Delaying the progression of CKD

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Broadly speaking treatments for CKD can be divided into those therapies that might delay progression of the kidney disease and those that just treat the symptoms. Treatments aimed at delaying disease progression are likely to be most effective in patients with Stage 2 & 3 CKD (mild-moderate azotaemia) when there are still a reasonable number of functional nephrons remaining.

Dietary Therapy

The best example of a treatment that delays progression of CKD is dietary therapy (primarily phosphate restriction). This ameliorates CKD – Mineral Bone Disorder [CKD-MBD] and is associated with increased survival time. The term CKD-MBD is preferred to that of renal-secondary hyperparathyroidism because it reflects that the problem is multi-faceted with mineral imbalance (primarily calcium and phosphate), multiple hormone derangements (PTH, calcitriol and fibroblast growth factor-23; FGF-23) and abnormalities of soft tissue mineralisation and bone loss all occurring simultaneously. All of these abnormalities are highly inter-related. Recent work has shown that increases in FGF-23 concentration may be one of the first changes to occur in cats with CKD and that this may be detectable even before patients are azotaemic. The concentration of FGF-23 at the time of diagnosis of CKD in cats is related to survival time,¹ and the concentration of this hormone (and of PTH) can be reduced by feeding of a phosphate-restricted, renal-care diets.² Less data is available from dogs but both PTH and FGF-23 concentrations have been shown to increase in relation to IRIS stage.³

Renal-care diets have been shown in numerous studies, conducted in different countries and by different research groups, to improve survival of cats,⁴⁵ and dogs,⁶ with azotaemic CKD. What has still to be established is whether these treatments can also be of benefit in selected patients with non-azotaemic CKD or if additional benefit can be gained by the use of target-driven therapy (for example normalisation of phosphate, PTH or FGF-23) in management of CKD. The potential role for phosphate-binding agents is also an area that warrants further study; when given to patients consuming an unrestricted diet they may be of little benefit because there is just so much phosphate in the gut to bind, but they are likely to be of more use when given in combination with a renal-care diet in patients where this is not enough, in isolation, to ameliorate CKD-MBD.

There is currently a group of feline specialists that question the benefit of dietary therapy in cats with mild azotaemic CKD, claiming that the degree of protein restriction is too great for obligate carnivores. However, review of the available epidemiological studies shows that there is a clear survival benefit, even when cats with IRIS stage 2 CKD are considered in isolation. In the author’s opinion, dietary therapy is indicated in all patients with azotaemic CKD.
In practical terms, it is important to realise that the commercially available dry and wet renal diets are complete and so patients should be offered the formulation that they prefer to eat. Although it is sometimes said that dry diets are ‘bad’ for patients with renal disease there is no evidence to support this contention.

**Drugs Acting on the Renin-Angiotensin System**

Proteinuria has been shown in many species, including the cat and the dog, to be associated with shorter survival times. This could be due to injurious effects of the proteins themselves, some of which get reabsorbed following filtration and passage through the tubulo-interstitium, or it could relate to the fact that proteinuria is a surrogate marker for glomerular hypertension. In either situation treatment with ACE-inhibitors (such as benazepril) or ARBs (such as telmisartan) could be beneficial because they reduce either the production of angiotensin II (ACE-inhibitors) or its receptor binding (ARBs); angiotensin II has a preferential constrictive effect in the efferent arteriole, blocking its actions reduces pressure across the glomerular capillaries and so decreases proteinuria.

The evidence for the use of angiotensin converting enzyme (ACE)-inhibitors and angiotensin receptor blockers (ARBs) in management of patients with tubulo-interstitial CKD is less strong than for dietary therapy. These agents have been shown to reduce proteinuria but have not been proven to extend survival in feline patients. In dogs, treatment with ACE-inhibitors has shown to be beneficial in patients with glomerulonephritis, whether this benefit extends to canine patients with tubulo-interstitial disease is unknown.

There are various theoretical advantages to treatment with ARBs rather than ACE-inhibitors. Although in health ACE is the main mechanism for conversion of angiotensin I to angiotensin II other pathways for conversion exist. There is some evidence that after a period of treatment with ACE-inhibitors conversion via these alternative routes increases, particularly if there is a resultant increase in renin activity. This is one mechanism for the phenomenon sometimes called ‘aldosterone escape’. Since ARBs act downstream of this conversion by blocking receptor binding, angiotensin II formed by non-ACE dependent pathways will not be an issue. In addition, ARBs inhibit the binding of angiotensin II to the angiotensin-1 (AT1) receptor exclusively. Binding to the AT2 receptor is unimpeded. This may be of relevance because broadly speaking agonistic actions at the AT2 receptor are weaker, but opposite to those that follow activation of the AT1 receptor; therefore receptor binding has potentially beneficial effects including vasodilation and natriuresis. In spite of these theoretical advantages there is no consistent demonstrable advantage shown to treatment with ARBs over treatment with ACE-inhibitors in humans with CKD. The main indication for the preferential use of ARBs is when side effects of ACE-inhibitors (such as cough) are proving intolerable - but these do not seem to occur in veterinary patients. Use of the two classes of drug in combination is generally not recommended because it increases the risk of side-effects without a clear increase in efficacy.
An alternative approach to interference with the RAS in patients with CKD would be the use of aldosterone antagonists such as spironolactone, either alone or in addition to treatment with an ACE-inhibitor or ARB. The potential benefit of this is yet to be investigated in either dogs or cats with spontaneous, naturally occurring CKD.

References

Symptomatic management of CKD

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Monitoring and Treating Urinary Tract Infections

Urinary tract infections (UTIs) are common in cats with CKD. Infection may in some instances ascend to the patient’s kidneys resulting in pyelonephritis and then the patient may become systemically unwell. Pyelonephritis is difficult to definitively diagnose so specific data on its incidence are lacking. Patients with CKD have traditionally been considered likely to have ‘complicated’ UTIs and have been treated with relatively long courses of anti-bacterials. Whether this is really necessary is unknown especially since many patients (particularly cats) with CKD that develop UTIs are asymptomatic. In humans asymptomatic bacteriuria (ASB) is common and it is not recommended that ASB is treated since this has not been found to reduce the incidence of subsequent symptomatic UTIs, incidence of pyelonephritis, patient morbidity or mortality. One study found no difference in survival of cats with CKD with and without UTI.1

Treatment of Anaemia

Anaemia is common in patients with CKD but it is not usually severe until azotaemia is relatively marked; IRIS stage 4 is typical. Treatment is usually only considered once the PCV is <20% in cats, 25% in dogs. The cause of the anaemia is multifactorial with a lack of erythropoietin being an important factor. Recombinant human erythropoietin has been used to treat anaemia although cross-reacting antibodies may develop in some patients. Darbepoetin is a modified molecule with a long half-life and it is postulated that this results in a lower incidence of cross-reacting antibody formation.2 The recommended starting dose for darbepoetin is 1 µg/kg (SQ or IV) weekly with a tapering of the dose and/or frequency of administration once the PCV rises. Iron supplementation should also be given initially.

Fluid Therapy and Feeding Tubes

Some patients with CKD have a tendency to become dehydrated causing a pre-renal component to their azotaemia and clinical deterioration. This can result in a patient that responds to intravenous fluids when hospitalised but decompensates after a few days at home. In these patients subcutaneous administration of fluids by the owner at home may be beneficial. Alternatively, if the patient has a feeding tube placed then additional water can be given via this route. Feeding tubes are generally very well tolerated by patients and have the advantage that as well as allowing optimal nutrition to be delivered, medications can also be given by the tube in a stress-free manner.
Potassium Supplementation

About 20 to 30% of cats with CKD are hypokalaemic. Chronic hypokalaemia induces histological lesions in the kidneys of experimental animals and the concept of hypokalaemic nephropathy emerged from these observations. Whether or not this phenomenon plays a role in the primary insult to the feline kidney or as a factor perpetuating progression of renal damage remains to be proven in clinical cases of feline CKD. Nevertheless, treatment of significant hypokalaemia may lead to a clinical improvement in the cats’ appetite and level of muscle strength and activity.

Laxatives

Constipation is quite common in patients with CKD and may contribute to anorexia. Judicious use of stool-softening agents can be helpful but it is important to ensure the patient does not develop diarrhoea which may exacerbate dehydration. Liquid paraffin (in the form of palatable paste e.g. katalax) and lactulose have traditionally been used but while dogs are quite accepting of the sweet taste of lactulose this is not well accepted by cats. Miralax (polyethylene glycol 3350) is much better accepted and can be dosed at ¼ teaspoon per meal, either mixed in the food or dissolved in water.

Appetite Stimulants

Recent work has been done to evaluate the most suitable appetite stimulants for use in cats with CKD. Maropitant was found to reduce vomiting but there was no increase in appetite compared with the placebo group and no weight gain. Mirtazapine, has been evaluated in several studies; firstly to determine the appropriate dosing strategies (1.88mg [1/8 tablet] per cat every other day appears optimal) and then to assess its efficacy as an appetite stimulant. Mirtazapine was found to increase appetite, with weight gain and a reduction in vomiting. At present this appears to be the preferred treatment in cats with CKD although it should be noted that all these studies were very small.

Anti-Hypertensive Therapy

Control of hypertension in cats has not been shown to directly impact upon survival; however, if it can be implemented before the development of end-organ damage (TOD; primarily blindness) this should reduce patient morbidity. Since hypertension is often a silent, slowly progressive, condition requiring life-long therapy, it is important to be as certain as possible of the diagnosis before initiating treatment. In cats with characteristic changes of hypertensive retinopathy/choroidopathy or hyphema the decision to implement treatment is straightforward. In patients without these signs the decision to treat hypertension is based on the probability of the patient developing TOD, weighed against the probability that the patient has white-coat hypertension for which treatment is unnecessary. The risk of TOD increases as blood pressure increases; however, there is no absolute cut-off value above which it can be said that a patient cannot have white-coat hypertension.
Multiple different classes of drugs would be predicted through their pharmacological actions to reduce blood pressure. In cats, however, clinical experience and data from clinical trials have provided substantial evidence in support of the use of amlodipine as the first-line treatment. In fact this species seems to be unusual in that monotherapy in most instances results in a profound reduction in blood pressure (often 40-60 mmHg) without attendant adverse effects. This contrasts with the situation in dogs and humans where multiple medications are often required to achieve only modest reduction in blood pressure.

Amlodipine is a dihydropyridine calcium channel blocker, with preferential affinity for the L-type channels that are found in vascular smooth muscle, rather than the calcium channels present in the myocardium or nodal tissue. Its main effect is to reduce total peripheral resistance. Since the L-type (long acting) calcium channels produce currents of long duration and inactivate slowly, drugs acting on this channel tend to have long duration and slow onset of action. This is clinically important because it means that once daily dosing is possible and patients do not suffer from initial hypotension with reflex tachycardia immediately after dosing as occurs with other classes of drugs with more rapid onset of action, such as hydralazine. Amlodipine has the potential to reduce blood pressure in both normotensive and hypertensive animals but effects in normotensive cats are modest at best. Amlodipine has a very long terminal elimination half-life (53 hours in cats). Its metabolites are eliminated through urine and faeces and this process is not affected by reduced renal function so it can be safely used in cats with CKD. It is metabolised in the liver and so should not be used in cats with significant hepatic dysfunction. Peak plasma level of the drug is seen 3-6 hours post dosing and steady-state is reached 2 weeks after treatment is started.

Treatment of hypertensive cats with agents other than amlodipine is rarely indicated, except in the emergency management of very severe hypertension of rapid onset; in this situation hydralazine (a direct acting arteriolar dilator) has been used to good effect. In most feline patients rapid reduction in blood pressure is not required, even if retinal detachment or other ocular pathology has only just been diagnosed it is likely that hypertension has been present for a considerable period of time.

The other classes of drugs that are sometimes used to aid in the management of hypertension in include beta-blockers and drugs that interfere with the actions of the renin-angiotensin-aldosterone-system (RAAS). Beta-blockers have mainly been studied in the management of hypertension in cats with hyperthyroidism but have not been found to be very effective and amlodipine treatment is preferred in this clinical situation. Angiotensin converting enzyme (ACE)-inhibitors have not been found to be very effective in reducing blood pressure in cats, a fact that might be predicted from the observation that plasma renin activity is usually low. Recently there has been some clinical interest in the use of angiotensin-receptor blockers (ARBs), such as telmisartan, for management of hypertension but again the efficacy of this drug in the treatment of ‘low-renin’ hypertension as is thought to occur in the cat is uncertain. In dogs, treatment of hypertension is much more difficult and combination therapy with multiple different agents is usually required.
The aim of anti-hypertensive therapy is to reduce blood pressure to a level at which further ocular injury (and TOD in other organs) will not occur. Generally reduction of systolic blood pressure to <160 mm Hg is advocated for this. Control of blood pressure has not been shown to directly impact on the survival time of treated cats, although the cats with the poorest responses to amlodipine therapy are those that are most proteinuric and these are also the patients with the shortest survival times. Treatment with amlodipine does reduce proteinuria.

References
Protein losing nephropathy

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There are no specific guidelines for how marked proteinuria needs to be before it is termed protein-losing nephropathy (PLN). However, in general this term is used for proteinuria of sufficient magnitude that it may result in hypoalbuminemia. A urine protein creatinine ratio (UPC) of >3 is an arbitrary cut-off for this.

Patients with PLN may present in several different ways. The proteinuria may be an incidental finding on a screening urinalysis, the patient may present due to illness or the animal may be being investigated because it is from a breed with an increased risk of glomerular disease. Signs of PLN vary from very non-specific (malaise, weight loss, poor appetite), signs of an underlying triggering condition (e.g. Leishmania) or signs of nephrotic syndrome (the constellation of proteinuria, hypoalbuminemia, hypercholesterolemia and ascites/subcutaneous oedema). Some patients with PLN present with signs of thromboembolic disease. Whatever the presentation several steps need to be taken: firstly the proteinuria needs to be quantified so that a representative baseline value is obtained that can be monitored to evaluate response to therapy. UPC is the most useful measure of proteinuria but shows a great deal of day-to-day variability.\(^1\) It is therefore recommended that 3 samples are obtained to get a representative baseline.\(^2\) This can be quite expensive but it is possible to collect 3 different specimens (can be free catch), aliquot 1 ml from each into a single container and only pay for a single measurement.\(^3\) One of the samples however should be obtained by cystocentesis and a culture performed to rule out a post-renal cause for the proteinuria. The effect of UTI on UPC is highly variable however so it should not be assumed that if a patient has a UTI that treating that will resolve the proteinuria, especially if hypoalbuminemia is also present.

In a patient with significant proteinuria they should also be evaluated for the presence of azotaemia while recognising that a patient can have significant proteinuria, even nephrotic syndrome, and still be non-azotaemic. Albumin and cholesterol also need to be measured. In reality, a complete haematology and biochemistry should be performed to look for any underlying or concomitant diseases. Additionally diagnostic imaging of the thorax and abdomen should be performed. This is primarily to look for underlying triggers for glomerular disease; sometimes referred to as NIN - neoplastic, infectious, non-infectious inflammatory. A triggering condition is found in less than half of all patients with PLN, neoplastic diseases are most common being found in about 20% in one study.\(^4\) Serology needs to be performed in view of the patient’s location/travel history; this might include agents such as *Borrelia*, *Dirofilaria*, *Ehrlicia* and *Leishmania* for example.
Non-specific Therapy

Treatment usually consists of feeding a renal diet with restricted but high-quality protein content and omega-3 polyunsaturated fatty acid supplements and either an angiotensin converting enzyme (ACE)-inhibitor or an angiotensin receptor blocker. The aim with all of these treatments is to reduce glomerular capillary pressure and so reduce the amount of protein that passes through the glomerular barrier. Patients with PLN are predisposed to thromboembolism so are often treated with either aspirin or clopidogrel, however implementation of these treatments should be delayed if a biopsy is to be performed. Blood pressure should be measured and anti-hypertensive therapy instigated if appropriate. It is mandatory that hypertension is controlled before performing renal biopsies.

Renal Biopsies

Renal biopsies are considered in patients with PLN in order to determine whether there is any evidence that the disease process is immune-mediated and therefore would potentially benefit from immunosuppressive therapy. In a recent series of biopsies in dogs with PLN, collected under the auspices of the WSAVA renal biopsy standardisation project, immune complex glomerulonephritis (ICGN) was documented in just under half of the samples that were submitted. Other less common reasons to biopsy patients with glomerular disease would be to characterise familial diseases so that the individuals can be removed from the breeding pool. It is also suggested that prognostic information might be obtained from the biopsies although, at present, there is very limited knowledge of the behaviour of different types of glomerular disease seen in dogs and cats. Before contemplating a renal biopsy careful consideration should be given to the patient’s signalment. There are some breeds of dog where the likely diagnosis is predictable (e.g. amyloidosis in a middle-aged Shar pei) or can be identified by specific genetic tests (e.g. hereditary nephritis in cocker spaniels, podocytopathy in soft coated wheaten terriers). In these cases a diagnosis may be reached without the risks and expense of performing a biopsy.

In general, it is not recommended that biopsies are performed in patients that are significantly azotaemic (certainly no more than IRIS Stage 2) or where the kidneys are reduced in size. This is because these patients have very little to gain from collection of a renal biopsy as they are unlikely to benefit from immunosuppression because their disease is too advanced and likely to be irreversible.

Renal biopsies can be obtained by a number of different methods; the most common are ultrasound-guided tru-cut biopsies, wedge biopsies taken at laparotomy or more recently by a laparoscopic approach. The laparoscopic biopsies can be sub-optimal because they tend to be very superficial and there are very few glomeruli just under the renal capsule. Biopsies should be obtained with the patient under general anaesthesia (even if ultrasound guided) because this allows the patient to be kept very still, including if necessary temporarily preventing respiratory movement. The left or right kidney may be biopsied at the preference of the ultrasonographer. The right kidney is less mobile.
but the left kidney is more caudal so may be more accessible. A variety of commercially available automated biopsy devices can be used; an appropriate diameter and length of throw of the biopsy needle should be selected for the individual patient. In general 18-gauge biopsy needles are used in cats and small dogs and 16-gauge needles in larger dogs. A short-throw (i.e. 11mm throw, 7mm specimen notch) should be used in small patients or when the cortex is thin. A biopsy guide may be used attached to the ultrasound probe or the biopsy may be obtained ‘free-hand’. Considerable experience of biopsying other organs is required before kidney biopsy is attempted; the kidney is quite mobile, the capsule is tough and there is little margin for error with the possibility of causing severe (even fatal) haemorrhage if a major renal vessel is lacerated. Typically two or three needle core biopsies are obtained from a single kidney. If the cores are 10mm in length two will be sufficient, usually three are required. The biopsy samples should be visually inspected; sometimes it is obvious that peri-renal fat rather than kidney has been obtained. Muscle is more difficult to differentiate. It is possible to use a dissecting microscope at very low magnification and ensure that the sample is of cortex rather than medulla by identifying spherical glomeruli within the sample and also that the tubules appear jumbled (cortex) rather than organised and linear (medulla). Biopsies should not intentionally be collected from the medulla since there will be no glomeruli to evaluate and there is a high risk of damaging the arcuate arteries in the corticomedullary junction.

It is imperative that the biopsy samples are handled as little as possible to avoid crush artefact. Ideally renal biopsies will be evaluated by light microscopy (formalin), immunofluorescence (Michel’s) and electron microscopy (glutaraldehyde). Nephropathology is a very specialist field and there are probably only half a dozen specialist veterinary nephropathologists worldwide. The importance of complete evaluation was illustrated in the recent series of 501 renal biopsies evaluated by the WSAVA scheme; 27.4% of the cases with ICGN required electron microscopy for definitive diagnosis and in 5.8% of cases ICGN was not even suspected prior to electron microscopy being performed.\(^5\)

Complications following renal biopsy have been reported to occur in 13.4% of dogs and 18.5% of cats.\(^6\) Most often this was haemorrhage and required no specific treatment but was more serious in a small number and there were occasional deaths. Complications were most frequent in patients with marked azotaemia (which are not recommended for biopsy in any case) and in dogs <5 kg having tru-cut biopsies. Therefore in very small patients consideration should be given to collecting surgical wedge biopsies in preference.

**References**

Appropriate management of urinary tract infections (UTI)

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Urinary tract infection (UTI) is a major reason for antibiotic prescription in small animal practice. Despite this there is great uncertainty regarding optimal treatment for this condition. The emerging problem with multidrug resistant bacteria has increased awareness of antibiotic use and misuse in small animals. The International Society for Companion Animal Infectious Diseases (ISCAID) has published guidelines to promote prudent use of antibiotics in canine and feline UTIs.\(^1\)

**Does this patient have a UTI?**

Diagnosis of a UTI usually occurs either because a patient presents with compatible lower urinary tract signs (dysuria, stranguria, pollakiuria, haematuria) or because a patient is considered to be at increased risk of infection and urinalysis and/or culture are performed, even in the absence of clinical signs. Conditions where pre-emptive screening for UTI may be performed include in patients receiving steroids or other immunosuppressive drugs, patients with diseases such as CKD, diabetes mellitus or hyperadrenocorticism, and in patients with compromised anatomical barriers to infection such as those with incontinence, perineal urethrostomy, recent urinary catheterisation and neurogenic bladder for example.

It is important to recognise that most cats (and certainly almost all young-to-middle aged cats with good urinary concentrating ability) that present with lower urinary tract signs do not have a UTI and should not be treated with antibiotics. These cats are most likely to have idiopathic feline lower urinary tract disease (fLUTD), or could have urolithiasis, but rarely have infection.

Urinalysis can be very helpful in documenting the presence of infection. In most patients with UTI haematuria, pyuria and/or bacteriuria are noted on examination of urine sediment. This is a test that can either be performed by diagnostic laboratories or in-house. The significance of haematuria alone should not be over-interpreted as iatrogenic blood contamination is common in samples collected by cystocentesis and haematuria has many other potential causes. Documentation of pyuria (>5 WBCs/hpf) on sediment examination is usually indicative of infection; however leukocyte esterase pads on urine dip-sticks are worthless and these results should be disregarded; these are often negative in dogs even when infection is present and are almost invariably positive in cats. Inflammatory changes in the urine sediment may be absent in patients receiving steroids or with naturally occurring hyperadrenocorticism. A positive culture from a sample obtained by cystocentesis is the ‘gold-standard’ for diagnosing bacterial UTI. Ideally (and according to the ISCAID guidelines) this would be obtained prior to starting treatment in every patient, even if treatment was then started prior to the results being available.
A single bacterial pathogen is isolated from at least 75% of infections. *E.coli* is the most common isolate in both dogs and cats accounting for more than half of all infections. Gram-positive cocci (*Staphylococcus* and *Enterococcus* particularly) are the next most common organisms, and a variety of other isolates are occasionally encountered (*Proteus, Klebsiella, Pasteurella, Pseudomonas, Mycoplasma*).

In most small animal practices culture is performed by sending samples to diagnostic laboratories. Occasionally this can lead to frustration when negative cultures occur in spite of clinical suspicion that infection is present either to the clinical signs a patient is showing or because of the findings of urine sediment examination. It is possible for organisms to die during transport to the laboratory although this probably not common; however, transport of specimens in boric acid may sometimes result in negative cultures so when specimens have been collected by cystocentesis submission of samples in plain tubes is advised. Recently two different systems for in-house culture of urine specimens have been developed and marketed to practitioners. The first is a urine dipstick paddle system, ‘Uricult Veterinary System’, which has been shown to be reliable in detecting whether or not bacteria are present, although less reliable at speciation of the bacteria that are grown. It is therefore recommended that if this system is being used when growth occurs the urine sample is submitted to the laboratory for identification and to provide antibiotic sensitivity testing. The second system (‘Flexicult Vet’) allows identification of organisms, and testing of antibiotic sensitivity, following overnight incubation at 37°C.

**Treatment of Uncomplicated Infections**

It is recommended that uncomplicated infections are treated with either amoxicillin or trimethoprim-sulfonamide in the first instance. These antibiotics have excellent penetration of the urine and achieve high concentrations. It is recommended that drugs such as amoxicillin-clavulanate, fluoroquinolones and cefovecin be reserved for complicated or resistant infections. Duration of treatment of UTI in veterinary medicine has traditionally been 10-14 days. In human medicine much shorter (e.g. 3 day) antibiotic courses are often used with the potential improvement in patient compliance, decreased cost and less selection pressure for antimicrobial resistance. There have been two prospective, randomised clinical trials evaluating the effectiveness of short-duration treatments of UTI in dogs, although unfortunately neither study evaluated the same antibiotic in both arms of the trial. The first study, compared 3 days high-dose enrofloxacin (20 mg/kg q24h) with 14 days amoxicillin-clavulanate (14-20 mg/kg q12hours) and the second, compared 3 days trimethoprim-sulphonamide (15 g/kg q12h) with 10 days cephalexin (20 mg/kg q12h). In both instances there was no difference in either the clinical or bacteriological cure rates.
Complicated Infections

Infections should be considered complicated in any situation in which appropriate short-term treatment for a UTI does not result in a clinical or microbiological cure, or in any patient in which this improvement is transient. Infections are also considered complicated when comorbidities are present that are likely to make eradication of infection more difficult; these may relate to compromised anatomy (e.g. ectopic ureters), immunological defences (e.g. hyperadrenocorticism) or concurrent treatments (e.g. steroids). UTIs should also be considered to be complicated in any patient with pyelonephritis or any entire male due to the inevitable involvement of the prostate.

In patients with complicated infections treatment with antibiotics, on the basis of the results of culture and sensitivity, should usually be considered for 4-6 weeks. In addition to culture being performed prior to treatment this should be repeated 7 days into treatment and 7-10 days after completion of the antibiotic course and again 1 month later. Results of these cultures can then be used to differentiate between refractory/persistent infections, relapsing infections and re-infection as outlined in the table below.

<table>
<thead>
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<th>culture</th>
<th>resistance</th>
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<th>re-infection</th>
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<tr>
<td>5-7 days on therapy</td>
<td>+ve (same organism)</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>7-14 days post-therapy</td>
<td></td>
<td>+ve (same organism)</td>
<td>+ve (different organism)</td>
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<tr>
<td>Post-therapy (previous -ve culture)</td>
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<td></td>
<td>+ve (same or different organism)</td>
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If the infection is resistant this is usually due to either inherent bacterial resistance, barriers to antibiotic penetration of the urine or non-compliance of either the owner or the patient. If the infection is relapsing this is usually due to a deep-seated niche of infection; for example calculi, polypoid cystitis, neoplasia or prostatic involvement. Re-infection may occur due to poor immunological or anatomical defences against infection.

Asymptomatic bacteriuria (ASB)

ASB is a common and usually benign finding in healthy women. Antimicrobial treatment of women with ASB is not recommended except during pregnancy. Treatment has not been found to reduce the number of episodes of symptomatic UTI or development of pyelonephritis, even in patients with diabetes. There is some evidence to suggest that infection with strains of bacteria with low pathogenicity actually may reduce the risk of infection with organisms likely to result in symptomatic infections. ASB also seems to be very common in female cats with CKD and does not seem to be related to the cats overall survival time (although the cats were treated).
References


Management of urinary incontinence

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Urinary incontinence is defined as the inability to control micturition with the involuntary passage of urine. This problem is relatively common in bitches but less common in male dogs and in cats of both sexes. Treatment of incontinence should start with diagnostic investigation to determine the most likely underlying cause, although in many bitches this will only consist of a complete history and physical examination to determine that sphincter mechanism incompetence (USMI) is the most likely diagnosis. Urine culture is indicated in all incontinent patients because urinary tract infection (UTI) can cause, or exacerbate, incontinence and patients with incontinence are predisposed to ascending infections. Careful history and physical examination should be sufficient in most instances to differentiate incontinence from inappropriate urination, behavioural problems and paradoxical incontinence due to urethral obstruction. It is also important to establish if the patient is polyuric, if so then an appropriate investigation for the underlying cause of this is indicated.

Further diagnostics should be performed in any patient in which an anatomical cause for the incontinence is suspected, or where surgical intervention is being considered. In most patients this will consist of some form of diagnostic imaging; most often intravenous urography (using either conventional radiography or CT) and/or a retrograde vagino-urethrogram. Cystoscopic examination of the lower urinary tract is very useful for direct visualisation of the anatomy and can also be used to direct therapy (for example in laser ablation of ectopic ureters). Urodynamic procedures can also be helpful but have limited availability.

Urethral Sphincter Mechanism Incompetence

The presence of urinary incontinence in an otherwise healthy female dog that was previously continent is often adequate for presumptive diagnosis of USMI and a trial of empiric therapy. This usually will consist of treatment with α-adrenoceptor agonists such as phenylpropanolamine (1.0-1.5 mg/kg/q8-12 hours) or a synthetic oestrogen such as estriol (1-2mg/dog/q24 hours initially, then every other day at minimum effective dose). Although the approach has not been systematically evaluated these drugs have been used in combination where either alone is insufficient to maintain continence. The effectiveness of these treatments may dissipate with time. Anecdotally weight loss can also be beneficial in bitches that are overweight.

The increased risk of urinary incontinence in bitches has been attributed to spaying (ovariohysterectomy), and is sometimes referred to as hormone-responsive incontinence for this reason. Some studies have suggested that early-neutering in particular increases the risk of incontinence.
developing. However, the epidemiological association with spaying is not universally accepted and has been questioned by some authors. ¹ Bitches >25kg are at increased risk of developing incontinence and a recent study suggested that the risk associated with neutering was only evident in larger dogs. ²

Numerous surgical treatments for USMI have been described. These treatments are usually reserved for patients that are non-responsive to, or intolerant of, medical therapy. The aim of surgical treatments such as colposuspension and urethropexy is to move the bladder neck into a more intra-abdominal position, increasing functional urethral length. These procedures have had variable outcomes and are considered to have poor long-term efficacy, particularly in animals with normal bladder position. ³ The most promising surgical procedure for USMI is placement of an artificial urethral sphincter that may be adjusted via a subcutaneous port. Recent studies have shown it to lead to a significant increase in continence in male and female dogs that had failed medical therapy for USMI, although significant complications have also been reported as a result of this procedure. ⁴

**Detrusor Instability (Overactive Bladder)**

This is the most common form of urinary incontinence in people, but it has been poorly characterized in dogs and/or cats. It is characterized by sudden urgency to urinate and involuntary loss of urine associated with bursts of detrusor contractions at bladder volumes far less than capacity. Diagnosis can be challenging and is only definitively made using urodynamic studies such as cystometrography. Response to therapy with antimuscarinic drugs such as oxybutynin or imipramine is sometimes used to presumptively diagnose detrusor instability in veterinary species.

**Ectopic Ureters**

Ectopic ureter is the most common anatomical cause for urinary incontinence in the dog. It may be seen in combination with other anatomical abnormalities and can be unilateral or bilateral. The ureteral entrance may be located in the bladder neck, urethra, uterus, or vagina, but in most cases the ureter apposes to the bladder in the normal position at the trigone but does not open into the bladder and continues to run caudally in an intra-mural position until it opens in the urethra.

Diagnosis of ectopic ureter is most often suspected in patients with a history of having never been continent, however in some cases incontinence may only develop later in life, often due to development of concurrent urinary tract infection. In male dogs signs relating to UTI may sometimes be the only presenting signs. Patients with ectopic ureter will normally posture to urinate and pass urine normally but dribble urine at other times too.

Conventional surgical treatment for ectopic ureter has been surgical re-implantation of the ureter into the trigone or ureteroneocystostomy (creating a connection between the ureter and the bladder lumen in the trigone) either with or without dissecting the distal extension of the ureter. ⁵ If the ectopic ureter is intra-mural it is also possible to perform laser guided ablation of the ectopic
ureter without the need to recourse to surgery. Whatever method is employed it is important to caution owners that many dogs will have continued incontinence following repair of the ectopic ureter, although this is usually of reduced severity and in many cases can be managed with medical management for associated USMI.

**Urinary Incontinence in Cats**

Urinary incontinence is uncommon in cats. In cats the bladder is typically located in a relatively cranial position with a long intra-abdominal urethra. Manx cats may have neurological incontinence associated with a lack of urethral tone. Perhaps the most common anatomical cause of incontinence in cats is urethral hypoplasia/genitourinary dysplasia; a condition in which the urethra and vagina are not separated from each other. A good response to surgery has been reported.7

**References**

Non-surgical management of stone disease

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The recent ACVIM consensus statement concluded that optimal management of urinary tract stones in most cases was by dissolution or use of minimally invasive procedures rather than by surgery.\(^1\) Their rationale was that incision-less procedures are associated with shorter hospitalisation, shorter anaesthesia time, and faster patient recovery.

**Medical dissolution**

Medical dissolution of stones requires that these are bathed in dilute urine for a period of weeks to months. Many stone types are amenable to dissolution; of the commonly encountered stones in dogs and cats only calcium containing stones (oxalate and phosphate) and silica cannot be dissolved. Stones that are causing obstruction are generally not suited to medical dissolution although stones in the urethra can be returned to the urinary bladder and then dissolved, but patients managed in this way should be carefully observed for signs of re-obstruction.

**Struvite**

Struvite stones should be suspected in dogs (especially females) with moderately radiopaque stones and urinary tract infections with urease producing bacteria (*Proteus, Staphylococcus*). These dogs will usually have alkaline urine, provided they have not received treatment with antibiotics. *E.coli* is not a urease-splitting bacteria and so when UTI with this bacteria is diagnosed it should be suspected that the patient has stones that have become secondarily infected, rather than the infection being the cause. It is important to understand that control of the UTI is key to dissolution of infection-related struvite. Antibiotic therapy has to be continued until the stones have been totally dissolved since viable bacteria may be present throughout the stone and as this dissolves bacteria will be liberated. In addition to antibiotics, low-protein, acidifying diet will ensure that dilute urine is produced and solubility of struvite is maximised. Infection related struvite stones can be very large and dissolution of stones can take some time (sometimes months) which can lead to owner/veterinary surgeon reluctance to employ medical therapy. It should be recognised though that once the UTI is controlled with antibiotic therapy the patient is usually asymptomatic, and even if surgery were performed concurrent medical therapy of the UTI would also be required. Therefore surgical treatment confers no real advantage and increases patient morbidity.

In cats struvite stones are usually sterile. The stones may be suspected because they are in the lower urinary tract, are less radiopaque than calcium-containing stones and relatively large and sometimes disc-shaped. These stones dissolve very quickly (within a few weeks) of commencing a diet designed to
dissolve feline struvite stones. If the stones are non-obstructive and the diagnosis of stone type uncertain it is often worth a trial period with diet prior to considering cystotomy as a way of confirming the diagnosis.

**Urate/xanthine**

Most dogs with urate stones will either be of a breed known to harbour the mutation in the SLC2A9 transporter (e.g. Dalmatian, Russian black terrier, bulldog) or will have portosystemic shunts (PSS). Urate stones can be dissolved by feeding a diet low in purine precursors that is relatively alkalinising, in combination with treatment with allopurinol (15 mg/kg/q12hours), a xanthine oxidase inhibitor. This treatment will be required in any case because otherwise these patients will form more stones. Patients with urate stones need to be monitored very carefully because the small, round stones can easily pass into the urethra and cause obstruction. It is very important that if patients are treated with allopurinol that dietary management occurs concurrently, otherwise xanthine stones may form.

Stones that form in patients with PSS are not considered to be amenable to conventional methods of dissolution, although they may resolve with surgical correction of the PSS.

**Cystine**

Dissolution of cystine stones with dietary alkalinisation and 2-mercapropionylglycine (Thiola; 15-20 mg/kg PO q12 h) has been described as an effective treatment for cystine stones. Unfortunately, at least in the UK, Thiola is prohibitively expensive so this approach is not really viable. Like urate, cystine stones also often cause urethral obstruction; sadly, after repeated episodes and multiple surgeries, many of these dogs have ended up being euthanised. The recent observation that in many dogs with cystine stones the problem appears to be androgen-responsive has resulted in the recommendation that these dogs be neutered; anecdotally, this seems to be effective in preventing stone recurrence.

**Voiding Urohydropropulsion**

Voiding urohydropropulsion is a relatively non-invasive method for removing small stones from the lower urinary tract. It is particularly valuable in female dogs and cats because of their relatively short and wide urethra. It can be used to remove all the stones that are in the bladder or to collect a representative stone for mineral analysis to guide appropriate medical dissolution strategies (for example in bulldogs where both urate and cystine stones can form).
To perform voiding urohydroprolpulsion the patient is anaesthetised and then held in a position such that the urethra is vertically orientated. The bladder is agitated to allow the stones to drop into the urethral outlet and then the bladder squeezed to initiate voiding. Once the bladder is empty the patient is catheterised to re-fill the bladder and the procedure repeated until all the stones have been passed.

**Lithotripsy**

Lithotripsy is the fragmentation of uroliths by use of shock waves (extracorporeal shock wave lithotripsy; ESWL), electrohydraulic lithotripsy (EHL) or laser energy. ESWL uses repeated shock waves to fragment stones located in the upper urinary tract (kidney or ureter) until they are small enough to pass spontaneously through the urinary tract. Use of ESWL is limited because of the cost and limited availability of the equipment that is required. EHL has been used in veterinary patients with lower urinary tract stone disease but has been largely superseded by the use of a Holmium: yttrium-aluminum-garnet laser which is associated with a higher rate of stone clearance.\(^5\) Reported success rates for laser lithotripsy are 100% in females and 80% in males,\(^6\) but careful selection of cases is required; removal of large stone burdens in male dogs is very time consuming. Treatment is therefore generally limited to urethroliths in male dogs and urethroliths and cystoliths in females.

**Benign neglect**

A decision is sometimes made to leave non-obstructive, non-infected stones in-situ when they are not causing clinical signs. This may be the best course of action in patients with concurrent disease.

**References**