Proudly Presents:

**Nephrology/Urology**

With:

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Chronic kidney disease (CKD) is common in dogs and cats with the incidence increasing with age. The term CKD is preferred over chronic renal failure and renal insufficiency, because CKD has a spectrum of severity from asymptomatic kidney disease to end stage uremia. The International Renal Interest Society (IRIS) has developed a classification scheme for CKD with the concept of implementation of specific treatments in different stages. The dog or cat is staged on the basis of stable serum creatinine concentration in a well-hydrated patient. Ideally 2 creatinine determinations should be obtained at least 2 weeks apart along with blood pressure and urine protein/creatinine ratio also obtained at each time point. Patients are sub-staged on the basis of blood pressure and proteinuria. An evidence-based approach to treatment of CKD in dogs and cats has been published.\(^1\)\(^2\)

### TABLE 1. IRIS CKD Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine mg/dl</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.4 dogs&lt;br&gt;&lt;1.6 cats</td>
<td>Non-azotemic&lt;br&gt;Confirmed renal disease present</td>
</tr>
<tr>
<td>2</td>
<td>1.4-2.0 dogs&lt;br&gt;1.6-2.8 cats</td>
<td>Mild renal azotemia (overlaps w reference range)&lt;br&gt;Clinical signs usually mild other than PU/PD</td>
</tr>
<tr>
<td>3</td>
<td>2.1-5.0 dogs&lt;br&gt;2.9-5.0 cats</td>
<td>Moderate renal azotemia&lt;br&gt;Many extrarenal clinical signs may be present</td>
</tr>
<tr>
<td>4</td>
<td>&gt;5.0 dogs and cats</td>
<td>Severe renal azotemia&lt;br&gt;Many extrarenal clinical signs are usually present</td>
</tr>
</tbody>
</table>

### TABLE 2. IRIS Substaging by UP/C Ratio

<table>
<thead>
<tr>
<th>UP/C value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2 dogs and cats</td>
<td>Non-proteinuric (NP)</td>
</tr>
<tr>
<td>0.2-0.4 cats&lt;br&gt;0.2-0.5 dogs</td>
<td>Borderline proteinuric (BP)</td>
</tr>
<tr>
<td>&gt;0.4 cats&lt;br&gt; &gt;0.5 dogs</td>
<td>Proteinuric (P)</td>
</tr>
</tbody>
</table>
TABLE 3. IRIS Substaging by Blood Pressure

<table>
<thead>
<tr>
<th>Risk*</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>&lt;150</td>
<td>&lt;95</td>
</tr>
<tr>
<td>Low</td>
<td>150-159</td>
<td>95-99</td>
</tr>
<tr>
<td>Moderate</td>
<td>160-179</td>
<td>100-119</td>
</tr>
<tr>
<td>High</td>
<td>≥180</td>
<td>≥120</td>
</tr>
</tbody>
</table>

*Risk = likelihood that high BP will further damage the kidney and other end organs.
Further information on the IRIS staging system is available at www.iris-kidney.com.

Dietary Treatment of Chronic Kidney Disease

Recent randomized clinical trials show that renal diets result in lower mortality from uremia compare to maintenance diets in both dogs and cats with stage 2-3 CKD. There is no evidence that dietary protein restriction per se slows progression of CKD, so it is not known exactly why renal diets were beneficial in these clinical trials. Reasons that renal diets may be beneficial include restriction in dietary protein or phosphorus content, ω-3 fatty acid supplementation, alkalinizing nature of the diet, potassium content or other factors.

Anorexia is a common clinical problem in dogs and cats with CKD. It is important that animals with CKD maintain adequate caloric intake to avoid protein-calorie malnutrition and maintain body condition. A recent study in dogs with CKD comparing survival and body condition score (BCS) showed that dogs with low BCS have significantly shorter survival than dogs with normal BCS and those that were overweight.

Introduction of renal therapeutic diets may initially result in decreased food intake. The method of introduction of the diet is important. Gradual transition to the renal diet over 2-4 weeks resulted in excellent acceptance of the diet in cats with stage 2-3 CKD in one clinical trial. Dogs and cats with stage 4 CKD often fail to eat sufficient food voluntarily, regardless of the palatability or nutrient content. Monitoring for evidence of protein-calorie malnutrition should include monitoring for weight loss, hypoalbuminemia, anemia, poor hair coat quality, muscle wasting and declining body condition scores. Diet consumption may be encouraged by minimizing uremia by maintaining hydration and treating for uremic gastritis and uremic nausea.

Cats with CKD have increased a serum gastrin concentration, which contributes to the pathogenesis of uremic gastritis. Uremic gastritis contributes to anorexia in addition to vomiting. Famotidine (5 mg per cat PO q 24 h) is recommended for treatment of uremic gastritis secondary to CKD in stage 2-3 CKD. For more severe uremic gastritis or during a uremic crisis, oral omeprazole (0.7 mg/kg PO q 24 h), IV pantoprazole (0.7-1 mg/kg q 24 h), ondansetron (0.5 mg/kg PO or IV q 12 h) or maropitant (Cerenia 0.5-1 mg/kg SQ or PO q 24 h) are more effective for reducing uremic gastritis and uremic-induced nausea. Maropitant is general used once daily for 5 days, although clinical studies are evaluating longer-term administration for CKD patients.
During a uremic crisis with active vomiting, do not feed CKD animals orally and avoid force-feeding of renal diets because these approaches are likely to induce food aversions. Once the vomiting has stopped and azotemia reduced, food is reintroduced as frequent small meals. It is better to introduce new renal diets once the dog or cat is discharged rather than during hospitalization. For some cats, heating the food to room temperature, or adding small amounts of water, tuna water or clam juice to the diet may increase dietary acceptance. However, these may supplements contain large amounts of sodium and may worsen hypertension.

**Subcutaneous fluid therapy / Assisted Feeding tubes**

For dogs and cats with stage 3-4 CKD, administration of subcutaneous fluids such as Plasmalyte or LRS daily or every other day may be beneficial. Subcutaneous fluids should not be implemented too early in the progression of CKD (stage 2 CKD) because of the sodium content of isotonic fluids may contribute to development of hypertension in some animals with sodium responsive hypertension. Subcutaneous (SQ) fluid therapy does not increase GFR above what the kidneys are capable of provided they are normally perfused. Subcutaneous fluids help keep the animal well hydrated and allow some increased elimination of BUN through increased tubular flow rates.

If therapy for uremic gastroenteritis and administration of SQ fluids fail to restore adequate caloric intake, administration of mirtazapine (1-3 mg PO q 72 hours) or cyproheptadine (1-2 mg PO q 12-24 hours) to stimulate appetite should be attempted. It is important to confirm that any apparent response sufficiently enhances food intake to meet nutritional needs (increasing or stable body weight and BCS). If food intake remains inadequate or BCS is low (< 3/9), assisted tube feeding should be considered. Long-term PEG or esophagostomy tubes are useful for delivering food, extra water and medications to dogs and cats with CKD. Tube feeding can reverse progressive weight loss associated with CKD and animals can have extended periods of improved quality of life. Tube feeding of CKD animals may be much easier than management with SQ fluids and numerous oral medications. Assisted tube feeding of animals with CKD is an important therapeutic approach that should be considered in any animal when medical management does not effectively eliminate anorexia and for CKD patients with declining BCS.

**Renal secondary hyperparathyroidism**

Phosphate binding agents should be instituted when dietary phosphorus restriction fails to maintain serum phosphorus and PTH concentrations within the target range. Aluminum hydroxide (30 to 100 mg/kg/day PO with meals) is the traditional phosphate binder. Hypercalcemia may occur when calcium-containing phosphate binders are combined with calcitriol therapy. A chitosan-based product has also been used as an intestinal phosphate binder in a case series of cats with spontaneous CKD and induced CKD. Lanthanum carbonate was also an effective phosphate binder resulting in reduced serum phosphorus concentrations in cats with induced CKD. None of these studies were examined the effect of phosphate binders on survival of dogs and cats with naturally occurring CKD.

A placebo controlled, double-masked study confirmed that calcitriol to treat renal secondary hyperparathyroidism is beneficial in dogs with CKD compared to placebo. There was a 68% reduction in mortality in the calcitriol treated dogs. Calcitriol (3.5 to 6ng/kg/day PO) should be initiated in dogs once the serum creatinine concentration is above 5 mg/dl and if elevated PTH concentrations are documented. Calcitriol should only be administered after dietary phosphorus restriction and addition of phosphate binders. Also, this therapy requires regular monitoring of ionized calcium and PTH levels and
should not be used unless the owner will comply with follow-up recommendations. If hypercalcemia occurs, the dose of calcitriol should be decreased or changed to pulse therapy. An alternative approach is to give a larger dose (3X dose) once every third day. Monitoring of ionized calcium and PTH concentrations is the preferred method of monitoring calcitriol therapy. Calcitriol dose maybe gradually increased as needed to 6ng/kg to reduce PTH levels or until ionized hypercalcemia occurs, whichever occurs first.

Anemia of CKD

Treatment of dogs and cats with anemia secondary to CKD using recombinant human erythropoietin (r-HuEPO) corrects the anemia in a dose dependent fashion. r-HuEPO is a human protein and is antigenic to dogs and cats resulting in development of anti-EPO antibodies that cross react with the endogenous EPO causing a severe nonregenerative anemia and transfusion dependency. Because of this potential side effect, administration of darbepoetin has been suggested as a less antigenic alternative to r-HuEPO. Anecdotal evidence suggests that the incidence of antibody formation occurs in less than 5% of dogs and cats treated with darbepoetin. The initial dose of darbepoetin is 1.0 mcg/kg SQ once weekly. Once the hematocrit is at or near the low end of the reference range, the dose is reduced to every other week and decreased to 0.5 mcg/kg if needed. Iron deficiency is a potential sequela of darbepoetin therapy resulting in poor responsiveness. Therefore, iron supplementation is recommended for all animals treated with darbepoetin using oral ferrous sulfate at a dose of 100 - 300 mg/dog/day and or iron dextran injections (10 mg/kg IM q 3-4 weeks) in cats.

Management of hypertension and proteinuria in CKD patients

Hypertension and low-level proteinuria are relatively common in dogs and cats with chronic kidney disease (CKD) and they may contribute to progression of the renal dysfunction. Treatment of hypertension should be considered with systolic blood pressures above 160 mmHg. ACE inhibitors slows the rate of decline of the renal function in animals with induced CKD; therefore, ACE inhibitors are recommended if the animal has low to moderate risk of hypertensive injury with concurrent proteinuria.

Amlodipine is generally more effective than ACE inhibitors for controlling blood pressure in cats and dogs with high risk of hypertensive injury. For cats, amlodipine should be the initial antihypertensive (0.18-0.25 mg/kg or 0.625-1.25 mg/cat PO q 24 h), and then increase the dose up to 0.5 mg/kg/day if it is not effective. If hypertension still is not controlled, then an ACEI such as Benazepril should be added to the amlodipine. Benazepril dosage for cats is 0.5-1 mg/kg once daily and there is no need for dosage reduction based on degree of renal dysfunction. Dogs are treated with amlodipine (0.2 mg/kg PO q 12-24 h) initially. If hypertension still is not controlled, then add an ACE inhibitor (e.g., enalapril at 0.5 mg/kg PO q 12 h or benazepril at 0.5-1 mg/kg PO q 24h), and then double the dose of ACE inhibitor if not effective. A loading dose protocol for amlodipine may be used for dogs with malignant hypertension by administering 0.2-0.4 mg/kg PO q 2-4 until systolic blood pressure decreases to < 180 mmHg (usually 2-3 doses total). Control of hypertension with amlodipine alone may not preserve renal function due to changes in intraglomerular pressures. In feline CKD, proteinuria that persists despite control of hypertension is important in progression of CKD. If blood pressure is controlled with amlodipine alone but proteinuria persists, then add an ACE inhibitor to reduce the proteinuria. Lifelong serial monitoring of blood pressure for patients on anti-hypertensive medication is required.
In some clinical patients, measurement of SBP yields results that are questionably elevated. Normal animals may have SBP in the low end of the moderate risk category from excitement-induced elevations in SBP (“white coat effect”). If dogs or cats with CKD that have “moderate risk” of hypertensive injury without evidence of end-organ damage (160-179 mmHg SBP), ACE inhibitors may be used instead of amlodipine initially. Reductions in BP with ACE inhibitors alone are only modest and will not control SBP in animals with documented severe hypertension. If the blood pressure remains elevated despite ACE inhibitors at full doses, then consider adding or changing to amlodipine.

Recent studies in cats have shown that even low levels of proteinuria (UP/C ratio >0.2), which were previously thought to be clinical irrelevant, may be related to poor long term survival. However there is significant overlap of the magnitude of between cats with progressive renal disease and those which have stable renal function. ACE inhibitors lower intraglomerular capillary pressures which may lessen proteinuria, thereby potentially slowing progression of CKD. Protein in the ultrafiltrate is reabsorbed by endocytosis in the proximal tubule. Excessive protein reabsorption ultimately damages the tubules resulting in tubulointerstitial injury and progression of CKD.

In 2 recent clinical trials of cats with CKD, benazepril reduced proteinuria but did not slow progression of CKD. For dogs with PLN, treatment with enalapril reduced proteinuria and slowed progression of CKD. An ACVIM panel consensus statement on proteinuria recommends treatment of dogs with UP/C > 0.5 and cats with UP/C > 0.4 with a renal diet and ACE inhibitors. ACE inhibitors are most beneficial in stages 1-3 and should be used with caution in dogs or cats with stage 4 CKD because substantial decreases in GFR may occur in patients with advanced stage 4 CKD in response to ACE inhibitors.

References


ACUTE KIDNEY INJURY (AKI) OR CHRONIC KIDNEY DISEASE (CKD)?
IMPLICATIONS FOR TREATMENT

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Introduction
Acute kidney injury (AKI) spans a spectrum of injury from subclinical, non-azotemic injury to fatal oliguric acute renal failure (ARF). AKI may be reversible or irreversible depending on the degree of damage. AKI must be differentiated from CKD and other causes of acute azotemia. Recovery from AKI may be complete resulting in normal renal function, or recovery may be incomplete with residual chronic kidney disease (CKD) that is subsequently classified as stage 1-4 based on the IRIS classification scheme for CKD patients. AKI manifests as either rapid rise in serum creatinine or oliguria indicating rapid deterioration of renal function.

AKI must be differentiated from other causes of acute azotemia. Patients with severe acute azotemia may have AKI, decompensation of CKD or so-called acute on chronic renal failure, hypoadrenocorticism or obstructive ureteroliths, so veterinarians should consider all these possibilities before assuming a patient has AKI. Prerenal causes of acute azotemia include dehydration, hypoadrenocorticism, and low-output CHF. With prerenal azotemia due to dehydration, the pre-treatment urine specific gravity is > 1.030 in dogs and > 1.035 in cats, and rehydration usually corrects the azotemia within 24-48 hours (thus also termed volume responsive azotemia). Hypoadrenocorticism (or Addison’s disease) mimics AKI because dogs with hypoadrenocorticism often have azotemia and urine specific gravity below 1.030. One major clue to hypoadrenocorticism is often that the dogs have hyperkalemia with adequate (or increased) urine output. Dogs with AKI generally do not develop hyperkalemia unless there is concurrent reduction in urine output to the oliguric range (<0.5 ml/kg/hr). Renal causes of acute azotemia include AKI, acute renovascular problems, or decompensation of CKD potentially resulting in AKI (acute on chronic renal failure). AKI results from infection (leptospirosis, Lyme nephropathy), ischemia or nephrotoxicity. Acute inflammatory diseases include acute pyelonephritis, immune mediated glomerulonephritis, and acute interstitial nephritis. Although leptospirosis can cause AKI along with acute liver disease (or liver failure), AKI without liver disease have become the most common clinical presentation of the predominant serovars of leptospirosis affecting dogs.\textsuperscript{1,2} Postrenal causes include obstructive uropathy (ureteroliths) and urinary tract rupture. Ureteroliths (and concurrent ureteral stricture) have become a very common post renal cause of azotemia in cats with a markedly increased incidence.\textsuperscript{3,4}

AKI can be classified as oliguric (<0.5 ml/kg/hour) or nonoliguric (>0.5 ml/kg/hour). Nonoliguric patients may be or may become profoundly polyuric. Nonoliguria indicates less severe damage than oliguric AKI. Oliguria is associated with complications as a result of low distal tubular flow rates leading to hyperkalemia, severe metabolic acidosis, and overhydration from fluid therapy.

Diagnosis of AKI
The clinical signs of AKI are similar to CKD, but often more severe. They include anorexia, vomiting, dehydration, diarrhea, oliguria or PU/PD, oral ulceration, lethargy, extreme depression, coma, seizures, hypothermia, and bradycardia (from hyperkalemia). Neurologic signs are frequently more severe with AKI because there is less time for the animal to adapt to the uremia. Indications of AKI (versus CKD)
include cylindruria, known exposure to nephrotoxin, or an episode of severe hypotension/shock (especially in animals receiving NSAIDs). Rapid declines of renal function over 24-48 hours without prerenal and postrenal factors, or recent lab data demonstrating normal real function are also suggestive of AKI.

Laboratory abnormalities for AKI are similar to CKD but there are some differences. Anemia on the CBC result is not characteristic of AKI but may occur with acute blood loss. Therefore the presence of concurrent anemia alone cannot be used to confirm a diagnosis of CKD. Hyperkalemia is common with oliguric AKI, as is severe metabolic acidosis. Conversion of oliguria to polyuria will assist in the correction of hyperkalemia. A markedly increased anion gap in a patient with AKI is a diagnostic clue of ethylene glycol toxicity. Hypocalcemia may be severe with ethylene glycol toxicity, but is usually not symptomatic. Inappropriate urine specific gravity (< 1.030 in dogs or < 1.035 in cats) is seen with AKI (and CKD). Isosthenuria is common in AKI. Although calcium oxalate crystalluria may be normal, calcium oxalate crystalluria in an animal with AKI is strongly suggestive of ethylene glycol toxicity. "Hippurate" crystals or calcium oxalate monohydrate crystals may be present in ethylene glycol toxicity. There are also commercial test kits available that detect ethylene glycol in serum or urine. Increased amylase and lipase (up to 4 times normal) may occur with marked decreases in GFR from either AKI or CKD.

Urine enzymes (NGAL, GGT) compared to urine creatinine (NGAL/creatinine ratio or GGT/creatinine ratio) may also be used for early detection of AKI. Recent studies also suggest that either serum NGAL or urinary NGAL/creatinine ratio may help differentiate between AKI and CKD.5,6

The pathophysiology of hyperkalemia is important. Principal cells in the distal nephron are responsible for potassium excretion under the influence of aldosterone. Three main factors affect potassium excretion in the distal nephron: aldosterone, distal tubular flow rate, and distal tubular lumen Na+ concentration. Aldosterone permits sodium reabsorption and potassium excretion into the tubules. Potassium diffuses passively into the tubular lumen and must be washed downstream by distal tubular flow to prevent a buildup of potassium. Adequate tubular lumen Na+ is also required for exchange with K+ to generate an electrical gradient for K+ diffusion into lumen. Therefore, the major disease mechanisms that result in hyperkalemia include deficiency of aldosterone (hypoadrenocorticism), inadequate distal tubular flow rates (urinary obstruction or oliguric AKI), and inadequate distal tubular lumen sodium content (from reduced renal perfusion with avid Na+ reabsorption in proximal tubule and loop of Henle).

**Causes of AKI in dogs and cats**

Leptospirosis has become the most common cause of AKI in many parts of the US.1,2,7-12 Common toxins causing AKI include ethylene glycol, grapes, raisins, Easter Lily plants, arsenic, zinc, and lead. Antibiotics that may cause AKI include aminoglycosides, amphotericin B, and oxytetracycline. Miscellaneous drugs that may cause AKI include thiacetarsamide, cis-platinum, methoxyflurane, and rarely radiographic contrast agents. Pigment nephropathy from hemoglobinuria or myoglobinuria is uncommon in dogs and cats, but may occur combined with dehydration leading to slow tubular flow rates. Diet-induced AKI occurred from pet food contaminated with melamine and cyanuric acid resulting in a major pet food recall. Recently, treat associated Fanconi syndrome leading to AKI has also been recognized with increasing frequency.
Aminoglycoside nephrotoxicity is an important cause of AKI in dogs and cats. Some factors that increase nephrotoxicity of aminoglycosides are hypokalemia, acidosis, advanced age, pre-existing renal disease, fever, sepsis, dehydration (furosemide-induced), liver disease, concurrent nephrotoxic drugs, and over dosage of aminoglycosides. Therefore, one should correct predisposing factors before initiating aminoglycosides if possible or select an alternate antibiotic. When using aminoglycosides, one should monitor the therapy appropriately and discontinue at first indication of renal damage. Monitoring the serum concentration of the drug may be helpful for prevention of toxicity. Monitoring the urine GGT/creatinine or urinary NGAL/creatinine ratios are most sensitive than other parameters such as serum creatinine for detecting early AKI. The urinary GGT/creatinine ratio or urinary NGAL/creatinine ratio will increase 2-5 days before other parameters.\textsuperscript{13,14}

**NSAIDs and AKI**

Nonsteroidal anti-inflammatory drugs (NSAIDs) have a minimal effect on renal blood flow (RBF) and GFR in a normal animal. If dehydration or hypovolemia are present, it can lead to an increase in renin release that causes an increase in the conversion of Angiotensin I to Angiotensin II, which leads to vasoconstriction. Angiotensin II causes a local release of vasodilatory prostaglandins (PGE\textsubscript{2} and PGI\textsubscript{2}), which preserves GFR and RBF during states of activation of renin-angiotensin axis. This helps prevent ischemic damage to the nephron. NSAIDs block renal vasodilatory prostaglandin production, which allows intense renal afferent and efferent arteriolar vasoconstriction leading to ischemic damage and, potentially, clinical AKI. Therefore, one should exercise caution with NSAIDs during surgery, shock, and dehydration. Ibuprofen overdose may lead to GI ulceration, which can cause dehydration, which in turn can lead to AKI from the lack of vasodilatory prostaglandins. Also, phenylbutazone and flunixin meglumine have been reported to cause AKI in dogs at routine doses. In cats, meloxicam may cause AKI without concurrent dehydration or hypotension.

**Prognosis of AKI**

Nonoliguric AKI has a better prognosis than oliguric AKI that reflects less severe damage and less severe complications. Prognosis for nonoliguric AKI is guarded to fair. Prognosis for oliguric AKI is guarded to poor depending on severity and cause unless renal replacement therapy is available. The prognosis for oliguric AKI caused by Leptospirosis is fair depending on urine output. The prognosis for oliguric AKI caused by ethylene glycol is poor. Severe hyperkalemia, acidosis, and overhydration that accompany severe oliguria contribute to poor prognosis in patients treated conservatively. These complications often necessitate hemodialysis. Prognosis of nonoliguric AKI not requiring dialysis is best determined by response to therapy. Factors that negatively impact prognosis are advanced age, underlying renal disease, and infection. One should avoid nosocomial infections by aseptic placement/care of all IV and urinary catheters.

**Leptospirosis and AKI**

Leptospirosis is important to recognize because it is potentially reversible and because of the potential for zoonosis to owners and veterinary personnel. Leptospirosis is one of the most common causes of AKI with serovars *grippotyphosa, bratislava, and pomona* being the most common infective serovars.\textsuperscript{11} Unlike traditional leptospirosis (*canicola* and *icterohaemorrhagiae*), hepatic involvement with these serovars may be absent, minimal or delayed compared to the onset of AKI. Leptospirosis is important to recognize because it is potentially reversible and because of the potential for zoonosis to owners and veterinary personnel. Clinical presentations may include AKI, acute hepatic disease, fever, myalgia,
uveitis, and vasculitis. Some serovars of leptospirosis in Europe commonly cause pulmonary hemorrhage, but this is not usually observed in the US. Common laboratory findings in dogs with leptospirosis include azotemia with inappropriately dilute urine specific gravity, elevated liver enzymes, hyperbilirubinemia, neutrophilic leukocytosis, thrombocytopenia, and renal glucosuria with normoglycemia.

Diagnosis of leptospirosis is usually made by demonstrating antibody response to non-vaccine serovars. Baseline titers > 1:800 to non-vaccine serovars or a 4-fold increase in convalescent titers (> 2 weeks later) with compatible clinical signs are considered diagnostic. The exact role of urine PCR testing for diagnosis of leptospirosis is unclear. While the initial urine PCR tests had high false positive rates, newer urine PCR testing is more specific and very sensitive.

Treatment of leptospirosis should include routine treatment for acute renal failure plus ampicillin (22 mg/kg IV q8h for 2-3 weeks) during the acute phase followed by doxycycline (5 mg/kg PO q12h) for 2 weeks. Because the diagnosis if often made retrospectively, all dogs with AKI should be considered leptospirosis suspects unless another cause is known.

References

MANAGEMENT OF RECURRENT URINARY TRACT INFECTIONS

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Recurrent urinary tract infections (UTI) are a common problem in dogs. Many resistant UTI are secondary to resistance acquired with recurrent UTI. There are 2 major types of UTI recurrence: relapse and reinfection. The implications of relapse versus reinfection are important for diagnosis and management of recurrent UTI. Relapses are defined as UTI recurrence of the same species and serologic strain of microorganisms within several weeks of withdrawal of therapy. Reinfections are recurrent infections caused microorganisms that are different than the prior UTI. Dogs with positive urine culture during antibiotic treatment have either super-infection or persistent infection. Super-infections are infections with resistant bacteria acquired during treatment of an initial UTI. Persistent infections occur when the original organism persists during treatment.

Causes of recurrent UTI

Most UTIs occur from ascending bacterial infection from the vaginal vestibule or prepuce. There are normal host defenses that protect the urinary tract from infection. Normal voiding washes bacteria out of the urinary tract before they can establish an infection. Normal canine and feline urine is bactericidal from high osmolality and extremes in pH (< 6.0). Urothelium has also intrinsic antibacterial properties. Mechanical factors including the high-pressures in the urethra, length of urethra, ureteral peristalsis, and ureterovesical "flap valve" effect act as mechanical barriers to ascending UTI.

Interference with normal host defenses may contribute to recurrent ascending infections. Common contributing factors include incontinence, incomplete voiding, urine stasis or reflux, disruption of or damage to the urothelium, anatomic abnormalities, morbid obesity, perivulvar dermatitis, alterations in immune competence, alterations of urine composition (dilute urine, glucosuria), or iatrogenic causes (perineal urethrostomy, indwelling urinary catheters). Young adult cats rarely have bacterial UTI unless prior procedures predispose them to acquired UTI, older cats are more commonly affected by UTI because of concurrent diseases that cause dilute urine and or impair immune competence.

Common causes of UTI relapse include inappropriate antibiotic use (incorrect dose or duration, poor owner compliance), persistence of infection within a urinary tract nidus (uroliths, neoplasia, pyelonephritis, prostatitis), and emergence of drug-resistant pathogens. Common causes of reinfection include failure to eliminate predisposing causes for UTI (perivulvar hooing with perivulvar dermatitis, vaginal septa, morbid obesity), incontinence, systemic illness (e.g., CKD, diabetes mellitus and hyperadrenocorticism), and spontaneous reinfection. A rare cause of UTI is recto-urethral fistula, which presents usually with reinfections and multi-organism infections.

Diagnostic approach for animals with recurrent UTI

The standard diagnostic evaluation for dogs with recurrent UTI should include history, physical examination, CBC, serum biochemistry profile, urinalysis, urine culture, abdominal radiographs and ultrasound (if available). The history should be reviewed to assess client compliance with prior treatments, for diseases or drugs that could contribute to immunosuppression, for evidence of urinary incontinence, or skin issues including perivulvar licking/dermatitis. Physical examination should include careful examination of the vulva and perivulvar skin for evidence of recessed or “hooded” vulva with
periretinal dermatitis that may contribute to reinfection of the urinary tract. Subtle abnormalities of the periretinal region is easily overlooked during routine physical examination and should be carefully evaluated in dogs with recurrent UTI. Rectal examination should also be included as a standard part of the physical examination to evaluate the urethra for masses or uroliths that could contribute to recurrent UTI.

Testing for hyperadrenocorticism should be performed if there is data that might support the presence of hyperadrenocorticism in dogs with a signalment compatible with hyperandrenocorticism. Cystoscopy is recommended for diagnostic evaluation for dogs with recurrent UTI if an underlying cause has not been identified during initial work-up. Cystoscopy helps rule out anatomic abnormalities, polyps, neoplasia or uroliths and permits mucosal biopsy for culture, cytology and histopathology.

Cultures of tissue or uroliths are more sensitive than routine urine culture for detecting chronic UTI especially in dogs previously treated with antibiotics. Bacteria were isolated from bladder mucosal cultures or urolith cultures in 18 to 24% of dogs despite concurrent negative urine cultures. Cultures of mucosal biopsies are readily obtained during cystoscopy. Cytology and histopathology of cystoscopic biopsies are required to differentiate benign polyps or polypoid cystitis from neoplasia such as transitional cell carcinoma.

Therapeutic approach for animals with resistant UTI

Treatment of recurrent or resistant UTI should include attempts to obtain a specific diagnosis first followed by a systematic treatment approach. Treatment of recurrent UTI should be based on aerobic culture and sensitivity testing of urine samples obtained by cystocentesis or from culture of mucosal biopsies. A follow-up “therapeutic” urine culture should be obtained approximately 7 days after initiation of antibiotic therapy to prove in vivo efficacy of the drug selected on the basis of the initial in vitro susceptibility testing. This “therapeutic” culture will be positive in dogs that have persistent infections that may show in vitro susceptibility to the administered antibiotics, yet treatment fails to resolve the resistant infection. Positive “therapeutic” cultures necessitate change in antibiotic treatment. Alternatively, if this “therapeutic” culture is negative, antibiotic therapy is continued at full doses for a total of 4 to 6 weeks depending on location and type of infection. Duration of antibiotics should to be 6-8 weeks for suspected kidney or prostate infections. Follow-up urinalysis and urine culture should be repeated 1 week and 1 month after completion of antibiotic therapy to confirm resolution of UTI.

Male dogs with UTI should be assumed to have infection of the prostate; therefore, antibiotics selected for treatment of UTI in male dogs should achieve good prostate penetration. Examples of antibiotics with poor prostate penetration include penicillin, ampicillin, cephalosporins, and aminoglycosides. Antibiotics that achieve good prostate concentration and are more likely to be effective for treatment of UTI complicated by bacterial prostatitis in dogs include fluoroquinolones (enrofloxacin, marbofloxacin, and ciprofloxacin), trimethoprim-sulfa, carbenicillin, and chloramphenicol. Bactericidal antibiotics such as fluoroquinolones are generally preferred over bacteriostatic antibiotics for treatment of chronic prostatitis.

Episioplasty is often effective for resolving re-infections that occur secondary to periretinal dermatitis. Weight loss and control of active UTI are also recommended prior to episioplasty. Resolution of
relapsing UTI secondary to infected uroliths usually requires removal of the uroliths in order to achieve resolution of the UTI.\(^9,10\) Urinary incontinence may also contribute to recurrent UTI: if urine can leak out of the bladder, then bacteria may be able to ascend through the urethra from the lack of a tight seal. Effective treatment of urinary incontinence may reduce the risk of recurrent UTI in dogs. For dogs with vaginal septal remnants, laser or surgical transaction of the remnant may be beneficial to preventing future ascending UTIs.

**Preventative therapy** for repeated re-infection (> 2 per 6 months) should only be utilized after an extensive search for any underlying cause. Preventative therapy will not be effective for relapses of the same organism from a nidus within the urinary tract. Administration of cranberry juice or cranberry extract is suggested to reduce recurrence of UTI in humans, although not all studies support efficacy of these products in humans. Cranberry extracts containing proanthocyanidins (PACs) inhibit the attachment of the P-fimbriated *E. coli* to uroepithelial cells in vitro. A recent study confirmed that cranberry extract administered to normal dogs resulted in excretion of PACs in their urine, which inhibited attachment of UPEC to canine uroepithelial cells in vitro. There are no placebo controlled clinical trials evaluating efficacy of cranberry extracts containing PACs for prevention of recurrent UTI in dogs. The main application of cranberry extracts would be for prevention of re-infection in dogs with a history of UTI with gram-negative organisms. Cranberry extracts would not be effective for elimination of established infections nor would they be effective for UTI relapse in cases where there is a nidus within the urinary tract such as an infected urolith.

Preventative antibiotic therapy used to be recommended, but newer information suggests that this approach may only reduce UTIs on the short-term and contributes to emergence of more resistant strains of bacteria and more UTIs in the long-term. Pulse antibiotic therapy for 3-5 days every few weeks is also not an effective strategy for management of recurrent UTI. These misuses of antibiotics are likely to induce multiple drug resistance in the organisms causing the UTI and limit the number of effective antibiotic options available for treatment of recurrent infections.

An alternative therapy for recurrent UTI is use of a rarely used urinary antiseptic methenamine hippurate.\(^1\) Methenamine is converted to formaldehyde in an acidic urine pH. Because bacteria cannot acquire resistance to formaldehyde, it may be efficacious in patients with re-infections. The dose is not well established but recommended doses are 10-20 mg/kg PO q 8-12 h. If necessary, urine pH may need to be lowered by use of an acidifying diet and/or urinary acidifiers. The major concern with this approach is that formaldehyde is a carcinogen, so long-term use might promote development of TCC. Therefore, this drug is used most often in older dogs or dogs with TCC and recurrent UTI.

**Difficult organisms causing resistant or recurrent UTI**

Urinary tract infections with *E. coli* warrant some specific comments concerning treatment. Because of their ability to acquire antibiotic resistance through plasmid-mediated resistance, *E. coli* UTIs can become multi-drug resistant. Therefore, appropriate follow-up is especially important with this common uropathogen. Follow-up urine cultures are recommended for any dog or cat with recurrent UTI due to *E. coli*. For multi-drug resistant *E. coli*, antibiotics to consider if testing suggests they are effective include amikacin, ceftiofur, imipenem or meropenem. Aminoglycosides are excreted in the urine and achieve very high urine concentrations but are also nephrotoxic. Therefore, aminoglycosides should only be used for shorter durations and with appropriate monitoring for nephrotoxicity. Monitoring for
nephrotoxicity should include routine urinalysis and monitoring of urine GGT to creatinine ratios.\textsuperscript{11} Cumulative once daily dosing of amikacin is preferred over more frequent dosing of gentamycin. Ceftiofur or cefoxitin are effective alternatives to aminoglycosides provided the \textit{E. coli} isolated is sensitive in \textit{vitro}. Imipenem or meropenem are highly effective against many strains of \textit{E. coli} and may be required in animals with preexisting renal disease and resistant gram negative UTI. However these antibiotics should be reserved for documented multi-resistant infections when other antibiotics have failed and renal disease prohibits the safe use of aminoglycosides. A novel approach that is being investigated for treatment of multi-drug resistant strains of \textit{E. coli} is treatment with fosfomycin, which is a natural antibiotic produced by \textit{Streptomycyes fradiae}.\textsuperscript{12} Fosfomycin is not affected by beta lactamases, it is effective against beta lactamase producing bacteria. Potential side effects include anorexia and diarrhea. The suggested dose is 40 mg/kg PO q 12 h.\textsuperscript{12}

\textbf{Enterococcus spp} are isolated from urine in dogs more commonly that in the past, especially in dogs that have been treated with fluoroquinolones. There are several important features of this organism that are important to consider. Most animals with enterococcal ‘UTI’ have no clinical signs of lower urinary tract irritation (unless other organisms are present), notable absence of pyuria, and are considered to have ‘asymptomatic bacteruria” rather than UTI per se; thus treatment is not recommended or beneficial. Also, during laboratory \textit{in vitro} susceptibility testing, Enterococcus often appears to be susceptible to fluoroquinolones, although it is usually resistant to fluoroquinolones \textit{in vivo}. In some dogs, treatment of any concurrent organisms may resolve the enterococcal UTI without specific treatment of the Enterococcus. In dogs with asymptomatic, resistant enterococcal ‘UTI’, \textbf{not} treating the Enterococcus is the best approach.

\textbf{Recurrent UTI in cats}

Cats less than 8 to 10 years of age uncommonly have bacterial UTI as a cause of lower urinary tract signs unless they have had perineal urethrostomy surgery or indwelling urinary catheters.\textsuperscript{3,14,15} The incidence of lower urinary tract disease in geriatric cats is very different than young adult cats. In one study, 46\% of geriatric cats with lower urinary tract disease had UTI, 17\% had UTI and uroliths, 10\% had uroliths, 7\% had urethral plugs, 7\% were due to trauma, 5\% had idiopathic cystitis, and 3\% had neoplasia.\textsuperscript{4} Many geriatric cats with UTI have concurrent CKD, diabetes mellitus or hyperthyroidism\textsuperscript{4,15}

\textbf{Conclusion}

The key to successful management of recurrent UTI is to accurately diagnose the reason(s) for the recurrent nature of the problem in each case. Cystoscopy is an underutilized tool in the diagnosis of recurrent UTI. Appropriate follow-up cultures are required for successful management of recurrent UTI and resistant UTI.

\textbf{References}


MANAGEMENT OF UROLITHS IN DOGS AND CATS
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Introduction
Effective management of uroliths always involves removal of the uroliths and prevention of recurrence. Removal of bladder and urethral stones has traditionally been by open cystotomy and urethrotomy. Surgical removal is usually effective for uroliths in the bladder and urethra, although post-operative radiographs should be performed to confirm complete removal. Uroliths may be inadvertently left in the urinary tract in up to 20% of patients treated by open cystotomy, with the majority of the uroliths remaining in the urethra. These remaining urethroliths may be removed by laser lithotripsy to avoid a second surgery. Minimally invasive management techniques often can be used to replace open surgical removal of uroliths. Minimally invasive techniques include medical dissolution, voiding urohydropropulsion, laser lithotripsy and laparoscopic-assisted cystotomy. Prevention of recurrence should be based on quantitative analysis from a veterinary urolith center. Retrograde urohydropropulsion of urethral stones is preferred over attempts to push urethral stones back into the bladder using a urinary catheter.

Medical dissolution
Medical dissolution is effective for certain uroliths locations and types. Urocystoliths and nephroliths are amenable to dissolution whereas ureteroliths and urethroliths are not. Struvite, urate, and cystine uroliths may be medically dissolved whereas calcium oxalate and silica uroliths cannot be medically dissolved. For dissolution to occur, uroliths must be surrounded by under-saturated urine to allow the crystals to go back into solution. Medical dissolution of urocystoliths in male animals is associated with risk of urethral obstruction once the uroliths are small enough to pass into the urethra.

Struvite uroliths in dogs are usually infection-induced from infection to urease producing bacteria. Over 90% of struvite stones in dogs are caused by UTI with Staph, Proteus. Other urease-producing organisms that infrequently cause struvite uroliths include Pseudomonas spp, Klebsiella spp, Corynebacterium urealyticum and mycoplasmas such as Ureaplasma urealyticum. While cats also develop infection-induced struvite uroliths, most struvite uroliths in cats are sterile and are considered dietary-induced uroliths. Medical dissolution of infection-induced struvite urocystoliths requires a combination of appropriate antimicrobial and calculolytic dietary therapy. Antimicrobial selection should be based on urine culture obtained by cystocentesis prior to antimicrobial therapy. Antimicrobial therapy must be given throughout the entire dissolution period because viable bacteria are contained within the layers of struvite uroliths. For sterile struvite uroliths in cats, antimicrobial therapy is not necessary. Commercial calculolytic diets for dissolution of struvite uroliths in dogs include Hill’s Prescription diet s/d® and Royal Canin® S/O Lower Urinary Tract Support Diet. Antimicrobial and dietary therapy should continue approximately 1 month beyond radiographic resolution of struvite urolithiasis (because uroliths too small for radiographic detection may still be present) or until resolution of all uroliths on ultrasonography. The animal should not be in renal failure and should not have evidence of obstruction. One week after initiation of antimicrobial therapy, urine should be obtained by cystocentesis for urinalysis and culture. Urinalysis should reveal decrease of the urine pH to <7.0 and the urine culture should be negative for bacterial growth. If the UTI is persistent, antimicrobial therapy should be changed on the basis of urine culture and sensitivity testing. Monitoring of dissolution therapy should consist of
abdominal radiographs and urinalyses every 4 weeks. If bacteriuria, pyuria or inappropriate alkaline urine pH are present, the urine should be cultured for aerobic bacteria and mycoplasma.

Commercial calculolytic diets for struvite uroliths in cats include Royal Canin® S/O Lower Urinary Tract Support Diet, Purina UR st/ox Diet, and Hill’s Prescription diet s/d® and c/d-multicare diets. Struvite preventative diets are preventative for sterile struvite uroliths in cats. Prevention and treatment of recurrent UTI is critical for prevention of infection-induced struvite uroliths in dogs and cats.

**Voiding urohydropropulsion**

Voiding urohydropropulsion is the removal of smaller urocystoliths by inducing voiding while the dog is positioned vertically so that urocystoliths pass during voiding. General anesthesia facilitates complete urethral relaxation, preventing development of high intravesicular pressures that could cause iatrogenic trauma to the bladder wall. If the bladder is not distended with urine, it is distended with sterile saline via cystoscopy or urethral catheterization. The dog is positioned so that the spine is roughly 25 degrees caudal to a line perpendicular to the effects of gravity, such that a line drawn through the urethra into the bladder is approximately vertical. The bladder is agitated side to side to cause the urocystoliths to settle in the trigone by gravity. The bladder is palpated and the intravesicular pressure is gradually increased by manual compression of the bladder to initiate a detrusor contraction. Once voiding begins, the bladder is compressed more firmly to attempt to maintain maximum urine flow to flush out the cystoliths. The bladder is refilled with sterile saline through the cystoscope or a urinary catheter and the process is repeated until no urocystoliths are passed with the expelled fluid. Then post-procedural radiographs are performed to confirm complete removal of the urocystoliths.

**Laser lithotripsy**

If available, laser lithotripsy using the holmium: YAG laser is an option for fragmentation of cystoliths that are too large for voiding urohydropropulsion. The holmium laser energy is absorbed in <0.5 mm of fluid, allowing it to safely fragment uroliths within the urethra or bladder without damage to adjacent mucosa. Our results with laser lithotripsy using the holmium laser have been excellent especially for female dogs and larger male dogs. Laser lithotripsy may be preferred over urethrotomy for removal of urethroliths. Most dogs are clinically normal within 12 to 24 hours of the procedure. Male dogs with large stone burdens are not good candidates for removal of cystoliths by laser lithotripsy. Likewise, male dogs smaller than 5-7 kg may be too small for this transurethral cystoscopic technique. Therefore, we often utilize laparoscopic-assisted cystotomy for male dogs.

**Management of urolith recurrence**

Calcium oxalate uroliths tend to recur in most dogs with recurrence rates of up to 50% within 3 years of initial diagnosis. Therefore preventative measures such as diet and medications should be utilized to reduce the risk of recurrence. Dietary changes should be attempted; additional medications are recommended if there is persistent calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis. Increased water intake though feeding a canned diet or by adding water to the diet may be the most important recommendation to help prevent recurrence of calcium oxalate urolithiasis in dogs.

The commercial diets recommended to reduce the risk of calcium oxalate urolith recurrence in dogs include Royal Canin Canine Urinary S/O Diet, Purina UR, and Hill’s Prescription diets c/d MultiCare, and u/d. Alternative diets suggested for dogs with history of pancreatitis, obesity, diabetes mellitus or
hyperlipidemia are Royal Canin Canine Urinary S/O Moderate Calorie diet and Hill’s Prescription diet g/d or w/d.

Dietary therapy alone will not always prevent calcium oxalate urolith recurrence. Hydrochlorothiazide (2 mg/kg PO q12h) should be considered in dogs that have persistence of calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis despite diet therapy. Thiazide diuretics cause subclinical volume depletion resulting in increased proximal tubular reabsorption of sodium and calcium. Once dietary and hydrochlorothiazide therapy have been implemented, if calcium oxalate crystalluria is persistent or calcium oxalate uroliths recur, potassium citrate should also be given to effect to achieve a urine pH of 6.5—7.0 using a starting dose of 50—75 mg/kg PO q12h. The serum potassium should be initially monitored monthly during potassium citrate supplementation and the dose reduced if hyperkalemia occurs.

Because calcium oxalate uroliths commonly recur, appropriate surveillance should be utilized to document recurrences before the uroliths become too large to void. If small recurrent urocystoliths are diagnosed, many recurrences may be managed by voiding urohydropropulsion. Although some dogs with recurrent calcium oxalate urocystoliths may be asymptomatic for extended periods of time, removal of urocystoliths is recommend to prevent urethral obstruction.

**Feline Ureteroliths-Subcutaneous Ureteral Bypass**

Subcutaneous ureteral bypass (SUB) is a new option for management of obstructive ureteroliths. A SUB is a nephrostomy tube connected to a cystostomy tube by a subcutaneous port (Figure 1). There is a learning curve associated with SUB placement, so most complications are associated with leakage or kinking of the tubing in the immediate post-operative period. One advantage of the SUB over ureteral stents is the ability to flush the SUB system to remove transient occlusions by cellular debris. The urine from the bladder and renal pelvis may be sampled for urinalysis and urine culture by insertion of a Huber needle into the SUB port. Another advantage of the SUB is the much larger diameter (6 Fr) compared to ureteral stents (2.5 Fr), such that occlusion due to encrustation of the lumen is much less likely with a SUB than with ureteral stents. In our hospital, SUB placement is currently the preferred technique for intervention for majority of cats with ureteroliths.

*Figure 1: Post-operative radiograph of SUB placement in a cat with bilateral ureteroliths. Note the iodine contrast in the urinary bladder that has drained from the right kidney into the bladder through the SUB system.*
Long-term survival in cats treated with ureteral stent or SUB placement is dependent on the degree of recovery of renal function after relief of the ureteral obstruction. On the basis of renal function following relief of obstruction, cats with Stage 1-2 CKD had more prolonged survival than cats with stage 3-4 CKD. Therefore, earlier intervention should be considered in cats with complete ureteral obstruction to preserve as much renal function as possible. The optimal time wait to allow for passage of ureteroliths using medical management prior to intervention should be determined for each individual cat. Factors indicating need for quicker intervention include multiple ureteroliths, hyperkalemia, refractory metabolic acidosis, severe azotemia and marked distention of the renal pelvis and ureter.

References
FELINE IDIOPATHIC CYSTITIS

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Introduction

Feline idiopathic cystitis (FIC) is a lower urinary tract disease (LUTD) of undetermined etiology characterized by hematuria, dysuria, and periuria, with possible urethral plug formation in male cats.\(^1\)\(^-\)\(^6\) Idiopathic cystitis is one of the causes for dysuria/pollakiuria in cats with LUTD. The problem with assuming all cats with LUTD have FIC is that other diseases with similar signs will be misdiagnosed and not treated effectively.

Diagnosis of Idiopathic Cystitis

Diagnosis of FIC is based on ruling out other known causes of LUTD, thus FIC is an exclusion diagnosis. The minimum work-up consists of a urinalysis, urine culture, and abdominal radiographs to rule-out radiopaque uroliths and UTI. Ultrasound or contrast radiographs should be used to evaluate cats with clinical signs that that are highly recurrent or that persist for more than 7 days to rule out radiolucent uroliths and neoplasia. Cystoscopy may be used to confirm a diagnosis of FIC and to exclude other causes on LUTD.\(^7\)\(^,\)\(^8\) Urine concentrations of fibronectin were increased and urine concentrations of trefoil factor 2 were decreased in cats with FIC compared to normal cats and cats with urolithiasis or UTI.\(^9\)\(^,\)\(^10\) These findings may eventually serve as biomarkers for diagnosis of FIC, although there is overlap of the concentrations of these biomarkers between cats with FIC, cats with other LUTD, and normal cats.

Non-obstructive FIC usually resolves spontaneously within 5 to 7 days regardless of treatment. Recurrence is common but unpredictable; cats can be normal from days to years between episodes. Recurrences occur in up to 65% of cats within 1-2 years. Therefore, placebo-controlled clinical trials are essential for evaluation of therapies for treatment or prevention of FIC.

Obstructive FIC is seen almost exclusively in males, and is caused by urethral "plugs". Urethral plugs are not uroliths. Urethral plugs differ from uroliths in that they lack organized internal structure. They are semi-solid plugs composed of primarily of protein matrix and may also contain struvite crystals.\(^11\) The matrix consists of varying quantities of protein and cellular debris. If obstruction is due to true uroliths, the disease is urolithiasis, not idiopathic cystitis. Urethral obstruction from urethral pugs may occur abruptly without prior clinical signs. Urethral matrix plugs may begin to form in female cats and non-obstructed male cats, but they pass out the urethra without becoming obstructed. Increased crystals in plugs may solidify the plug causing obstruction. Urethral spasms contribute to obstruction as evidenced by the fact that drugs designed to facilitate urethral relaxation may allow cats to pass the urethral pug without need for urethral catheterization.\(^12\) Urethral obstruction tends to be recurrent with subsequent episodes of FIC.

The etiology of idiopathic cystitis is unknown.\(^1\) Some authors have suggested that FIC is "feline interstitial cystitis", similar to interstitial cystitis which occurs in humans (mainly women).\(^1\)\(^,\)\(^3\) Cats with FIC have abnormal size and function of their adrenal glands.\(^13\) Cats with FIC also have elevated catecholamine levels that normalize after periods of environmental enrichment.\(^14\) The exact clinical relevance of these observations is not clear.
Treatment of FIC

There is no proven effective therapy for treatment to shorten the duration of an episode of FIC.\textsuperscript{1,15-17} FIC episodes usually resolve spontaneously over 5-7 days in non-obstructed cats. Antibiotics are only indicated for documented UTI or prophylaxis following urethral catheterization, preferably after removal of the catheter. While many different treatments have been suggested for FIC, none are more proven to be more effective than placebo to shorten the duration of an episode of FIC. Antibiotics are not effective in treatment of FIC.\textsuperscript{17,18} Methylene blue containing products and phenazopyridine are contraindicated in cats, because they may cause Heinz body hemolytic anemia and methemoglobinemia. Corticosteroids have been suggested to reduce inflammation in FIC, but a double-blinded clinical trial showed no improvement with steroids compared to a placebo.\textsuperscript{19} Prednisone also did not reduce inflammation in an experimental model of FIC and predisposed the cats to UTI and pyelonephritis.\textsuperscript{16,18} Meloxicam was also not beneficial compared to placebo in cats with FIC. Propantheline is an antispasmodic that may reduce the severity and frequency of "urge" incontinence in cats with non-obstructed FIC. However, this is symptomatic only and does not affect the rate of recovery. Intravesical DMSO was not effective, and it may predispose the cat to UTI and pyelonephritis.\textsuperscript{18} Treatment with sublingual buprenorphine (0.01-0.03 mg/kg PO q 6-12h) may reduce clinical discomfort from FIC while waiting for the disease to spontaneously resolve.

Prevention of FIC

Previous clinical trials suggest that dietary therapy designed to prevent crystalluria, such as a canned dietary therapy, may reduce the incidence of recurrent FIC episodes and urethral obstruction.\textsuperscript{20} Adding water to the diet and/or feeding canned diets appears to reduce recurrence of FIC.\textsuperscript{1} In a recent prospective clinical trial, cats fed either dry or canned “therapeutic urinary food” showed significantly less clinical signs of FIC compared to a control diet.\textsuperscript{21} The therapeutic diet was effective as both a canned or dry formulation.

Amitriptyline (5-10 mg per cat q24h) may prevent recurrence of FIC based on a non-controlled study, but this is not consistently effective.\textsuperscript{22} Perineal urethrostomy (PU) has been advocated for prevention of recurrent urethral obstruction. Perineal urethrostomy surgery reduces the risk of obstruction; however, it does not address the underlying disease process. PU can also predispose to UTI, which can lead to infection-induced struvite urolithiasis, along with potential complications including urethral stricture.\textsuperscript{23,24} Although glucosamine has been recommended for treatment of FIC, studies have not demonstrated any benefit over placebo-treated cats.\textsuperscript{25} In this study, most cats were fed more canned food during the study and both glucosamine-treated and placebo-treated cats improved to a similar degree.\textsuperscript{25} In a multicenter clinical trial of GAG therapy, Elmiron (pentosan polysulfate) had a small beneficial effect on cystoscopic scores in cats with FIC, but no difference in clinical signs. In this study there was a large placebo effect that prevented any measurable benefit on clinical signs. Similarly, a placebo-controlled study of pheromone therapy also failed to demonstrate any benefit.\textsuperscript{26} A recent uncontrolled observational study suggested that environmental enrichment along with other behavioral modifications (so-called multimodal environmental modification) resulted in improvement of the clinical signs of FIC and warrants further study.\textsuperscript{27}
Summary

Feline idiopathic cystitis is an exclusion diagnosis; so appropriate tests must be done to rule out other common causes of LUTD. Dietary therapy is effective for prevention of idiopathic cystitis and is the mainstay of therapy for FIC.

References


URINARY OBSTRUCTION

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Introduction
Urinary obstruction is a common clinical presentation in dogs and cats and must be differentiated from functional urinary retention. Mechanical obstruction can be intraluminal due to uroliths, urethral plugs, and blood clots. Urinary obstruction can also be intramural from neoplasia (TCC) and urethral or ureteral strictures. Extramural mechanical obstruction can be caused by neoplasia (prostatic) or bladder herniation into a perineal hernia. Urinary retention can also be caused by functional urinary retention disorders such as neurologic disorders, urethral spasms in male cats and reflex dyssnergia. Before concluding that a patient has functional urinary retention, one should always thoroughly diagnostically evaluate the patient for mechanical urinary obstruction.

Metabolic effects of urinary obstruction
Severe hyperkalemia is the usual cause of death from complete urethral obstruction. Findings on ECG from hyperkalemia include tall T waves, prolonged P-R, QRS, and Q-T intervals, bradycardia, and ventricular asystole. Severe metabolic acidosis also occurs due to lack of excretion of metabolic acids. Hypothermia and dehydration are also common with severe postrenal uremia.

Urinary obstruction causes increased tubular pressure, which impairs glomerular filtration, renal blood flow, and tubular function. Tubular function is often impaired for several days after the relief of obstruction. Post-obstructive diuresis may result in massive polyuria for several days. The exact mechanism of post-obstructive diuresis is not known, but it may include tubular dysfunction, solute diuresis, volume expansion, humoral factors or atrial natriuretic factor.

Obstruction to urine flow limited to one ureter or kidney will not cause postrenal azotemia/uremia provided the other kidney and ureter are functional. The degree of renal damage from chronic obstruction depends on the degree, duration, and site of obstruction. Complete ureteral obstruction (without infection) can lead to irreversible renal damage within 2 to 4 weeks. Chronic, partial obstruction will lead to hydroureter, hydronephrosis and potential for severe renal damage of the obstructed kidney. In some animals with unilateral ureteral obstruction, reductions in renal blood flow to the kidney during obstructive uropathy results in a small, irregular kidney rather than hydronephrosis. Damage from urinary obstruction is accelerated if UTI is also present. Urinary obstruction with UTI may result in sepsis (urosepsis). An obstructed, infected kidney may be irreversibly damaged within days. The degree of reversibility of decreased renal function is variable and difficult to predict in clinical patients.

Urethral obstruction may cause excessive bladder distension resulting in detrusor atony or weakness, which disrupts tight junctions between muscle cells. This is common in obstructed cats, and usually resolves over several days if the bladder is kept decompressed.

Treatment of urinary obstruction
Patient Stabilization: The goals in treating urethral obstruction are to re-establish urine flow via low pressure excretory pathway, treat metabolic consequences of obstruction, treat/prevent UTI, and preserve renal function. In the treatment of complete urethral obstruction, the bladder should be
decompressed by careful cystocentesis with samples saved for urinalysis and culture. This reduces intravesical pressure, allows the kidneys resume urine production, and makes relief of obstruction easier. Intravenous fluid therapy is needed to correct the azotemia, hyperkalemia, acidosis, and dehydration. The estimated deficit is replaced IV with Plasmalyte or LRS over 6-12 hours unless cardiac or pulmonary disease prevents rapid replacement. Intravenous bicarbonate was previously recommended to correct the acidosis and to decrease serum potassium levels; however this will also decrease serum ionized calcium concentrations, which are commonly decreased with obstruction. Therefore, IV bicarbonate is not the safest or most effective means to treat hyperkalemia. A more effective means to correct hyperkalemia by transcellular shifts is intravenous glucose and insulin therapy. Intravenous calcium gluconate may be necessary to treat ionized hypocalcemia and to counteract the cardiac effects of hyperkalemia in patients at risk for dying from cardiac arrhythmias. Hypothermic animals should be placed on a warm water blanket until the temperature is normal.

**Relief of urethral obstruction:** Urethroliths should NOT be pushed back to the urinary bladder using a urinary catheter. This is an extremely common error made by many experienced veterinarians. Successful passage of a urinary catheter often occurs without displacing the urethroliths from the urethra by the catheter passing to the side of the urolith(s). Then when the urinary catheter is removed, the patient often re-obstructs with the urethrolith. Urethroliths should be retropulsed back into bladder for medical dissolution or surgical removal. If the urethrolith cannot be retropulsed into bladder, laser lithotripsy is a highly effective for removal of urethroliths.¹³

**Retrograde urohydropropulsion of uroliths:** General anesthesia is usually required for retropulsion. If the bladder is overdistended, decompressive cystocentesis (using a 22-gauge needle connected to a 60-mL syringe by extension tubing and a three-way valve) is performed and fluid therapy should be administered to correct acid-base and electrolyte imbalances before anesthesia. The largest urinary catheter possible is gently passed into the distal urethra and the urethral orifice is compressed gently around the catheter with sterile gauze sponges. An assistant compresses the urethra against the pubis via digital rectal palpation. A 2:1 mixture of sterile saline and sterile aqueous lubricant is rapidly flushed into the urethra while compressing the urethral orifice around the catheter to prevent fluid leakage from the penis. An estimate of the total volume of flush required is 6 ml/kg of body weight or 60 ml, whichever is less. Once the urethra begins to dilate, the rectal compression is released while flushing continues. If the urethroliths pass retrograde, the catheter is gently advanced to the trigone. If the calculus does not move retrograde, the degree of bladder distention should be assessed prior to repeating the procedure. Subsequent retrograde flushes are done with sterile saline alone, because the urethra is well lubricated. Successful retrograde movement of the urethroliths should be confirmed by cystoscopy or radiography. The aim of retrograde urohydropropulsion is to flush the uroliths into the bladder, not to push them with the urinary catheter. Pushing against urethroliths with rigid polyethylene catheters may result in mucosal trauma, urethral perforation, or the catheter being passed round the urolith. Catheter induced trauma predisposes to future urethral stricture formation.

**Urethral plugs:** Urethral plugs should be dislodged manually or flushed back into bladder. After flushing urethral plugs back into the urinary bladder, thoroughly lavage the bladder with warmed sterile saline if needed to remove debris (matrix and crystals) to reduce risk of recurrent obstruction. Perineal urethrostomy is rarely required for acute urethral obstruction by urethral plugs. If necessary, an indwelling urinary catheter should be maintained connected to a closed collection system. Indwelling
urethral catheters predispose to UTI, and may promote urethral inflammation, edema, and potentially, urethral stricture formation. Indications for an indwelling urethral catheter in cats are: inability to produce adequate size and force of urine stream by bladder compression following urethral flushing, repeated episodes of obstruction occurring over a period of hours, severely azotemia cats with severe electrolyte abnormalities, and cats with large amounts of urine sediment and/or blood clots in the urine.

Recent observations of cats with urethral plugs indicate that urethral obstructions by plugs are due at least partially from urethral spasms which prevent passage of plugs.\(^4\) One recent study documented that sedation may facilitate passage of urethral plugs in most cats.\(^4\) Therefore, an alternative approach may be attempted for cats without severe dehydration, azotemia or acid-base and electrolyte abnormalities. The urinary bladder is decompressed by cystocentesis, and the cat is sedated with a combination of narcotics and high-dose acepromazine. The cat is placed in a quiet environment and monitored for passage of urine. Decompressive cystocentesis is repeated every 4-8 hours as needed. If spontaneous voiding does not occur, then traditional relief of obstruction is indicated.

In a recent pilot study of obstructed male cats with feline idiopathic cystitis, intravesical infusion of glycosaminoglycans (GAG) was well tolerated. While not statistically different than the control group, intravesical GAG treatment tended to reduce the incidence of urethral obstruction following removal of the urethral catheter.\(^5\) This therapy warrants additional study to determine clinical efficacy.

**Urethral Stents:** Urethral stents are most commonly indicated to relieve urethral obstruction by neoplasia such as transitional cell carcinoma (TCC).\(^6\)-\(^8\) Urethral stents may also be useful for management of severe, refractory urethral obstruction from proliferative urethritis, but this has not been reported. Self-expanding nitinol urethral stents are preferred for palliative stenting of malignant urethral obstructions because they have more outward expansile strength than balloon expandable stents.\(^6\) In 19 dogs with complete urethral obstruction from TCC, 17 dogs were successfully stented allowing the dogs to void and be discharged from the hospital.\(^8\) Median survival was 78 days, and 59% of the dogs had metastasis at the time of death. While 39% of the dogs had some degree of incontinence post-stenting, owner satisfaction with their dog’s quality of life was high with 94% indicating they would recommend urethral stent placement.

**Functional urinary retention**

Animals with suspected functional urinary retention should be thoroughly evaluated for mechanical causes on urethral obstruction before concluding that the condition is caused by functional obstruction. There are several causes of functional urinary retention. One of the most commonly encountered causes of functional urinary retention is neurogenic disruption of normal innervation of the micturition reflex by spinal cord disease. Depending on the neurologic localization, there may be several different clinical presentations. Other less common causes of functional urinary retention include reflex dyssnergia, bladder atony from prolonged overdistension, and side effects of medications. Functional obstruction may result from failure of coordination of urethral relaxation with detrusor contraction referred to as reflex dyssynergia.\(^9,10\)

Neurogenic causes of urinary retention most often are due to spinal cord diseases that disrupt communication of the brain stem with the lubosacral spinal segments. Therefore, careful neurologic examination should be performed in dogs with suspected functional urinary retention. Some dogs with
apparent reflex dyssynergia have subtle disease in the lumbosacral spine. Urethral spasms during urethral pressure profilometry are supportive evidence of reflex dyssynergia.\textsuperscript{10} Treatment of suspected reflex dyssynergia should begin with the \(\alpha\)-adrenergic antagonists phenoxybenzamine, prazosin or tamsulosin. If these drugs do not resolve the urinary retention, then bethanechol is added to facilitate detrusor contraction. Then, benzodiazepine may be added as a skeletal muscle relaxant, although response is often poor. In some patients, these therapies are not effective and urinary retention continues. Advanced imaging (MRI) of the caudal spinal cord may reveal an underlying cause in some refractory patients. In refractory patients, salvage procedures may include tube cystotomy or urethral stent placement.\textsuperscript{11}

Cats with urethral plugs and cats after removal of urethral catheters often have substantial urethral spasms that contribute to the urethral obstruction. In cats with plugs, it may be a combination of functional urethral spasms along with the mechanical plug resulting in the obstruction. Relaxation of the urethral spasms facilitated passage of the plug without the need for urethral catheterization in 11 of 15 cats in one study.\textsuperscript{4} Urethral spasms following removal of urinary catheters are the most common cause of functional urinary retention in small animal practice. Administration of \(\alpha\)-adrenergic antagonists is often required in these cats to resolve the ongoing urethral spasms and avoid repeated catheterization.

\textbf{References}

MANAGEMENT OF REFRAC TORY URINARY INCONTINENCE

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Urinary incontinence is defined as loss of voluntary control of urination resulting in leakage of urine. Urinary incontinence must be differentiated from inappropriate urination associated with dysuria and pollakiuria. Diagnosis and management of the majority of cases are routine; however, treatment of refractory urinary incontinence may present a challenge to the clinician. A thorough physical examination should be performed of dogs with refractory urinary incontinence including a rectal examination and a neurologic examination focusing on the rear limbs and perineal reflexes. Dogs with severe urinary incontinence may have urine scald around the vulva or prepuce. The diagnostic evaluation of dogs with refractory urinary incontinence should include a medical history, physical examination, serum biochemistry profile, urinalysis, urine culture, abdominal radiographs and ultrasonography. If available, cystoscopy and urodynamic testing should be also performed. Urodynamic tests include urethral pressure profile (UPP) and cystometrograph (CMG). The UPP permits evaluation of urethral function during the storage phase and the CMG evaluates detrusor function during the storage and voiding phases.

Urethral incompetence

Urethral incompetence (or urethral sphincter mechanism incompetence) is the most common cause of incontinence in adult female dogs. Urethral incompetence is usually "hormonally responsive" and usually occurs months to years after neutering. Congenital anatomic or functional abnormalities of the urethra may result in urethral incompetence prior to neutering.

The pathogenesis of urethral incompetence after neutering is controversial but likely involves the effects of estrogen on α-adrenergic receptors. Estrogen has a permissive effect on α-adrenergic receptors of the internal urethral sphincter, thereby promoting increased urethral tone and continence. With decreased estrogen concentration, α-adrenergic receptors require greater stimulation to maintain urethral tone. This forms the basis of treatment with α-adrenergic agonists or estrogen. While the dog is awake, the external urethral sphincter may maintain continence. When the dog is sleeping or with muscle relaxation, the internal sphincter fails maintain continence resulting in incontinence.

The α-adrenergic agonist phenylpropanolamine (1.1-1.5 mg/kg PO q 8 h) is effective in approximately 85% of female dogs with urethral incompetence. Clinical response to pseudoephedrine is inferior to phenylpropanolamine. The dose-related side effects of phenylpropanolamine in dogs include excitability, panting, restlessness, irritability, and hypertension. Phenylpropanolamine should not be used in patients with concurrent hypertension. Estrogen therapy is presumed to increase urethral closure pressure by increasing the density and responsiveness of α-adrenergic receptors in urethral smooth muscle. Estrogen therapy is effective in approximately 65-70% of female dogs with urethral incompetence. Excessive doses of estrogen may cause severe bone marrow suppression; therefore owners should be cautioned not to exceed recommended doses.

Estriol is a now FDA approved for treatment of urethral incompetence and should be used instead of diethylstilbestrol. Estriol (Incurin) has been marketed for veterinary use in Europe since 2000 and was approved by the FDA for the US market in 2011. The incidence of adverse effects associated with use of
this product appears to be quite low with less than 1% showing signs of estrus, and there was no evidence of bone marrow toxicity even with 5X dosing. Approximately 70% of dogs were improved with estriol. Estriol is administered at a dose of 2 mg PO daily for 2 weeks, and then the dose is reduced at weekly intervals to the minimal effective dose (0.5 - 2.0 mg/dog given daily or every other day).

Treatment of refractory urethral incompetence:
Because estrogen therapy up-regulates the α-adrenergic receptors that phenylpropanolamine stimulates, combination therapy with these medications is synergistic. Therefore female dogs that are refractory to either medication alone may respond to combination therapy. For dogs that are refractory to combination therapy, urodynamic evaluation is recommended. Alternative therapies for dogs with refractory urinary incontinence due to confirmed urethral incompetence include cystoscopic injections of collagen or surgical methods to increase urethral resistance.

Periurethral injection of collagen narrows the urethral lumen and allows for more effective closure of the urethra by existing urethral pressure. Periurethral injection of collagen resolved urinary incontinence in 53 to 69% of dogs without medication. Overall, 75 to 93% of these dogs were improved after collagen injection with or without concurrent administration of phenylpropanolamine. The mean duration of continence following peri-urethral collagen injections was 17 months in one study. Repeat cystoscopic injections of collagen is required in some dogs months to years after initial injections to maintain continence.

Surgical methods for treatment of refractory urinary incontinence include colposuspension and urethropexy. A novel approach the surgical management of urinary incontinence is the placement of a peri-urethral hydraulic urethral cuff or so-called artificial urethral sphincter (AUS). At our hospital, placement of these AUS devices have replaced other surgical options for treatment of refractory urethral incompetence. The AUS is initially injected at 2-week intervals to adjust the cuff pressures, which resolves incontinence in more than 70% of dogs.

A report from Europe indicates that treatment with GnRH analogues may resolve refractory urinary incontinence in female dogs. In subsequent studies response has been reported to be quite variable with some dogs responding well and others not responding.

Detrusor instability and urge incontinence
Although urethral incompetence is the most common cause of urinary incontinence, incontinence may also occur due to detrusor contraction during storage of urine or due to low compliance of the detrusor muscle, which may be confirmed by cystometry. When decreased detrusor compliance occurs secondary to inflammatory conditions affecting the lower urinary tract (e.g., urolithiasis, UTI), this is termed urge incontinence. Clinical signs of dogs with urge incontinence may also include pollakiuria, stranguria and dysuria. If no identifiable cause of decreased detrusor compliance is identified, this is termed idiopathic detrusor instability.

Treatment of detrusor instability is by anticholinergic medications (oxybutynin, imipramine or dicyclomine) to decrease detrusor contractions during storage of urine. Although oxybutynin (0.2 mg/kg PO q 8-12 h) has been most commonly recommended, dicyclomine appeared to have a greater effect on detrusor compliance in normal dogs than oxybutynin. Imipramine is a tricyclic antidepressant...
medication that has anticholinergic effects to facilitate urine storage and also increases urethral closure pressure. Therefore, imipramine may be effective for dogs with mixed incontinence due to detrusor dysfunction and concurrent urethral incompetence.

**Ectopic ureters**

Ectopic ureters are a common cause of urinary incontinence in young dogs. Ectopic ureters may also be diagnosed in adult dogs with refractory urinary incontinence, especially dog with ectopic ureters located in the proximal urethra. Most canine ectopic ureters are intramural in location, meaning the ureter enters the serosal surface of the bladder wall in the correct location, but the intramural ureter tunnels in the wall of the bladder and urethral submucosa with one or more openings in the urethra or vaginal vestibule.

Although ectopic ureters have traditionally been diagnosed by contrast radiography, cystoscopy is the preferred technique for diagnosing ectopic ureters as the clinician is experienced with the procedure. In studies comparing the diagnostic accuracy of excretory urography, contrast enhanced CT scans and cystoscopy for detection of ectopic ureters, contrast enhanced CT scans and cystoscopy were the most accurate diagnostic methods for detection of ectopic ureters. During cystoscopy, the anatomy of the urethra and vaginal vestibule are also evaluated. Most dogs with ectopic ureters have an abnormality of the vaginal vestibule called paramesonephric septal remnant (or vaginal septa) which is a broad band dividing the vaginal opening into 2 parts and lifting the urethral opening dorsally.

Urethral incompetence frequently occurs concurrently (~50% of dogs with ectopic ureters) and can result in treatment failure after repair of ectopic ureters. Traditionally, ureteral openings have been moved into the bladder by various surgical techniques. A new technique for treatment of intramural ectopic ureters is to use a diode or Ho:YAG laser to remove the wall between the urethra and parallel ureter. Laser ablation of intramural ectopic ureters results in resolution of urinary incontinence in approximately 50% of female dogs after laser correction without medications. Additionally, the majority of female dogs were continent with medication or periurethral collagen injections for concurrent urethral incompetence. Likewise, laser ablation of ectopic ureters resolved urinary incontinence in 4 of 4 male dogs.

Some dogs with concurrent urethral incompetence have improved continence after correction of the ectopic ureter if treated with PPA. Our approach is to correct the ectopic ureter via laser ablation, and either perform UPP before laser correction or as a follow-up evaluation for dogs with persistent refractory incontinence. Dogs with urinary incontinence due to urethral incompetence following correction of ectopic ureters may not be responsive to medical management. The potential surgical approach to dogs with congenital refractory urethral incompetence is surgical placement of a periurethral hydraulic cuff. Periurethral collagen injections are also a minimally invasive option for congenital urethral incompetence. Placement of a periurethral hydraulic cuff is a longer lasting option than collagen injections, but requires surgery and has potential complications such as obstruction from urethral stricture formation.

**References**