COMMON QUESTIONS FROM RDVMS REGARDING THE GASTROINTESTINAL AND IMMUNE SYSTEMS IN DOGS AND CATS
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What is this new lipase?

Pancreatitis in the dog is relatively common but can be frustrating to definitively diagnosis. History, clinical signs and physical examination findings lead to the differential diagnosis; however, the presentation can be nonspecific and variable. A diagnosis is generally based on the combination of these signs plus clinicopathological and imaging findings.

Imaging of the pancreas depends on operator experience, equipment and degree of inflammation in the pancreas and surrounding tissues. The specificity of abdominal ultrasonography was only 68% in one study.

The original serum lipase was a catalytic assay that used a 1, 2 diglyceride assay. This test was unreliable for the diagnosis of pancreatitis because of low sensitivity and specificity. Lipase is produced by tissues other than the pancreas. Serum amylase concentration also lacks sensitivity and specificity.

The canine pancreatic specific lipase is available as a SNAP cPL and as a quantitative test Spec cPL. Sensitivity of Spec cPL concentrations vary for mild pancreatitis (21%), moderate to severe pancreatitis (71%), and pancreatitis overall (64–94%). Currently, serum cPL concentration is considered the most specific serum biomarker for the diagnosis of pancreatitis in dogs. Specificities range from 71–100%.

The new lipase test, 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) assay, was validated in dogs in 2005. The DGGR lipase test was recently compared to the Spec cPL and found to have high agreement. The DGGR lipase assay may be less expensive and have a faster turn-around time than the Spec cPL depending on the laboratory used.

It must be remembered that any lipase test is not 100% sensitive nor specific and the only true method of diagnosis is histopathology. As an example, in a study that we completed at the University of Tennessee, dogs with HAC but without clinical pancreatitis were more likely to have abnormal SPEC cPL concentrations and SNAP cPL results than dogs with normal ACTH stimulation test results. Based on this study, abnormal cPL results should be interpreted with caution in dogs with HAC in the absence of clinical signs of pancreatitis. Further studies are warranted to determine the pathophysiology behind this association.

Is there a new parvovirus?

Canine parvovirus (CPV) was first reported in the late 1970’s in North America (NA). This disease is caused by strains of CPV-2 (2, 2a, 2b, 2c). This is a single stranded DNA virus that has a higher mutation rate than other DNA viruses. The original strain CPV 2 mutated to develop the new strains CPV 2a, 2b and 2c over the next few years (1980, 1984, and 2000
respectively). The CPV-2b and 2c are the predominant strains in NA. CPV-2c differs from CPV-2b by a single amino acid. Tests and vaccinations work for both strains.

Acute infections can occur in any age dog but are more likely in puppies between 6 weeks and 6 months. There have been reports of outbreaks of CPV-2c infections in adult dogs (over 6 months of age). Severe cases may also be affected by co-infections of parasites and other viruses.

Initial testing for parvovirus includes fecal ELISA antigen tests and PCR methods. The point of care ELISA tests detect viral antigen in feces or rectal swabs but both false positives and negatives can occur. False negatives occur due to low concentrations of viral particles in the feces either due to decreased shedding in later stages of disease or dilutional effects of the diarrhea. False positives may occur following vaccination with modified live vaccines. PCR can also be false positive following vaccination. Virus isolation, hemagglutination and electron microscopy can be used to demonstrate infection but availability and turn-around time may be limiting for confirmation or group situations.

Treatment for CPV has not changed significantly over the years as it is supportive care. Fluid therapy and oncotic support are the mainstays of therapy. Antiemetics and antibiotics are added as needed. Management of nutrition has improved outcome. Immunotherapy with convalescent plasma has anecdotally been reported to help. Oseltamivir (Tamiflu) has been used as a treatment for influenza infection but has no theoretical basis for treatment. One study showed improved weight gain and maintenance of white blood cells in the oseltamivir treatment group compared to the control group. However, there was no significant difference in survival or clinical signs.

**How do you approach chronic small bowel diarrhea?**

Diarrhea can be described originating from small or large bowel or both. Small bowel diarrhea can be caused by nongastrointestinal disease such as endocrine, renal, liver, pancreatic, heart failure, metastatic cancer and toxins or drugs. A patient with small bowel diarrhea must be examined with this in mind and evaluated with basic laboratory and imaging assessment. It also must be remembered that there can be small bowel disease without diarrhea. Small bowel disease may have other clinical signs such as vomiting, weight loss, abdominal discomfort or altered appetite. Melena indicates blood has been digested in the small intestine – either through ingestion or localized gastrointestinal bleeding in the stomach or small intestine.

History and signalment will determine the initial approach. Differential diagnoses for a puppy may initially include foreign body (partial obstruction), infectious (parasitic, viral), diet, or even congenital abnormalities. Differential diagnoses for an old dog would more likely include neoplasia or inflammatory as primary. History is important. If several animals in a household are affected with diarrhea, the differential diagnoses are more likely to be infectious or dietary as a common cause.
Basic causes of diarrhea include malassimilation (maldigestion/malabsorption), secretory, osmotic, dysmotility or mixed. Dysmotility is seen with hyperthyroidism in cats. Secretory causes include bacterial enterotoxins or chemical toxins and possibly intestinal inflammation. Osmotic diarrhea results from unabsorbed products that lead to the osmotic draw. Malabsorption is a common cause of diarrhea and can be seen with many disorders (liver disease, bacterial overgrowth, lymphangiectasis, EPI, villous atrophy). A permeability or malabsorption diarrhea is also caused by intestinal inflammation or neoplastic infiltration.

Depending on the case, the approach to chronic diarrhea may vary. However, nongastrointestinal causes must be ruled out through blood work and imaging. Abdominal ultrasonography can evaluate bowel wall thickness and presence of masses. Fecal examination for parasites is absolutely necessary (direct smear, flotation, concentration methods). If these results are negative, deworming with a broad spectrum drug is still advised prior to more expensive and invasive diagnostic techniques.

Rectal cytology may reveal a large number of neutrophils which can indicate a bacterial problem. This test may help to decide if a bacterial culture would be useful. Rectal scraping may indicate the presence of histoplasmosis and the diagnosis is made!

Bacterial cultures are very confusing to interpret because of normal gut flora. If the animal is febrile, has an inflammatory leukogram, has hemorrhagic diarrhea and has increased neutrophils on rectal cytology, culture may be used (Salmonella, Campylobacter). Interpretation of the culture results must be carefully considered.

Common serum laboratory panels for GI include: TLI, PL, folate and cobalamin. TLI will rule in or out exocrine pancreatic insufficiency and the PL may rule out pancreatitis. Decreased serum folate concentration may indicate disease affecting proximal small intestine and increased concentration may indicate bacterial overgrowth. Serum cobalamim concentration is decreased with bacterial overgrowth or distal small intestinal disease. However, serum folate and cobalamin concentrations are insensitive and non-specific for detecting bacterial overgrowth. Also, bacterial overgrowth is better defined as antibiotic-responsive enteropathy (ARE). This syndrome is probably a result of increased bacteria in the upper small intestine and the resulting host response. The bacteria are not obligate pathogens and can be ones that are usually found in that area. The host response may be inflammatory or dysbiosis. ARE is difficult to definitely diagnose and empirical antibiotic therapy may be chosen as a means of diagnosis. However, antibiotic choice is difficult because any bacteria species can be present in the small intestine and the species may change over time. Tylosin is a popular antimicrobial choice. Also, metronidazole can eliminate many anaerobic bacteria and may also be immunomodulating. An antibiotic trial should be done for at least 2 – 3 weeks. The patient may respond to concurrently feeding a therapeutic diet trial.

If the patient can tolerate a therapeutic diet trial, this is worthwhile to rule out food sensitivity. There is no perfect trial diet but a careful examination of historic diets may help determine the initial elimination diet. A novel protein diet or a hydrolyzed diet are good initial choices. It must be stressed that during this trial, no other foods or treats can be given. This includes flavored heartworm or flea control products. This diet should be implemented for a minimum of
2 – 4 weeks. It is rare that longer periods are required as a trial. If the diet resolves the diarrhea, continue for another 3-4 weeks to ensure that it was not a transient improvement. It has been seen that up to 50% of case of chronic diarrhea will resolve with a diet change. Also we have seen that 50% of those case may be able to be changed back to the original diet with time.

Failure of response to diet change, antibiotic trial, or deworming can then indicate that endoscopy and biopsy are necessary. Some diseases will have normal biopsies including ARD, food intolerance, dietary indiscretion, toxic diarrheas, motility disorders, or systemic disease. Endoscopy allows visual examination of the gastrointestinal tract but does not include the mid jejunum and ileum. Colonoscopy may allow retrograde examination through the ileocolic valve into the ileum. Biopsies of the intestines should always be taken with chronic diarrhea and the result depends on the quality and quantity of samples obtained. Full thickness biopsies via surgical means may be necessary when endoscopic mucosal biopsies are non-diagnostic.

Protein losing enteropathy (PLE) in dogs can cause a chronic diarrhea and can result from inflammation, neoplasia, lymphangiectasis, infection or endoparasitism, and intussusception. There are breeds predisposed to PLE: Yorkshire terrier, soft-coated Wheaten terrier, Shar-Pei, Basenji, and Lundehund. These cases usually require biopsy for diagnosis.

Treatment of small bowel diarrhea depends on the underlying cause. If the diagnosis is inflammatory bowel disease or lymphocytic plasmacytic inflammation and diet, antibiotic, anthelminthic treatment does not help, then immunosuppression can be tried. This is usually corticosteroids, but other treatments may be useful. Cats can respond to chlorambucil.

The diagnostic approach to large bowel diarrhea is similar to small bowel. However, other infectious diseases such as trichuris, giardia, tritrichomonas (in cats), pythium and prototheca can occur in the large bowel. An inflammatory histiocytic ulcerative colitis or granulomatous colitis occurs most frequently in young Boxer dogs but can occur in other breeds. This disease has been linked to adherent and invasive E. coli (AIEC). This was diagnosed with biopsies that were tested by FISH (fluorescent in situ hybridization). Therefore if this disease is considered, mucosal biopsies can be submitted for histopathology, FISH test and also cultured for antimicrobial susceptibility. These cases have responded to long term enrofloxacin therapy (7 mg/kg/day for 9 – 10 weeks) but antimicrobial resistance is becoming common.

What about probiotics?

The intestinal microbiota is the new exciting hot topic. The complexities of this system are overwhelming and the research in human medicine is exploding. The inter-relationship between the microbiota and the host is fascinating. Because of this complexity it is not possible to give specific recommendations for the use of probiotics. For basic treatment, the probiotic must survive passage into the gut, adhere to the gut, and also proliferate. The probiotic does not survive long in the gut and therefore must be given on a regular basis. There is also variation between type and number of organism in different products. Different products have been used in veterinary medicine and have been used with clinical improvement in chronic diarrhea. However, remember that these are bacterial organisms that can be susceptible or resistant to antibiotics administered to the patient.
Megacolon in cats – what to do?

Constipation and megacolon in cats is a challenge and must be fully evaluated to exclude underlying causes. With recurring cases, after history and basic physical examination, examination of the anorectal area and neurologic system is necessary. Basic laboratory assessment and abdominal and pelvic imaging are next to be evaluated. Laboratory results may indicate metabolic or endocrine problem. A rectal exam is difficult in a conscious cat and is reserved for heavy sedation or general anesthesia during removal impacted feces. Neural deficits may reveal a neurologic cause such as neuromuscular dysfunction. Other mechanical causes can include pelvic stenosis, colonic neoplasia or perineal hernia. When all is ruled out, idiopathic constipation is diagnosed and medical management can be done to prevent obstruction. This treatment consists of removal of impacted feces, maintaining hydration, laxative therapy and prokinetics agents. Diets may be individualized for this problem and diet recommendations depend on how much motility is present in the large intestine. If there is some motility present, a diet such as Royal Canin Gastrointestinal High Fiber® is advised. If using other food, fiber supplementation with psyllium (1-4 tsp per meal) or pumpkin (1-4 tbsp per meal) may help. Canned food can increase water intake and can have supplements added. If the patient starts impacting on the high fiber diet then try a high digestible diets with low residue such as Purina EN®, Hills ID® or homemade diets. Lactulose (0.5 ml/kg q 8 – 12 hr.) is a good hyperosmotic laxative. Polyethylene 3350 Powder (Miralax®) has been also used in these cats (1/8 – 1/4 tsp BID with food). There is no good evidence based in vivo studies to show that the prokinetic cisapride is effective, but anecdotally it probably helps with mild to moderate constipation in the cat. Megacolon may not be medically controlled and surgical colectomy can be performed.

What tests do I submit for immune mediated disease?

Immune-mediated diseases include non-organ specific (systemic lupus erythematosus) to organ specific (immune mediated hemolytic anemia [IMHA]) disease. Inquiries about IMHA and immune mediated thrombocytopenia (IMT) are common.

Cases with IMHA are usually presented for weakness, lethargy and possibly icterus. General examination can show pale yellow mucous membranes, tachycardia and heart murmur. Basic laboratory work (CBC, serum biochemistries, urinalysis) submitted shows a regenerative anemia, polycythemia, spherocytosis, neutrophilia, increased liver enzymes and hyperbilirubinemia. In acute disease, reticulocytes may not be increased as it take 3 – 5 days for their appearance in the circulation. A cage-side slide agglutination test can confirm IMHA. A Coomb’s test may not be necessary if the slide agglutination test is positive. The etiology of IMHA can be infectious, neoplastic, drug/vaccine administration or primary. These differential diagnoses must be ruled out prior to a diagnosis of primary IMHA. Canine infectious agents that are known to cause IMHA include: rickettsial (Ehrlichia canis), protozoal (Babesia species) and bacterial (Mycoplasma, Leptosporosis). Therefore tests that are
routinely submitted include tick borne diseases (Rickettsial, Ehrlichia, and Babesia). We also start the patient on doxycycline on admission while awaiting results. In middle-aged or older animals, imaging should be completed to investigate neoplasia. This imaging includes chest and abdominal radiographs as well as abdominal ultrasonography. Immunology testing can include Coomb’s test and anti-erythrocyte antibodies. ANA does not test for IMHA and should only be used if SLE is suspected due to multiple organ involvement.

IMT can also be caused by infectious, neoplastic, drug administration or primary. Infectious agents that can cause IMT include *Anaplasma phagocytophilum, Erhlichia canis, Anaplasma platys, Babesia species.*

Immune mediated polyarthritis (IMP) is another disease seen in dogs that can be caused by infectious, neoplastic, vaccine/drug or be idiopathic. These dogs present with short-gaited strides, painful joints and possible fever. Infections with bacteria (*Borrelia, Mycoplasma*), rickettsia (*Ehrlichia ewingii, Anaplasma phagocytophilum*), protozoa (*Leishmania*) and viruses (*Calicivirus in cats*) can cause polyarthritis. Other antigen sources such as endocarditis, discospondilitis, pyelonephritis or urinary tract infection, periodontal disease, skin disease, gastrointestinal disease or heartworm disease must also be ruled out.

**What is the best immunosuppressive for immune mediated diseases?**

Due to the lack of evidence based studies in IMHA and ITP, there is no true recommendation for immunosuppression except for corticosteroids. Glucocorticoids are the mainstay of treatment. Dosage of prednisone (or prednisolone) is not standardized and ranges from 0.5 - 4 mg/kg/day. The usual initial dose is 1-2 mg/kg/day. There is a reported high dose pulsed approach but no clinical studies have been completed to assess effectiveness. In any immune mediated disease, the dose of glucocorticoids should not be tapered until normalization has occurred and then the tapering should be done slowly over weeks. If the tapering is too rapid, the disease may return and be more difficult to control.

The immunosuppression from glucocorticoids may not be sufficient in some immune mediated cases and a second drug can be considered. Azathioprine, cyclosporin and mycophenolate are the most common drugs chosen. The addition of these drugs may allow for increased immunosuppression and faster tapering of the glucocorticosteroid.

Azathioprine is a thiopurine which interferes with purine synthesis. DNA and RNA syntheses are inhibited. The effect is on cell mediated immunity and causes a reduction in lymphocyte numbers and T cell dependent antibody synthesis. There is a lead-in time for effect and may be up to 7 days or longer. The adverse effects recorded include: myelosuppression, acute pancreatitis, gastrointestinal problems and hepatopathy. There is a breed related variation in metabolism of the drug due to an enzyme (thiopurine methyltransferase) activity. Giant schnauzers may be more sensitive to the drug as this enzyme activity is lower than in other breeds.

Mycophenolate is another drug that blocks the purine synthesis. It was developed as an alternative for azathioprine. Therefore, do not use the two drugs simultaneously. It has a faster
onset of action and lower toxicity than azathioprine. However, there have been reports of gastrointestinal effects in dogs.

Cyclosporin reduces IL-2 production from T cells and thus reduces proliferation of T cells and consequently B cells. Most research has been done with immune mediated skin disease but cyclosporin is being used more commonly with other immune mediated diseases. The adverse reactions include gastrointestinal effects, possible renal toxicity and emergence of oral papillomatous lesions.

Vincristine is not utilized for immunosuppressive effects but is used for management of IMT. Vincristine stimulates megakaryocytes to increase release of platelets and impairs phagocytosis of opsonized platelets. The action is through binding to tubulin and disrupting mitosis. This drug is used as an initial therapy and not continuous.

Leflunomide is a drug that decreases pyrimidine production and inhibits T and B cell proliferation. It has been used in cases refractory to conventional drugs or when glucocorticoids are contraindicated or non-acceptable.

Human Intravenous gammaglobulins (IVIG) competitively inhibits the binding of IgG to monocytes due to saturation of Fc receptors. It has been used in dogs with IMHA and IMT with life threatening disease. A benefit was seen in one study with IMT but no controlled studies have been done with IMHA. This is an expensive treatment and may cause allergic reactions.

Remember that cases of IMHA are hypercoagulable and may benefit from aspirin or clopidogrel therapy.

Do cats get IMHA?

Yes. Remember that infectious causes such as Mycoplasma and Cytauxzoonosis must be ruled out or treated.

References:


Why is this patient drinking so much??
Polyuria/polydipsia is a presenting complaint for many conditions and in fact one article in the literature lists 28 causes. When the mechanism of urine concentration is reviewed, then one can look at different areas that can affect that concentrating ability. The renal tubule concentrates using the concentration gradient that is developed and maintained by the loop of Henle with sodium and urea and also the presence and response to ADH. The tubule is also prone to osmotic diuresis which is seen when the proximal tubules are not able to resorb or have reached the maximal transport ability as seen with glucosuria. With the understanding of these mechanisms a system of looking at the causes can be used to develop a list of differential diagnosis.
An apparently healthy dog can present for PU/PD with no abnormal physical finding. History must be thorough to investigate diet, drugs and possible toxins. Also important information is spay status, other health problems or any environmental or behavioural changes.
Initial diagnostic approach includes a complete blood count, serum biochemistries with electrolytes and a urinalysis with culture. These simple tests can rule out many common diseases.
The urinalysis can confirm polyuria by examining the specific gravity. A urine with low specific gravity is difficult to evaluate for infection and therefore culture is required to rule out pyelonephritis. If the urine is concentrated, the complaint is not a polyuria but may be a pollakiuria and diagnostics for that problem can be pursued. Glucosuria may be an indication for diabetes mellitus or a tubulopathy such as primary renal glucosuria or Fanconi’s syndrome. Chronic renal failure, liver disease, electrolyte imbalances (sodium, potassium) and hypercalcemia are hopefully identified on the basic blood work. Endocrine diseases may be investigated with further testing (thyroid, Cushing’s, Addison’s disease).
Other differential diagnoses include: partial ureteral obstruction, splenomegaly, intestinal leiomyosarcoma, polycythemia, pyometra, leptospirosis, primary aldosteronism, acromegaly, pheochromocytoma, post-obstructive diuresis and renal medullary solute washout.
Diabetes insipidus is also a cause but can be difficult to diagnosis. When other differential diagnoses are ruled out, the usual suspects are DI, primary psychogenic polydipsia or Cushing’s. Water deprivation tests can be time consuming and for safety for the animal should only be done once major differential diagnoses have been ruled out. Prior to water deprivation testing, a trial with DDAVP can be done, but it must be remembered that other diseases can respond to the supplementation with ADH.

How do I diagnose Cushing’s disease?
Cushing’s disease in dogs may present with PU/PD, polyphagia, skin disease (alopecia), pot-bellied appearance, hepatomegaly, muscle weakness, or hypertension. Other less common signs include hyperpigmentation, thin skin, poor hair regrowth, insulin resistant DM, urine leakage and possible recurrent urinary tract infections. Initial blood work may reveal an increased serum
alkaline phosphatase (ALP), increased ALT, hypercholesterolemia, hypertriglyceridemia, neutrophilia, lymphopenia, eosinopenia, thrombocytosis and mild erythrocytosis. Cushing’s disease can result from either a tumor in the pituitary gland (Pituitary dependent hyperadrenocorticism – PDH) or the adrenal gland.

The screening tests for hyperadrenocorticism that are available include: ACTH stimulation, low dose dexamethasone suppression and urine cortisol/creatinine ratio (UCCR). However, no test has 100% diagnostic accuracy. The UCCR ratio is used frequently in Europe and has not been embraced in North America. Urine should be collected at home, in the morning and at least 2 days after a visit to the veterinary hospital. The urine can be pooled and brought in to be tested. Other diseases or stress can falsely elevate this test result.

The ACTH stimulation can be used to diagnosis Cushing’s disease, hypoadrenocorticism and to confirm iatrogenic Cushing’s disease. It can be done at any time of the day but the effect of feeding is unknown. Synthetic ACTH preparation should be used and compounded should be avoided. The dosage is 5 microgram/kg IV with blood samples drawn before and 60 minutes after administration. Post values about the laboratory cut-off range indicates hyperadrenocorticism and further testing is necessary to differentiate PDH from adrenal origin. Low dose dexamethasone suppression is done using 0.01-0.015 mg/kg dexamethasone sodium phosphate or polyethylene glycol IV. Blood samples are taken at time 0 (prior to administration) and then 4 hours and 8 hours after administration. Avoid feeding and try to decrease stress during the day (ie. No other diagnostic testing). Normal dogs suppress below the cut off values of the lab. If minimal suppression or an inverse (escape) pattern is seen, then further differentiating testing should be done.

Some cases can be very difficult to diagnosis because clinical signs indicate Cushing’s disease but the screening tests do not support the diagnosis. These are referred to as “occult” cases. An ACTH stimulation test including sex hormones is offered at the endocrinology lab at the University of Tennessee. However, sex hormones have not been proven to cause “occult HAC”. An indication to use this test is if there is inappropriately low cortisol concentration on the screening tests. Further investigation into the role of excess basal cortisol secretion is currently under way at the University of Tennessee. Differentiating tests include: High dose dexamethasone suppression test, endogenous ACTH and abdominal ultrasound.

**How do I treat Hyperadrenocorticism?**

Once Cushing’s disease is diagnosed and determined to be either PDH or adrenal origin, treatment options can be explored. PDH treatment is aimed at controlling the hyperadrenocorticism resulting from the pituitary tumor. Surgery or radiation of the primary tumor is not considered an option at this time in North America. To control the excess corticosteroid production, the medical options are mitotane, ketoconazole and trilostane. Medical treatment may be individualized as not all patients respond to each treatment. Trilostane is the only FDA approved drug for veterinary use. Initial dosage of trilostane is low (1-2 mg/kg q 12 hr) and can be monitored and adjusted.

If an adrenal tumor is found, surgery may be considered. Medical management is an option for stabilizing a patient. A CT scan should be done prior to surgery to determine the extent of
growth and invasion of the tumor into surrounding structures such as the caudal vena cava. Some tumors are not resectable.

**What is a pheochromocytoma?**

An adrenal mass can arise from the cortex (corticosteroid or aldosterone producing) or the medulla (catecholamine producing) of the adrenal. Pheochromocytoma is a tumor of the adrenal medulla that secretes catecholamine. The pheochromocytoma has become more recognized with the increasing use of ultrasound in veterinary medicine. Pheochromocytomas are slow growing and vascular. The size can vary and can grow large and invasive to the adjacent vessels (caudal vena cava).

This secretion of epinephrine is episodic and causes vague clinical signs. Weakness and collapse are key signs but panting, tremors, anxiety, PU/PD, gastrointestinal signs, and hemorrhage have been reported. Hypertension may be recorded on a physical examination but because of the episodic nature, obtaining a normal blood pressure does not rule out this condition. There are no consistent physical examination or basic laboratory abnormalities for this disease. Initial diagnosis of an adrenal mass is made with ultrasonography as these masses are not usually palpable. Adrenal cortical masses are usually suspected due to the signs of hyperadrenocorticism and ultrasonography is part of the differentiating testing for this disease. However, abdominal ultrasonography may be completed for other medical reasons and an adrenal mass may be incidentally discovered.

To diagnosis pheochromocytoma, urine catecholamine concentrations can be measured. To differentiate between pheochromocytoma and hyperadrenocorticism, serum inhibin can be measured in neutered animals.

Treatment for pheochromocytoma is surgery. A CT scan is usually performed prior to surgery to evaluate the extent of vascular invasion. Medical management includes controlling blood pressure and arrhythmias.

**When should I think about Addison’s disease or hypoadrenocorticism?**

Hypoadrenocorticism is the great pretender. It is not common in dogs but it is not rare. Hypoadrenocorticism results from atrophy or destruction of the adrenal cortices and results in deficiency of both glucocorticoids and mineralocorticoids. Atypical hypoadrenocorticism is defined as having only recognized glucocorticoid deficiency. However these cases may have minimal mineralocorticoids and probably need supplementation.

Causes include primary (Addison’s), idiopathic (which may be immune-mediated), iatrogenic, or destruction (metastatic neoplasia, granulomatous, or hemorrhage).

Most cases are young to middle aged dogs but the range reported is 2 months to 14 years. Breeds that have a predilection include standard poodles, bearded collies, and leonbergers. However many other breeds have been identified.

Clinical signs can be chronic waxing and waning or can be an acute crisis. Chronic signs can be vague and can include the gastrointestinal or renal systems. These signs may be brought on by
stressful situations. Knowing that many breeds can be affected and that age is not always typical, one should consider this disease in many cases that are having vague clinical signs. Acute cases can present with dehydration, hypotension, shock, painful abdomen, hypothermia, bradycardia with history of gastrointestinal signs. Those cases must be dealt with on the emergency basis with aggressive fluid therapy and correction of electrolyte and acid/base abnormalities.

Initial diagnosis is based on history, physical and clinical signs and basic blood work. A complete blood count (CBC) should be examined for a stress leukogram. Absence of lymphopenia or neutrophilia in a stressed, ill dog should be a flag. A normocytic, normochromic anemia may occur. Serum biochemistries can show an azotemia with an inappropriately concentrated urine leading to an incorrect diagnosis of primary renal failure.

Hypoadrenocorticism is a cause of polyuria/polydipsia with a non-concentrated urine. In a stressful condition, the dog can become dehydrated causing increased BUN and creatinine which leads to the misdiagnosis of renal failure. The azotemia usually resolves quickly with fluid therapy. The electrolyte abnormalities are the usual flags for suspicion. The increased potassium and the decreased sodium with a sodium/potassium ratio of less than 27 is the classic presentation. However, in atypical cases, the electrolytes can be normal. It must also be remembered that there are other causes of increased potassium and decreased sodium. These include gastrointestinal disease, effusive disorders, renal disease and acid/base disorders.

Baseline serum cortisol concentration can be a screener for the suspicious cases. If the resting cortisol is above 2 microgram/dl the case is unlikely to have hypoadrenocorticism. However, definitive diagnosis requires an ACTH stimulation test. This test can be done even in the critical patient. If exogenous glucocorticoids are required in the crisis, dexamethasone can be used as it does not interfere with the cortisol assay. Other glucocorticoids (prednisone, hydrocortisone) will interfere with the test.

**What is best way to measure blood pressure?**

Blood pressure is being recognized as part of a complete physical examination in veterinary medicine. However not all veterinary clinics have the instruments to make this a reality. Direct blood pressure measurement is the gold standard but is not practical for practitioners. Indirect blood pressure measurement can be obtained using ultrasonic Doppler flow monitors or automated oscillometric devices. The oscillometric method uses an automated system with a cuff that records the oscillations of the vessel wall at different pressures and computes the systolic, diastolic, and mean arterial pressures. The Doppler flow method requires the use of an inflatable cuff attached to a sphygmomanometer placed on an appendage or tail and a piezoelectric crystal positioned over an artery distal to the cuff. Systolic (SAP) and diastolic (DAP) pressures can be obtained, though diastolic pressures readings can be inaccurate with Doppler flow method and require increased training to determine. Size of the cuff used is important to obtain the most accurate measurement. The width should be approximately 40% the circumference of the appendage. If the width is too small, an increased pressure is measured and if too width, then the pressure can be measured incorrectly low.
Positioning of the patient is a key factor for correct blood pressure reading. The cuff should be positioned at the level of the heart to most accurately reflect the arterial pressure. When using the Doppler flow method, the paw or tail may be clipped to allow a better contact with the crystal but should be done well in advance of the procedure to decrease stress. The patient should also be acclimated to the room for at least 5 – 10 minutes to decrease stress. In cats, the limbs may be used, but the tail may be a better option. The first measurement should be discarded and then the average of 3 – 7 consistent measurements should be calculated. The appendage used, the cuff size and the readings should all be recorded in the medical record so consistency can be used for future measurement and comparison.

Different studies have reported normal pressures but most record a normal < 160 mm Hg. However, healthy sight hounds may have a resting systolic blood pressure that is greater than 15 mmHg higher than other breed.

**Why do I care about hypertension?**

Hypertension can result from “white-coat” stress and this should be determined by decreasing any possible stress for the patient during measurement and repeated measures over time. Hypertension can be primary or secondary. In our veterinary patients, we recognize secondary hypertension more commonly and this is associated with renal disease, hyperadrenocorticism, diabetes mellitus, and hyperthyroidism. Other less common causes are pheochromocytoma, primary aldosteronism and acromegaly.

Hypertension may be a reason to test for the mentioned conditions but in itself it is damaging to the body. The target organs are the eyes, the kidneys, the brain and the cardiovascular system. Acute blindness in cats may result from retinal hemorrhage or detachments and may be the reason for presentation. Hypertension causes proteinuria which is very damaging to the tubule; however, renal disease can lead to hypertension.

Controlling documented hypertension along with the underlying disease can decrease further progression of complications of hypertension.

**What’s the best test to diagnose a hyperthyroid cat?**

Hyperthyroidism usually affects older cats but the age range is reported to be 4 – 22 years. Most cats present with clinical signs of PU/PD, polyphagia, weight loss, gastrointestinal signs and skin changes. Other clinical signs include: respiratory signs, weakness, tremors, decreased appetite, and decreased activity. General examination may reveal weight loss, a palpable thyroid gland, tachycardia or gallop rhythm, heart murmur, skin changes and hypertension.

Since other diseases are considered with many of these clinical signs, a complete blood count, serum biochemistry and urinalysis should be completed. Serum biochemistries may show increased liver enzymes (ALT, ALP) and increased blood glucose. The urine is usually concentrated unless renal insufficiency is also present. The hyperthyroidism may mask underlying kidney disease due to the increased GFR.

The screening test for hyperthyroidism is a total T4 (TT4) concentration. The RIA method is the gold standard for measuring TT4. There are other methods for measuring that are employed by different laboratories (chemiluminescent immunoassay, ELISA, enzyme immunoassay method – EIA).
Free T4 (fT4) should not be used as a screening test as the specificity is poor (false positives). Be cautious of the method of measuring fT4 as not all laboratories use the same methods (equilibrium dialysis, RIA, chemiluminescent immunoassay). fT4 should be used in conjunction with TT4 and clinical signs.

Serum T3 concentrations are not useful for diagnosis because in one study by Peterson et al, one-third of the hyperthyroid cats had normal T3 concentrations. TSH measurement is also a test that should not be used routinely to diagnosis hyperthyroidism in cats as results can be over interpreted. If used, it should be interpreted with TT4.

Thyroid scintigraphy uses nuclear medicine to display functional thyroid tissue. This can be used in suspected cases that have normal or borderline TT4. It could be considered the gold standard; however availability is the challenge.

There are cases in practice that have all the clinical signs of hyperthyroidism, have other differential diagnoses excluded but do not have abnormal TT4. If scintigraphy is not an option, then a T3 suppression test can be considered. This test measures serum T3 and TT4 concentrations prior to testing. T3 (liothyronine) is given orally (20 micrograms q 8 hr for 7 doses). A blood sample is then taken 2 – 4 hours after the last dose and the TT4 and T3 serum concentrations are measured. The T3 concentration confirms that the cat received the drug. The T3 should suppress TT4 in normal cats. Therefore if TT4 is >20 nmol/l +/ - <35% suppressed from baseline, hyperthyroidism is diagnosed.

**What is the best treatment for a hyperthyroid cat?**

Hyperthyroidism can be treated either medically, surgically or with radioactive iodine. Medical management with methimazole can be challenging in that the cat must be medicated once to twice a day for the rest of its life. Methimazole can be administered as an oral tablet or liquid or as a transdermal form. The transdermal may have less gastrointestinal side effects than the oral form. However, it may be necessary to increase the dose with long term treatment. Medical management requires routine blood monitoring to insure no biochemical abnormalities and adequate treatment.

Medical management may also unmask underlying renal insufficiency. The return to normal GFR may reveal an azotemia and therefore these cases must be monitored closely for renal failure. Management of both diseases is then undertaken.

Some cats cannot tolerate methimazole and will have clinical side effects such as gastrointestinal upset, facial pruritus or biochemical side effects such as increased liver enzyme concentrations, thrombocytopenia, neutropenia or anemia. These cases may not be able to tolerate medical management.

Surgical treatment is an option if the thyroid gland or glands can be palpated. The glands may not be palpable if they have moved into the thoracic inlet. The surgical cases may be managed medically initially to evaluate renal function as well as to stabilize weight and heart issues. Anesthesia is a concern as well as postoperative monitoring. These cases require intensive care post surgically to monitor for hypocalcemia as the parathyroid glands can be damaged during surgery as well as the recurrent laryngeal nerve.
Radioactive iodine is a non-invasive method of treatment but requires authorized facilities. These cases must also be stable for this treatment. Medical management with methimazole is suggested to unmask renal disease and to stabilize the patient. The cat is treated for 14 days and then the serum TT4 is measured. If the TT4 concentration is in the normal range, a serum biochemistry is done to evaluate the renal function. If the renal function is normal, then the methimazole is discontinued for 2 weeks prior to radioactive iodine treatment. This allows uptake of the iodine by the abnormal thyroid tissue. The disadvantage of radioactive iodine is that the cat is in radiation isolation for many days depending on the State. These cats cannot be handled, evaluated or treated with other medication during this time. This fact adds to the decision of treating cats with predisposing illnesses. A second radioactive iodine treatment may be required in a low percentage of cats (2-5%). However, radioactive iodine treatment is less stressful, does not require anesthesia and will end medical treatment.

**Why is this Diabetic not controlled?**

A diabetic pet may require increased insulin doses to remain regulated or may become unregulated while on insulin therapy. Insulin resistance is suspected if the insulin dose is greater than 2.2 U/kg to maintain control. Loss of control and persistent marked hyperglycemia can occur and doses of 1.5 U/kg may not have any effect on the blood glucose measurement.

The clinical signs of uncontrolled DM can include polyuria, polydipsia, polyphagia, weight loss or a more severe presentation of diabetic ketoacidosis. The approach to the patient depends upon the presentation. All cases are evaluated with a physical examination and basic blood work and urinalysis. The less critical cases may also be evaluated with a blood glucose curve and/or serum fructosamine concentration. If the blood glucose curve or serum fructosamine indicate non-regulation, then the investigation begins.

The first questions to ask are in regards to the owner and insulin. The age, the care, handling, and administration of the insulin are important. Has there been a change in caretaker of the pet? Is the pet on other medications? Is the pet neutered? These are easy questions to rule out simple answers to the problem.

The next question is whether or not this animal is being overdosed with insulin and is experiencing the Somogyi effect. This can occur when the insulin dose is slowly increased without regular blood glucose measurements. The Somogyi effects effect can occur soon after insulin administration and must be measured at that time, as the blood glucose level will rapidly increase due to the counter-regulatory hormone secretion and. If the blood glucose is only spot checked throughout the day, it would appear that the blood glucose remains high. If the animal is experiencing this Somogyi effect, the simple answer is to lower the insulin dose back to the initial dose and start the regulation again.

If the Somogyi is not occurring and the blood glucose is truly increased throughout the day, then causes of insulin resistance must be explored. The most common causes of resistance include endocrine diseases and infections. In dogs, these causes include hyperadrenocorticism, bacterial infections, hypothyroidism and diestrus. In cats, the causes include hyperthyroidism, bacterial
infections, and organ insufficiency (renal, liver, cardiac), and other less common causes
(acromegaly, hyperadrenocorticism).
Infections cause secretion of the counter regulatory hormones (glucagon, cortisol, and
epinephrine). Diabetics are prone to urinary tract infections due to the low urine concentration
and the glucosuria (great media for bacterial growth). Evaluation of just a urinalysis for
infection in not adequate for diabetics. A bacterial culture must be submitted to rule out an
infection. Other sites of infection/inflammation such as periodontal disease and skin infections
must be ruled out.

Endocrine diseases cause insulin resistance. Hyperadrenocorticism is most common in dogs and
hyperthyroidism in cats. The challenge of identifying concurrent hyperadrenocorticism and
diabetes can be challenging. An uncontrolled DM, may have a falsely increased cortisol with
either ACTH stimulation test or LDDS test. If possible, stabilizing a DM with increased insulin
dose can help with interpretation of these tests. However, once diagnosed with
hyperadrenocorticism, treatment for that disease will drastically decrease the insulin
requirements and close monitoring must be done to avoid insulin overdosing.

Other causes of insulin resistance include obesity, acromegaly, hypothyroidism, chronic
pancreatitis, pheochromocytoma, other cancers, hyperlipidemia and renal insufficiency.

The production of insulin antibodies can occur but is not the usual cause of insulin resistance.
Therefore, all other causes must be ruled out prior to diagnose.

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COMMON QUESTIONS FROM RDVMS REGARDING THE URINARY SYSTEM IN DOGS AND CATS
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How do I treat canine urinary incontinence not responsive to standard therapy?

Standard initial treatment for urinary incontinence in spayed female dogs is with reproductive hormones (e.g. estriol, premarin or diethylstilbesterol) or sympathomimetic drugs (phenylephrine, pseudoephedrine and phenylpropanolamine). Combining these two classes of drugs can be attempted to achieve continence if single treatment is not effective. Further diagnostic tests should be explored for dogs that are not responding to pharmacological treatment. Basic urinalysis plus culture should always be completed to evaluate for concentrating ability and possible infections. A patient with polyuria/polydipsia may be misdiagnosed as primary incontinence. Additionally, CBC and serum biochemistries should also be performed. Imaging of the bladder (radiology and ultrasonography) can determine if anatomical abnormalities may be contributing. In select cases, contrast urethral radiology can determine intra or extra-luminal problems. Urethral pressure profile (UPP) is useful to determine the pressures at different locations in the urethra. However, this test is only done at select locations. Urethral scoping can visualize the urethral and bladder mucosa and can determine if ectopic ureters are present. If there is no underlying problem found, urethral bulking or surgical placement of a percutaneously adjustable hydraulic urethral occluder may be considered as treatment options.

When should I worry about urine crystals in an asymptomatic patient?

Urinary crystals can indicate an underlying problem or may be insignificant. In the bladder, crystals are formed in supersaturated urine. Once urine is collected, crystals can form or dissolve with changes in pH, temperature, or technique of preparation. Importantly these changes can alter interpretation of results. Evaluation of recently acquired urine samples is preferred to determine crystal significance. Crystals should be interpreted in view of the entire urinalysis in relation to pH and specific gravity. Crystalluria may indicate a potential risk for urolith formation. While crystalluria does not predict urolith formation, there is an increased risk if heavy crystalluria in a fresh urine sample is present. If this occurs, dietary changes are not always indicated; however, increased water intake and increased surveillance are warranted. Early detection of uroliths may aid in removal by noninvasive means if the uroliths are small.

Magnesium ammonium phosphate (struvite) crystals can be found in urinalysis of normal dogs and cats. These crystals also can occur with urinary bacterial infection due to urease-induced production of ammonia. Therefore the finding of these crystals in dogs or especially in pediatric dogs and cats in addition to finding pyuria or bacteriuria in the urinalysis should prompt automatic culture of the urine sample. Urolithiasis should be investigated if there is an infection plus crystals noted on the urinalysis. However, mature cats with struvite crystalluria usually do not have an underlying infection. Feline lower urinary tract disease (FLUTD) or feline
interstitial cystitis (FIC) sometimes presents with excessive struvite crystalluria and struvite crystals remain the most common mineral component of urethral plugs.

Calcium oxalate crystalluria can be a normal finding but if significant quantities are present then diseases such as hypercalcemia or ethylene glycol toxicity should be explored. Interestingly, patients with calcium oxalate urolithiasis only have crystalluria 50% of the time. To decrease risk of stone formation in cases of persistent crystalluria, medical management with diet and oral potassium citrate may be necessary.

Normal dogs and cats do not usually have urate crystals but they can occur. Dalmatians and English Bulldogs are breeds that are prone to this type of crystal and therefore are at risk for urolithiasis. In other breeds and cats, if urate crystals are present the animal should be evaluated for underlying liver disease such as portal vascular anomalies (shunts).

**When to worry about proteinuria in an asymptomatic dog or cat?**

Proteinuria discovered on a urine dipstick or by screening microalbuminuria test may be an incidental finding but should be further investigated. Presence of protein should be confirmed with SSA (sulfosalicylic acid); however, SSA may still yield inaccurate results. The source of the protein must be investigated. Positive results occur with hemoglobinur ia and myoglobinuria. For a true proteinuria due to glomerular disease, urine sediment must not contain cells or bacteria. The first step is to microscopically evaluate urine sediment and to perform a urine culture. If there is inactive urine sediment and culture is negative, then a urine protein/creatinine ratio (UPC) should be performed to verify and quantitate the proteinuria. To verify true persistent proteinuria, serial UPC measurements are recommended as daily variations can occur. UPC is considered abnormal at >0.5 in a dog and >0.4 in a cat; however, most healthy dogs and cats have UPC < 0.2.

When post-renal proteinuria is excluded, confirmed proteinuria is usually an indication of glomerular protein loss. The exception is seen with some tubular disorders such as Fanconi’s syndrome. Glomerular disorders can be either primary or secondary in origin and proteinuria should be investigated. Secondary causes of glomerular disease can be due to antigenic reactions; therefore a search for underlying antigenic stimulus such as non-renal infection or heartworm disease must be made. Hypertension can damage the glomerulus leading to proteinuria and therefore systemic blood pressure measurement is indicated. Cushing’s disease or oral corticosteroid therapy in dogs will cause a mild to moderate proteinuria that can resolve with treatment or cessation of therapy.

If an underlying cause cannot be found, renal biopsy should be considered. Since glomerulonephritis has different histopathological forms, analysis will help with descriptive analysis as well as determination of future therapy.

**How to deal with nephroliths?**

The best treatment plan for a nephrolith depends on the type, the impact on the patient, and the potential morbidity of available treatment options.
Nephroliths can vary in size from small to staghorn and must be differentiated from renal mineralization. Nephroliths may be part of the primary problem or may be an incidental finding on survey radiographs. Mineral composition may be difficult to determine without removal and analysis. In cases where this is not possible, the most likely composition can be inferred from radiographic appearance, urinalysis (crystalluria and pH), presence of infections and evaluation of serum mineral levels (calcium).

Calcium oxalate are the most common nephroliths in cats. Surgical removal can cause renal damage and therefore feline calcium oxalate nephroliths are best managed medically; however, with proximal ureteral obstruction, surgery may be necessary. As dissolution is not possible, the goal is to prevent growth of the nephrolith. Use of lithotripsy (extracorporeal) is not indicated because the feline kidney is unlikely to tolerate the shock wave dosage required for complete fragmentation and ureteral passage of stone material. Medical management of cats includes evaluation for hypercalcemia or chronic kidney disease. Mild hypercalcemia, azotemia and calcium oxalate nephrolithiasis commonly co-present in feline patients. Therapy for idiopathic hypercalcemia is aimed at decreasing serum calcium concentration which includes diet, fiber and possibly bisphosphonates. Nephroliths in a solitary functioning kidney (big kidney-little kidney syndrome) may pose additional concern but still are usually best managed with medical strategies.

Many dog breeds seem predisposed to calcium oxalate nephroliths. However, suspecting this type of nephrolith in dogs should also lead to investigation of underlying disease such as hypercalcemia or endocrinopathy (Cushing’s). Treatment is similar to cats with the exception that extracorporeal lithotripsy may be used if conditions are suitable (size of nephrolith and patient stability). Surgical removal also may be indicated when a nephrolith is associated with pain, infection, or obstruction and renal pelvic dilation.

If struvite nephroliths are suspected they can be treated with dissolution diets and antimicrobial therapy (if infection-induced). Ureteral obstruction is a possibility as the nephrolith becomes small enough to drop into the ureter; however, this appears rare in actual practice.

Are there any new treatments for feline lower urinary tract disease?

Many differential diagnoses show similar clinical signs for feline lower urinary tract disease (FLUTD). It is important to rule out these diseases prior to making a diagnosis of feline idiopathic cystitis (FIC). Diagnostic tests including urinalysis, urine culture, basic blood work (CBC, serum biochemistries) and imaging should be completed in all cases, with prioritization of the urinalysis and survey radiographs. A presumptive diagnosis of FIC can be made if no underlying disease is found. Triggers for FIC episodes are not always known and could include stress or neurogenic stimuli. Therefore multi-modal management to prevent these recurrences includes stress reduction (environmental enrichment, facial pheromones) and more traditional therapies of diet (moist food), increasing water intake and analgesics.

Chronic cases of FIC include those that continue to have clinical signs without remittance or that have frequent recurrences even after multi-modal management. These cases should be provided appropriate pain management to break the pain cycle using short acting analgesics such as buprenorphine, butorphanol or NSAIDS (meloxicam, robenacoxib). Amitriptyline treatment may
reduce recurrence by decreasing stress or via other pharmacologic effects. Feline facial pheromones may be useful by decreasing stress. Treatment with the oral glycosaminoglycan, pentosan polysulfate (Elmiron®), given long term (months to years) may reduce clinical signs in some cats, despite a lack of strong evidence based research. If successful, it is a lifelong therapy. Other glycosaminoglycan drug usage in these FIC patients is also antidotal and future studies are necessary. Each cat therapy must be individualized to find the best management.

**When to do a perineal urethrostomy on a cat?**

Urethral blockage with mucous or mucocrystalline plug in a male cat can be very frustrating in both initial and long term management. When the initial blockage is difficult to resolve, urethral spasm can make recovery of voiding function difficult. The irritated urethra can spasm at any location and can involve smooth or striated musculature or both. Because of these spasms, prolonged recovery can involve multiple urinary catheter placements and therefore pharmacological therapy can help decrease the urethral spasm.

After this initial blockage, management with diet, increased moisture intake, and multi-modal environmental management may help prevent recurrence of urethral plugs. If several recurrences occur despite appropriate management, a perineal urethrostomy may be considered. For example, I will be more likely to recommend a PU be performed after a cat’s third blockage. In other situations, a PU may be indicated as a salvage procedure when severe urethral trauma has occurred, or to alleviate blockage by a urethral stricture.

Perineal urethrostomy surgery is not innocuous. With loss of the distal urethra, normal barriers are lost; bacterial infection can occur and may ascend into the kidneys. Incidence of bacterial urinary tract infections increases with PU surgery and has been reported to occur in up to 50% of patients depending on the technique employed. PU surgery is delicate and if not done correctly, urethral leakage or stricture can occur. Finally, the cat may still suffer from episodes of non-obstructive lower urinary tract signs if medical management is not applied and continued.

**Why are urine cultures always negative when I send them to the diagnostic laboratory?**

Many practitioners do not submit urine for culture because it is expensive and they receive “false negatives” even when urinary tract infection is suspected. True and false negatives can be related to procedural and biological reasons.

Negative urine cultures are often accurate and reflect a sterile sample. In house use of urine dipsticks may give false information on the presence of leukocyte in dog or cat urine. Microscopic urine sediment examination may falsely overestimate “bacteria” as many artifacts mimic bacteria and even bacterial motion. The best sediment examination is achieved by using routine stains (clean Gram stain or new methylene blue) and qualified personnel.

Timing is important. Whenever possible, samples should be collected prior to antimicrobial treatment in new cases. If this is not possible then the diagnostic laboratory should be notified of current treatments. Antimicrobial administration may inhibit bacterial growth in culture but may not be bactericidal in vivo. Additionally, the laboratory must be notified if anaerobic and
mycoplasma organisms are suspected as these organisms will not grow with standard aerobic methods.

Adverse effects may occur with handling of the urine sample prior to transport. Samples should be refrigerated and transported as soon as possible. Do not ship formalin biopsy samples with urine samples for culture. During transportation, temperature may affect culture outcome. Long delays or high temperatures may affect the viability of bacteria.

Finally, it must be remembered that not all lower urinary tract signs are caused by bacterial infection. Other etiologies such as urolithiasis, neoplasia and idiopathic cystitis should be considered and investigated in patients with persistent signs and repeated negative culture results.

**How to treat those urinary tract infections that keep coming back?**

Repeated urinary tract infections can be classified based on the species and pattern of bacteria observed. Sequential urine cultures are invaluable in sorting out these bacterial urinary tract infections. Recurrent signs caused by the same organism are usually due to a relapse of the original infection. Signs due to a new reinfection are usually caused by a different organism. However, repeated *Escherichia coli* infections can be challenging to interpret as there are different strains of the bacteria. *E. coli* is a common urinary tract infectious agent as well as a common persistent organism in some patients.

“Recurrent” infection must be evaluated in relation to previous treatment. In a relapse (same bacteria), the effectiveness of the prior treatment plan is questioned: Was adequate treatment given to the patient (appropriate drug, dosage and duration)? Was urinalysis and culture rechecked after treatment completion to ensure clearance of infection? Was this a simple or complicated infection (especially pyelonephritis, prostatitis or UTI with concurrent disorders)?

With reinfections (different organisms), underlying predisposing causes must be investigated. These include problems with host defense such as anatomical abnormalities of the lower urinary tract (vaginal urine pooling, recessed vulva, or masses), urethral incompetence, neurological impairment of micturition, and alteration in urine volume and concentration. Uroliths can also act as a nidus for relapse or reinfection at any location in the urinary system. Other underlying systemic predispositions include immunocompromise such as endocrine diseases (hyperadrenocorticism or diabetes mellitus) or corticosteroid therapy. Unfortunately, an underlying disorder may not be detected in many cases.

Management of recurrent urinary tract infections can still be challenging even when a distinct reason or underlying cause can be identified. Surgical problems can be corrected and manageable systemic disorders can be addressed. Other predisposing disorders may or may not be able to be eliminated (e.g. poorly controlled endocrine disorders, irreversible neurological impairment). These cases should be managed as a complicated UTI with long term appropriate antimicrobial therapy. Pulse or low dose daily antibiotic therapy or other prophylaxis can be considered once the initial infection is cleared.
Many of these recurrent infections involve *E. coli*. These bacteria must first adhere to the cell and may actually be internalized. Oral therapies that may be used to prevent adhesion include cranberry extract and D-mannose. Cranberry extract contains proanthocyanidins that inhibit *E. coli* adhesion to epithelial cells. D-Mannose may also be an adhesion deterrent, but clinical studies of its efficacy are lacking.

**How do I treat those highly resistant urinary tract infections?**

Patients with unidentified or unmanageable underlying disease can develop resistant UTI. These cases have had many different classes of antimicrobials prescribed and as a result the bacteria have become resistant. As with recurrent UTIs, an underlying disease or condition should be investigated and treated if possible.

The diagnostic laboratory can be of great help in maximizing effective antimicrobial choices. Antibiotic susceptibility is reported via agar disc diffusion (Kirby Bauer) or by antimicrobial dilution technique (MIC – minimum bacteriostatic bacterial concentration). With MIC, each antibiotic is evaluated in respect to serum levels; however, urinary concentrations may be significantly higher. Therefore renally excreted antimicrobials may be effective even if the lab result reports intermediate susceptibility or resistance. Short term use of injectable antimicrobials may be necessary to eliminate the infection. If aminoglycosides are used, urinalysis should be monitored frequently for early renal tubular damage by using cast identification. If susceptible, infections can be treated with the antiseptic therapy nitrofurantoin but potential side-effects must be recognized. As discussed in the previous section, oral cranberry extract and D- mannose may be useful in management of some *E. coli* infections.

**How about those asymptomatic (silent) urinary tract infections?**

A patient may not show clinical signs of lower urinary tract disease even with a positive bacterial culture. Urine contamination must be ruled out first and bacterial numbers should be evaluated. Significant infection is likely if one or two high growth organisms are isolated from an appropriately handled cystocentesis urine sample. Patients with silent infections usually have an uncontrolled underlying disorder. In the course of frequent, deliberate urine cultures as part of a monitoring plan, infection may be discovered.

Initially, standard treatment approaches for complicated infections are pursued. These cases can be very frustrating because the infections may not be cleared and resistance may occur. These patients still do not show clinical signs but the concern is for ascending infection or if bacteria are urease producers for possible formation of struvite uroliths. In some cases, no treatment is successful in eliminating the organism. Inhibitory antimicrobial treatment (low dose, once daily administration) has been recommended to prevent complications. In other cases, all antimicrobial therapy may be discontinued and hopefully with time, resistant bacteria may be replaced with other susceptible bacteria. The urine should be re-evaluated and cultured after 1 to 2 months with hopes of finding a treatable infection. In other cases, treatment is withheld unless clinical signs of infection or urosepsis occur.
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COMMON QUESTIONS FROM RDVMS REGARDING THE RESPIRATORY SYSTEM IN DOGS AND CATS
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When faced with a kennel cough outbreak, what is the best method for testing?

Kennel cough is the old term for what is now called canine infectious respiratory disease (CIRD). The disease is commonly seen with kenneled dogs and is transmitted by direct or indirect methods. The list of infectious agents that have been recognized to contribute to this disease is growing. The most common bacteria identified are *Bordetella bronchiseptica* and *Mycoplasma*. *Streptococcus zooepidemicus* has been identified as a cause of serious pneumonia in some cases of CIRD. These bacteria can be cultured from a transtracheal wash (TTW) but special requests must be made for mycoplasma culture. The well known viruses involved include: parainfluenza, adenovirus-2, and respiratory coronavirus, and canine influenza virus. Other viruses identified include: canine hepacivirus, bocavirus, pneumovirus, and pantropic canine coronavirus. Distemper virus can be mistaken for CIRD. These CIRD cases must be treated as infectious and if possible on an outpatient basis. If hospitalized they must be isolated.

For individual dogs, testing is determined by the seriousness of the condition. Most cases are uncomplicated with no fever, anorexia or lethargy. These cases are sent home and treated with antibiotics and antitussives. However, cases can become complicated if immunocompromised or have overwhelming infectious exposure. Those cases have a productive cough, naso-ocular discharge and fever. An interstitial and/or bronchopneumonia is identified on thoracic radiographs and blood work reflects the infectious/inflammatory nature. These serious cases are first radiographed and then washed to obtain samples for cytology and bacterial culture. For viral diagnostics, serology is used for canine influenza, urine PCR is used for distemper and PCR or virus isolation can be used for other viruses.

In a kennel situation, an outbreak of CIRD can be devastating. Most dogs are noncomplicated and recover with minimal to no treatment. However, since the transmission is through direct or indirect contact, many dogs become infected. To identify the pathogenic organism, affected dogs can be tested. Influenza may not be present at the time of clinical signs and paired serology may be needed to positively confirm diagnosis. Nasal swabs for virus and bacteria can be done but remember that some bacteria are part of the normal nasal flora. Finding a positive diagnosis does not always implicate the causative agent.

Management of a kennel outbreak is aimed at environment and isolation control. To decrease transmission, new dogs should not be admitted to the kennel. Affected dogs should be isolated from non-infected dogs and strict isolation standards followed.

**What to do about chronic nasal discharge in a dog?**

Chronic nasal discharge in dogs can be frustrating. History and signalment can aid in the approach. Unilateral discharge may lead one to consider a foreign body or a tumor but this is not always the case. Bilateral discharge can occur from infectious, inflammatory or neoplastic
causes. Epistaxis can be a local problem or indicate systemic disease (hypertension, thrombocytopenia and vasculitis).

Initial diagnostics depend on history and signalment and thus may involve basic blood work, urinalysis and thoracic imaging. More specific diagnostics involve nasal CT, rhinoscopy and biopsy. Skull radiographs do not provide information to the same degree as CT. CT allows evaluation of the nasal cavities, sinuses and also the extent of the disease. It can guide post-imaging rhinoscopy, biopsy procedures and also plan for future radiation therapy.

Nasal aspergillosis is the most common fungal infection in the nasal passages and is usually seen in young to middle aged dolichocephalic dogs. The fungal hyphae are confined to the surface of the mucosa and the body’s inflammatory response results in bony destruction and turbinate loss. Treatment consists of local debridement and topical antifungal infusion. The frontal sinuses may be affected and must be included with treatment. Oral antifungal therapy is much less effective but may be used if the cribiform plate has been penetrated.

Idiopathic lymphoplasmacytic rhinitis is common but an underlying etiology is seldom discovered. This inflammatory response is likely an aberrant immune response to multiple antigenic factors. Other causes of nasal discharge must be ruled out prior to diagnosing this condition. Treatment is frustrating. Allergen avoidance is not usually helpful unless blatant exposure is known (secondhand smoke). Corticosteroids do not seem to help. NSAID therapy combined with antibiotics may help (piroxicam and doxycycline for 4 – 8 weeks if possible). Oral itraconazole can also be tried as hypersensitivity to commensal fungal organisms may be contributing to the condition.

Nasal neoplasia occurs in middle aged to older dogs. The majority are malignant and arise from within the nasal cavity. These are aggressive and cause destruction of nasal turbinates and surrounding bone. Metastasis occurs late in the course of the disease. Radiation treatment is the treatment of choice.

**Anything new with upper respiratory disease in cats?**

Upper respiratory disease in cats is one of the most frustrating conditions for a veterinarian. The most common cause is viral disease (herpes or calicivirus) with secondary bacterial infection. However, one must not ignore other differential diagnoses. Once these are ruled out with serology, nasal CT, rhinoscopy and biopsy, the usual disappointing result is probable viral disease with secondary bacterial infection. If the cat was infected as a kitten with virus, the nasal turbinates may have been infected with resulting loss of normal anatomy and defense methods. This will lead to a chronic discharge from secondary bacterial infection. The virus may not be able to be isolated in these cases in the chronic state.

How to treat these chronic cases? These cats can have bacterial infection resulting in copious nasal discharge. Submitting for bacterial culture of either discharge or nasal swab is not useful as the infections are opportunistic and will change with time. Periodic flushing of the nasal cavities under general anesthesia may relieve the buildup of discharge and this material is a better representation to culture. Be sure to use an endotracheal tube and pack off the nasopharyngeal area to avoid aspiration.
Broad spectrum antibiotics are indicated and should be based on the bacterial culture. However, the numerous times of flushing with anesthesia to obtain a culture is not practical and trial broad spectrum antibiotics can be used for 6-8 weeks. Repeat antibiotic use usually leads to resistant bacteria and *Pseudomonas* usually appears. Antiviral drugs such as famciclovir will not work if the virus is not present. If the infection is recurring and is caused by herpesvirus, the drug may be a benefit. Oral lysine has been used but may not always be beneficial. This drug is also only indicated for herpesvirus infections.

Decongestants can improve mucosal edema through vasoconstriction but the use leads to a rebound effect. Antihistamines may dry out the nasal passage and this may lead to further inspissated material; however, some cats may respond. Other recently published research on intranasal vaccination to aid immunological response needs further work to advocate its use.

**What about fungal pneumonia?**

Fungal pneumonia is not rare in our region. Blastomycosis is the usual suspect. The cases are usually young male, larger breed dogs. However, we have seen cases in older, small breed dogs and even in indoor cats. The fungus lives in the soil and can be brought into the house on shoes or in house plants. The most sensitive and specific test is the urine antigen which is done by Miravista® laboratories. This measures the level of antigen and can be used for monitoring treatment. There is a new blastomycosis antibody test that when used in conjunction with antigen levels can aid in diagnosis.

Treatment is usually with itraconazole or fluconazole. Do not use compounded itraconazole. Our studies in both cats and dogs have shown that there is no absorption of compounded itraconazole and therefore the drug does not achieve therapeutic blood levels. In severe cases of blastomycosis or those with neurologic involvement, amphotericin can be used as a fungicidal treatment.

**Anything new on feline asthma/bronchitis?**

Research into feline asthma is continuing. The immune system’s response to antigenic stimulation causes the hyper-reactivity and the inflammation associated with the condition. Treatment including antigen avoidance, anti-inflammatory corticosteroids and bronchodilators is still the main stay of therapy. Decreased exposure to trigger antigens would be ideal but not easily done. Changing cat litter from clay to paper will eliminate dust. Second hand smoke can also be a trigger as can perfumes, cleaning solutions or air fresheners.

Corticosteroids are the main anti-inflammatory drugs used for this condition but do have side effects. Oral prednisolone or prednisone are the usual initial systemic drugs chosen. Long acting injectable methylprednisolone acetate is not ideal and should be limited to those cats that are intractable or cannot be pilled. The use of inhaled corticosteroid (fluticasone) is a more targeted treatment but requires a cooperative cat and owner. When starting inhalation therapy, there must be overlapped with oral corticosteroids for 7 – 10 days. Anti-inflammatory treatment is important because it has been shown that even while on corticosteroids, subclinical inflammation is still present in the lungs.
Bronchodilators assist with the bronchoconstriction that occurs with asthma and bronchitis. Oral therapy with theophylline can be used. Continuous use of albuterol inhalers has been shown to be detrimental in humans and cats as the drug can cause increased inflammation. Therefore inhaled albuterol should be reserved only as a rescue emergency therapy only. Another rescue therapy that owners can administer at home is subcutaneous terbutaline.

Other therapies that have been used in humans do not always translate to feline medicine. Antihistamines (cetirizine) and antileukotrienes (zafirlukast) have not been shown to help. Cyproheptadine may be an adjunct therapy but is not as promising as once thought. Cyclosporin can be considered for use in asthmatic cats that may have conditions that contraindicate glucocorticoid therapy. The dose has not been determined but most use the same dose as that recommended for allergic dermatitis. Inhaled nebulized lidocaine has been used in human medicine and has been looked at in experimental cats. This may be another therapy that could be used as an adjunct to other treatments.

Skin testing for antigens is challenging because of the antigenic range that is possible. There have not been any studies to investigate the correlation between dermal reactions and inhalant antigens in clinical cats. Omega-3 fatty acids and luteolin supplementation may have some beneficial effects on airway responsiveness as shown in cats with experimentally induced asthma. This may also suggest that a diet change could be also tried.

**How to treat a chronic cough in a dog?**

Chronic cough in a dog can indicate inflammation, infection or neoplasia. Radiographs are always indicated. The next step in diagnostics depends on the results of the radiographs. If chronic bronchitis is suspected, a TTW is indicated for cytology and culture. Parasites can be the cause and should not be overlooked as they can be treated.

Collapsing trachea can be missed on radiographs even with inspiratory and expiratory exposures. Dynamic testing with fluoroscopy or endoscopy are used for diagnosis and to document the extent of the collapse. Initial treatment for collapsing trachea is usually weight loss and use of a harness. Medical management with antitussives and antibiotics (in case of secondary infections) can also be used initially. Short term anti-inflammatory doses of glucocorticoids can help with stabilization. Cerenia has been suggested for use as an antitussive for collapsing trachea but no evidence based studies support this treatment. Severe respiratory distress from tracheal collapse can be alleviated with sedation. Acepromazine is useful for this scenario. The last resort treatment is tracheal stenting. This provides structure to the trachea but does not alleviate chronic cough nor future collapse distal to the stent.

Another cause of chronic cough in dogs is chronic bronchitis. This is usually seen in middle aged to older dogs. Diagnosis is by exclusion of airway infection, airway collapse or foreign body. Thoracic radiographs are important and may show increased bronchial to interstitial patterns. However, chronic bronchitis may not be as evident on the radiographs. Bronchoscopy can reveal tracheal or bronchial collapse, as well as airway hyperemia or abnormal mucosa. Airway samples are important for cytology and culture. Chronic bronchitis has cytological abnormalities of inflammation (neutrophils, eosinophils or mixed) and increased mucus.
Anti-inflammatory is the mainstay of therapy for chronic bronchitis. If bacterial culture has not been done, a doxycycline trial should be done prior to corticosteroid therapy. This is a long term therapy with corticosteroids, so a tapering regime should be used. Inhaled corticosteroids can also be used although systemic absorption does occur. Bronchodilators can help clinically with these patients although there is no effect of these drugs on the large airways. Cough suppressants should not be used if the cough is productive as this is the main method clearing secretions from the airway. The use of these drugs should only be used when inflammation has cleared or if there is tracheal/bronchial collapse. Weight loss can also help with this condition if the dog is overweight.

Older, small breed dogs can also have a chronic cough from heart disease. The left atrium can cause compression of the bronchi leading to irritation and cough. These cases must be managed for the heart condition and the cough can be controlled with an antitussive.

References available upon request