blunted by antimicrobial therapy. Titers resulting from previous vaccination, exposure, or chronic infection generally change more slowly or not at all. Titers can persist for at least 1 year after natural infection, and in 1 study, generally declined by 4 months after vaccination.

Postvaccinal titers may persist for longer and be maintained at high levels if ongoing exposure to field strains occurs. Thus, although single positive titers can increase suspicion for the disease, even when high (>800), they do not confirm a diagnosis of leptospirosis. This is especially important in dogs with a history of
vaccination, because although postvaccinal titers tend to be low, high titers (>1,600) have the potential to persist after vaccination, and cross-reactivity to nonvaccinal serogroups can occur. In 1 study, the sensitivity of a single MAT titer >800 for diagnosis was 22–67% and the specificity was 69–100%.

False negative titers may occur if the infecting serovar is not including in the panel of serovars used to perform the test. MAT tests used for diagnosis of human leptospirosis generally include a larger panel of serovars (>20) than those used for veterinary diagnostic testing (5–7 serovars). MAT assays for canine leptospirosis should include serovars known to be circulating in the local dog population, although this information is not always readily available.

The MAT is a serogroup- rather than a serovarspecific test, because antibodies to serovars within the same serogroup cross-react extensively. Because of shared antigens, some cross-reactivity among different serogroups also occurs after human and canine exposure to leptospires. In the past, the serogroup with the highest titer has been interpreted as the infecting serogroup. However, studies of infected humans with culture-proven infections have shown that accurate prediction of the infecting serovar occurs in <50% of cases. Higher, crossreactive titers can occur to a noninfecting serovar. These so-called “paradoxical reactions” are especially common in early infection, and when multiple serovars circulate within the population. Furthermore, the MAT used to perform studies in humans included approximately 20 serovars, and the serovars included in the test reflected those circulating in the population. Even lower specificity could be predicted when the number of serovars included in the test is small and not reflective of actual serovars infecting the dog population in a specific geographic region.

The predicted identity of the infecting serogroup also has been shown to change over the course of infection in dogs. Previous vaccination can influence the pattern of serovar reactivity. In dogs, the serogroup with the highest titer also varies depending on which laboratory performs the MAT, again likely reflecting the lack of standardization of the assay. Thus, the results of the MAT are not recommended to predict serogroups circulating in the dog population. Instead, studies involving isolation of leptospires from dogs are recommended for epidemiological purposes, as well as for selection of antigens for diagnostic assay development and vaccine design.

Polymerase Chain Reaction (PCR) and Culture

Culture and PCR detect pathogenic leptospires or their nucleic acid, respectively, and have potential utility early in the course of untreated infection when antibody assays are frequently negative and antimicrobials have not yet been administered. They also can confirm active infection in animals with positive antibody test results that have a history of vaccination with leptospiral vaccines, because previous vaccination should not yield false positive results by these methods. They may detect infection in dogs with chronic renal or hepatic disease.

In the first 10 days of infection, organism numbers are highest in blood, and thus blood is the sample of choice during the first week of illness. After that time, organisms are present in highest concentration in urine.
When the time of infection is unknown, simultaneous testing of blood and urine may increase diagnostic sensitivity. Recent antimicrobial treatment can result in false negative test results for both culture and PCR, although multiple doses of antimicrobials may be required before PCR becomes negative, because PCR detects both viable and nonviable organisms.

Culture of leptospires requires special media. Organisms may be destroyed during transport to the laboratory. The growth of leptospires is slow, requiring incubation for up to 3–6 months, and consequently culture is not useful for early diagnosis. Overgrowth with other bacteria may occur in contaminated cultures. For optimal sensitivity, venous blood should be collected by aseptic technique and immediately inoculated (alongside the patient) into blood culture bottles containing culture medium for Leptospira before sending the inoculated bottles to the laboratory. After the 1st week of illness, urine should be collected by cystocentesis, and 1 drop of urine should be inoculated into 5mL of culture medium within 2 hours of collection. Cultures must be performed by laboratories with expertise in isolation and identification of leptospires, and the commercial availability of leptospiral culture is not widespread. However, a proper understanding of the epidemiology of leptospirosis depends upon serotyping and genetic typing after isolation, and thus attempts to isolate leptospires from dogs with leptospirosis are encouraged.

PCR assays for detection of leptospiral nucleic acid are increasingly offered by commercial veterinary diagnostic laboratories worldwide. Both conventional and real-time assays have been developed, and their use has been reported. Although PCR assays have been designed to detect only pathogenic leptospiral serovars, currently available assays do not differentiate between serovars or serogroups and thus are not useful for studying the epidemiology of leptospiral strains. Recent reports suggest that PCR typing methods may be used to some extent to identify infecting serovars. Not all PCR assays are alike and they vary considerably in their performance. Negative results do not rule out leptospirosis, because they may occur when organism numbers in a sample are low, or other factors, such as PCR inhibitors, are present.

Currently, there is limited information regarding the validity of PCR assays for detection of pathogenic leptospires infecting dogs, as well as their sensitivity, specificity, and positive predictive value, and so positive and negative test results should always be interpreted in conjunction with other diagnostic methods such as acute and convalescent phase antibody testing. The sensitivity of 1 assay on blood was greatest when whole blood, as opposed to sera, was used. Sensitivity was 90% in the first 5 days of illness, after which it decreased to 50%. Because apparently healthy dogs may shed leptospires, a positive PCR test result on urine may not necessarily correlate with illness but is useful to identify a chronic carrier state. Other methods that can be used to confirm the presence of Leptospira spp. in tissues include silver staining of biopsy or necropsy specimens (which lacks sensitivity), immunohistochemistry, tissue PCR, and in situ hybridization.

**Rapid SNAP and IgM detection tests**

Bed-side testing to support an early diagnosis of leptospirosis has been available for the past 2 years - SNAP test (Idexx) to detect LipL32, a major outer membrane protein of pathogenic Leptospira serovars, and an LFA assay (Witness-Zoetis) to detect IgM antibodies to serovars Canicola, Grippotyphosa, Icterohaemorrhagiae,
and Pomona in whole blood, plasma, or serum. Both tests have reasonable sensitivity (85%) and specificity (85%) in studies. Patients testing negative but with a high degree of clinical suspicion should be evaluated by other test methods while initiating therapy. Both tests may detect previous Leptospiral vaccination so positive test results should be confirmed with other test methods.

**Treatment Recommendations for Leptospiral infections**

The optimal treatment for leptospirosis is unknown. Penicillins or doxycycline traditionally have been the antimicrobials of choice for treatment of humans and dogs with leptospirosis. Ceftriaxone and cefotaxime are as efficacious as penicillin in human leptospirosis. Azithromycin also may be effective. First generation cephalosporins appear less effective, and leptospires are resistant to chloramphenicol. The use of fluoroquinolones has been controversial. Efficacy similar to doxycycline in hamsters has required doses >25 mg/kg/d. In a study that used quantitative PCR for leptospiral detection, ofloxacin was unable to clear leptospires from the kidneys and blood of a hamster model, ampicillin did not clear organisms from the kidney, but doxycycline cleared organisms from all sites within 3 days of infection. Orbifloxacin was ineffective in 1 dog with leptospirosis that responded to amoxicillin. Based on these data, the consensus panel recommends treatment of canine leptospirosis with doxycycline, 5mg/kg PO or IV q12h for 2 weeks, but the optimal duration of antimicrobial therapy requires further investigation. Treatment should not be delayed pending results of diagnostic testing for leptospirosis. If vomiting or other adverse reactions preclude doxycycline administration, dogs with leptospirosis should be treated with ampicillin, 20mg/kg IV q6h, with dose reduction for azotemic dogs. Penicillin G (25,000–40,000U/kg IV q12h) also could be used. Ampicillin should not be administered orally because it is not reliably absorbed from the gastrointestinal tract. Dogs should receive doxycycline for 2 weeks after gastrointestinal signs abate in order to eliminate organisms from the renal tubules. Concurrent fluoroquinolone use is not recommended in dogs with leptospirosis because it contributes to antimicrobial resistance in other bacteria.

Renal replacement therapy with intermittent hemodialysis or continuous renal replacement therapy (CRRT) can be life-saving for many dogs with severe anuric leptospirosis. More than 80% of patients that would otherwise die from the consequences of severe uremia survive with supportive renal replacement therapy. Recovery of adequate renal function usually occurs within 2–4 weeks of starting dialysis. Sometimes only 1–3 treatments are required before polyuria ensues and renal function begins to recover. Renal replacement therapy is indicated in dogs with inadequate urine output that are developing volume overload, hyperkalemia, BUN >80 mg/dL, or signs of uremia that are not responsive to medical management. Increased availability of hemodialysis will help more dogs survive this disease. Practitioners should consider early referral of dogs failing to produce adequate urine volume despite proper fluid therapy to centers with intermittent hemodialysis or CRRT facilities when client finances allow.

Dogs with Lepto-associated pulmonary hemorrhagic syndrome may require oxygen therapy and, if severe, mechanical ventilation. The role of immunosuppressive therapies is still undefined in dogs.
Provided severe respiratory complications are absent, the prognosis for dogs treated early and aggressively in the course of leptospirosis with appropriate antimicrobial drugs and IV fluids, with or without diuretics, is good, especially when intermittent hemodialysis is available. Survival rates of approximately 80% have been reported, both among dogs treated conservatively and those treated with dialysis, although virtually all dogs that are dialysis dependent and do not receive dialysis would be expected to die. The prognosis for dogs developing severe respiratory complications is poorer. A high prevalence of respiratory complications contributed to overall mortality rates of 48 and 36% in 2 studies from western Europe, respectively.

Successful treatment is associated with gradual return of serum urea and creatinine concentrations to reference ranges within 10–14 days, although regeneration of damaged renal tissue may continue for over 4 weeks after treatment of infection. The bilirubin concentration may decline more slowly than the activities of serum ALT and ALP. Platelet counts often improve within 1 week of initiating antimicrobial treatment. In some dogs, especially those treated late in the course of illness, permanent residual kidney damage may occur. IV fluid therapy should be tapered gradually before being discontinued, to ensure that polyuria is resolving and the patient is able to drink sufficient water to maintain hydration. Prolonged inappetence may require nutritional support by enteral or parenteral routes.

Treatment Monitoring

Dogs with acute leptospirosis ideally should have serum biochemistry panels performed every 24 hours during hospitalization to monitor renal function, liver enzyme activities, serum protein concentrations, and electrolyte and acid-base status. More frequent monitoring may be indicated for dogs with marked electrolyte and acid-base derangements. PCV should be monitored every 24 hours, and the CBC every 48 hours during hospitalization. Dogs with nonoliguric renal failure may be profoundly polyuric. Fluid therapy may be provided by the “outs and ins” method. Some patients may require fluid rates >200 mL/kg/d. For dogs with oliguric or anuric renal failure, close attention should be paid to urine output by use of a closed, indwelling urinary catheter and collection bag system. Initially, urine output should be monitored at least hourly. Referral to a 24-hour care facility is recommended if adequate time for monitoring is not available in the practice. Indwelling, rather than intermittent, urinary catheterization is recommended for dogs requiring urinary catheterization because of decreased risk of exposure to infected urine with indwelling catheterization. Serial physical examinations with frequent monitoring of body weight, respiratory rate, lung sounds, blood pressure, and, if possible, central venous pressure are indicated to assess for early signs of overhydration that might necessitate diuretic therapy or dialysis. Once a patient is appropriately hydrated, fluid administration must be adjusted to prevent life-threatening fluid overload. Although follow-up will vary from dog to dog, at a minimum, dogs should be reexamined no later than 1 week after discharge from the hospital, and a serum biochemistry panel and urine specific gravity
should be performed. If thrombocytopenia or anemia were present during hospitalization, a CBC could also be performed. This also represents an opportunity to obtain convalescent antibody titers.

**Public Health Implications of Canine Leptospirosis**

Leptospirosis in humans occurs after an incubation period of 2–25 days, and varies in severity. Infection in some humans is subclinical. Others develop a mild, influenza-like illness. The most severe manifestations of leptospirosis in humans are hepatic and renal failure (Weil's disease) or LPHS. Weil's disease typically occurs 1 week after recovery from an initial febrile illness that is accompanied by myalgia, headache, chills, and conjunctivitis.

The public health implications of canine leptospirosis vary geographically. In developing countries, stray dogs may represent a reservoir of infection for humans, although rodents also may play a role. In developed countries, most leptospirosis cases in humans result from recreational activities involving water. Individuals that contact farm animals are also at risk. In 1 study, 10% of 61 leptospirosis cases in humans in California over the last 20 years resulted from pet contact. Contact with adopted wild rodents also has resulted in human disease.

In general, animals developing acute leptospirosis are incidental hosts and do not develop a chronic carrier state. Transmission from incidental hosts to other animals is rarely reported, and the few reports suggesting transmission of leptospirosis from pet dogs to humans have not been substantiated by molecular methods. The extent of shedding of specific leptospiral serovars by dogs after infection requires evaluation. Anecdotal evidence suggests it is difficult to detect leptospires in the urine of dogs receiving penicillin or doxycycline treatment, and thus appropriate antimicrobial therapy may also decrease the possibility of zoonotic transmission. Nevertheless, the full impact of antimicrobial therapy on leptospiral shedding from infected dogs requires further study. Positive PCR results detected in animals receiving antimicrobial therapy may reflect nonviable organisms, which would not be a zoonotic risk.

**Risk of Zoonotic Transmission in the Veterinary Hospital**

Having a high index of suspicion for leptospirosis in dogs with renal injury and handling them appropriately may decrease zoonotic transmission of leptospires in the hospital. All personnel that may have had direct or indirect contact with a dog suspected to have leptospirosis should be informed of the risks. These people include radiology personnel and laboratory personnel handling blood, urine, or tissue samples from patients. All dogs with acute renal failure, including “acute-on-chronic” renal failure, should be managed as leptospirosis suspects until an alternate diagnosis has been made. Based on rodent model studies, viable organisms are most likely to be present in blood or urine before initiating antimicrobial therapy, and within the first 2–3 days of treatment. Leptospires might be shed for months in urine if appropriate antimicrobial treatment is not initiated.
Leptospires generally survive poorly in the environment and are susceptible to UV irradiation, dessication, and routine disinfectants, although the degree to which organisms could survive in urine-soaked hair is unknown. Caution is recommended when handling dogs suspected to have leptospirosis. The movement of dogs suspected to have leptospirosis around the hospital should be minimized, and areas of contact should be disinfected. Warning labels should be placed on cages of dogs suspected to have leptospirosis, and pregnant or immunocompromised humans should avoid contact with these patients. Because many of these dogs are critically ill and require frequent monitoring, and leptospires are not readily transmitted between dogs, housing in isolation is not necessary. If possible, patients should be placed in floor-level cages and housed away from high traffic areas. Care should be taken to avoid needle-stick injuries and other blood contact. Gloves and a disposable gown should be worn, and either protective eyewear and a facemask, or, alternatively, a full face shield should be worn if aerosolization of urine is possible, such as when manipulating urinary catheters or collection systems, or when cleaning areas of urine spillage. Pressure washing of runs should be avoided as it may contribute to urine aerosolization. An indwelling urinary catheter should be placed if urine output requires monitoring, or if urinary incontinence is present, to minimize urinary contamination of the environment. If a urinary catheter is not in place, dogs should be walked frequently enough that urination does not occur in the hospital, and preferably by a route that avoids common hallways. Patients also could be moved through the hospital on a gurney. They should be allowed to urinate in a restricted area, preferably one that can be easily and immediately decontaminated, such as on a hard, nonpermeable surface that is free of organic matter. If urine spills occur, they should be disinfected and cleaned immediately. Bathing of hair that becomes soaked in urine is recommended. Hand washing should be performed before and after handling each patient after glove removal, and cages should be thoroughly cleaned and disinfected daily. Gloves, a disposable gown, and face protection should be worn when handling soiled bedding and when cleaning cages or runs. Normal laundering of soiled bedding will inactivate leptospires, but individuals handling the bedding should wear protective clothing. Disposable bedding should be placed in biohazard bags and handled appropriately. Urine collected from dogs with leptospirosis can be inactivated with disinfectant solutions (eg, 1:1 aqueous dilution of 10% bleach solution) and should be disposed of properly. Iodine-based disinfectants, accelerated hydrogen peroxide, and quaternary ammonium solutions also are effective. In dogs with indwelling urinary catheters, disinfectant should be injected directly into the collection bag before disposing of the urine. In designated outdoor areas where infected dogs have urinated, treatment of the area with 10% bleach solution is recommended. All blood, urine, and tissues from dogs suspected to have leptospirosis should be treated as medical waste, and the handling of such material may vary depending on local regulations. If a dog dies or is euthanized, individuals handling the remains should be alerted of the zoonotic potential of the carcass.

**Risk of Zoonotic Transmission within the Home**

Treated dogs represent a low risk to household members. In addition, urinary shedding usually does not commence until 7–10 days after infection, and consequently dogs in the first few days of illness also may
not represent a clinically relevant source of infection. Nevertheless, until proper antimicrobial therapy is completed, owners should avoid contact with their dog’s urine and wear gloves when cleaning up urine. Routine household disinfectants should be used to clean areas of urine contamination in the home. Dogs should be taken to urinate and should urinate away from standing water, where no other animals and people, especially children, will have access. Owners should be advised to wash their hands after handling their pets. Upon diagnosis of leptospirosis, veterinarians should educate owners of the zoonotic potential of leptospirosis, and recommend they seek medical attention if illness occurs around the time their dog is diagnosed with leptospirosis or if they have questions about the disease in humans. Internet resources also can be provided. Immunocompromised humans should be referred to their medical practitioner for advice. Routine vaccination of dogs at risk of developing leptospirosis may decrease the risk of zoonotic transmission of the disease. Owners should be informed that their dog likely contracted leptospirosis by direct or indirect contact with wild or farm animals, which may represent ongoing risk factors.

**Leptospirosis Vaccination**

Currently, vaccines containing serovars Icterohaemorrhagiae, Canicola, Grippotyphosa, and Pomona are available in North America for prevention of canine leptospirosis. Current vaccines appear to effectively prevent disease resulting from experimental challenge and to a large degree prevent shedding caused by the serovars in the vaccine. They also protect for at least 12 months. Currently available bacterins elicit serogroup-specific immunity, but partial immunity to heterologous serogroups has been documented in some studies. Naturally occurring canine leptospirosis has been reported after vaccination with bivalent serovar Icterohaemorrhagiae and Canicola vaccines. The panel is unaware of leptospirosis in dogs that have been fully vaccinated with 4-serovar vaccines, but published data are lacking regarding the incidence of naturally occurring leptospirosis in such dogs. This may partly relate to the difficulty in definitively diagnosing leptospirosis in fully vaccinated dogs.

Annual vaccination with 4-serovar vaccines is recommended for at-risk dogs, regardless of breed, with the understanding that the definition of “at-risk” may vary geographically. In geographic locations in which infection occurs in urban, backyard dogs, all dogs may be at risk, and the vaccine may be considered part of a core vaccination protocol. In other locations, only dogs that contact wildlife, swim, hunt, or roam on farmland may be at risk. Other methods of prevention include decreased access to potential sources of infection, such as marshy areas and standing water, and minimizing wild animal contact by use of fencing and rodent control.

Concern has been raised regarding the development of anaphylactoid reactions in dogs after leptospirosis vaccination, especially small breed dogs, although such reactions may occur in any breed. There is anecdotal evidence from veterinarians and industry that the prevalence of these reactions is decreasing, and may be similar to the rate induced by vaccines for other pathogens. In a study of acute vaccine reactions in dogs utilizing a large database, vaccines containing leptospiral antigen were no more reactive than other vaccines for dogs.
Evidence of recurrent leptospirosis in dogs after proper treatment is lacking. Nevertheless, annual vaccination for dogs that have recovered from leptospirosis could be considered, because such dogs are at risk of ongoing exposure, and whether or not life-long immunity results from natural infection is unknown. The duration of immunity in dogs after natural infection is likely to be at least as long as that induced by vaccination, and thus initial vaccination after recovery should occur 1 year after recovery. Although natural infection may elicit only partial cross-protective immunity to heterologous serogroups, dogs are most likely to be reexposed to a similar serovar to that involved in the initial infection. There is little evidence supporting the need for immediate boosting with a multivalent vaccine after recovery from infection. More studies are required to establish the true duration of immunity and degree of crossprotection among specific serovars after natural infection in dogs.