DIAGNOSIS &TREATMENT OF ACUTE GASTROINTESTINAL DISORDERS - DOGS & CATS

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Introduction

There are numerous causes that result in dogs and cats presenting to their veterinarian with acute change of appetite (dysrexia, hyporexia, anorexia), vomiting and/or diarrhea. A thorough review of the vaccination status, diet, concurrent drug treatment, and potential exposure to toxins or exposure to infectious disease should be investigated.
The onset, duration and the severity of clinical signs should be considered when deciding whether to pursue a definitive diagnosis or simply initiate symptomatic therapy with the anticipation that the signs will resolve rapidly. Many clients seek veterinary care immediately upon recognizing GI abnormalities and in many of these cases a causative agent is not readily identified and not important as clinical signs resolve quickly without treatment. Similarly in human medicine, a high percentage of patients that develop acute vomiting and diarrhea experience self-resolution of signs and do not see their doctor. While this scenario may be academically unsatisfying, a lack of definitive diagnosis in dogs and cats does not matter to the patient or client if the problem resolves and does not recur.

The most frequent causes of acute GI tract disturbance in our patients include dietary, toxic, infectious, foreign body ingestion and drug reactions Dietary indiscretions related to ingestion of poor quality foods, spoiled foods, high fat foods and difficult to digest foods; sudden dietary change and food intolerance are common in dogs. Ingestion of foreign material is a common cause of acute signs in our patients. True food immunologic hypersensitivity usually result in chronic repeatable signs. Side effects from concurrent medication is a frequent cause of acute GI signs and should be suspected based on history. Additional rule-outs should be considered in patients presenting with an “acute abdomen” (severe GI signs) or when defining (pathognomic) clinical signs are present such as dilation-volvulus, intussusception, parvovirus. Acute GI signs caused by more serious enteric disorders (enteric viruses, pathogenic bacteria, pancreatitis), systemic infections (leptospirosis, toxoplasma, FeLV) or metabolic issues (liver, renal, hyperthyroidism) usually are accompanied by more serious clinical presentation.

Patients that are bright, alert, do not appear dehydrated, etc… on presentation may be treated symptomatically or require minimal diagnostic investigation especially if a cause for their GI disturbance is supported by recent medical history. A complete fecal examination (floatation, wet prep, and stained smear) and survey radiographs should be considered if indicated by history and physical exam findings. Further diagnostic investigation is necessary if the patient is listless, depressed, weak, febrile, dehydrated, has abdominal discomfort, melena, bloody mucoid stools, has frequent intractable vomiting, has an obvious intestinal mass, intestinal plication or exhibits discomfort on palpation and when has failed to respond to initial symptomatic treatment.

Symptomatic Out-Patient Treatment of the Acute Gastrointestinal patient

The initial management of an acute gastrointestinal disturbance is often symptomatic and supportive and intensity of therapy is directed on the basis of clinical findings. It is important that the patient is regularly re-evaluated to monitor their response to symptomatic therapy and to detect the development of other clinical signs.

Oral fluid and electrolyte replacement therapy may be sufficient if acute diarrhea is associated with only mild or insignificant dehydration and vomiting is infrequent or absent. Parenteral solutions containing glucose and electrolytes—sometimes with added glycine, glutamine, or pep-

tides can be considered. Subcutaneous fluid administration can be considered in affected patients especially when transient ongoing fluid loss is anticipated.

The dogma of “intestinal rest” has been challenged by studies that demonstrate that feeding during secretory diarrhea promotes recovery. An emphasis should be placed on stopping vomiting if present and then initiating frequent small volume easily digestible meals. Diet considerations should include feeding a bland high CHO, low fat, adequate protein content diet provided as small volume frequent meals every 4-8 hours for several days. Once the GI disturbance is resolved then the original diet is gradually reintroduced. Common choices are commercial veterinary prescription diets or home-cooked foods consisting of boiled or braised low fat content chicken, turkey or beef, white fish and low-fat cottage cheese, boiled rice, potato or pasta. Cats have a lower tolerance to dietary CHOs and benefit from a diet with protein and moderate fat content. The overall nutritional adequacy of home-prepared bland diets is not considered when fed in the short term.

Bismuth subsalicylate, kaolin-pectin, magnesium or aluminium binding antacids, barium suspension or activated charcoal products are often administered in acute diarrhea to bind toxins (bacterial -related or ingested) protecting the intestinal mucosa. They also bind water and may be anti-secretory. Therapy should not exceed 48 hours if there is no improvement with these products.

Antiemetic are beneficial to reduce/resolve vomiting when present. This allows for less GI flui loss, reduces patient discomfort and allows for re-established food intake (and makes owners happier!). Antiemetics can completely stop vomiting even in cases of GI foreign material ingestion and intestinal obstruction so further diagnostic testing is indicated if the patient does not exhibit a rapid and full recovery or has a strong history suggesting ingestion of foreign material Maropitant (Cerenia^{R}) is an excellent first-line broad spectrum antiemetic selection.

Anticholinergics and opiate drugs (loperamide, diphenoxylate) reduce intestinal motility and modify secretions and can be considered for short term symptomatic management of acute diarrhea; in more seriously ill patients, anticholinergic agents can potentiate ileus and are not recommended. These drugs reduce motility or stimulate segmental motility, thereby slowing transit, and also decrease intestinal secretion and promote absorption. They are contraindicated in cases involving known obstruction or an infectious etiology. Loperamide may have central nervous system side effects in dogs with the multidrug resistance 1 (MDR-1) gene mutation.

The routine use of short-term antibiotic treatment in acute GI disturbances, especially metronidazole, is questionable. A specific GI bacterial infection etiology is uncommon in apparent healthy acute GI disturbance cases. Routine use of antibiotic treatment in patients with unconfirmed infection may promote bacterial resistance or cause drug-associated side effects which may complicated recovery. Fecal cytology, culture or PCR evaluation may be useful to establish the presence of suspected GI pathogens, however, many of these organisms are also residents in the healthy GI tract. Antimicrobials indicated in patients with GI tract disease in which a confirmed bacterial or protozoal infection is documented or highly suspected and in patients in which a breach of intestinal barrier integrity is suspected. Leukopenia, neutrophilia, pyrexia, the presence of blood in the feces, and shock all are potential indications for prophylactic antibiotics in animals with GI tract disease. Initial choices in these situations include potentiated penicillins or a cephalosporin effective against gram-positive and some gram-negative and anaerobic bacteria. If systemic translocation of enteric bacteria is suspected, antimicrobials effective against anaerobic organisms, such as metronidazole or clindamycin, and an aminoglycoside effective

against “difficult” gram-negative aerobes, are indicated. To reduce renal sided effects aminoglycosides should not be given until the animal is fully hydrated.

Probiotics are orally administered living organisms that exert health benefits beyond those of basic nutrition. These “good” organisms have direct antagonistic properties against pathogenic bacteria and modulate mucosal immune response (reduce expression cytokines that alter intestinal permeability.) The evidence shows that the positive effect of probiotics is species specific and present only while the probiotic is administered. The traditional practice of feeding live yogurt as a way of repopulating the intestine with beneficial lactobacilli after an acute GI upset or antibiotics is unlikely to work in dogs and cats. Probiotics are available for use in each domestic species. Prebiotics are selective substrates used by a limited number of “beneficial” species, which therefore cause alterations in the luminal microflora. The most frequently used prebiotics are non-digestible carbohydrates—such as lactulose, inulin, fructooligosaccharides and immunomodulators such as lactoferrin. Combined use with probiotics to encourage the growth of organisms is termed symbiosis.

Select Disorders causing Acute Gastrointestinal signs.

Enteric viral, bacterial and parasitic infections often result in acute GI signs.

Feline Astrovirus is often subclinical but can cause diarrhea particularly in kittens that may last as long as two weeks. Feline rotaviruses can cause subclinical infections and occasionally mild enteritis in kittens. Feline coronavirus is divided into two groups: The pathogenic strains that cause feline infectious peritonitis (FIP) and those feline enteric corona viruses (FECV) that cause a subclinical or mild enteric signs. Feline panleukopenia virus (parvovirus) is a highly contagious viral disease of cats that is frequently fatal. The disease is seen most frequently in cats 3 - 5 months of age and is associated with high mortality. The virus is present in nasal secretions, feces and urine and is transmitted by contact with infected animals. Clinical signs include fever, anorexia, depression, weakness, sternal recumbency, nasal discharge, conjunctivitis, vomiting, and diarrhea.

Canine rotavirus occurs widely in the intestine of dogs but infections are generally subclinical. Canine coronavirus infection is a relatively mild enteric disease of mainly young dogs although all ages may be infected. The virus is relatively labile and can only survive outside the animal for 1 - 2 days. Clinical signs are anorexia, depression vomiting, and diarrhea.
Canine parvovirus (CPV-2) is a common viral enteritis of dogs. To date, the exact evolution and origin of CPV-2 remains elusive. Initially the emergence of CPV-2 in the naïve canine population resulted in high morbidity and mortality. In the 1980s a new strain of CPV-2 emerged, which was designated CPV-2a. That strain then mutated into CPV-2b, and more recently into CPV-2c. This strain is highly virulent and associated with high morbidity and rapid death. Young dogs particularly Doberman Pinschers and Rottweilers appear particularly susceptible. Clinical signs include vomiting, hemorrhagic diarrhea, fever, dehydration, and marked leukopenia. CPV infection has remained a relatively treatable and preventable disease with severe morbidity occurring in animal shelters and in unvaccinated dogs.

Campylobacter jejuni is a contagious disease characterized by enteritis and diarrhea of variable duration and severity. Dogs and cats can carry and shed C. jejuni, without showing clinical signs. C. jejuni is a small, fragile, gram-negative rod. Dogs less than six months of age are more severely affected and there is some question as to whether this organism causes enteritis and diarrhea in normal cats other than kittens although debilitated older cats may be more suscepti-

ble. Although C. coli and C. upsaliensis can occasionally be recovered from the feces of cats, their significance is not clear.

Salmonellosis is a contagious disease of animals and humans caused by many varieties of the enteric gram-negative bacterium Salmonella. Over 2000 serotypes of Salmonella have been implicated as causes of salmonellosis. The most common serotype recovered from dogs and cats is S. typhimurium. Concurrent enteric infection and immunosuppression may predispose to clinical salmonellosis. Salmonellosis is manifested by one of the following three syndromes: septicaemia, acute enteritis and chronic enteritis. Young animals most frequently develop the septicaemic form, whereas acute and chronic enteritis is seen most commonly in adult animals. Cats are highly resistant to salmonellosis but there are reports of outbreaks in kittens and infrequent clinical disease in adult cats. A considerable number of dogs and cats are carriers. Clinical signs vary with the severity of the infection and include acute to chronic gastroenteritis, episodes of fever, vomiting, depression, occasionally pneumonia and sometimes abscesses in lymph nodes and liver.

Giardiasis is a protozoal intestinal infection, caused by Giardia duodenalis. This flagellated protozoan inhabits the lumen of the small intestine where it produces microscopic lesions on villi. Transmission takes place when cysts are passed in feces and ingested. Contaminated food and water are frequently the source of infection. Cysts are resistant and can survive for long periods outside the host. Infections in adult dogs and cats can cause clinical disease including seen. Acute and chronic diarrhea occurs mainly in kittens and puppies. Clinical signs include diarrhea, flatulence and loss of or failure to gain weight.

Several species of Isospora coccidia have been associated with diarrhea in dogs and cats, particularly in puppies and kittens; however, most infections are subclinical. Infection is by ingestion of sporulated oocysts found in feces contaminated feed, water, and soil. Dogs and cats usually become infected before one year of age and may remain sub-clinically infected for long periods. Overcrowding, poor sanitation, nutrition, impaired immunity, and other stresses predispose to clinical coccidiosis. Clinical signs are intermittent diarrhea for several days and hematochezia. Clinical disease is uncommon in adults and an alternate diagnosis should be considered in an adult with clinical GI signs and coccidia identified on fecal exam.

Cryptosporidiosis is a widespread, worldwide infection of humans and domestic animals, caused by the coccidian parasite, Cryptosporidium parvum. Infection is by the oral-fecal route. Most infections are subclinical with clinical disease rare in dogs and cats. Kittens and puppies are most susceptible. When it occurs there may be other predisposing underlying infection, e.g., giardia, FeLV or FIV infections. The organism invades the microvillus border and there is mild to severe villous atrophy. Both the intestine and colon are affected. Clinical signs are mild to severe diarrhea.

Tritrichomonas foetus is a microscopic single-celled flagellated protozoan parasite. In cats the organism is an important cause of chronic diarrhea. It can infect and colonize the large intestine, resulting in prolonged and intractable large bowel diarrhea. Although the diarrhea may be persistent and severe, most affected cats are otherwise well, and show no significant weight loss. Although cats of all ages can be affected, it is most commonly seen in young cats and kittens, the majority being under 12 months of age. Infection is most commonly seen in colonies of cats and multi-cat households, where the organism is presumably spread between cats by close and direct contact. There has been no evidence of spread from other species, or spread via food or water.

Toxoplasma is a widespread protozoal disease of many warm-blooded animals and humans throughout the world. Toxoplasma gondii, a coccidia-like protozoan, completes its life cycle in epithelial cells of the intestine of the cat. Cats are the definitive host and serve as the main reservoir. Clinical disease may develop as a result of stress, impaired immunity and concurrent disease. In cats intestinal infections are usually subclinical with mild diarrhea infrequently seen. Cysts in tissues can cause diarrhea, vomiting, fever, anorexia, dyspnea, icterus, ocular disease, and neurological dysfunction. In dogs infections are acquired from eating uncooked meat and ingesting food and water that has been contaminated with infected feces. Some of the conditions attributed to toxoplasmosis are: neurological infections with abnormal reflexes, ataxia, paralysis, but rarely with ocular involvement; infections of the myocardium and skeletal muscle; pneumonia and hepatitis.

Comments on Treatment of Parvoviral Enteritis

Specific drug therapies do not kill parvovirus. The treatment of CPV is mainly supportive while the virus runs its natural course – managing dehydration, controlling secondary infections, reducing the intestinal signs, and ensuring adequate nutrition are mandatory to successful outcome. Antiviral treatment (oseltamivir) started after the onset of clinical signs does not result in a better outcome.

Fluid therapy with crystalloid fluid selection to replace dehydration deficit, provide maintenance daily fluid requirement and replace ongoing GI losses. Intravenous amino acid solutions such as ProcalAmine 3% can be beneficial in providing amino acids as a protein source, essential minerals, and glycerin for energy. Albumin infusion can be considered if significant hypoalbuminemia develops. Serum potassium and glucose should be monitored closely and supplemented as needed. Plasma or blood transfusions are rarely necessary but should be provided if necessary.

Broad spectrum injectable antibiotic therapy for 3-5 days during neutropenia period. There are many favorite combinations but a potentiated penicillin (ampicillin/sulbactam 35-50 mg/kg TID) + aminoglycoside or fluoroquinolone remain my combination choice until the hemorrhagic diarrhea resolves, the patient is eating and neutropenia is resolved. Monitor for urinary granular casts every 24-48 hours if using aminoglycoside therapy.

Fenbendazole therapy (50 mg/kg PO QD) is provided for 5 consecutive days to eliminate concurrent intestinal parasitism.

Maropitant (1 mg/kg IV q 24hr) plus metoclopramide CRI (1-2 mg/kg/24hr rate) will provide an excellent combination antiemetic and prokinetic function can be added if additional antiemetic support is required. Antacid therapy may be beneficial during active regurgitating and vomiting.

Initiate feeding once the patient is rehydrated and antiemetic therapy is provided (4-12 hours after admission in most case). Initiate approximate 1/3 of nutritional caloric requirements in first 24 hours and increase each subsequent day to meet full caloric needs.

SYMPTOMATIC TREATMENT CONSIDERATION FOR CHRONIC GASTROINTESTINAL DISORDERS IN DOGS & CATS

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Introduction

Many chronic gastrointestinal problems develop as a result of persistent inflammation within the mural layers of the gastrointestinal tract. Symptomatic treatment trials that target specific causes of GI inflammation should considered prior to intestinal tissue biopsy. These same symptomatic treatments should be considered in all patients with biopsy confirmed GI inflammation in which a primary etiology is not documented.

Deworming strategies – which drugs to consider?

Always review if and which drug an individual patient is receiving for heartworm prevention as macrocyclic lactones drugs are effective in controlling and eliminating common intestinal parasites such as roundworms, hookworms and whipworms.

Fenbendazole, a benzimidazole dewormer, is preferred in dogs and cats as it covers a wide spectrum of possible parasitic pathogens including roundworm, hookworm, whipworm (dogs) and giardia infections. A dosage of 50mg/kg PO QD for 5 consecutive days should result in rapid and significant improvement if occult GI parasitism is the cause of ongoing clinical signs. Repeat deworming monthly for 3 months is recommended to provide complete elimination of all parasite life cycles. Febantel products (label dose for 3-5 days) can also be used as this product is metabolized to fenbendazole by the liver and has been shown to be effective in parasite elimination.

Ronidazole is the preferred antimicrobial for treatment of Tritrichomonas fetus infection in cats. Ronidazole is given at 30 mg/kg PO QD for up to 14 days. It has a very narrow therapeutic range; higher doses or a longer duration can result in neurotoxicity. Ronidazole must be obtained through a compounding pharmacy. It is very bitter and therefore should be given via capsule; liquid solutions are not recommended. Treatment failure can occur, and a fecal PCR should be performed if a cat fails to respond to therapy; a post-treatment negative PCR result means that TTF is a less likely cause of the diarrhea. Cats that are untreated may eventually become normal, especially young cats under one year of age, usually with spontaneous resolution of diarrhea within two years of diagnosis; however, most remained TTF infected based on PCR results if retested for as long as two to five years after the initial diagnosis.

Diet strategies - What diet trials should I consider in chronic GI patients that are eating?

Resolution of chronic GI signs by simply changing the diet is common with clinical studies suggesting up to 50% response rate. Dogs with food-responsive diarrhea (FRD) tend to be younger with

predominantly large-bowel signs; however, some dogs have more small-bowel characteristics and can lose condition and develop hypoproteinemia in severe cases.

A diet trial is justified in patients that are eating and are not severely debilitated A positive response to a diet trial is referred to as food-responsive gastroenteropathy. Inflammation can be associated with dietary fat, true dietary allergies (immunologic) or a dietary intolerance (non-immunologic). Allergies generally result from a reaction to a specific protein antigen, while intolerance occurs in response to some substance in the diet such as a preservative or food coloring as examples.

Dietary trials using a test diet generally require 2 weeks or even less to appreciate a response; the GI tract seems to respond much faster than dermatologic conditions that may take as long as 8 weeks or more to improve. There is no single ideal diet that will consistently resolve chronic GI inflammation. The main options for diets include diets that optimize assimilation of nutrients (e.g., highly digestible, fat restricted or low fiber) or diets that favors antigenic modification (e.g., a novel protein source or a protein hydrolysate).

Highly digestible GI prescription diets may improve assimilation, promote GI health and modify the microbiota. Diets containing highly fermentable fibers such as those containing fructooligosaccharides (prebiotics) are often useful for colonic disease because fermentation products are shown to have beneficial effects on mucosal function and modify enteric microbiota promoting "good" bacteria and inhibiting certain pathogenic bacteria.

Hydrolyzed diets have gained favor with many gastroenterologists. The hydrolyzed diets are single-protein sources (usually soy, rice or potato based) and have undergone digestion producing low-molecular-weight protein derivatives that are highly digestible with low antigenic potential. In addition, they are very pure and contain little else that might contribute to a dietary intolerance.

Novel protein (“limited-ingredient”) diets containing a single protein antigen can also be used as a trial. True single antigen diets are becoming much harder to validate because of the widespread use of lamb, fish, venison in many dog and cat foods. When using novel protein diets, be aware that most over-the-counter novel protein diets and many veterinary prescription diets are not all that novel as they have been shown to contain other antigens not listed on the label. Prescription rabbit diet may be the most reliable hypoallergenic protein currently available (Royal Canin).

A challenge with the original diet would be necessary to confirm efficacy. Only a small percentage of dogs with GI signs appear to relapse on challenge so the incidence of true food allergy is likely low.

Cats may respond best to higher protein-lower carbohydrate formulations as dietary fat does not appear to be play an important role in feline intestinal disease.

Probiotics / Prebiotics. Are probiotics useful in managing chronic GI patients ?

The microbes used in probiotics are non-pathogenic organisms, such Bifidobacterium or Lactobacillus, or non-bacterial organisms such as Saccromyces spp. Criteria for probiotic organisms include resistance to low gastric pH, adherence to intestinal mucosa, ability to proliferate and colonize the colon, activity against pathogenic microorganisms, and modulation of the immune system. They must also have no pathogenic, toxic, mutagenic or carcinogenic effects. The proposed benefits of probiotics include

increased competition against pathogenic species of bacteria, reduction of bacterial translocation, and production of antimicrobial products. To date, there have been very few controlled clinical studies evaluating probiotic success in veterinary medicine.

Probiotic trials should be considered in any patient suspected of having intestinal microbial dysbiosis. Antibiotic therapy can be used with probiotics and more rapid and complete clinical improvement is sometimes seen when they are given in combination. No consensus has been reached on use in the management of idiopathic IBD patients.

Probiotics are not regulated in the USA. This can pose a problem when clients obtain and use human probiotic products as they may be ineffective based on the bacterial sp. or CFU/unit. Nutramax, Purina, Visbiome™ and other veterinary companies have introduced veterinary probiotic formulations and appear to be of benefit in some select chronic GI patients. Probiotics exert their effects as long as they are being given, but once stopped, the GI flora generally returns to the pretreatment state.

Antibiotic Treatment

Chronic small or large bowel disease is often responsive to antibiotic therapy (ARD). Intestinal dysbiosis describes conditions associated with an abnormal GI bacterial ecosystem (microbiome). GI dysbiosis is an imbalance in intestinal bacteria with less "good bacteria" and more "bad bacteria." Chronic GI patients that respond to antibiotic therapy likely have altered the overall intestinal bacterial ecosystem, promoting a more normal bacterial makeup, and have not eliminated a specific pathogen. Some cats and dogs with GI dysbiosis have decreased serum cobalamin (vitamin B12) concentrations. Elevated serum folate concentrations may be associated with dysbiosis. Cobalamin deficiency is also common either due to abnormally increased intestinal bacterial utilization or ileal disease causing inadequate cobalamin absorption.

Which antibiotics may be effective in treating suspected dysbiosis ?

Metronidazole has antibacterial, especially anaerobic, anti-protozoal, anti-inflammatory and anti-fibrotic activities. It can be effective as a sole agent in some chronic GI patients. An oral starting dose of 10-20 mg/kg q 12hr is suggested. Historically, it has been used long term in patients that relapse following initial treatment and can be tapered to the lowest effective dose and frequency. It also has been used in combination with other drugs in idiopathic IBD patients and may allow CCS dose reduction. Side effects include nausea and vomiting. Significant neurologic side effects can be seen in some patients. It has a bitter taste and can cause salivation especially in cats. Long term treatment has more recently been discouraged due to concerns with antibiotic resistance and possible enterocyte DNA disruption (cancer promotion).

Tylosin is a macrolide antibiotic with activity against gram-positive bacteria and Chlamydia and Mycoplasma spp. Tylosin is effective for most Clostridium perfringens and is considered by many to be the treatment of choice for suspected clostridial diarrhea.

It may be used successfully in dogs and cats with chronic dysbiosis. Tylosin may also have anti-inflammatory properties but the mechanism of action is unknown. It has a very bitter taste and is most easily administered mixed in can food or in gelatin capsules (cats and finicky dogs). A starting dose of 15-20 mg/kg PO BID is recommended and can be tapered to the lowest effective dose. 1/8 tsp of the poultry product equals 325mg tylosin base. A #3 gelatin capsule holds 130 mg, a #1 capsule holds 240

mg, a #0 capsule holds 345 mg, and a #00 capsules hold 430 mg. For cases that respond, the long-term dose can be reduced to as low as 5 mg/kg/day. Tylosin is less likely to promote antibiotic resistance or have serious systemic side effects. Following discontinuation, the original bacterial population often returns to its pretreatment state.

What other specific conditions may benefit from antibiotics ?

Fluoroquinolone
Enrofloxacin or other fluoroquinalone antibiotics may be useful in chronic bacterial-related gastrointestinal disease. These drugs have been used successfully in hemorrhagic ulcerative colitis cases in which Enterobacter sp (E.coli) have been shown to invade mucosal enterocytes (FISH) and cause chronic-active inflammatory response and disruption of enterocyte function. Antibiotic resistance has become an issue. Tissue culture and antibiotic sensitivity should be considered in chronic ulcerative colitis patients that do not respond appropriately.

Mesalamine Preparations Mesalamine or 5-aminosalicylic acid (5-ASA) may be beneficial when used specifically for colitis in dogs and cats. These preparations are delivered relatively intact to the distal small intestine and colon where intestinal bacteria break the azo bond and release the active molecules. 5-ASA is poorly absorbed and has produces a local anti-inflammatory effect. Doses must be adjusted for cats due to their salicylate sensitivity, but can be used safely at lower doses and for shorter durations as compared to the dog.

Sulfasalazine is composed of a molecule of 5-ASA linked to sulfapyridine via an azo bond. Side effects such as keratoconjunctivitis sicca (KCS), typical of sulfa drugs may be seen with prolonged use of sulfasalazine. The dose for sulfasalazine in dogs is 10-15 mg/kg q 8-12 hours for 2 weeks. The starting dose for cats is 10mg/kg q 24 hours tapered to the lowest effective dose. Other preparations of 5-ASA that do not contain sulfapyridine are available. Olsalazine has been used at a dose of 5-10 mg/kg q 12 hours. A dose for cats has not been established, but 5 mg/kg q 24 hours is suggested.

Fecal Transplantation

There has been a recent interest in veterinary medicine in fecal transplantation as a treatment for chronic unresponsive diarrhea. There are several small case series showing improvement in some patients with chronic diarrhea. The premise is that the transplant replaces good intestinal bacteria and restores normal fecal bile acid metabolism. The procedure is relatively easy and involves collecting feces from a young normal donor, mixing with saline, straining, and placed in the patient's colon via enema or upper intestine via NG intubation. Further studies and clinical experiences are necessary to better understand whether this low-cost, low-risk treatment will provide lasting benefit to dogs and cats with chronic diarrhea issues.

What to do with chronic GI patient when an owner won't allow biopsy collection ?

Gastrointestinal biopsy evaluation is indicated whenever the underlying cause for chronic GI disease has not been determined and a patient fails to respond to appropriate symptomatic treatment trials. However, for a variety of reasons, some owners will not consent to this next indicated step in the evaluation of their pet. What are your options ?

In dogs, the next logical step is to determine if the GI disorder is STEROID responsive. Further discussion of corticosteroid treatment for inflammatory GI disease will be presented in the "Use of corticosteroid and other immunomodulant treatment in GI inflammatory bowel disease."

In cats, the primary rule-outs still include idiopathic inflammatory bowel disease and chronic small-cell lymphoma. Corticosteroid and chlorambucil are the principle treatment options and may be effective in both disorders. Further discussion of corticosteroid and chlorambucil treatment for feline IBD and lymphoma treatment will be presented in the "Use of corticosteroid and other immunomodulant treatment in GI inflammatory bowel disease."

DIAGNOSTIC TESTING APPROACH FOR CHRONIC GASTROINTESTINAL DISORDERS IN DOGS & CATS

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Introduction

Veterinary patients commonly present with chronic intermittent or persistent gastrointestinal clinical signs that may include some combination of variable appetite change, weight and condition loss, vomiting and diarrhea. In many cases these clinical signs result from primary disorders involving the gastrointestinal tract and may also involve the liver and/or pancreas. The specific combination of clinical signs may be helpful in establishing the region of the GI tract involved in the disease process (i.e., regurgitation, vomiting character, feces character) and help direct the diagnostic exam.

A complete diagnostic evaluation to establish a definitive diagnosis or narrow the likely differentials is critical to successfully manage these patients. This can be an exhausting endeavor for patients (and for owners & doctors). Baseline diagnostic testing should be performed in all patients. Rational symptomatic treatment trials may be useful in many patients prior to more in-depth or invasive definitive testing. Some patients will require tissue biopsy of affected organs to establish a definitive diagnosis and determine the initial prognosis. The response to treatment is also important to confirm the diagnosis and better refine the associated prognosis.

Relevant Diagnostic Tests that can be perform in your practice

Routine Blood testing - CBC provides important information about the general health of the patient (i.e, anemia ?, white blood cell count and distribution) but in general does not provide specific information about the digestive system. CHEM panel provides important information about possible concurrent liver and/or pancreas involvement and possibly some clues about intestinal status (i.e., albumin, globulin). Thyroid baseline (T4) and routine infectious assays (FeLV, FIV) may prove to be important in feline patients with digestive disorders.

What should I know about liver enzymes (LEs) in GI disease? The liver is considered a "sympathy organ" as there is often a secondary hepatocellular response to other abdominal or systemic disease (i.e., elevations in ALT can occur with hypoxia, GI and pancreas disease, sepsis, chronic skin and dental inflammation, metabolic disorders, etc…). Increased serum ALT and ALP values are frequently present in patients with primary GI disease as the portal circulation serves both the GI tract and the liver. The finding of elevated liver enzymes in cats is usually indicative of concurrent hepatic disease. An elevated serum bilirubin value almost always confirms that significant primary or secondary hepatobiliary disease is present.

What about serum amylase and lipase values ? Many dogs and cats with gastrointestinal disease will have concurrent pancreatic involvement which may result in elevated serum amylase and/or lipase values.

In summary, the gastrointestinal tract organs, liver and pancreas should all be investigated in patients with gastrointestinal signs.

Routine Fecal tests - Chronic infectious gastroenteritis may result in vomiting and diarrhea, weight loss and appetite change. The following tests are useful to detect infectious agent in feces of patients with ongoing GI signs.

Fecal flotation. Cysts, oocysts, and eggs in feces can be concentrated to increase sensitivity of detection. Most eggs, oocysts, and cysts are easily identified after zinc sulfate centrifugal flotation. This procedure is considered by many to be optimal for the demonstration of protozoan cysts, in particular, Giardia spp. and so is a good choice for a routine flotation technique in practice. Sugar centrifugation can be used for routine parasite evaluation and may be superior to many techniques for the demonstration of oocysts of Toxoplasma gondii and Cryptosporidium spp.. Giardia cysts are distorted by sugar centrifugation but can still be easily identified. Fecal sedimentation will recover most cysts and ova, but will also contain debris. This technique may be superior to flotation procedures for the documentation of Eurytrema procyonis, the pancreatic fluke. Strongyloides larva may be easier to identify after concentration using the Baerman funnel technique.

Direct fecal smear. Liquid feces or feces that contains large quantities of mucus should be microscopically examined immediately for the presence of protozoal trophozoites, including those of Giardia spp. and Tritrichomonas foetus. The sample should be fresh. The material for evaluation should be collected from the surface of the fecal material, preferably mucous if present. Alternately, a rectal scraping could be used. A direct saline smear is made to potentiate observation of these motile organisms. The amount of feces required to cover the head of a match is mixed thoroughly with one drop of 0.9% NaCl. Following application of a coverslip, the smear is evaluated for motile organisms by examining it under 100X magnification. Giardia ("falling leaf") and Tritrichomonads ("shoot & dart") have specific motions that are useful in establishing their presence.

Stained fecal smear. A thin smear of feces should be made from all animals with large or small bowel diarrhea. Material should be collected by rectal swab if possible to increase chances of finding white blood cells. A cotton swab is gently introduced 3-4 cm through the anus into the terminal rectum, directed to the wall of the rectum, and gently rotated several times. Placing a drop of 0.9% NaCl on the cotton swab will facilitate passage through the anus, but not adversely affect cell morphology. The cotton swab is rolled on a microscope slide gently multiple times. Following air drying, the slide can be stained.
Bacteria morphologically consistent with Campylobacter app or Clostridium perfringens may be observed after staining with Diff-Quick or Wright's-Giemsa stains, however, there presence does not implicate these organisms as the absolute cause of clinical disease. Presence of neutrophils on rectal cytology can suggest inflammation induced by Salmonella spp., Campylobacter spp., or Clostridium perfringens; fecal culture is indicated in these cases. Histoplasma capsulatum or Prototheca may be observed in the cytoplasm of mononuclear cells. Methylene blue in acetate buffer (pH 3.6) stains trophozoites of the enteric protozoans. Iodine stains and acid methyl green are also used for the demonstration of protozoans. Acid-fast or monoclonal antibody staining of a fecal smear should be performed in cats with diarrhea to aid in the diagnosis of cryptosporidiosis. Cryptosporidium parvum is the only enteric organism of approximately 4 to 6 µ in diameter that will stain pink to red with acid-fast stain.

Specialized Fecal Tests.

Culture. Culture of feces for Salmonella spp., Campylobacter spp., and Clostridium perfringens is occasionally indicated in small animal practice. Approximately 2-3 grams of fresh feces should be submitted to the laboratory immediately for optimal results, however, Salmonella and

Campylobacter are often viable in refrigerated fecal specimens for 3-7 days. Appropriate transport media should be available through your laboratory. The laboratory should be notified of the suspected pathogen so appropriate culture media can be used. More than 1 culture may be needed to prove infection. Tritrichomonas foetus can be cultured from feces of cats in general practice using a commercially available kit (InpouchTM, Biomed Diagnostics) but diagnosis of this organisms has been widely replaced by PCR method. Some Giardia spp. isolated from cats will grow on culture media, but this technique is not generally performed in small animal practice.

Immunologic techniques. Parvovirus, Cryptosporidium parvum, and Giardia spp. antigen detection procedures are available for use with feces. Canine parvovirus antigen assays will detect feline parvovirus antigen (panleukopenia). An IFA for concurrent detection of C. parvum oocysts and Giardia cysts has been validated for use with dog and cat feces; this assay is commonly available at commercial laboratories. While Giardia spp. antigen assays appear to detect dog and cat genotypes, human Cryptosporidium antigen assays do not. The Giardia assays can be used to increase sensitivity in dogs or cats with diarrhea but should be interpreted in conjunction with results from fecal examination techniques.

Polymerase chain reaction

PCR assays are available to amplify and detect DNA of Giardia, Cryptosporidium, Tritrichomonas foetus, Salmonella spp., Campylobacter spp., Clostridium spp., parvoviruses, coronovirus and Toxoplasma gondii.

The diagnosis of Giardia spp. infection is generally made with the combination of fecal flotation techniques, wet mount examination with or without fecal antigen tests or IFA. Fecal PCR assays for Giardia are often falsely negative because of PCR inhibitors in stool and so PCR should not be used as a screening procedure for this agent. However, Giardia spp. PCR can be used to determine whether the infective species is a zoonotic assemblage. Genotyping is available at Colorado State University (http://dlab.colostate.edu/).

It is unusual to find C. felis or C. canis oocysts after fecal flotation. Acid-fast staining of a thin fecal smear is cumbersome and insensitive. Antigen assays titrated for use with human feces are inaccurate when used with cat or dog feces. Fecal IFA is the screening procedure for this organism. PCR may aid in the diagnosis of cryptosporidiosis in dogs and cats. Cryptosporidium spp. PCR assays are indicated in IFA negative cats or dogs with unexplained diarrhea or when the genotype of Cryptosporidium is to be determined (http://dlab.colostate.edu/). C. felis and C. canis organisms are common in the intestinal tract so positive tests results do not always prove that the agent is the cause of the clinical disease. Small animal strains are not considered significant zoonotic agents so PCR is never indicated in healthy animals.

Cats with Tritrichomonas foetus large bowel diarrhea can be readily identified with fecal PCR testing. DNA of T. foetus can be detected in healthy carrier cats and so positive results do not always prove illness from the organism.

Cases with suspected salmonellosis or campylobacteriosis should be cultured rather than assessed by PCR to determine the anti-microbial susceptibility patterns.

In dogs, the PPV of Clostridium spp. PCR assays on feces is low and if used, should be combined with enterotoxin assays. Information in cats is currently lacking.

There is no current evidence that parvovirus PCR on feces is superior to currently available antigen assays. In one recent study, approximately 40% of healthy cats vaccinated with a modified live FVRCP vaccine were PCR positive for panleukopenia virus DNA in feces one week after vaccination. Thus, the currently used assays cannot differentiate vaccine strains from natural infections which should be considered when making case management decisions.

Toxoplasma gondii is only shed for about 7-10 days and millions of oocysts are generally shed during this time making the organism very easy to identify. Thus, PCR assays are usually not needed to diagnosis this infection.

Because virus isolation is not practical clinically, RT-PCR is used most frequently to detect coronaviruses RNA in feces. However, positive test results do not differentiate FIP inducing strains from enteric coronaviruses and there is no association between diarrhea and positive test results for coronavirus in cat feces.

Specialized Blood Tests

Gastrointestinal Blood Panel. Gastrointestinal/Pancreatic-specific blood panels are comprised of serum cobalamin (vitamin B12), folate, TLI and PLI determination. These tests may be very helpful in evaluating patients with vomiting, weight loss, diarrhea, or in poor body condition. Submit fasted serum for this evaluation in chronic GI patients prior to recommending advanced GI diagnostics such as ultrasound, endoscopic (or surgical) biopsy or significant treatment trials (prednisone, immunosuppressants). The results may provide alternative treatment suggestions that will improve or resolve the GI issues in individual patients. Perform the entire panel as the serum cobalamin and folate levels are best assessed in conjunction with the pancreatic-specific assays as they may be abnormal in animals with EPI or chronic pancreatitis. The major commercial laboratories & GI Laboratory at Texas A&M are recommended providers of these tests.

Cobalamin is absorbed in the distal small intestine (specifically in the ileum). Values below the control range are seen in patients with EPI, bacterial overgrowth in the upper small intestine and especially mural diseases affecting the distal small intestine (ileum). Significant tissue-level cobalamin deficiency may develop in companion animal patients with gastrointestinal disease. Fasted serum cobalamin levels are reduced and reflect tissue cobalamin levels. Cobalamin is involved in many cellular and enzymatic processes including intestinal absorption of nutrients across the mucosal enterocytes. Reduced cobalamin levels impair intestinal absorption of essential calories and nutrients including cobalamin thus perpetuating tissue deficiency of this critical vitamin. Patients with chronic GI disease often become secondarily cobalamin deficient over time. This is significant as without acceptable cobalamin substrate many GI patients will experience sub-optimal treatment response regardless of their underlying GI disease. Primary cobalamin deficiency also develops in certain breeds such as Chines Shar Pei and Siamese cats.

As cobalamin deficiency in most of our patients is secondary to intestinal mucosal or mural disease which reduces cobalamin absorptive capacity, the use of dietary cobalamin supplementation is at best highly inefficient, and most likely ineffective in restoring bodily cobalamin stores. The route of choice for cobalamin supplementation is parenteral injection. Generic formulations of cobalamin are readily available and extremely cost effective. Most generic cobalamin preparations are 1mg/ml, i.e. 1000µg/ml. Multi-vitamin and B-complex injectable formulations contain much lower cobalamin concentration, and can cause pain at the injection site, so their use is not recommended. Cobalamin is non-irritating and may be given subcutaneously or intramuscularly.

A typical dose regime is weekly administration for six weeks then one additional dose after 30 day. Repeat testing is suggested 30 days after the last dose. If the underlying GI disease process has resolved and cobalamin body stores have been replenished, serum cobalamin concentration should be supranormal . However, if the serum cobalamin concentration is within the normal range, treatment should be continued at least monthly and the owner should be forewarned that clinical signs may recur sometime in the future. If the underlying intestinal disease cannot be completely resolved, it is likely that the patient will continue to require regular cobalamin supplementation.

Current dose recommendations -

250 mcg SQ per cat; 250 to 1500 mcg SQ depending on the size of the dog.

Dogs weight	Below 10 lbs	10 lbs-20 lbs	20 lbs-40 lbs	40 lbs-60 lbs	60 lbs-80 lbs	80 lbs-100 lbs	Above 100 lbs
Dose of Cobalamin	250 µg	400 µg	600 µg	800 µg	1000 µg	1200 µg	1500 µg

Folate (Vitamin B9) is absorbed in the proximal small intestine only. Values above the control range are suggestive of bacterial imbalance (dysbiosis) in the upper small intestine. Values below the control range are suggestive of non-bacterial disease affecting absorption of folate in the proximal small intestine.

Antibiotic therapy is suggested in patients with elevated serum folate levels since this finding suggests bacterial-mediated disease. Probiotic and intestinal diet therapy may also be of benefit in establishing and maintaining a healthy intestinal microflora.

A benefit of supplementing folic acid to dogs and cats with gastrointestinal disease and low serum folate has not been clearly demonstrated. Experimentally-induced folate deficiency can lead to clinical consequences and folic acid is cheap and safe so oral supplementation in animals with a decreased serum concentration is considered. Patients with severe hypofolatemia may be more likely to benefit from treatment. OTC folic acid supplements are readily available. Recommended dose of 200 mcg for cats and smaller dogs (<20 kg BW) and 400 mcg for larger dogs (20 kg BW) PO once daily for 4 weeks. The proximal small intestinal disease that is suspected as the underlying cause of the decreased serum folate concentration must also be addressed.

Trypsin-like Immunoreactivity (TLI). Exocrine pancreatic insufficiency (EPI) occurs when there is insufficient synthesis and secretion of digestive enzymes by the pancreatic acinar (exocrine) tissue. The pancreas has fairly good functional reserve with clinical EPI developing when the secretory capacity is reduced to less than 10 - 15%. When this degree of insufficiency occurs there is inadequate nutrient digestion and weight loss, diarrhea, and other clinical signs will become evident. EPI can be an inherited disorder with juvenile atrophy of the exocrine glands or may be a consequence of repeated episodes of or massive pancreatitis resulting in tissue destruction.

Small quantities of pancreatic proteases are present in the blood of normal animals. Trypsinogen is synthesized exclusively by the acinar cells of the pancreas, and measurement of this enzyme provides an excellent indirect index of pancreatic function. The assay detects both trypsinogen and trypsin (use of the term TLI to describe the total concentration of these two immunoreactive species), but the active enzyme (trypsin) is only present in the serum when there is pancreatic inflammation. EPI is often overlooked in both dogs and cats with chronic gastrointestinal disturbances and chronic weight loss. Cats in particular may not have clinical diarrhea (or steatorrhea) that is commonly observed in dogs. Cats also require intrinsic factor, a protein secreted by the exocrine pancreas, in order to assist cobalamin absorption in the feline ileum.

Administration of oral pancreatic extracts does not affect serum TLI concentrations in either normal dogs or cats with EPI, so withdrawal of enzyme supplementation prior to testing of dogs and cats that are receiving supplementation is unnecessary.

Imaging tests of the GI tract, Liver and Pancreas

Survey radiographs may be helpful in establishing a diagnosis in patient exhibiting chronic GI disturbances. Regurgitation is often difficult for owners to describe and discern from vomiting – evaluation of a survey lateral thoracic radiograph can be diagnostic for megaesophagus, focal esophageal disease, gastroesophageal or hiatal hernias or mediastinal masses. Gastrointestinal foreign objects or ingesta may be visualized or suspected based on radiographs. Regional or diffuse ileus may be apparent. Small intestinal obstructive patterns may be documented. Abdominal mass lesions are often discernible. Gastrointestinal thickening, gastric and intestinal luminal content and the "ground glass" appearance of pancreatitis are often over interpreted in my opinion. Mesenteric lymphadenomegaly can usually not be appreciated on survey studies.

Contrast radiography. I rarely find contrast radiography useful in diagnosis of gastrointestinal disease in my practice. Often the amount of barium necessary to provide complete filling of the stomach is not provided or the patient vomits prior to stomach emptying. Barium passage through the GI tract is dependent on multiple factors that influence motility so equivocal studies are very common. Barium food swallowing studies are the exception and can be very helpful in esophageal disorders but require fluoroscopy equipment. BIPS (barium impregnated spheres) have been of no value in my practice.

Abdominal cavity ultrasound exam. Ultrasound examination of the abdominal cavity is crucial in the evaluation of chronic GI patients. Information on all abdominal organs can be readily obtained. Specific evaluation for GI mass lesions, focal or diffuse gastric or intestinal thickening and enlarged regional lymph nodes (hepatoportal, omental and mesenteric) is achievable. Fine needle aspirates of masses, focal thickenings and lymph nodes can be performed which may provide a diagnosis without the need for more invasive surgical techniques. Gastrointestinal ultrasound interpretation has become much more specific for certain intestinal disorders with the ability to image and evaluate individual layers of the intestinal wall.

Endoscopy examination. GI endoscopy can be both rewarding and frustrating. Foreign body identification and removal is extremely rewarding. Gastric, duodenal and colonic mass lesions and ulcers can be readily identified and biopsied. However, many chronic GI disorders involve diffuse inflammatory changes which can often not be appreciated visually. Endoscopic biopsy samples may not provide an adequate tissue sample for complete evaluation and there is significant pathologist variation in biopsy interpretation despite standardization attempts. Lymph nodes and pancreatic tissue samples cannot be evaluated. In my experience many patients that do not have easily identifiable endoscopic abnormalities may have been better served with an exploratory laparotomy and full thickness intestinal and nodal biopsies. I find abdominal ultrasound examination to be of great help in determining whether to perform endoscopy vs. surgical evaluation.

DIAGNOSIS & TREATMENT OF PROTEIN-LOSING ENTEROPATHY (PLE) IN DOGS

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INTRODUCTION

Intestinal protein loss occurs as a consequence of impaired intestinal absorptive function that may result from severe intestinal inflammation (acute or chronic disease) or from disrupted intestinal chyle absorption and lymph flow. The exact mechanism leading to intestinal protein loss has not been determined in the dog, but three possible mechanisms are proposed. Intestinal protein loss may result 1) as a direct consequence of erosive or ulcerative mucosal lesions allowing protein exudation; 2) leakage of protein rich lymph into the intestinal lumen secondary to intramural lymphatic dysfunction; and/or 3) disruption of the "mucosal barrier", lining causing abnormal permeability and protein leakage into the lumen.

PLE is a consequence of intestinal disease and is not a specific diagnosis. There are varying causes of chronic intestinal disorders associated with intestinal protein loss in dogs. PLE is much less common in cats. In dogs, it is most frequently associated with severe chronic enteropathies such as idiopathic inflammatory bowel disease (IBD) or with idiopathic intestinal lymphangiectasia in specific breeds. It can also be associated with diffuse neoplastic infiltration of the intestinal wall or other infectious agents (i.e., fungal enteropathy). It is rarely associated with dietary hypersensitivity, intestinal parasitism or dysbiosis.

DIAGNOSTIC CONSIDERATIONS

PLE patients usually present with some combination of typical clinical signs including chronic intermittent to persistent small intestinal diarrhea and possible vomiting. However, significant intestinal protein loss and mild to moderate hypoproteinemia may occur without obvious diarrhea. Hypoalbuminemia may even be detected incidentally during regular heath screens in some patients (usually lymphangiectasia patients). Appetite change (hyporexia, anorexia), weight and condition loss is often present in severe cases. In the presence of significant hypoalbuminemia (serum albumin < 2.0 g/dl) the main complaint may relate to abdominal cavity dissension resulting from cavitary effusion

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The first diagnostic challenge consists in establishing the origin of the protein loss. To this effect, a minimal diagnostic database should be collected (CBC, chemistry panel, urinalysis). Renal protein loss (urine protein-creatinine ratio) and liver dysfunction (serum bile acids) must be ruled out. Third spacing of serum proteins due to other causes and hypoadrenocorticism should be considered but usually only result in mild hypoalbuminemia. Generally, PLE is associated with panhypoproteinemia due to non-selective protein loss of both globulin and albumin. Hypoalbuminemia with normal or increased globulin concentration can occur but other differentials should also be considered. While these guidelines are useful in practice, they should not be blindly relied upon since many exceptions occur (i.e., a dog with significant systemic or intestinal inflammation may present with hypoalbuminemia and hyperglobulinemia. Other common abnormalities present in PLE include hypocholesterolemia, hypocalcemia (total and ionized), hypomagnesemia, and lymphopenia.

Once the GI tract has been confirmed as the site of protein loss, further work-up should include abdominal ultrasound with a particular focus on the intestinal wall, in particular wall thickness and wall layering. The ultrasonographic appearance of the intestinal wall consists of 5 distinct layers. Hyperechogenic mucosal striations are frequently observed in dogs with PLE, and

appear to be a specific finding. This finding may represent dilated lacteals although they may also be due to dilated crypts often seen in PLE or to other mechanisms. Hyperechogenic mucosal speckles are a non-specific indicator of inflammation and not specific for PLE.
The definitive diagnosis as to the cause of PLE relies solely on histopathologic examination of intestinal biopsies collected during endoscopy or exploratory laparotomy. Dogs with severe hypoalbuminemia have increased anesthetic risks so it is sometimes preferable to postpone endoscopy or surgery and initiate presumptive treatment. Additionally, many dogs with PLE have bicavitary effusion, so thoracic radiographs are recommended to properly assess anesthetic risks. Synthetic (hydroxyethylated starches) and natural colloids (plasma, human or canine albumin concentrates) are very useful in order to temporarily increase oncotic pressure in critical cases. A slow infusion of 5% human serum albumin at 2 ml/kg/h over 10 hours (total daily volume of 20 ml/kg/day) has been successful for partial restoration of serum albumin concentration in order to minimize the risks of general anesthesia or in critically presenting cases. The decision as to a preferred biopsy collection technique depends on the preference, availability and surgical or endoscopic skills of the attending veterinarian. Advantages of a surgical exploration include the possibility of sampling several sites along the small intestine and obtaining full thickness specimen. Surgical collection of intestinal biopsies was not shown to be more risky in hypoalbuminemic patients, although a cautious approach is recommended (consider serosal patching). Endoscopy allows relatively non-invasive collection of biopsies limited to the mucosa, and good endoscopic skills are required to obtain quality specimen. Visualization of the mucosa is an advantage, and allows targeted sampling of mucosal lesions. Recent studies convincingly demonstrated that collecting both duodenal and ileal biopsies is essential, as lesion distribution may be irregular and severe ileal lesions may occur with only mild (or absent) duodenal lesions. This approach prolongs anesthesia time since a colonoscopy is required to properly evaluate the ileum and collect ileal mucosal biopsies. However, the improved diagnostic yield often outweighs the inconvenience of a prolonged procedure.

HISTOLOGIC FINDINGS

Diseases frequently associated with PLE include intestinal lymphangiectasia, idiopathic IBD, and chronic enteropathies characterized by significant mucosal architectural changes such as dilation of small intestinal crypts. Alimentary lymphoma and fungal infections (histoplasmosis) may result in PLE.

Intestinal lymphangiectasia (IL): Yorkshire terriers, Chinese Shar-peis, Maltese terriers, Norwegian lundehunds, and Rottweilers have been shown to be prone to primary IL. The pathogenesis of primary IL is still poorly understood but it results from obstruction to the flow of lymph in the intestinal wall, which could conceivably be due to congenital anomaly of intestinal lymphangiogenesis. Acquired obstruction to normal lymph flow is also a common occurrence, with the formation of granulomas impinging on intestinal lymphatics and/or intestinal lymphangitis. Secondary IL is commonly associated with significant intestinal mucosal inflammation (e.g. IBD) and neoplasia (alimentary lymphoma). Histopathologic mucosal changes include dilated lacteals in the mucosa, and deep-seated perilymphatic granulomas that can be seen in full thickness biopsies. Lacteals are essential for fat absorption and their obstruction leads to severe dilation and tear. Damaged lacteals empty their lipid- and protein-rich content into the intestinal lumen.

Inflammatory Bowel Disease (IBD): The term IBD describes “a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal (GI) signs and inflammation of the GI tract.. The inflammatory process located in the GI mucosa may lead to protein loss both by preventing the absorption of nutrients and by compromising the integrity of the intestinal mucosal barrier leading to exudation of proteins into the intestinal lumen. PLE of soft-coated

wheaten terriers is a specific form of IBD affecting this breed worldwide. In approximately 50% of these dogs, PLE and protein-losing nephropathy (PLN) occur concurrently. Mucosal lesions can be severe and include inflammatory infiltration, dilated lacteals, and deep-seated intestinal lymphangitis. While the pathogenesis is still poorly understood, a hypersensitivity component has been documented as specific proteins can trigger clinical episodes.

Crypt disease: Crypt dilation and necrosis have been frequently associated with PLE. Crypt dilation is a mucosal architectural change that is relatively frequently observed in dogs with IBD and IL. However, in some cases, crypt dilation and abscesses may be the only detectable mucosal lesions in dogs with PLE. Dogs with documented small intestinal crypt abscesses are more likely than dogs with no such lesions to experience significant hypoalbuminemia due to PLE, to show ultrasound changes of their intestinal mucosa, and to experience more severe clinical signs and a poorer response to treatment.

THERAPY SPECIFIC TO PLE PATIENTS

The two main components of treatment in dogs with PLE are dietary modification and management of the inflammatory process.

Dogs with PLE are in a catabolic state, and adequate nutrition is essential. In dogs with primary idiopathic IL, dietary modification centers on feeding a highly digestible diet with low to EXTREMELY low fat content (10-15% on a dry matter basis) to prevent further dilation and rupture of lacteals. Additionally, the diet should contain highly bioavailable dietary proteins and be low in crude fiber. Dietary therapy should probably be maintained for the length of the dog's life in patients that respond well. In dogs with PLE associated to underlying IBD, many veterinary gastroenterologists report good success with exclusive feeding of a diet consisting of hydrolyzed proteins. Novel protein diets are an alternative approach if other diets are unsuccessful. Acceptance of the diet is a critical issue in PLE dogs, particularly in the most severely affected animals, which may be anorexic. For each patient, the veterinary care team needs to identify the most palatable diet. Initially, it might be more important to feed a less optimal diet that the dog will be interested in eating, and progressively transition to a more desirable diet.

In dogs with primary IL, anti-inflammatory glucocorticoid therapy (e.g. prednisone 1 mg/kg/day or budesonide) is useful and often required for proper management of the disease. Its main desired effect is to decrease inflammation associated with lipogranulomas secondary to chyle leakage restoring an adequate intestinal lymphatics flow. In some dogs, anti-inflammatory treatment can be slowly weaned and discontinued over 2-3 months or longer.

Immunosuppressive therapy is the basis for treatment of severe idiopathic IBD with PLE. The A corticosteroid, such as prednisone or prednisolone should be initiated at 2 mg/kg q12 h for 3-5 days, then tapering to 2 mg/kg once daily until the dog's condition has significantly improved and appears stable. Subsequently the dose can be decreased in 2-week steps with 1 mg/kg/day, then 1 mg/kg every other day and so on. Side effects of steroid therapy may compromise owner's compliance. Budesonide has gained in popularity in the treatment of canine IBD. In humans, the drug is known to be locally efficient and undergo high first pass hepatic metabolism. Therefore, systemic complications of steroid treatment are less intense but there is still influence on the pituitary-adrenal axis. The recommended dose is 0.5-3 mg/dog daily (depending on the dog's size). The drug needs to be reformulated by a compounding pharmacist for use in many dogs. Concurrent use with other glucocorticoids is not recommended.

Azathioprine is a thiopurine drug that may be used in dogs with steroid-refractory IBD, and in those that relapse when prednisone treatment is weaned off. It may also be combined with prednisone in the initial treatment of severe cases of IBD. Azathioprine is generally well tolerated, but side effects include bone marrow suppression, hepatotoxicity and pancreatitis. Regular monitoring of CBC and biochemistry profile is advisable during the first weeks to months of treatment. The initial dose is 2 mg/kg daily for 3 weeks, then 1-2 mg/kg every 48 h. Up to 3 weeks of treatment may be necessary for the drug to reach maximal effect.

Chlorambucil is an alkylating agent that has been used in conjunction with prednisolone for low-grade alimentary lymphoma or refractory IBD. A study compared the survival of dogs with chronic enteropathies and severe PLE (serum albumin concentration < 1.8 g/dl) receiving a prednisolone/chlorambucil versus prednisolone/azathioprine. Dogs receiving chlorambucil and prednisolone gained more weight and serum albumin concentration was significantly higher. Survival was greatly improved using the chlorambucil combination. The recommended initial canine dose of chlorambucil is approximately 4 mg/m2 q 24-48h, and it comes in 2 mg tablets (the drug will need to be appropriately reformulated or compounded for small dogs). Side effects of chlorambucil are rare and include bone marrow suppression. A CBC should be performed after 1 and 3 weeks of treatment and repeated every 2-3 months or if the dog's condition changes to monitor for neutropenia.

Cyclosporine is an inhibitor of T-cell function. Pharmacokinetics of cyclosporine in dogs with IBD do not appear to be significantly different from those of normal dogs. In a clinical study more than half of dogs with steroid-refractory IBD went into complete remission within 4 weeks of cyclosporine treatment (5 mg/kg PO once daily). Additionally, several dogs experienced partial remission. Transient adverse effects were seen during the first 2 weeks of treatment in approx. 1⁄4 of the dogs and included vomiting and loss of appetite, hair coat changes, and gingival hyperplasia. Most side effects responded to temporary discontinuation followed by dose-reduction. Most responders remained free of clinical signs after discontinuation of cyclosporine treatment. Monitoring of whole blood or plasma concentration of cyclosporine is controversial but lymphocyte function impairment by cyclosporine can be performed at select laboratories.

ASSOCIATED CONSIDERATIONS

Low serum cobalamin (Vitamin B12) concentrations are commonly found in dogs with PLE, especially in the presence of underlying IBD. Deficiency in vitamin B12 has negative effects on the intermediary metabolism and may delay proper healing of intestinal inflammation. Hypocobalaminemic dogs are initially treated with weekly SC injections of vitamin B12 (from 250 to 1500 µg/dog based on body weight) for 6 weeks. If the treatment is successful, the interval between injections may be increased to 2 weeks for another 6 weeks.

Recent studies using thromboelastography have revealed the high prevalence of hypercoagulability in dogs with PLE, which significantly increases the risk of potentially fatal thromboembolic events. The problem may be compounded by the prothrombotic effects of glucocorticoids which are often used for treatment. Hypercoagulability does not appear to resolve after successful treatment of PLE, so this raises questions as to the pathogenesis of this complication. In dogs with documented hypercoagulability, administration of low doses of aspirin (0.5-1 mg/kg/day) and/or clopidogrel (1-5 mg/kg/day) should be considered in order to prevent thrombosis. However, there is currently no study confirming the beneficial effect of such a therapeutic regimen.

A significant decrease of total calcium is expected in dogs with moderate to severe hypoalbuminemia since 50% of total calcium is bound to albumin. However, ionized calcium

may also be abnormally low in dogs with PLE. Low serum ionized calcium concentration occurred in association with 25-hydroxyvitamin D loss from the intestine. Correct moderate to severe hypocalcemia with parenteral administration of 10% calcium gluconate (1 ml/kg slowly IV over15 to 30 min; or administered SC after 1:1 dilution with saline to a maximum daily amount of 9 ml/kg given in 3 to 4 doses). Oral vitamin D is advisable in order to prevent the onset of clinical signs when asymptomatic ionized hypocalcemia is documented . Concurrent hypomagnesemia may compromise the success of treatment and should be corrected.

PROGNOSIS

Studies are inconclusive regarding outcome correlated to severity of hypoalbuminemia. Patients with IL exhibit a variable response to strict diet therapy and anti-inflammatory doses of glucocorticoids. Unfortunately there are no known parameters that allow early identification of dogs likely to be refractory to dietary and steroid treatment. This would be useful to initiate early aggressive treatment in difficult cases.
Dogs with chronic enteropathy and crypt disease are associated with a poorer response to treatment and significantly shorter survival.

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ANTI-INFLAMMATORY & DIET THERAPIES FOR INFLAMMATORY BOWEL DISEASE IN DOGS & CATS

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Inflammatory bowel disease (primary IBD) is an idiopathic disorder that results in chronic gastrointestinal disease and associated clinical signs in dogs, cats and humans. Primary IBD is an appropriate diagnosis in an individual patients when other common causes of intestinal inflammation have been ruled out through diagnostic testing or treatment trials, inflammation is present within the mucosa, lamina propria and possibly deeper layers on intestinal biopsy examination (usually lymphoplasmacytic infiltrate). While the exact pathogenesis of idiopathic IBD remains unclear there are certain interactions between the intestinal microbiota and mucosal immune system, host genetic susceptibility, and environmental factors that clearly are disrupted and result in clinical disease. Histochemical and immunohistochemical techniques evaluating immune cell populations and cytokine expression in the intestinal mucosa have not been uniform precluding a generally accepted description of abnormalities in IBD patients. Tissue histopathology provides confirmation intestinal inflammation but specific architectural changes (i.e., villous atrophy) appear to be more reflective of severity and prognosis. The severity of inflammation and specific lesions can be vary throughout the intestine suggesting multiple biopsies by obtained from different regions for best evaluation.

Initial treatment of IBD is often a "best guess-least harm" symptomatic approach employing dietary modification, vitamin supplementation, antimicrobial agents and deworming treatment. Treatment is to some extent based on the severity of the disease in each individual patient. in patients with less severe clinical signs, the above symptomatic treatment trials are often completed prior to intestinal biopsy. When symptomatic treatment as outlined above does not result in a favorable response then immunosuppressive therapy is often necessary to reduce intestinal inflammation and lessen clinical signs. When a positive therapeutic response is achieved then the disorder is often designated as a “steroid-responsive” IBD.

There are several steroidal and non-steroidal immunosuppressive drugs that can be considered in the treatment of canine and feline idiopathic IBD.

Canne Inflammatory Bowel Disease Treatment

The classification of canine IBD is generally based on the region of the GI tract affected and on the predominant cell type in the inflammatory infiltrate. Lymphocytic-plasmacytic enteritis is the most common type of IBD observed in dogs. Other forms include eosinophilic, neutrophilic, and granulomatous enteritis. There are also breed-specific forms of IBD best recognized in soft-coated Wheaten terriers having a protein-losing enteropathy (PLE), in Basenjis with an immunoproliferative enteropathy, in Norwegian Lundehunds with IBD and PLE.

It is estimated that 30-50% of dogs failing appropriate diet, antibiotic and deworming treatments will respond to corticosteroids. Oral prednisone is the most common selection at an initial immunosuppressive dose of 2 mg/kg PO QD (50 mg/m^2) for 2-3 weeks. If clinical improvement is achieved then the dose is decreased by 25-50% every 2-3 weeks over an 12-16 week period. The side effects of glucocorticoids can be marked so the initial dose is often limited to 40 mg PO QD larger breed dogs. Budesonide, an oral glucocorticoid with a high first-pass hepatic

metabolism, reportedly exerts a "local effect" on the intestine and could also be considered a first-line corticosteroid for IBD patients. A potential advantage with budesonide is the there is less systemic absorption which may lessen systemic effects. A prescription human enteric-coated formulation (Entocort EC, 3mg capsule) is available. Compounded non-coated formulation is available and has been used in most veterinary patients. Recommended dose is 1 mg PO QD in toy breeds, 2 mg PO QD in medium-breed dogs and up to 3 mg PO q 12-24hr for large-breed dogs.

If the response to glucocorticoids is poor or the initial side effects are severe, then an adjunctive immunosuppressant is recommend. Oral modified cyclosporine at 5–10 mg/kg PO QD is my choice. If effective this dose should be used for for at least 2-3 months before considering dose reduction. Gastric side effect (vomiting after administration) may be reduced by freezing the capsule prior to administration.

Other immunosuppressive drugs, such as azathioprine, chlorambucil and mycophenolate, may be considered in combination with prednisone depending on the individual patient response.

Many cases of IBD can be managed, but unless the underlying etiology can be identified and removed, it is usually a chronic ongoing treatment. It is suggested that about one-fourth of canine IBD cases progress to complete remission; intermittent clinical signs remaining in approximately half of cases, and 5-10% of patients are completely uncontrolled and euthanized because of their disease. Hypoalbuminemia and hypocobalaminemia are suggested as poor prognostic indicators.

Feline Inflammatory Bowel Disease Treatment

In cats, oral prednisolone (2-4 mg/kg PO QD, average 10mg per cat daily) is the initial drug of choice. It is administered at the initial immunosuppressive dose for 3 weeks and if clinical improvement is sustained then decreased by 50% in 3 weeks; if a satisfactory clinical remission is maintained then the dose can often be reduced to 5mg PO/cat every 48 hours. Further dose reduction may be possible after 2–3 months of successful therapy, however, many patients will require daily to QOD continual treatment to maintain clinical remission.

If the clinical response is poor, chlorambucil (Leukeran) at 6 mg/m^2 PO q 48 hours (which is 2 mg dose for a 4-5 kg cat) is prescribed along with prednisolone (5 mg PO QD). As chlorambucil is also considered a preferred chemotherapy treatment for cats with small cell intestinal lymphoma, a positive clinical response may occur with refractory IBD or intestinal lymphoma patients. This drug is generally safe for long term use in cats; blood cell counts (CBC) should be periodically evaluated and the dose/frequency should be reduced if persistent leukopenia is noted.

Other immunosuppressive agents (cyclosporine, mycophenolate) have not been used extensively in cats with IBD but could be considered in refractory cases. Azathioprine is toxic to cats (irreersible marrow damage) and should not be used in this species. Metronidazole has frequently used in conjunction with corticosteroids to modify intestinal microflora and reduce inflammation. However, metronidazole is a potential mutagen and as such I prefer to avoid long term therapy with this drug.
Successful treatment is accompanied by a decrease in clinical signs and weight and condition improvement. Once a patient has had 2–3 months remission from clinical signs it may be possible to gradually withdraw immunosuppressive therapy. Other supportive treatments (diet,

probiotics, cobalamin) should be continued if they appear to be beneficial. If clinical signs recur after stopping anti-inflammatory therapy then daily medication is resumed until signs improve, then gradually reduced again to the lowest dose and frequency that provides satisfactory control. In patients who respond poorly to therapy or relapse after an initial response lymphoma still remains the major differential.

Feline Intestinal Lymphoma

Alimentary lymphoma is now the most common anatomic form in cats and predominantly affects middle age to older felines. In feline patients with chronic GI signs, ultrasound is useful for evaluating intestinal thickness/layering, presence or absence of muscularis layer hypertrophy, evaluating mesenteric lymph node appearance and abnormalities in liver, kidney, spleen, and pancreas. Although certain sonographic changes are suggestive of lymphoma infiltrate, ultrasound findings cannot distinguish lymphoma from IBD. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates from enlarged mesenteric lymph nodes, spleen or liver but is more often made by tissue biopsy of the intestine. The absence of lymphoma in a fine needle aspirate does not rule it out. There is a high degree of discordance between FNA and biopsy results of LN aspirates from cats with confirmed alimentary lymphoma. Endoscopic visualization and biopsy may enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of "lymphoplasmacytic enteritis." Full thickness biopsies from multiple intestinal locations obtained at the time of exploratory laparotomy can circumvent the endoscopy vs surgery debate.

Feline alimentary lymphoma is predominantly low grade T cell immunophenotype. The response to therapy is often favorable, with a long duration median survival time in low-grade lymphoma versus weeks to months in high-grade large cell lymphoma. In one study of low grade lymphoma cats, cancer was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems; extra-gastrointestinal sites involved included mesenteric lymph nodes, liver, spleen, and pancreas; 89% were determined to be of T-cell origin; 55% achieved a complete response to therapy and 37% achieved a partial response; the majority of cats received prednisone 5 mg, PO, q 12–24 h and most received chlorambucil at a dose of 2 mg, PO, every other day; 8% experienced no response; there was no association between any risk factors and response to therapy; overall median remission duration was 948 days; partial response to therapy was associated with shorter remission duration; overall median survival time was 704 days; no factors were significantly associated with survival time (Kiselow MA, Rassnick KM, McDonough SP, et al. Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995-2005). J Am Vet Med Assoc. 2008).

DIAGNOSIS & TREATMENT OF PANCREATITIS IN DOGS & CATS

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Introduction

Acute pancreatitis is a commonly encountered canine issue presenting with typical gastrointestinal signs including repeated vomiting, lethargy, weakness, anorexia, abdominal discomfort and diarrhea. The clinical spectrum and severity can vary dramatically from patient to patient. Significant fresh hemorrhagic stool may be present due to inflammation of the transverse colon that lies in close proximity to the pancreas. Severe cases frequently develop systemic clinical signs including fever, acute renal failure and possible cardiovascular shock. Cats also develop acute pancreatitis but the clinical signs are often subtle and different compared to dogs leading to less confirmed cases of this disorder in felines.

Cats frequently present with ongoing GI signs relating to chronic pancreatitis which is often part of a more generalized inflammation of the intestines and in some cases the liver as well (feline IBD, triaditis). Clinical signs related to chronic pancreatitis is encountered less commonly in dogs.

Pancreatitis involves activation of intracellular glandular digestive enzymes with subsequent tissue autodigestion; the exact inciting mechanism is often unclear. Overnutrition, ingestion of high-fat diets and trash ingestion, especially in an obese patient, are recognized risk factors that likely cause excessive acinar enzyme secretion. Select drugs (thiazides, furosemide, tetracycline, asparaginase, azathioprine) are also associated with pancreatitis; corticosteroids as a cause of pancreatitis has been suggested but remains controversial and unproven.
In many cases the inciting cause is never determined.
Tissue involvement may be mild when associated with edematous pancreatitis or may become more severe when associated with pancreatic tissue necrosis. More severe pancreatic necrosis tends to be associated with severe clinical signs and can result in systemic disease, such as systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction (MODS) thus warranting a guarded to poorer prognosis.

Hyperlipoproteinemia is common with pancreatitis; it is postulated that high triglyceride concentrations may be activated by pancreatic lipase and result in pancreatitis. Pancreatitis is common in Schnauzers and other dogs that have a primary hyperlipidemia.

• How can I quickly & accurately assess the pancreas in acute GI disturbance?

This is still a point of valid concern in veterinary medicine as there is no one “gold standard” pancreatitis test that is always reliable. Appropriate diagnosis of acute and chronic pancreatitis in dogs and cats still requires a thorough clinical history and diagnostic evaluation to build a case for pancreatic disease and exclude other reasonable differentials. Diagnostic evaluation should include routine screening laboratory tests, pancreas-specific blood testing and imaging tests. In rare cases pancreatic tissue aspiration or biopsy may be required.

Routine laboratory evaluation (CBC/CHEM) may reflect signs of pancreatic inflammation (leukocytosis, mild hypoalbuminemia, hypocalcemia) but are not specific for pancreatitis.

Serum lipase and amylase have poor specificity and sensitivity for the diagnosis of pancreatitis due to variable half-life, multiple tissue sources and influence of other medical disorders.

Radiographic changes consistent associated with pancreatitis are non-specific. Reported findings include increased soft tissue density in the cranial abdomen with diminished contrast (ground-glass appearance). Lateral displacement and gas dilation of the proximal duodenum is also described. Loss of detail due to regional peritoneal effusion may be appreciated. In cats with acute severe pancreatitis, pleural effusion and pulmonary fluid accumulation may be evident.

Ultrasound imaging allows better differentiation of pancreatic tissues compared to radiology. The normal pancreas has a non-specific sonographic appearance and blends in with normal omental tissue. With acute pancreatitis, the tissue appears as a nonhomogeneous hypoechoic soft tissue due to edema, hemorrhage and inflammatory exudates; the surrounding peripancreatic omental fat becomes hypoechoic. Chronic pancreatitis causes subtle histologic changes and is often not recognized on ultrasound exam.

Computed tomography is the preferred imaging technique for diagnosis of pancreatitis in people. Studies in dogs have not shown CT to be sensitive or specific for diagnosis of pancreatitis.

- **What do pancreatic-specific lipase tests really tell me? Which PL test is reliable?**

Assays for measurement of **pancreatic lipase immunoreactivity** in dogs and cats (cPLI, fPLI, DGGR, Fuji Dry-Chem lipase, respectively) have been developed and validated. In contrast to catalytic assays for the measurement of lipase activity, use of immunoassays allows for the species-specific measurement of lipase originated only from the exocrine pancreas.

Serum pancreatic-specific lipase assay concentration offers improved sensitivity and specificity for the diagnosis of pancreatitis in dogs and cats when interpreted in conjunction with other clinical data. The PL test was developed at the Gastrointestinal Laboratory at Texas A&M University (www.cvm.tamu.edu/gilab). A commercial assay for measurement of feline and canine PLI (Spec fPLI & cPL™) is available from a major diagnostic company (Idexx) and is marketed to increase the ability to accurately and quickly evaluate for pancreatic disease. A bed-side SNAP PL test is also available for rapid in-hospital use. The DGGR test is another pancreatic-specific lipase assay offered by Antech Diagnostics (Precision PSL).

Studies confirm these tests have a high individual sensitivity compared to other pancreatic tests. PLI is a very sensitive cellular “leakage” enzyme indicating pancreatic disease but it is not specific for pancreatitis only. Elevated PL values are supportive of but not definitive for a diagnosis of pancreatitis. A diagnosis of pancreatitis should be based on a combination of appropriate clinical signs and complete diagnostic testing including PL evaluation and imaging studies to also rule-out other disorders causing similar GI clinical signs.

Using the SpecPL assay, a value less than 3.5 ug/L is normal and a value greater than 5.4 µg/L is consistent with pancreatic inflammatory disease in cats; a value less than 200 µg/L is normal and a value greater than 400 ug/L is consistent with pancreatic inflammatory disease in dogs. Studies indicate Spec PL testing identifies approximately 80% of pancreatitis cases (80% specificity) and excludes pancreatitis in approximately 80% of cases (80% sensitivity).

The Antech Precision PSL correlates closely with the Spec PL assay in published studies. A value of > 140 U/L is considered positive in dogs and > 26 U/L is considered positive in cats.

Using the SNAP PL assay, a value less than 3.5 ug/L is normal and a value greater than 3.5 µg/L is consistent with pancreatic inflammatory disease in cats; a value less than 200 µg/L is normal and a value greater than 200 ug/L is consistent with pancreatic inflammatory disease in dogs. Specificity differs with this test because the cut-off value is at the bottom end of the grey zone. Thus SNAP PL testing identifies approximately 70% of pancreatitis cases (70% specificity) but excludes pancreatitis in approximately 94% of cases (94% sensitivity). Positive SNAP PL results should be confirmed with SPEC PL assay unless all other clinical data is consistent with pancreatitis.

Trypsin-like Immunoreactivity (TLI). Pancreatic inflammation can lead to an increased release of trypsin into the vascular space thus serum TLI concentration can be increased in dogs and cats with pancreatitis. A significantly increased serum TLI concentration (> 50 µg/L in dogs and > 100 µg/L in cats) is highly specific for pancreatitis but has a limited sensitivity of 30-60%. Elevated TLI values are also frequently seen in chronic renal disease and malnourished patients (dogs usually) without evidence of pancreatitis and in some cats with patchy pancreatic hypertrophy/atrophy (generally considered to be a benign age-related change). Therefore, elevated serum TLI concentration is of little clinical use for the diagnosis of canine or feline pancreatitis as superior diagnostic tests are available (i.e. cPLI, fPLI).

How do I treat acute pancreatitis in dogs and cats ?

1) supportive fluid therapy to restore and maintain intravascular volume and pancreatic perfusion,
2) recognize and intervene to reduce or prevent systemic complications, and
3) pain management.
4) restore enteral nutrition as soon as possible

Based on human studies there is likely an important and short therapeutic window in the first 36-48 hours for successful management; survival rates decrease and complication rates increase when treatment is delayed. Restoration of fluid volume to maintain adequate pancreatic microcirculation and prevent inflammatory cytokine release is critical. Experimental studies of pancreatitis found aggressive fluid replacement prevented progression of edematous to more severe necrotizing pancreatitis.

Fluid and electrolyte therapy should be provided in all symptomatic pancreatitis patients to improve local pancreatic perfusion, correct fluid loss occurring into the peritoneal cavity, replace vomiting losses and counteract vasoactive factors producing hypovolemic or possibly endotoxic shock. A balanced crystalloid electrolyte solution (LRS, Normosol-R) is indicated in almost all cases. Careful monitoring of electrolyte concentrations and patient hydration and renal output is essential in the severe pancreatitis case. Pancreatitis patients usually develop metabolic acidosis with depletion of total potassium stores. Extensive fluid losses through vomiting occasionally may result in a hypochloremic metabolic alkalosis. Glucose should be monitored and corrected if indicated; insulin therapy is reserved for prolonged consistent hyperglycemia that does not correct with supportive treatment.

Colloids such as Hetastarch have been recommended in the past but recent information suggests it is associated with acute kidney injury and consequently the use of these products is contraversial.

The use of fresh frozen plasma to replace protease inhibitors and improve oncotic pressure has been reported but unsubstantiated. A recent study failed to demonstrate a benefit in patients given plasma compared with those only given crystalloids. Plasma use would be considered for treatment of secondary coagulopathies or DIC associated with severe pancreatitis.

Pain management should be considered for all patients with pancreatitis, even if there is a low score on a physical pain score. Phenothiazine drugs are contraindicated initially due to hypotensive potential. Parenteral narcotics are preferred in our clinic. For mild pain, buprenorphine (0.1- 0.2 mg/kg IV q 4-6hr as needed) is usually satisfactory especially when combined with maropitant. For moderate to more severe pain, hydromorphone, morphine or fentanyl can be considered. With severe intractable pain, increasing narcotic dosages along with either ketamine (0.2–0.4 mg/kg/hour CRI) or lidocaine (5– 30 µg/kg/min CRI) may provide better pain management. Patients are closely monitored for side effects, particularly respiratory depression. Narcotics do decrease gastrointestinal motility so dosages should be reduced or drugs discontinued with improving status.

Empiric use of **antibiotics** may not be necessary as bacterial infection is not a routine complication especially in milder pancreatitis cases. However, prophylactic antibiotic therapy is warranted in the severe case or whenever there is evidence of sepsis or pancreatic infection. Broad-spectrum antibiotic therapy effective against aerobes and anaerobes is used; a second-generation cephalosporin (cefoxitin) or a combination of ampicillin and enrofloxacin are suggested.

Anti-inflammatory treatment is controversial but studies suggest no benefit is provided in acute pancreatitis patients.

While vomiting is actively present, NPO status is indicated. However, injectable **antiemetic treatment** to reduce/control vomiting, reduce additional GI fluid loss and provide patient comfort should be instituted as soon as possible so that feeding can be initiated and complications with gastrointestinal villus atrophy, bacterial translocation out of the gut, and gastrointestinal ileus can be minimized. Restoring oral nutrition is critically important in cats as high incidence of concurrent hepatic lipidosis is seen after 2-3 days of anorexia. The ideal antiemetic therapy for pancreatitis should provide both central and peripheral activity. Maropitant (Cerenia) is a neurokinin-1 antagonist that blocks receptors found in the emetic center, CRTZ, and in peripheral afferent nerves. It is an effective broad-spectrum antiemetic that works both centrally and peripherally (1 mg/kg every 24 hours given SC or IV slowly; 2 mg/kg every 24 hours given PO). Maropitant also has been shown to blockage/reduce peripheral visceral pain. Serotonin antagonists, ondansetron and dolasetron, provide central antiemetic activity but may also have some effect in decreasing GI motility. Metoclopramide has been traditionally used for antiemetic effects and to improve gastrointestinal motility (0.01–0.02 mg/kg/hr CRI). However, more recent information's documented that metoclopramide, a dopamine antagonist, has poor prokinetic effects and weak central antiemetic effects; in addition dopamine antagonism may decrease pancreatic perfusion. More severe pancreatitis cases may require a combination of the above antiemetics providing synergistic activities. Phenothiazine antimetic/sedative drugs are not recommended due to potential drug-induced hypotension. Anticholinergic antiemetics are not recommended due to effects including decreased stomach emptying and ileus promotion. **Antacid therapy** (famotidine, PPA) can be used temporarily while the patient is actively vomiting or regurgitating/refluxing. Prolonged antacid therapy once vomiting has been controlled is unnecessary.

What/When do I feed pancreatitis patients during treatment ? Nutritional supplementation in pancreatitis patients is very important. Re-establishment of enteral nutrition is favored over

parenteral nutrition. Pancreatic rest in the form of fasting has been a traditional recommendation by giving nothing per OS (NPO) for several days based on the belief that feeding results in stimulation of pancreatic secretions and exacerbate the pancreatitis. Studies have shown, however, that adequate nutrition improves survival and improves gut integrity in experimental and human pancreatitis patients. Feeding a highly digestible low-fat diet given in small frequent meals is ideal. If well tolerated, and accepted by the patient, this diet can be continued for 2 weeks and the reintroduction of the patients' regular diet can be considered. Cats can be fed a higher protein, moderate fat, restricted carbohydrate diet immediately following resolution of vomiting.

If the patient is not vomiting but will not eat then placement of an enteral feeding tube (nasoesophageal, esophageal) should be considered. Patients with severe vomiting despite antiemetic therapy and/or pain associated with eating would be the only reasons to provide continued NPO fasting. If a patient is not expected to be eating on its own within 3 days nutritional support is indicated. Intravenous parenteral nutrition (TPN) could be considered but it is expensive, complicated and has high risk potential. Placement of a jejunostomy feeding tube could also be considered in severe cases in which the stomach and duodenum may be affected for a more prolonged time period.

Surgery for pancreatitis is controversial and indications would include peritoneal lavage in septic peritonitis, treatment of pancreatic abscesses, feeding tube placement, or possibly for treatment of an associated distal biliary obstruction. Surgery for pancreatitis or obstructive biliary tract disease generally has a guarded prognosis. Most obstructive biliary complications will resolve as the pancreatic inflammation obstructing the common bile duct resolves.

How do I treat chronic pancreatitis in dogs and cats ?

Treatment of chronic pancreatitis in cats has been discussed with feline chronic inflammatory bowel disease as both disorders result from idiopathic lymphocytic inflammation and have identical presentations. Corticosteroid therapy is indicated in most patients. Dietary fat restriction does not appear to be necessary or beneficial in feline pancreatitis. Since many feline patients have concurrent intestinal and hepatic inflammation as well it is important to address these organs as well as the pancreas. Maintaining normal intestinal vitamin levels, i.e. cobalamin (vitamin B12) is helpful in maintaining normal intestinal function and absorption. SAM-e and urosdiol may be of benefit in feline patients with concurrent liver involvement.

In dogs, unlike acute pancreatitis, chronic pancreatitis is a challenge to diagnose, as clinical signs are vague and often intermittent. Laboratory tests can yield equivocal results. The most reliable test to confirm chronic pancreatitis is biopsy, but this is an invasive diagnostic. A restricted fat diet is prescribed to reduce pancreatic inflammation and prevent acute “flare-ups”. Any of the prescription restricted fat diets such as Science Diet ID, Purina EN and Royal Canin Low Fat can be used in these patients. With chronic pancreatitis or in patients with hyperlipidemia, the restricted fat diet should be continued indefinitely. Hypertriglyceridemia is common in the Schnauzer breed and contributes to secondary pancreatitis. Triglycerides >500 mg/dL present after a 12- to 18-hour fasted sample should be treated with a low fat diet (RC Low Fat or Hills I/D Low fat) and omega-3-fatty acid dietary supplementation. Anti-lipid medications can be considered if fasting TG levels remain elevated.

Antioxidant therapy may play a role in scavenging free oxygen radicals that are produced during the inflammatory process and thus reducing acute “flare-ups” and reducing chronic pancreatic fibrosis. Vitamin E and S-adenosylmethionine (SAM-E) are excellent considerations.

There is no evidence that NSAID therapy or corticosteroids are indicated or beneficial for chronic pancreatitis in dogs.

Pancreatic enzyme supplementation has been reported to decrease the pain that accompanies chronic pancreatitis in humans by the feedback inhibition by endogenous pancreatic enzyme secretion. It is not known if the same benefit is provided in dogs.

Diabetes mellitus or exocrine pancreatic insufficiency may develop over time as a long-term complication of chronic pancreatitis, and may further complicate management.

DRUG TREATMENTS COMMONLY USED IN GASTROINTESTINAL DISORDERS OF DOGS & CATS

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Appetite Stimulants, Antiemetic, Antacid, Mucosal Protectants "The Good, The Bad & The Ugly".

HOW TO INCREASE FOOD INTAKE - Appetite Stimulants

Cyprohepatadine and benzodiazepine derivatives are no longer suggested for routine use as appetite stimulants in dogs and cats due to the availability of more reliable and safer agents.

MIRTAZAPINE (Remeron^{TM}) is a centrally-acting serotonin antagonist (primarily $5HT_3$ antagonist) which aids in reducing nausea, reducing vomiting and stimulating appetite. This drug has potential GI benefit in both dogs and cats. It has become a common chronic treatment for cats with poor nutritional status relating to chronic kidney disease. A FDA-approved transdermal product (Mirataz) has recently been introduced for cats.

Several recent publications highlight the dosing and benefit of this drug in cats:
The Pharmacokinetics of Mirtazapine in Healthy Cats. ACVIM 2009 Quimby, Lunn.
Mirtazapine 1.88 mg dose PO q 24hr . A single low dose of mirtazapine was well tolerated and resulted in a half-life that is compatible with 24 hour dosing intervals in healthy cats. Higher doses may result in delayed metabolism of the drug.

Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial. Vet J. September 2013;197(3):651-5 Quimby, Lunn (CSU). Mirtazapine 1.88 mg dose PO q 48hr to CRF patients vs placebo. In a placebo-controlled crossover study in cats with CKD, mirtazapine-treated cats had increased appetite, decreased vomiting and increased activity.

The mirtazipine dose for appetite stimulation in dogs is 0.6 mg/kg PO q 24 hr.

CAPROMORELIN (Entyce^{R}) is a newly released FDA approved (dogs) pharmaceutical that mimics the action of ghrelin. Ghrelin is a naturally occurring peptide produced in the stomach and is a centrally-acting growth hormone secretagogue receptor agonist. It is secreted and accumulates in bloodstream between meals, reaching highest concentration as time since the previous meal extends. The label dose is 3 mg/kg PO q 24 hr in dogs. In recent feline abstracts and pilot studies, administration of capromorelin was safe and resulted in increased food intake and body weight in CKD cats over a 90 day trial period (Allen et al. ACVIM abstract 2015). Elimination is primarily fecal so dose adjustments are not suggested in CKD; the suggested dose in cats is 2 - 6 mg/kg PO QD. Ptyalism, lip smacking, emesis, and head-shaking were observed at the higher dose but resolved within 5 minutes of oral dosing.

Pathophysiology of Vomiting

Nausea and vomiting are common encountered issues in practice of small animal veterinary medicine. Although vomiting is a complex event, it is a reflex act that is initiated by stimulation of the "vomiting" ("emetic") center located in the medulla oblongata of the brain. The vomiting center can be activated via detection of blood-borne substances or through various neural pathways. Stimulation of the vomiting center can arise through local vagal afferent, sympathetic, vestibular, or cerebrocortical pathways.

Activation of various peripheral receptors found throughout the body can stimulate these neural pathways. Disease or irritation of the gastrointestinal tract, other abdominal organs (especially pancreas), or peritoneum can directly stimulate vomiting through vagal afferent pathways. The vomiting center can also be stimulated indirectly via humoral or blood-borne factors that activate the chemoreceptor trigger zone (CRTZ) located in the area postrema. In this area, the blood-brain barrier is limited, which allows the CRTZ to be exposed to chemical stimuli found in the circulation. Blood-borne substances that can stimulate the CRTZ include certain drugs (apomorphine, cardiac glycosides), uremic toxins, bacterial toxins, electrolytes, osmolar and acid-base disorders, and a number of metabolic derangements. Vestibular stimulation activates the vomiting center. Motion sickness, inflammation of the middle ear labyrinth and lesions in the cerebellum can result in vomiting via this vestibular pathway.

A thorough diagnostic evaluation including history, physical exam findings, laboratory testing and imaging studies (radiographs, ultrasound) are often needed to define the cause of vomiting. In some cases direct tissue examination (endoscopy, surgery) and tissue biopsies may be necessary to establish the underlying cause. Treatment is directed at the underlying primary disease.

In otherwise healthy acute vomiting patients, antiemetic treatment and a temporary diet change (restricted fat "GI" diet) may be all that is necessary to resolve this issue. Chronic vomiting patients, especially those with associated debilitating medical signs, should be investigated and treated aggressively with antiemetic and other appropriate treatments.

"**Don't let emesis be your nemesis" - How to stop vomiting and nausea.**

Antiemetic and antinauseant drug therapy plays a critical management role in many different disorders. Antiemetics are indicated when vomiting of any cause is severe (as may result in clinical dehydration, electrolyte loss and acid base disturbances) and for the prevention of motion sickness (e.g. car sickness, vestibular disease). These drugs can also be useful for preventing vomiting associated with radiation or chemotherapy treatment, and some are useful in the management of nausea resulting in inadequate nutritional intake and to enhance patient comfort especially with chronic illnesses.

Because antiemetics and antinauseants work either peripherally, centrally or both, an understanding of the basic mechanisms and receptors involved in vomiting provides the rationale for selection of an appropriate drugs. The CRTZ contains dopamine (D2), histamine (H1), muscarinic cholinergic (M1), alpha adrenergic (α2), serotonin (5HT3), enkephalin (ENKμ,ē) and neurokinin 1 (NK1) receptors that are activated by blood-borne substances. Vestibular activation or motion sickness associated with vomiting is associated with M1, histamine (H1) or NK1 receptors. There are a number of different mechanisms by which stimuli within the gastrointestinal tract (such as inflammation, stretching or distention) activate the emetic center. The 5HT3 and NK1 receptors appear to play a pivotal role in the process of

vomiting, being abundant on vagal afferent neurons, other neurons and smooth muscle within the abdominal cavity. The emetic center contains 5HT1, NK1 and α2 receptors to aid in regulation of vomiting.

Metoclopramide, ondansetron and maropitant are the most commonly used antiemetics in most clinics. Maropitant is a preferred choice for several reasons. First, it is FDA approved for dogs and cats, is broad-spectrum, has proven clinical efficacy, and there is substantial research on its role in control of both vomiting and visceral pain. Mirtazapine, an appetite stimulant, may also be a clinically applicable antiemetic, antinauseant and promotability drug.

METOCLOPRAMIDE (Reglan) provides antiemetic effects through several mechanisms. At low doses, it inhibits dopamine (D2) receptors and at higher doses inhibits serotonin (5HT3) receptors in the CRTZ. Metoclopramide may be useful for the control of CRTZ-mediated vomiting from such things as chemotherapy, azotemia, or endotoxemia. Cats are reported to have few if any CRTZ dopamine receptors and consequently it is a poor antiemetic choice. Metoclopramide is rapidly metabolized through the liver, and the best results are observed when given via continuous-rate infusion. At high doses, it causes CNS excitement from dopamine antagonism. It is reported to have prokinetic effects, but they are weak. Metoclopramide has no effect on distal esophageal sphincter pressure in the dog. Metoclopramide should be avoided in epileptics or in animals receiving other drugs that are likely to cause extrapyramidal reactions and should not be used in conjunction with phenothiazine tranquilizers due to an additive effect. Metoclopramide can be used in combination with a second antiemetic with severe uncontrollable vomiting, such as in dogs with parvovirus, pancreatitis or patients treated with chemotherapy.

MARAOPITANT (Cerenia^{TM}) is the first veterinary FDA-approved antiemetic for the control of acute vomiting and motion sickness in the dog and cat. It is an excellent broad-spectrum antiemetic. Maropitant is approved for injectable use (1 mg/kg QD) SQ in dogs over 4 weeks of age and IV use in dogs over 16 weeks of age; SQ and IV use is approved for cats over 16 weeks of age. Oral dosing at 2 mg/kg PO q 24 hr is approved in dogs for the duration of need as pharmacokinetic studies have shown a high margin of safety given SQ, PO or IV and given for up to 30 days. The oral form has not been approved for use in cats but is widely used off-label. It does sting in some patients when given SQ, and some recommend refrigeration or diluting the drug in saline before administration with mixed results. Maropitant can be administered IV if the patient has an IV catheter. It should be given slowly IV over 1-2 minutes as rapid administration has been reported to cause transient hypotension. Because this drug requires hepatic metabolism, it should be used with caution in patients that have hepatic dysfunction. The dose should be reduced by approximately 50% in patients with advanced hepatic disease (there are no reported pharmacokinetic studies in patients with hepatic compromise). For prevention of motion sickness, maropitant is given at a dose of 8 mg/kg PO for two days; some dogs may respond to a lower dose for motion sickness.

Maropitant also is my choice of an antiemetic for cats. The recommended dose is 1mg/kg IV, SQ and 1-2 mg/kg PO. Cats should be over 16 weeks of age. The same higher dose is used for prevention of motion sickness.

Maropitant is very effective in preventing vomiting associated with chemotherapy, in management of parvovirus cases and many other causes of significant vomiting such as pancreatitis. Maropitant has been shown to decrease vomiting when given with preanesthetic narcotics. In a feline chronic kidney disease (CKD) study, the investigators found maropitant vs. placebo given orally for two weeks significantly reduced vomiting episodes and may be helpful in nutritional management of cats with CKD. Clinically many patients appear more comfortable

when given maropitant, and investigation of maropitant's role in blocking visceral pain has been conducted. Visceral pain pathways contain many NK1 receptors and maropitant likely also blocks those pain receptors. Dogs pretreated with maropitant had a significantly lower post-op pain score at the time of extubation and ate significantly more during the three- hour post-op recovery period than dogs that were not pretreated with maropitant. Maropitant has no effect on GI motility.

There are numerous anecdotal reports of maropitant for the treatment of many other conditions (dermatologic, rhinitis, respiratory), but they lack critical evaluation with convincing data. There are ongoing studies to assess maropitant's effect on visceral pain associated with feline interstitial cystitis. In an experimental feline asthma model, using maropitant was ineffective.

ONDANSETRON (Zofran) and DOLASETEON (Anzemet) are serotonin antagonists developed as antiemetics primarily for the control of vomiting and nausea in humans receiving chemotherapy. They are effective at blocking 5-HT3 receptors found peripherally, in the CRTZ and EC, but not very effective in relieving motion sickness. Ondansetron HCl can be given PO or IV (0.1 - 1 mg/kg q 12 hr); oral bioavailability is a concern in cats. Dolasetron mesylate can be given SQ or IV (0.6 - 1 mg/kg q 24 hr); a tablet form is available for larger dogs. These drugs are frequently given alone or combined with maropitant or metoclopramide in animals with parvovirus, pancreatitis or azotemia. Dose-related ECG interval prolongation (PR, QTc, JT prolongation and QRS widening) has been observed in humans but has not been a clinical concern in dogs and cats.

MIRTAZAPINE is a serotonin 5HT3 antagonist which reduces nausea, reduces vomiting and stimulates appetite. In a placebo-controlled crossover study in cats with CKD, mirtazapine treated cats had a significantly increased appetite and decreased vomiting. Recent studies also confirm increased gastric motility in dogs.

Phenothiazine derivatives (antiemetic/sedative) and Anticholanergics are rarely indicated any longer as they have been replaced by the above improved and safer antiemetic drugs.

GASTROINTESTINAL PROKINETIC DRUG THERAPY

There are several drugs that possess GI prokinetic activity and may be useful in management of select upper and lower gastrointestinal disorders in dogs and cats.

CISAPRIDE increases lower esophageal peristalsis and sphincter pressure and accelerates gastric emptying. It also enhances colonic peristalsis and is useful in the treatment of constipation disorders. It enhances detrusor contractility in dogs and may be helpful in management of micturition disorders. Prokinetic activity is via enhanced release of acetylcholine at the myenteric plexus, however the exact mechanism is still undefined as does not induce nicotinic or muscarinic receptor stimulation or inhibit acetylcholinesterase activity. In humans, the drug was removed from the US market due to concerns with cardiac QT-interval prolongation. Cisapride appears to be safe in small animals at the dosages recommended. Occasionally vomiting, diarrhea, and abdominal discomfort are noted. Dosage may need to be decreased in patients with severe hepatic impairment.

Canine dose 0.1 - 1.0 mg/kg PO q 8-12hrs. Feline dose 2.5 mg per cat PO twice daily with upward dose titration as tolerated to 7.5 mg per cat PO q 8 hr if necessary.

RANITIDINE HCl may stimulate gastric motility by inhibiting acetylcholinesterase providing increased acetylcholine exposure at myenteric muscarinic receptors. Lower esophageal sphincter pressures may be increased by ranitidine. A dose of 2 - 4 mg/kg PO q 8-12hrs may be necessary to enhance GI motility.

ERYTHROMYCIN is a macrolide antibiotic that can be used as a prokinetic agent. At sub-antimicrobial doses, erythromycin mimics the effects of motilin and 5-hydroxytryptophan3 (5-HT3) which stimulates the migrating motility complex and antegrade peristalsis with subsequent enhanced gastric emptying. Erythromycin also increases lower esophageal pressure. Erythromycin is reported to stimulate colonic activity in dogs, but not in cats.

A dose of 0.5 – 1 mg/kg PO q 8 hr is suggested. Prokinetic activity may diminish with chronic use (tachyphylaxis). Oral erythromycin may occasionally cause GI disturbances such as diarrhea, anorexia, and vomiting.

WHEN SHOULD OTC ANTACID THERAPY BE USED IN DOGS AND CATS?

Over the counter (OTC) antacid therapy has emerged as a common treatment in dogs and cats over the past 20 years. Until recently, use of antacid drugs has been largely anecdotal in the veterinary field but evidence-based published studies are now emerging to guide veterinarians in properly selecting individual OTC antacids and dosages for our patients. There is a limited spectrum of veterinary disorders in which antacid therapy is necessary. These include gastric and duodenal erosions and ulcers, hypertrophic gastritis, gastrin-secreting neoplasia (Zollinger-Ellison syndrome), esophagitis and hypergastrinemia associated with advanced hepatic disease. Gastric mucosal damage related to uremic gastritis has not demonstrated in dogs and cats so an indication for antacid therapy is questioned in CKD patients.

There has been an overall trend in the veterinary medical field to prescribe antacids for many other gastrointestinal and metabolic issues in which gastric acid suppression is not necessary and is unlikely to benefit the patient. The wide spread use of OTC antacids is likely based on the perception that they have a wide safety margin even with chronic daily use. In other words, why not use them as they might help and certainly won't hurt my patient. However, recent concerns have arisen as to potential detrimental issues arising from the chronic use of this class of medication in people and the same issues are may occur in our dogs and cats receiving these drugs.

Gastric cellular physiology and gastric acid secretion

The gastric mucosa may come in direct contact with numerous noxious substances that can create substantial damage to the metabolically-active lining tissue of the stomach. Hydrochloric acid (HCl), pepsin, bile acids, and lysolecithin are examples of endogenous agents that can insult the gastric mucosa. Drug therapies, in particular non-steroidal and steroidal anti-inflammatory drugs, also can cause direct damage to the gastric mucosal lining. Ingested items (foreign material, sharp objects, etc.…) may directly injure the stomach wall.

A low intragastric pH (<3) is maintained via luminal hydrochloric acid production by gastric parietal cells. Secretion is mediated via complex nervous and hormonal mechanisms that involve a number of second messenger systems involving different gastric mucosal cell populations. From a therapeutic standpoint, the 2 most important cell populations are enterochromaffin-like (ECL) and parietal cells. ECL cells synthesize histamine which stimulates gastric acid secretion by parietal cells. Parietal cells release gastric acid via a "proton pump"

(H+, K+-ATPase) exchange. Maintenance of a low intaluminal pH associated is essential for normal gastric digestive function.

Medical conditions associated with gastric acidity

The continued presence of normal gastric acid levels (low pH) can result in the formation and perpetuation of gastric and gastroduodenal ulceration when the gastric mucosa is damaged by intrinsic or extrinsic events. Mechanical damage (foreign bodies), drug therapies (NSAIDs), lack of regulatory glucocorticoids and prostagladins, severe hepatic dysfunction and pancreatic gastrinoma may result in clinically relevant ulceration of the gastroduodenal mucosa. Reflux of normal gastric acid causes varying degrees of esophagitis and possible esophageal stricture formation which may result in clinical signs (anorexia, hypersalivation, difficult swallowing, regurgitation). Reducing gastric acid in patients afflicted with these diseases is desired and is associated with mucosal tissue protection, healing and resolution of clinical signs.

How do antacids work ?

Antacids can reduce gastric acid secretion and increase gastric luminal pH via several mechanisms. Antacids comprised of calcium carbonate and aluminum hydroxide gel directly bind with and inactivate gastric acid. Antacids such as cimetidine, ranitidine and famotidine are classified as histamine2-receptor antagonists and reduce gastric acid secretion by blocking ECL histamine production. These drugs generally require 24 to 48 hours to provide a suitable increase in gastric pH. Antacids such as omeprazole and pantoprazole are proton-pump inhibitors (PPI) and reduce gastric acid secretion by directly blocking parietal cell function. PPIs generally require 3-5 days to maintain a stable increase in gastric pH.

Which OTC antacids provide predictable and reliable benefit in dogs and cats ?

OTC antacids have been clinically investigated in dogs and cats over the past decade. Multiple studies have determined gastric acid suppression associated with the administration of 4 antacids (ranitidine 2 mg/kg IV q 12 h; famotidine 0.5 mg/kg IV q 12 h; pantoprazole 1 mg/kg IV q 12 h; and omeprazole 1 mg/kg PO q 24 h or 1 mg/kg PO q 12 h). Famotidine, pantoprazole, and omeprazole significantly suppressed gastric acid secretion compared to saline placebo; ranitidine did not. Omeprazole PO administered q 12 hr has a significant effect on gastric acid secretion and was the only drug tested that provided therapeutic efficacy comparable to study criteria used for humans. The antacid effect of famotidine has been shown to diminish rapidly within a week and when given every 8 hrs did not affect gastric pH significantly, suggesting that increased frequency of administration of this H_2RA is of no benefit in dogs.

Tolbert et al compared the antacid effects of equine omeprazole paste (Gastrogard®) vs. omeprazole tablets and famotidine tablets (1.0–1.3 mg/kg q 12 h) in healthy adult dogs. The omeprazole formulations (1.5 – 2.5 mg/kg PO q 24 h) were superior compared to famotidine or placebo (intragastric pH > 3 was 62.5 ± 6.1% for omeprazole tablet, 54.1 ± 8.3% for omeprazole paste, 21.5 ± 13.6% for famotidine, and 6.1 ± 16.8% for placebo). Famotidine and placebo were not significantly different from each other in this study.

Williamson et al evaluated the efficacy of omeprazole (0.85 mg/kg q 24 h), famotidine (1 mg/kg q 24 h) and famotidine (2 mg/kg q 12 h) administered orally in Alaskan sled dogs. These dogs have been shown to be at higher risk for gastric erosions and ulcerations. These studies demonstrated: a) famotidine at the standard dose of 1 mg/kg q 24 h was not as effective in lessening the severity of gastric lesions; b) high-dose famotidine (2 mg/kg q 12 h) was similar to standard dose famotidine; and c) omeprazole did lessen the severity of gastric lesions.

Thus, omeprazole is the preferred oral OTC antacid capable of providing a level of gastric acid suppression comparable to that associated with therapeutic efficacy in people (gastric pH >3 for 75% of the day). A minimum dose of 1 mg/kg PO BID is required to achieve and maintain this target pH in dogs.

There are also recent studies evaluating antacid effects in cats. Parkinson et al. measured intragastric pH after BID omeprazole (fractionated tablet or reformulated equine paste) versus famotidine (1 mg/kg PO q 12 h). Intragastric pH was ≥ 3 for 68.4 ± 35.0% for fractionated omeprazole tablet, 73.9 ± 23.2% for reformulated omeprazole paste, 42.8 ± 18.6% for famotidine, and 16.0 ± 14.2% for placebo. Both omeprazole formulations were in a range associated with acid suppression. This study also shows that fractionated enteric-coated omeprazole is effective despite disruption of the enteric coating.

What are the possible detrimental effects of chronic antacid use in dogs and cats ?
The long-term effects of PPI and H_2RA antacid administration has been well reported in people in the past several years. Several significant medical concerns are reported in humans on chronic PPI antacid treatment including include vitamin B12 deficiency, bile acid alterations, ionized hypocalcemia, hypomagnesemia, diarrhea, enteric infections (particularly Clostridium difficile infection), increased risk of hospital acquired pneumonia, and increased risk of fractures in geriatric people. Emergent studies have not yet been reported in dogs and cats but similar concerns can be extrapolated from the human experience.

UPPER GI MUCOSAL BARRIER TREATMENT

Indications and drugs for upper GI mucosal protection.

Superficial ulceration of the distal esophagus, gastric and proximal duodenal mucosa is commonly encountered in patients with a variety of GI diseases and as a direct toxic effect with certain drugs. Confirmation is generally made via endoscopic exam of the upper GI tract. Therapy can be directed at physically coating the lesions to protect the underlying tissue while it heals and/or at producing physiologic antacid products to lower gastric pH levels.

SUCRALFATE is useful in the treatment of oral, esophageal, gastric, and duodenal ulcers. After oral administration, sucralfate reacts with gastric hydrochloric acid to form a paste-like complex that will bind to the proteinaceous exudates that found at ulcer sites. This complex forms a superficial barrier at the ulcer/erosion site to protect the tissue from further damage caused by pepsin, acid, or bile. Sucralfate can inactivate pepsin and bind bile acids. The duration of action (binding to ulcer site) may persist up to 6 hours after oral dosing. Sucralfate may have some cytoprotective effects, possibly by stimulating mucosal prostaglandin E2 and I2 production. Sucralfate does not significantly affect gastric acid output, or trypsin or pancreatic amylase activity. Adverse effects are uncommon but constipation has been reported in dogs receiving the drug for several consecutive days. Vomiting has been an issue in cats.

Sucralfate is empirically dosed at 250 – 500 mg for toy breed dogs and cats up to 1 gram per large dog PO 2-4 times a day. A commercial suspension is available. The tablet can be crushed and suspended in water or compounded into a suspension.

Sucralfate may impair the oral absorption of the certain drugs; separate dosing by at least 2 hours to minimize this effect. Adverse effects are uncommon but constipation has been

reported in dogs receiving the drug for several consecutive days. Vomiting has been an issue in cats.

MISOPROSTOL is a prostaglandin E1 analog used for treatment or prevention of gastric ulcers. It has a direct effect on parietal cells inhibiting basal and nocturnal gastric acid secretion as well as gastric acid secretions that are stimulated by food, pentagastrin or histamine. It also has a cytoprotective effect on gastric mucosa by increasing production of gastric bicarbonate, and increasing turnover and blood supply of gastric mucosal cells. It can be used in patients that are sensitive to the gastric effects of NSAIDs and other drugs.

2019 Current Concepts in the Diagnosis and Treatment of Chronic Kidney Disease

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CHRONIC KIDNEY DISEASE UPDATE

Has SDMA become the preferred means of diagnosing CKD?

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

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

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

Evaluating for protein loss (albumin) as a biomarker of chronic renal disease is recommended as part of a standard diagnostic screening evaluation in healthy geriatric patients and all sick patients. A patient identified with consistent proteinuria should undergo further diagnostic evaluation to determine the origin and cause of the renal protein loss. The detection of persistent proteinuria serves as a warning that renal damage is present and both specific and general supportive treatments to reduce ongoing renal damage should be implemented. Timely identification and treatment of any secondary underlying disease could make a huge impact on a patient's future prognosis. Underscoring its importance as a routine screening test, multiple studies conducted in humans, dogs and cats demonstrate an increased mortality in patients with chronic proteinuria. Once it has been determined that the proteinuria is of true renal origin, each individual should be evaluated to determine whether a primary renal disease (chronic interstitial

renal disease, glomerulonephopathy) is ongoing vs. some secondary disease process located in another organ system (not of primary renal origin). Findings of elevated serum BUN, creatinine, SDMA; renal imaging abnormalities and possibly more detailed renal function testing (iohexel clearance) can be used as supportive criteria for a primary kidney disease. Identification of extra-renal disorders, such as underlying chronic inflammation (teeth, skin, ears, immune-mediated); infection (HWD, tick-borne, other regional); endocrine (adrenal, diabetes, thyroid) or neoplastic disease, that cause glomerular entrapment of circulating immune complexes and subsequent renal damage should be undertaken. This diagnostic evaluation may be comprehensive depending on the potential infectious diseases present in the geographic region the patients resides.

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

How important is blood pressure determination in chronic renal patients?

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

limitations of obtaining precise and accurate readings in our patients.

When should renal biopsy be considered?

Renal biopsy allows for histologic diagnosis and should only be considered when the information obtained is likely to alter patient management. Examples of such clinical situations might include evaluation of diffuse uniform renomegaly in dogs (lymphoma, fungal) and cats (lymphoma, FIP, fungal) and discreet nodular infiltrates and masses (tumors).
While ideal, using tissue evaluation to differentiate type of protein-losing glomerular diseases, ARF etiology, determination of the tubular basement membranes in ARF, and determination of the patient's response to therapy or the progression of previously documented renal disease is rarely performed in clinical practice.
In my practice we rarely biopsy kidneys in chronic renal disease as my experience has been that the information obtained is usually academic (see The Ohio State University Renal Lab) and as of this time rarely alters patient treatment. approach The complication rate even with an experienced operator is real and should not be underestimated. Renal biopsy can result in severe hemorrhage in up to 10% of dogs and 15% of cats that have normal coagulation profile results; hemorrhage contributed to death in 1% of dogs and 3% of cats. (J Vet Int Med 2005 Renal Biopsy: A Retrospective Study of Methods and Complications in 283 Dogs and 65 Cats. Vaden SL, et al.).
If you still feel it is necessary to obtain a renal biopsy then consider the blind percutaneous needle, ultrasound-guided needle, laparoscopic needle, and surgical keyhole or open (laparotomy) techniques. The choice of technique depends largely on the experience and technical skill of the veterinarian. If the operator is relatively inexperienced with renal biopsy or if a larger sample is required, wedge biopsy by means of laparotomy is recommended. Laparotomy offers the surgeon the advantages of being able to inspect the kidneys, choose a biopsy site and provide excellent hemostasis. Needle biopsy specimens of the kidney can be obtained from dogs and cats under ultrasound guidance using one of several sedation protocols. Ultrasound-guided technique is most appropriate for larger patients in which you cannot palpate and immobilize the kidney. The biopsy needle should be directed along the long axis of the kidney as the goal is to biopsy the cortex and avoid the renal hilus and major vessels within the medulla to avoid iatrogenic infarction and fibrosis within the biopsy region. The blind percutaneous technique is often advocated in cats and small dog when the kidney can be readily palpated and immobilized; however needle guidance is impossible with this technique.
The most common complication of renal biopsy is hemorrhage. Subcapsular hemorrhage commonly occurs at the site of biopsy, and many patients experience microscopic hematuria during the first 48 hours after biopsy. Severe hemorrhage into the retroperitoneal cavity can occur associated with improper technique. Such hemorrhage must be treated aggressively by compression bandage of the abdomen, fresh whole blood transfusion, and exploratory surgery if necessary.

Which treatments reduce urine protein loss and improve blood pressure in patients with non-azotemic CKD?

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

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

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

Telmisartan (dogs) 1.0 mg/kg PO QD.

Semintra^{R} (cats) 1.5 mg/kg PO BID X 14 d, then 2.0 mg/kg PO QD

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

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

What are the realistic goals in treating chronic kidney disease?

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

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

co-morbid conditions (diabetes, hyperadrenocorticism, heart failure).

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

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

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

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

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

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

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

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

Aluminum Hydroxide Concentrated Gel Liquid: 600 mg/5 mL; AlternaGEL®, generic; (OTC)

Aluminum Hydroxide Gel, Dried Powder, tasteless bulk powder to mix in food is available from a variety of sources including many veterinary distributors.

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

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

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

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

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

Calcitriol (1,25-dihydroxyvitamin D) is a vitamin D analog may be useful in dogs and cats for treatment of renal secondary hyperparathyroidism and in the management of chronic renal disease. This specific vitamin formulation replaces the production loss of naturally occurring vitamin D in CRF patients. Unlike other forms of vitamin D, calcitriol does not require renal activation to be effective. Vitamin D has multiple actions including enhancing calcium absorption from the GI tract, promoting reabsorption of calcium by the renal tubules, and regulating calcium metabolism in bone. Vitamin D levels and ionized claim levels are gradually reduced in CRF patients and effects are documented as early as IRIS-2 disease stage during which increasing levels of compensatory parathyroid hormone (PTH) is noted. PTH is a potent uremic toxin and has detrimental effects in the well-being of CRF patients. Oral calcitriol provides for a rapid onset of increased vitamin D activities but has a short duration of action. This is an advantage in CRF patients as its use has a mild impact on blood calcium but a potent and longer acting effect in reducing serum PTH production. Surveys and clinical impressions suggest use of this drug in CKD dogs results in clinically improved mentation, activity, appetite and longer survival times in CRF patients. A positive effect in cats is postulated but has not been proven to date. The possible development of hypercalcemia and hyperphosphatemia is a concern, however, hypercalcemia is unlikely unless a concurrent calcium-containing phosphorus binder is being used. Hyperphosphatemia is best avoided by normalizing serum phosphate levels before therapy is begun. Periodic monitoring of serum calcium and phosphorus levels is mandatory when using this drug.

A formulated daily dose of 2.5 to 3.5 ng/kg PO q 24hr is recommended in dogs and cats. A pulse dosing strategy (giving 3x dose every 72 hours) is suggested as this approach will minimize acute GI calcium absorption and maintain prolonged PTH suppression. This drug is best obtained via a formulating pharmacy to ensure proper dosing as the human capsules and solution are at much higher dosages then required by most veterinary patients.

Appropriate use of erythropoieitin analog drugs in anemic CKD patients.

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

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

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

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

The use of gastrointestinal medications for uremic CRF patients is extremely important. Antiemetic (maropitant) and/or antinauseact (ondansetron, dolesetron) drugs may can be crucial in improving appetite/water intake by reducing nausea and vomiting. Antacid therapy is controversial in CKD as uremic gastritis has not been documented in dogs and cats. Appetite stimulation therapy (mirtazapine, capromorelin) is also of great benefit in many advanced CKD

patients. Subcutaneous fluid therapy may also be of significant importance in uremic patients that are not achieving adequate oral hydration.

DIAGNOSIS, TREATMENT AND PREVENTION OF CANINE URINARY INCONTINENCE

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INTRODUCTION

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

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

History, Physical Exam and Diagnostics

A focused and thorough history is essential when speaking with an owner complaining of an abnormal urinary issue. There are many disorders, including behavioral conditions, polyuria, pollakiuria, etc…, that may be confused with or promote incontinence. It is critical to establish that a pet is unaware of the passage of urine. The timing of the incontinence episodes and the observed ability of a dog to initiate and maintain urination while emptying the bladder are important in determining the probable cause.
Congenital anomalies such as ectopic ureter should be suspected in very young dogs that have never been continent or have been “difficult to house train”. Patients with UI and concurrent increase in water intake should be evaluated for disorders causing polyuria and polydipsia. Patients whose UI and concurrent pollakiuria or stranguria should be evaluated for bacterial UTI, urolithiasis or infiltrative LUTD disease.

Physical examination should focus on the caudal abdomen and lower urinary tract; exam should include a digital rectal examination with careful palpation of the urethra and prostate. Urethral infiltrative/obstructive disease, including urethral/prostatic neoplasia and prostatic hyperplasia, may be best detected on this exam. Always make it a priority to observe the dog while it is actively urinating. Dogs with urethral sphincter incompetence will urinate normally. Male dogs often have overflow incontinence associated with structural or functional urethral obstruction as a common cause of UI. Residual urinary bladder volume should be determined when incomplete or disrupted urination is observed. Neurologic and orthopedic examination are conducted if a dog has difficulty posturing normally to urinate, as this can lead to interrupted urination, incomplete emptying of the bladder and overflow UI.

Complete urinalysis is performed in all patients with UI or any time UI relapse occurs in a previously continent dog. Urine leakage may be exacerbated by a bacterial urinary tract infection (UTI) and incontinence itself may predispose a patient to the development of UTI.

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

DISORDERS OF URETHRAL MUSCLE COMPETENCE

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

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

Risk factors associated with USMI have been identified but the exact mechanism for development remains unclear. Multiple factors including the pituitary-gonadal axis, the anatomic structure of the lower urinary tract, and the integrity and tissue characteristics of the lower urinary tract supporting structures all likely play an integral role in USMI development.
Urethral muscle tone, the strength of supporting pelvic structures, and the position of the urinary bladder contribute to bladder neck and urethral closing pressure. Following ovariectomy, the subsequent decline in estrogen levels is associated with an increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in females. These hormones may affect and decrease smooth muscle tone in the lower urinary tract. Estrogen also has trophic effects on the vasculature and tissue matrix of the lower urinary tract and its supporting structures; a decline in post-neutering estrogen level may reduce blood flow to the urethra and its supporting tissues which reduces urethral closing pressure.
Bladder position within the caudal abdomen also plays a supporting role in maintaining closing pressure to the bladder neck and urethra. Intra-abdominal pressure normally transmits equal pressure to both the urinary bladder and the proximal urethra favoring normal urinary continence. A caudally malpositioned urinary bladder (“pelvic bladder”) still is effected by abdominal pressure but pressure is relieved on the pelvic urethra; an increase in abdominal pressure occurring with movement, barking, and coughing may create enough of a pressure gradient between the bladder to urethra resulting in urine leakage.

Adrenergic alpha-receptors within the urethra muscle can be targeted to effectively increase urethral muscular tone in a post-neuter female dogs with UI. These receptors reduce in number and have diminished sensitivity following decrease in estrogen exposure. Pharmacologic alpha-receptors agonists can increase contractile tone of the urethral smooth muscle. This effect can be promoted by either increasing the number of receptors (with estrogen supplementation) or increasing stimulation (with α-agonist drugs) and forms the basis for medical therapy of acquired USMI in dogs.

Orally administered **estrogen replacement therapy** has been used for many decades in the treatment of USMI in dogs. Estrogen increases alpha-receptors and improves urethral vascularity as well as other urogenital mucosal characteristics. **Diethylstilbestrol (DES)** is available at veterinary compounding pharmacies as it is no longer manufactured for humans. Oral DES treatment is safe and reasonably effective (40–65%). Estriol (**Incurin™, Merck Animal Health**) is an FDA approved estrogen replacement product for dogs; estriol is reported to have a 93% response rate. The human drug Premarin administered at 20 mcg/kg po q 4 days is a potential alternative to DES, however, the drug does not seem to be as effective for most patients.
Multiple treatment schedules are described for DES treatment. I prescribe DES at 0.5 – 1.0 mg dose (0.5mg for dogs <15kg and 1mg for dogs > 15kg) PO q 24hr x 7 days, then q 48hr x 7 days, then q 72hr for 7 days with the dosing frequency then tapered to q 5-7 day dosage. Incurin is started at 2 mg PO q24h initially and subsequently reduced to 0.5–2 mg PO q 2–3d based on clinical response.
Once urine continence has been maintained estrogen treatment may discontinued; subsequent UI relapse would require reinitiating and continuing drug therapy. Off-label injectable estrogens should never be used as they pose a much greater risk for bone marrow toxicity. Potential side-effects include estrus signs, gynecomastia and attractiveness to male dogs; these effects generally resolve when the medication dose is decreased or stopped. The risk of bone marrow suppression is extremely minimal when oral DES is used appropriately; a 1940s experimental study in Beagles required a 1mg dose every day for > 200 days to cause pancytopenia.

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

Phenylpropanolamine HCl (Proin™, PRN Pharmacal) is an alpha-adrenergic agonist useful in increasing internal urethral sphincter tone via its effect on smooth muscle. Reported success rate associated with PPA ranges from 85% to 97%. The maximal alpha-receptor effect of this drug likely occurs 2-6 hours following oral administration. The FDA label dose is 2 mg/kg PO BID, however some dogs may be adequately controlled on once daily treatment while others may require TID dosing. It has been reported that some dogs will regain continence but later relapse while still receiving the drug; alpha-receptor down regulation with continued drug use has been proposed; in this event temporarily discontinuing the medication followed by reinitiating may be effective by allowing for receptor upregulation.
Hypertension is a potential adverse effect of α-adrenergic therapy. Systolic blood pressure should be determined prior to and monitored initially after starting treatment especially in older or high-risk patients. Other side effects are uncommon but can include restlessness, insomnia, decreased appetite and aggression.

With refractory, PPA and an estrogen supplement can be given together and may provide for a synergistic effect on the alpha receptor and clinical improvement. If incontinence cannot be controlled with either an estrogen drug or PPA then the diagnosis should be re-evaluated.

Abdominal ultrasund exam, CT contrast imaging and urethrocystoscopy should be considered; urethral dynamic testing can be considered if available. In cases in which USMI is still likely adjunctive treatment such as urethral collagen injection or surgical treatments to increase urethral pressure (colposuspension, cystopexy, urethropexy, cystourethroplasty) may also be effective. Colposuspension, which attaches the uterine remnant to the pelvic ligament and drawing the bladder neck and proximal urethra farther into the abdomen, has variable success. More recently surgical treatments have centered on placement of urethral hydraulic constrictors to increase urethral luminal pressure.

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

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

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

Male dogs with urinary incontinence issues

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

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

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

Conclusion

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

Treatment Considerations and Prevention Strategies for Simple and Complex Bacterial Urinary Tract Infections

"Stopping the Repeat Offender"

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INTRODUCTION

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

DIAGNOSIS AND TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTION.

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

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

antibiotic should be discontinued and treatment with an alternative drug begun based on the culture and susceptibility result.

DIAGNOSIS AND TREATMENT OF COMPLICATED URINARY TRACT INFECTION.

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

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

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

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

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

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

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

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

MULTIDRUG RESISTANT INFECTIONS

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

SUBCLINICAL BACTERURIA

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

Antibiotic treatment of subclinical bacteruria may be considered if there is concern that there is a particularly high risk of ascending or systemic infection (e.g., immunocompromised patients, patients with underlying renal disease) or in patients that are unable to display clinical

signs of UTI (e.g., spinal injury). The presence of multidrug-resistant bacterium does not represent an absolute indication for treatment. Multidrug-resistant organisms may be replaced with susceptible organisms if treatment is withheld, and subsequent treatment with routine antimicrobials may be more practical if bacterial decolonization is desired or if clinical disease develops. Treatment of subclinical *Corynebacterium urealyticum* should be considered because of its association with encrusting cystitis.

UPPER URINARY TRACT INFECTION (PYELONEPHRITIS)

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

PREVENTON OF RECURRENT URINARY TRACT INFECTIONS

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

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

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

Phenylpropanolamine (PPA) is approved for the control of urinary incontinence due to urethral sphincter hypotonus. This drug acts via sympathomimetic agonist activity which results in an increase in urethral sphincter tone and closure of the bladder neck. PPA treatment trial (1.25 mg/kg PO q 8-12 hr) should be considered in any individual that has recurrent UTI and clinical evidence of even subtle involuntary urinary incontinence. Promoting enhanced urethral tone helps restore an effective urethral defense mechanism to prevent ascending bacterial translocation. Long term therapy is generally safe so if a decreased incidence of UTI results with PPA treatment then continued indefinite use should be considered. PPA stimulation of

alpha and beta-adrenergic receptors can result in increased vasoconstriction, heart rate, coronary blood flow, blood pressure, mild CNS stimulation, and decreased nasal congestion and appetite. Oral estrogen replacement therapy can also be considered in younger females that develop recurrent UTI following ovariectomy.

Cranberry extract supplementation has been suggested for UTI prevention. Initially it was thought that this extract produced an inhospitable acidic urine environment. However, it has now been shown that the American cranberry (Vaccinium marcocarpon) contains a natural bioactive tannin (proanthocyanidin, PAC-A) which inhibits E. coli fimbriae adhesion to the uroepithelium. This activity results in reduced bacterial numbers via bacterial elimination through urinary wash-out and reduced pathogenic colonization and infection. A similar activity has been shown against Enterococcus faecalis. Pharmaceutical cranberry extract with PAC-A is available in concentrated formulation in veterinary medicine. Recent in vitro and in vivo studies in dogs have demonstrated efficacy and safety.

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

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

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

Antibiotic considerations for urinary tract infections in the dog and cat

(adopted from Antimicrobial Use Guidelines for Treatment of Urinary Tract Disease in Dogs and Cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. Veterinary Medicine International Volume 2011, Article ID 263768, 9 pages; revised ACVIM Forum presentation 2016)

Amoxicillin 11–15 mg/kg PO q 8h

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

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

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

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

Consideration for treatment of confirmed multi-drug resistant organisms. Potentially nephrotoxic. Monitor renal status. Avoid in animals with renal insufficiency.

Ampicillin

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

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

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

Cefovecin 8 mg/kg single SC injection.

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

Cefpodoxime proxetil 10 mg/kg PO q24h

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

Ceftiofur sodium 2 mg/kg q12-24h SC

Approved for treatment of UTIs in dogs in some regions. May be effective against organisms that exhibit resistance to other cephalosporins. Enterococci are resistant.

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

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

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

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

Doxycycline 5 mg/kg PO q12h

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

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

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

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

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

Marbofloxacin 2.7–5.5 mg/kg PO q24h

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

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

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

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

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

Pradofloxacin 7.5 mg/kg susp PO q 24hr (cats); 3 - 5 mg/kg tab PO q 24hr (dogs)

Excreted in urine predominantly in active form. Reserve for documented sensitive chronic UTIs. Good first-line choice for pyelonephritis. Expanded anaerobic spectrum not likely to be beneficial in UTI. Limited efficacy against enterococci. Retinal damage has not been reported in cats. Bone marrow suppression has been reported in dogs.

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

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

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