Diagnostics and Management of Pyelonephritis

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Introduction

Pyelonephritis can be an acute life-threatening condition or a chronic condition, which results from bacterial or fungal invasion of the renal parenchyma. The remainder of this article refers specifically to bacterial pyelonephritis. The true prevalence of bacterial pyelonephritis in dogs and cats has not been reported. Bacterial pyelonephritis usually results from ascending infection by fecal commensals in the face of inadequate host defense mechanisms, but less commonly can follow hematogenous spread of bacteria to the renal parenchyma and pelvis. Clinical signs and physical examination findings of pyelonephritis can include lethargy, hyporexia, anorexia, polyuria, polydipsia, pain upon kidney palpation, and other signs associated with acute kidney injury (AKI). Furthermore, fever may be documented in the patient. A diagnosis of pyelonephritis can be suspected based on positive aerobic bacterial urine culture when accompanied by these clinical signs, as well as clinical laboratory findings of azotemia, cylindruria, and peripheral neutrophilia with or without bandemia (in the absence of another identifiable cause); and supportive ultrasonographic findings such as renal pelvic dilation or blunting of the renal papilla.[1] These ultrasonographic findings are not specific for pyelonephritis and renal pelvic dilation can be noted in patients with clinically normal renal function with diuresis and early ureteral obstructions. Pyonephrosis, a collection of sloughed urothelium and inflammatory cells in the dilated renal collecting system is a complication that can be noted in severe prolonged urinary stasis and secondary infection. It was reported that in the majority of 18 dogs with suspected pyonephrosis, the renal pelvis was distended with hyperechoic contents; hyperechoic retroperitoneal mesentery and effusion was noted in 11 dogs suggestive of retroperitoneal inflammation.[2] This complication appears to be more common in dogs with ureteral obstruction.[3]

In many cases, the diagnosis of pyelonephritis, particularly if the animal is not presenting with AKI, can be a diagnostic challenge. Some animals with pyelonephritis have negative bacterial urine cultures due to intermittent shedding of bacteria in the urine, systemic signs and laboratory abnormalities may be absent, and ultrasonographic findings suggestive of pyelonephritis may be absent. While nephropyelocentesis can be performed, this may not be possible in the absence of significant pyelectasia. Data evaluating the sensitivity and specificity of this procedure for pyelonephritis have not been published. There have been many publications evaluating the diagnostic utility of various urinary and serum biomarkers for evaluation of AKI in dogs and cats. For example, spot urinary N-acetyl B D- glucosaminidase (NAG) and γ-glutamyl transferase (GGT)/creatinine

were reported to be helpful in the diagnosis of early AKI in experimental dog models.[4] More recently, we have reported that neutrophil gelatinase-associated lipocalin (NGAL), a protein induced marker during AKI, may permit detection of AKI sooner than creatinine. NGAL/creatinine was an early marker of gentamicin-induced AKI; further its decrease documented the onset of recovery.[5] Moreover, NGAL/creatinine was found to be specific for naturally occurring AKI and can be used to screen patients that are at risk for AKI.[6] Serum symmetric dimethylarginine (SDMA) can also support the presence of chronic kidney injury in association with bacteriuria. Unfortunately none of these biomarkers are specific for pyelonephritis and only SDMA is currently clinically available for use.

In humans, increased concentrations of urine NGAL, urine kidney injury molecule-1 (uKIM-1), serum cystatin C (sCysC), plasma C-reactive protein, procalcitonin, erythrocyte sedimentation rate among others have been used to support a diagnosis of pyelonephritis in patients with bacteriuria, although they lack high sensitivity and specificity.[7-10] Other biomarkers that may have value for diagnosis of pyelonephritis in humans include urine heparin-binding protein (HBP) and urine interleukin-6 (IL-6), the concentrations of which are significantly higher in elderly humans with suspected pyelonephritis when compared with those that have asymptomatic bacteriuria.[11] Clearly, there is a need for a sensitive and specific marker in humans and veterinary medicine to confirm the diagnosis of pyelonephritis.

Diagnostics

In all dogs and cats with suspected pyelonephritis, urine collected by cystocentesis should be submitted to the laboratory for aerobic bacterial urine culture and susceptibility testing. If the patient is severely thrombocytopenic or has another coagulopathy, a urine sample can be obtained by midstream free-catch collection or aseptic urinary catheterization, although these methods are not preferred because of increased likelihood of contamination with commensal organisms. Results need to be interpreted with all other clinical signs and using quantitative bacterial counts (CFU/mL) if urine is collected in this manner. As mentioned above, if the urine culture is negative, urine collected by pyelocentesis could be submitted if renal pelvic dilation is present and the suspicion for pyelonephritis remains high. Blood cultures are recommended at the same time as urine cultures in immunosuppressed patients. Blood culture should also be considered for diagnosis of pyelonephritis if fever and azotemia are present but urine sediment examination is unremarkable and/or the urine culture is negative. Other general principles of diagnosis for simple bacterial cystitis apply for pyelonephritis. Interpretation of susceptibility data should be based on antimicrobial breakpoints for serum rather than urine drug concentrations because high tissue drug concentrations are needed to treat pyelonephritis effectively. If multiple organisms are isolated, the suspected relative relevance of these should be considered, especially for urine specimens collected by free-catch or catheterization.

Treatment

The treatment for patients suspected of pyelonephritis should begin prior to the availability of urine culture results, particularly in those patients that are azotemic, febrile and/or systemically unwell. Initial treatment should involve antimicrobial drugs known to have local or regional efficacy against Enterobacteriaceae, based on the predominance of those organisms in pyelonephritis. If regional data are

supportive, treatment with a fluoroquinolone excreted in urine in the active form (i.e., not difloxacin) is a reasonable first choice. If ascending infection is suspected, any recently obtained urine culture results might be the basis for initial therapy. If the upper UTI results from hematogenous spread, initial therapy should be based on cultures of blood or the infected site, whenever available. Oral antimicrobial therapy may be sufficient in animals that otherwise appear systemically well and have normal appetite. Intravenous therapy is recommended for animals that are dehydrated, hyporexic, or lethargic.

Once culture and susceptibility results are available, treatment should be revised if necessary. If combination therapy was initiated and the isolate is susceptible to both drugs, one should be discontinued. If resistance is reported to one of the drugs, that antimicrobial should be discontinued. Depending on the time elapsed, consideration should be given to substituting a drug to which the isolate is susceptible if the patient has not responded sufficiently; substitution is not necessary if patient response has been sufficient. If resistance is reportedto both antimicrobials and clinical evidence of improvement is not evident, antimicrobial treatment should be changed to a drug to which the offending organism is susceptible *in vitro*. Consultation with a specialist with an interest in microbiology, urinary or clinical infectious diseases is recommended for treatment of multidrug-resistant organisms. If resistance to the drug(s) that are used is reported but there has been good clinical response, continuation with the initial therapy could be considered, provided there are no other reasons (such as fluid therapy) that might explain clinical improvement. The clinician can confirm eradication of the bacteria by submitting another aerobic bacterial urine culture 5–7 days after antimicrobial therapy in such a scenario to confirm microbiological cure if clinically indicated. Failure of treatment response in the face of bacterial susceptibility to the initially chosen drug should also result in re-evaluation of the diagnosis and other potential reasons for treatment failure (e.g., non-infectious cause of azotemia such as ureteroliths and neoplasia accompanied by bacteriuria). At that time, consideration should be given to discontinuing antimicrobial therapy.

Treatment for 4–6 weeks has previously been recommended for veterinary patients with pyelonephritis. However, as with simple (uncomplicated/sporadic) urinary tract infections, shorter duration therapy has been investigated in humans with pyelonephritis and should be considered in veterinary patients. A recent study in humans evaluated short-duration IV levofloxacin or conventional IV and oral levofloxacin in adults with complicated UTI and acute pyelonephritis. Treatment with IV levofloxacin for 5 days was not found to be inferior to treatment with conventional therapy (IV/oral regimen of levofloxacin for 7–14 days).[12] While even the "conventional" therapy may seem short to most veterinary clinicians, the recommended duration of therapy for acute bacterial pyelonephritis in children is 7–14 days[13] and the recommendation for adults is 10–14 days for beta-lactams or trimethoprim-sulfamethoxazole and 7 days for ciprofloxacin[14]. There is no reason to suspect that a longer duration would be necessary for dogs and cats, and a recommendation for 10 to 14 days of treatment is currently under consideration by the Antimicrobial Use Working Group of the International Society for Companion Animal Infectious Disease as part of revised guidelines for treatment of urinary tract infections in dogs and cats.[15] Antimicrobial prophylaxis in preventing recurrence is still debated in humans and children with pyelonephritis and due to the risk of antimicrobial resistance the authors do not recommend it.

Monitoring the Patient

A recheck examination that includes physical examination, serum creatinine, urinalysis, and aerobic bacterial urine culture is recommended 1 to 2 weeks after discontinuation of treatment. However, if clinical signs and azotemia have resolved, consideration has to be given to the clinical relevance of a positive urine culture, as it may represent subclinical bacteriuria. Re-isolation of the same bacterial species as that identified initially should stimulate an investigation for reasons for treatment failure. If clinical signs persist, blood values do not return to within the reference range, or subclinical bacteriuria is present, further diagnostics should be considered to investigate the patient for bacterial resistance, urolithiasis, anatomic defects or immune deficiency.

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CKD: Updates on Diagnosis, Treatment and Prevention of Progression

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Measurement of serum creatinine concentration is the most commonly used surrogate to estimate GFR in the clinics, as it is not technically feasible or practical to measure GFR directly. Serum creatinine is generally preferred over BUN for evaluation of renal function since creatinine has fewer non-renal variables. Symmetric dimethylarginine (SDMA) is a molecule that is also a surrogate for the evaluation of GFR in the dog[1] and the cat[2] that has some advantages over measurement of serum creatinine. SDMA results from methylation of arginine that occurs in all nucleated cells. SDMA is excreted exclusively into urine and consequently increases in blood when GFR decreases. SDMA is not influenced by lean muscle mass whereas serum creatinine is related to lean muscle mass. Since creatinine arises from muscles, animals with decreased muscle mass will have lower serum creatinine concentrations than would otherwise develop. During progression of CKD, loss of lean muscle mass can parallel loss of renal function which results in little change in serum creatinine concentration. This phenomenon reduces the ability for serum creatinine to detect ongoing CKD progression early. It is important to remember than any surrogate for GFR will be influenced by pre-renal, primary renal, and post renal factors. It is also important to remember that the finding of normal serum creatinine, BUN, and/or SDMA concentrations does **not** exclude the presence of primary renal disease. In a patient with primary renal disease, a serum creatinine concentration above the reference range (>2.0 mg/dl) is often interpreted to be associated with a loss of >75% of renal mass and GFR. When a lower value for the upper limit of serum creatinine such as 1.4, 1.5, or 1.6 mg/dl is used, an increased serum creatinine concentration is associated with a loss of about 50% renal mass and GFR. It appears that on average SDMA increases at a time when about 40% of renal mass and GFR has been lost. SDMA can increase in CKD patients when there is as little as 25% loss of renal mass and GFR at times.

Concentrations of SDMA have been shown to increase above the reference range before serum creatinine increased in multiple studies of dogs and cats eventually diagnosed with azotemic CKD.[1,3-5] SDMA increased many months before serum creatinine when relatively high values for the upper limit of creatinine reference (above 2.0 mg/dl) ranges were used to diagnose the onset of CKD. When lower creatinine values were used for the upper limit as the comparator, SDMA still increased before creatinine but by a shorter time. Initial studies were reported in dogs and cats living in colonies at a pet food company and in a colony of dogs with hereditary nephritis. Recent reports in client owned dogs and cats show that SDMA

is a more sensitive diagnostic indicator for the development of azotemic CKD than is serum creatinine. LC/MS has been used as the gold standard to measure SDMA in most studies in dogs and cats but an automated clinical biochemistry method offered by a commercial veterinary laboratory is now available for use by practicing veterinarians. SDMA is increased much more frequently than serum creatinine in both dogs and cats when measured on the same sample (diagnostic discordance),[6] but it is not yet clear how many of these patients will progress to azotemic CKD.

IRIS CKD Staging now includes an "At Risk" category. This category is based on increased risk for a future diagnosis of CKD based on history and signalment that includes exposure to nephrotoxicants, breed, high prevalence of infectious disease in the area, and old age. IRIS CKS Stage 1 is the most difficult to assign with certainty. Since these patients are nonazotemic, some other index of renal disease must be present. This could include some combination of sub-maximally concentrated urine without identification of a non-renal cause, abnormal renal palpation or renal imaging, renal proteinuria, trend of serum creatinine to increase within the reference range, cylindruria and decreased or decreasing GFR (iohexol clearances). CKD Stages 2–4 are easily assigned, based on the magnitude of increased serum creatinine in a stable hydrated patient. Sub-staging is then based on the magnitude of UPC and systemic blood pressure.[7] SDMA has been added to the IRIS staging system to further characterize CKD in patients in which serum creatinine concentration is likely to underestimate a more appropriate stage assignment. The finding of a serum creatinine concentration <1.6 mg/dl for the cat and <1.4 mg/dl for the dog and an SDMA that is increased (>14 ug/dl) provides one entry point into IRIS Stage 1 CKD and should trigger further diagnostic evaluation of the patient to verify or exclude the presence of primary renal disease (urinalysis, systemic blood pressure, UPC, renal imaging).[7] An SDMA ≥25 µg/dl in patients with IRIS CKD Stage 2 and low body condition scores may indicate underestimation of renal dysfunction; these patients may be more appropriately staged as Stage 3. Similarly, an SDMA ≥45 µg/dl in patients characterized as IRIS Stage 3 with low body condition scores may be more appropriately staged as Stage 4.[7]

Progression of CKD refers to further loss of functional renal mass and accumulation of primary chronic renal lesions (tubulo-interstitial nephritis, fibrosis, and nephron drop-out) associated with decreasing GFR. When enough nephron mass occurs, increases in BUN, creatinine, SDMA, and phosphorus will be detected. Progressive loss of excretory renal function will occur if the cause of the initial renal injury is not detected and stopped, as can occur with various types of immune-complex glomerulonephritis, familial glomerular disease, and renal amyloidosis. The "inexorable progression" of CKD occurs after a substantial amount of renal mass has already occurred. This type of progression can continue even when the original cause of the renal injury has been stopped. Based on experimental data, this type of self-progressive destruction of the kidney likely occurs in the dog and cat when there is loss of at least 75% of the original renal mass. Glomerular hyperfiltration and glomerular hypertension are considered to be important players that exist in the surviving single nephrons in advanced CKD that contribute to this type of progression. Systemic hypertension, PTH, CKD- BMD (bone mineral disease associated with phosphorus, FGF-23, Klotho, ionized calcium) and oxidative stress are also likely to contribute to progression.

Treatment

The feeding of a renal diet is usually the first step in treatment of stable CKD dogs and cats that are in IRIS CKD Stage 2–4. Studies involving the feeding of renal diets in dogs and cats with CKD have included mostly overtly azotemic patients. Increased survival and decreased uremic crises in general occur when renal diets are fed to these CKD patients. The feeding of lower protein diets to cats with CKD is considered controversial by some but is still considered the standard of care by most when the degree of protein restriction is modest.[8,9] Recently it has been suggested that the feeding of a renal diet to both geriatric dogs and cats in IRIS stage 1 could exert benefits. Serum creatinine and BUN decreased while SDMA did not increase in cats following the feeding of a renal diet for 6 months. In dogs fed a renal diet for 3 or 6 months, creatinine and SDMA decreased. Whether this was the result of improved excretory renal function or other factors was not determined.[10,11] It remains to be determined if the feeding of any renal diet can prevent progression of IRIS stage 1 CKD to higher stages.

A renal diet confers major benefits to decrease progression of CKD and increase survival in large part from its degree of phosphorus restriction for those in IRIS Stage 2 to 4. Little is known about the possible benefits of feeding a phosphorus restricted diet to patients in IRIS CKD stage 1. The feeding of a moderate protein and phosphate restricted renal diet to non-azotemic geriatric cats had some benefits to limit PTH and fractional urinary excretion of phosphorus but did not impact how many cats converted to azotemic CKD.[12] Phosphorus retention in the body occurs during progressive CKD with serum phosphorus initially maintained within the reference range, likely due to the correcting effects of PTH and FGF-23 that increase phosphaturia. Hyperphosphatemia develops as CKD advances and overcomes these correcting forces.

It is important to evaluate phosphorus content on an energy content basis (mg/100 kcal) in order to determine the current phosphorus intake and what diets will provide considerably less phosphorus intake. Other factors must also be considered such as the biological availability of the phosphorus in these diets, which can vary despite similar concentration in mg/100 kcal. Animal sourced proteins are usually higher in phosphorus content than proteins from vegetable sources.[13] Phosphorus restriction to a targeted level of serum phosphorus is achieved through feeding a veterinary diet restricted in phosphorus and intestinal phosphate binders. Renal diets may provide sufficient dietary phosphate restriction during early stages of CKD but often the addition of dietary phosphate binders will be needed to reach targeted control of serum phosphorus. An initial goal is to maintain serum phosphorus concentration within the reference range but a more optimal goal is to achieve a circulating concentration of phosphorus that is in the lower half of the reference range to achieve more salutary effects on ionized calcium, PTH, and FGF-23.[14-17]

A total calcium-phosphate product >70 mg^2/dl^2 was associated with a higher mortality rate compared to those with a lower product in a study of dogs with naturally occurring CKD; this finding appeared to be independent of serum creatinine.[18] As single variables, serum phosphorus, total calcium, or ionized calcium at the time of diagnosis did not predict survival in these dogs. The risk of death was 4.2 times higher for CKD dogs with a calcium-phosphate product >70 mg^2dl^2 compared to a lower product. IRIS Stage 3 and 4 CKD dogs with a >70 mg^2/dl^2 calcium phosphate produce survived a median of 30 days. The median survival for IRIS Stage 1,2 and 3 CKD dogs with a calcium-phosphate product <70 mg^2/dl^2 could not be determined, as over 50% of these dogs were still alive at 450

days. A targeted calcium-phosphate product <55 mg^2/dl^2 has been recommended in human nephrology. This study of CKD dogs did not evaluate outcomes for those with <55 mg^2/dl^2 or from 55 to 70 mg^2/dl^2 calcium-phosphate products.[18] Indexing serum FGF23 to urinary phosphorus excretion (fractional or absolute mg/day) has recently been reported in human nephrology as a method to assess the efficiency or appropriateness of urinary phosphorus excretion in relation to nephron mass and signal for phosphaturia. Decreases in this ratio reflect a declining number of nephrons and are associated with vascular mineralization.[19,20] Survival time in CKD dogs was adversely affected by a decreased ratio of urinary fractional phosphorus to serum FGF23 as reported at this Forum.[21]

Intestinal phosphate binders are mixed in the food. The goal is to bind or decrease the absorption of phosphates in the food so that they are not available to be absorbed across the intestine into the circulation. Aluminum salts are the most commonly prescribed intestinal phosphate binders in veterinary medicine since they are inexpensive and bind phosphate well. Aluminum retention is known to be toxic in humans with CKD and evidence is emerging that there is toxicity in dogs with CKD as well.[22] Calcium salts (carbonate and acetate) are alternative phosphate binders to aluminum, but they are not as good at binding phosphates and there is the potential for ionized hypercalcemia to develop. Calcium salts should be avoided when calcitriol treatment will be prescribed in the same patient. Sevelamer is an organic polymer that contains no aluminum or calcium and is used extensively in people, but reports are lacking as to its efficacy and safety in veterinary CKD patients. Lanthanum carbonate is an excellent phosphate binder with little known toxicity but it is expensive. A previously available affordable veterinary formulation of lanthanum carbonate is no longer manufactured.[13] A new oral phosphate binder based on iron oxide has been developed for use in cats but is not yet marketed.[23]

Calcitriol is either absolutely or relatively deficient in dogs and cats with azotemic CKD. Calcitriol treatments decrease PTH or prevent its increase during CKD. This occurs mostly by genomic effects to block PTH synthesis in addition to a mild calcemic effect, and antiproliferative effect that prevents parathyroid gland hyperplasia. During treatment of CKD patients with calcitriol, simultaneous monitoring of serum ionized calcium, serum phosphorus and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism. Calcitriol should not be administered until hyperphosphatemia has been controlled. If the Ca x P solubility product exceeds 60–70, calcitriol should be avoided because of the risk of soft-tissue mineralization. The beneficial effects of calcitriol are also lessened within the parathyroid gland when ionized calcium remains low. Phosphorus restriction relieves phosphate-mediated inhibition of the renal 1α-hydroxylase system, resulting in enhanced endogenous synthesis of calcitriol and subsequent inhibition of PTH synthesis. Though the PTH lowering effect following calcitriol administration has been emphasized as a central benefit from this treatment, many other effects can follow binding of calcitriol to the VDR (vitamin D receptor) in various tissues including the kidney. Calcitriol binding to VDR in the renal tissue exerts anti-inflammatory and anti-fibrotic effects as well as reducing the generation of intra-renal RAAS activity all of which are independent of any effect to decrease circulating PTH.[14]

Intermittent rather than daily dosing calcitriol treatment protocols have emerged as the standard of care since less hypercalcemia occurs. The equivalent daily dose of 2.5 to 3.5 ng/kg daily is given instead every 3.5 days at 9 to 12 ng/kg. This is the

longest time in between dosing that will still suppress PTH synthesis within the parathyroid gland. This method of dosing is especially attractive for cat owners since medication will only be given twice weekly but this is also offered as the first option for dogs. Calcitriol treatment for azotemic CKD dogs increased survival to a median of 365 days compared to 250 days in dogs treated with placebo in one study.[24] A similar study was done by the same investigators who concluded that there is no advantage to calcitriol treatments in cats with azotemic CKD, but this study followed cats for just one year which is likely not enough time to demonstrate a treatment effect due to the inherently slow nature of CKD progression in cats.

It is common in some human nephrology practices to treat CKD patients with BOTH activated vitamin D metabolites like calcitriol and parent vitamin D (cholecalciferol).[25] Survival of human CKD patients correlates better with 25(OH)-vitamin D concentrations than to that of calcitriol, likely due to vitamin D receptor activation in local cells that then generate intracellular 1,25 $(OH)_2$-vitamin D. Low circulating 25(OH)-vitamin D is common in humans with CKD and this has also been observed in dogs with azotemic CKD.[26] In a recent study, 25(OH)-vitamin D, 1,25$(OH)_2$-vitamin D and 24,25$(OH)_2$-vitamin D concentrations were low in CKD dogs, with deficits more severe with advancing IRIS stage.[27] Low 25(OH)-vitamin D could be due to decreased dietary intake, decreased intestinal absorption, decreased hepatic hydroxylation of vitamin D to 25(OH)-vitamin D, or to increased loss in urine. 25(OH)-vitamin D and 1,25$(OH)_2$-vitamin D are reabsorbed along the proximal tubule following glomerular filtration - this process is mediated by megalin receptors that are upregulated by calcitriol-VDR interactions.[14] Regimens to best replete 25(OH)-vitamin D status have not yet been well developed in veterinary medicine for animals with or without CKD. Oral administration of 25(OH)-vitamin D achieved FDA approval in 2016 for repletion of 25(OH)-vitamin D status and control of secondary hyperparathyroidism in humans with CKD. Repletion of 25(OH)-vitamin D status in experimental dogs without CKD was more efficient when supplemented with oral 25(OH)-vitamin D compared to supplementation with parent vitamin D (cholecalciferol).[28] Vitamin D status based on 25(OH)-vitamin D concentrations can vary widely in normal dogs eating the same diet, so it is likely that repletion status will depend on measurement of 25(OH)-vitamin D post treatment and titration of dose to the targeted level of 25(OH)-vitamin D desired.[29] Whether baseline 25(OH)-vitamin D status predicts survival for CKD dogs and cats is not yet known. Also yet to be determined is the effect of 25(OH)-vitamin D repletion on survival time and stability of GFR in dogs and cats with CKD.

Inactivation of the RAAS (renin-angiotensin-aldosterone-system) can provide renoprotection to dogs and cats with CKD. This protection is provided by some combination of reducing intraglomerular hypertension and single nephron hyperfiltration, reducing systemic blood pressure, and by reducing damaging signals from angiotensin-II and aldosterone that promote renal inflammation and fibrosis. Most nephrologists advocate RAAS reduction in patients with renal proteinuria 30, but it is possible that benefits could be achieved in those without renal proteinuria also, but this is controversial. Most canine and feline CKD patients undergo reduction in UPC during treatment with enalapril or benazepril and some maintain higher GFR in the long term, but this does not necessarily translate into increased survival time. The angiotensin receptor blocker (ARB) telmisartan (Semintra® Boehringer Ingelheim) was approved by the European Commission in 2013 for use in the European Union as a drug for use in cats with CKD and is

available for use in Canada but not yet in the USA. Semintra was found to be at least as effective as benazepril in reducing proteinuria in cats with CKD and was well tolerated.[31,32] It is not clear when or if an ARB should be chosen to reduce RAAS activity instead of an ACE-Inhibitor for treatment of CKD in veterinary patients to reduce proteinuria, systemic blood pressure, or intra-renal inflammation.

Most animals with azotemic CKD have normal serum potassium concentrations. Hyperkalemia more readily develops when the animal becomes oliguric or anuric. Hyperkalemia in CKD dogs with normal urine production or polyuria may, however, occur more commonly than generally appreciated. In one study 47% of CKD dogs experienced 1 or more episodes of hyperkalemia, with 16% experiencing 1 or more episodes of severe hyperkalemia (>6.5 mEq/L). Some of the development of hyperkalemia in these CKD dogs was attributed to the potassium content of commercial renal diets, as serum potassium declined in dogs fed diets specifically formulated to be lower in potassium content.[33]

Hypokalemia may occur in 10–30% of dogs and cats with azotemic CKD due to some combination of anorexia, loss of muscle mass, vomiting, and polyuria. A significant body deficit of potassium can exist without the development of hypokalemia (kaliopenia). Serum potassium levels can underestimate total body potassium since most of the body's potassium lies within the cells. As potassium is lost excessively from the plasma, potassium leaches out of the cells down a concentration gradient masking the initial loss of potassium. One study of cats with azotemic CKD and normokalemia revealed decreased potassium content of muscles.[34] Hypokalemic (kaliopenic) nephropathy has been described as a specific syndrome in clinical cats either as a result of CKD or resulting in CKD. Whether kaliopenia without hypokalemia can result in CKD in cats has not been established. In one study of experimental cats, the development of azotemic CKD and hypokalemia was discovered at the same time in cats fed a marginally replete urinary acidifying and magnesium restricted diet.[35] Hypokalemia can contribute to anorexia, depression, and weakness independent of the effects of CKD. Severe muscle weakness (the "hanging-head" posture, truncal ataxia) is seen in many cats with serum potassium less than 2.5 mEq/L and in some with less than 3.0 mEq/L. The fractional excretion of potassium into urine is high despite the low serum potassium. Cats with normokalemic CKD also have high fractional excretion for potassium as part of the adaptive nephron response to maintain potassium balance.

Hypokalemia can be associated with functional and/or structural changes in the kidneys. These changes include a reduced ability to concentrate the urine - initially functional, structural later. Decreased GFR initially can be a result of hemodynamic changes, but later due to structural changes. Structural lesions of tubulointerstitial inflammation and fibrosis associated with azotemic CKD have been reported to develop in cats fed marginally potassium replete diets that are highly acidifying and magnesium restricted. Some cats with azotemic CKD and hypokalemia will improve their excretory renal function following correction of the hypokalemia. Whether this improvement is due to correction of pre-renal factors, intrarenal hemodynamics, or resolution of some intrarenal lesions is not clear. Some cats with azotemic CKD periodically develop hypokalemia during the course of their disease. Hypokalemia in dogs and cats with azotemic CKD may be treated with oral potassium gluconate or citrate. The dosage of potassium for cats usually is 2–4 mEq/day, whereas dogs may require as little as 2 or as much as 40 mEq/day depending on their body size.

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UTI Treatment and Prevention: What You Need to Know to Help

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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 a genuine concern about the use, misuse and overuse of antibiotic therapy in our patients, especially in regard to the development of antibiotic resistance. There have been numerous individual studies and reviews regarding the diagnosis, treatment and prevention of canine 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 likely normal urinary tract anatomy and function. Typical clinical signs of a lower UTI are present, characterized by dysuria, pollakiuria, and/or increased urgency of urination. Whenever possible, urine should be collected via cystocentesis when a UTI is suspected. 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 and initial therapy with amoxicillin (11–15 mg/kg PO q 8h) or trimethoprim-sulfonamide (15 mg/kg PO q12 h) 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. 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, 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) or advanced imaging (contrast-enhanced CT), particularly in females, should be considered to further investigate underlying causes. Any underlying concurrent causes identified on 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).

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, or DMSO 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 pathogenic organisms, when possible. If more than one bacterial species is identified on culture, the relevance of the 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 is recommended 5–7 days after initiation of antibiotic therapy to assess the efficacy of the particular antibiotic, especially in patients with previous relapsing or refractory infection, or those at high risk for ascending or systemic infection. Any bacterial growth during treatment indicates treatment failure and should prompt immediate re-evaluation. A second urine culture is recommended 7–14 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.

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 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 4–6 weeks is generally recommended. Treatment efficacy and monitoring is generally the same as for a complicated UTI (i.e., multiple cultures).

Multidrug-Resistant Infections

There are individual patient and public health concerns with regard to resistant pathogens. Multidrug-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 multidrug-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. Infection must be documented based on clinical, cytological, and culture abnormalities. Antibiotic use in multidrug-resistant infections for the treatment of subclinical infection 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 Bacteriuria

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. Quantitative culture result does not 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. Subclinical bacteriuria has no association with subsequent UTI development. Antibiotic treatment may not be necessary in patients with no clinical signs of UTI and no evidence of UTI (pyuria) 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.

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 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 h) 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 macrocarpon*) 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 effected 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 500 mg PO q 12 h; methenamine mandelate usually range from 10–20 mg/kg PO q 8–12h (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. Human 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.

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