Getting Nutrition into a Cat

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Our understanding of feline nutrition has advanced significantly from the day when we simply considered them small dogs, and the number of options we now have for dietary intervention in this species has expanded exponentially. But neither the knowledge of feline metabolism nor the number of available diets helps us, or the cat, one bit, if we can't get the stuff into them. When a Labrador retriever refuses to eat we know the prognosis is grave: when a cat refuses to eat it may well be that they have decided that the presentation of their latest meal was not up to standards. Unlike Labrador retrievers, cats are one-trial learners, so make the mistake of trying sneak a medication into the one particular flavor of food the cat will tolerate, and that may well be the last time you get anything into that cat's mouth. Try to switch diets on a Labrador and you might get a brief pause as the dog considers the phrase "fool me once, please!". Try to switch diets on a cat, for its own good mind you, and suffer an expression of disdain and an attitude of incredulous indignation. So of course, what is perhaps the single most common clinical expression of almost anything wrong with a cat? A decreased-to-absent appetite. And what are the consequences of anorexia in a cat compared to a Labrador? Well cats have their own specific condition for just that – hepatic lipidosis. This presentation should be considered a "group effort" as collectively the veterinary profession aspires to be more clever than a single cat and we explore a plethora of possible strategies for getting nutrition into a cat.

Terminology and differentials

Hyporexia is the term for a reduced appetite and Anorexia is complete inappetence. Large category differentials for Anorexia are: Primary anorexia, Secondary Anorexia, and Pseudo-Anorexia. Primary anorexia is most often associated with brain disease, trauma, or tumor, including "anosmia" or the inability to perceive odor – a particularly important sensation for cats. Pseudo-anorexia is any condition where the cat actually wants to eat but is extremely reluctant to do so because of other pressing problems. Examples of pseudo-anorexia would include dental disease, musculoskeletal disorders, pain (of the some component of the oral cavity and GI tract, or an unrelated but uncomfortable condition), stress, anxiety, depression, even environmental ques. Secondary anorexia is everything else, and the category that is most commonly the reason for presentation of a cat that's not eating.

Consequences

Anorexia leads to malnutrition, and malnutrition has significant consequences for cats. The cat's unique metabolic make-up is not particularly well suited for adapting to different nutritional planes, their metabolic rate and preferential metabolic pathways do not alter their activity level to a great extent in response to changes in nutrient content. When their diet or lack of dietary intake fails to provide their preferred nutrients they may turn to their endogenous supply (muscle protein leading to cachexia) or over-produce harmful metabolic by-products (ketoacidosis). A poor nutritional plane leads to immunosuppression, proteolysis, hepatic lipidosis, and an increase in mortality. Importantly, Reynolds et al. (2010) showed that for cat owners the quality of life is more important than longevity, and appetite ranked as one of the key components in a cat owner's perception of their cat's quality of life. Cats are also particularly prone to stress, whether obvious to us or only perceived by the cat, and Stella et al. (2011) demonstrated that one of the consequences of stress in cats is anorexia.

Veterinary clinics and hospitalized cats

The advent of Feline Friendly Practice standards (www.catvets.com) from the American Association of Feline Practitioners goes a long way towards helping clinicians design environments and interactions that can reduce stress and decrease the incidence of hospital acquired anorexia in our feline patients. Unfortunately there are still too many scenarios where cats who are already feeling ill are stuffed into a carrier and exposed to a room full of predators just before being introduced to the healing hands of the veterinary staff, potentially for restraint, target practice, and indignity before being transferred to a metal box with none of the comforts of home. But an active appreciation and the motivation to change can go a long way towards relatively simple (a hiding box, an elevated perch, the appropriate temperature, the line-of-sight) or complex (feline-only reception area, cat-only exam rooms, specially trained and qualified "crazy cat" nurses) measures to reduce the stress of your feline patients and the anxiety of their owners. While hospitalized it should be routine for cats to be weighed daily and assessed in terms of body condition score, muscle score, amount of food and water consumed, evidence of urination and defecation, including fecal characteristics. Consideration of who is feeding the cat, what and in what, when and where, texture (it is often mistakenly assumed that every cat would prefer wet food to dry…not so) and social setting (some will only eat when witnessed, others only when alone). Remember that cats are "neophobic", they are very suspicious of new things and most everything in a veterinary clinic is new to a cat. Ironically, the veterinary hospital is probably the worst place (and time) to attempt to introduce a cat to a new "prescription diet", and as mentioned, hiding medication in what a cat will eat is, unfortunately, often a quick way to add that to the list of what a cat will not eat. Consider a "sacrificial" diet first.

Guideline for how much to feed a cat

Resting Energy Requirement (RER) = 30 x weight (kg) + 70 Kcal for cats < 5 kg

= 70 x weight (kg)$^{0.75}$ Kcal for cats > 5 kg

5 kg cat: 220 kcal/day, with > 5 gm protein/kg/day

KEY = Monitoring!

Non-pharmaceutical intervention in anorectic cats

Dr. Google, the Popular Press, Cat Fancy magazine, YouTube, and the Crazy Cat Lady next door, the number of reliable sources for ideas on how to convince a cat to eat are almost boundless! Much of it common sense, some of it is cat sense, some of it is Oscar Myer Bologna. At first do no harm, but as long as you observe that Golden Rule, Kitty-bar-the-door because it is open to most whatever your imagination can come up with. From obvious (palatability, smell, temperature, texture, freshness, presentation) to open-mindedness (acupuncture, slippery elm, B vitamin complex) to absurd (wafting wonderous odors under their noses while blowing CatNip bubbles into their faces…), all are worthy of consideration.

Pharmacology

Several recent pharmaceutical advances are of tremendous benefit to the cat with some form of gastrointestinal disease as a reason for anorexia, and the clinician attempting to care for that patient. Metoclopramide still may have a place as a pro-motility agent in the cat, but it has largely been replaced by cisapride (5mg per cat, two to three times daily) for that function. The pharmacology of the cat's emetic center is simply not amenable to metoclopramide as an effective feline anti-emetic. Fortunately, ondansetron (0.5 mg/kg IV or PO once daily) and maropitant (1mg/kg daily, subcutaneously or orally – 1/4th of a 16mg tablet) appear to be very effective anti-emetics in the cat. So if needed, we can stop the cat with acute gastritis from vomiting. What about getting them to eat? Cyproheptadine (2-4mg per cat, once or twice daily) has long been used as an appetite stimulant in cats, with variable success. More recently, mirtazapine (1/8th of a 15mg tablet once daily, reduce the dose to every other day in cats with chronic kidney disease to) has been shown to be an effective appetite stimulant in many cats, and may have some anti-emetic properties as well. Contrary to the original dosing information (every 3 days), research by Dr. Quimby at Colorado State University has shown that the pharmacokinetics of mirtazapine in cats would require daily administration of the drug for full effect. It appears safe to mix and match the various anti-emetics and appetite stimulants, and the most effective combination will likely differ for different patients.

Finally, if a feline patient at CSU is approaching 48 hours without having been convinced to take on nutrition voluntarily (or with the help of pharmaceutical intervention), we will move relatively quickly towards "assisted feeding" through either a nasoesophageal feeding tube (liquid diet such as CliniCare at 1 kcal/ml, or the human product Ensure, also 1 kcal/ml), or quite frequently, an esophageal feeding tube (E-tube) with a blenderized diet, particularly if we are trying to get the cat out of the hospital.

E-tube placement: (a number of excellent demonstrations available as YouTube videos)

- 20-24 French Argyle Catheter
- Surgical scrub & alcohol; sterile gloves; 3cc syringe; 2-0 or 3-0 Nylon suture
- Clippers & blades, Sterile instrument pack (towels, drape, clamps, scalpel #10 blade, 4x4s
- Curved blunt-tipped forceps
- General anesthesia, right lateral recumbency for left-sided placement
- Aseptic prep of lateral mid-cervical area, extend neck, place mouth speculum
- Premeasure feeding tube from mid-cervical to 7th-8th intercostal space (place mark on tube)
- Cut end of feeding tube at an angle to enlarge diameter of delivery
- Large curved forceps through oral cavity, into esophagus, push outward to id entry point
- 1-2 cm incision over Forceps bulge in neck, avoid vessels
- Blunt dissection of subQ, esophagus & esophageal mucosa to visualize forceps
- Forceps grasp end of E tube and pull that portion out of the mouth to pre-marked length
- Reinsert tip of tube through mouth, into esophagus, and feed distally
- Outer portion of E-tube will "flip", showing that inner portion is running in aboral direction
- Chinese finger trap and bandage

Summary

- Anorexia leads to malnutrition relatively quickly in the feline and should be addressed
- Abundant numbers of unproven strategies exist for encouraging cats to eat, use common sense.
- Pharmacological intervention should be temporary while underlying conditions are addressed
- The Esophageal Feeding Tube is an excellent way to empower an owner to help their cat.

References

Reynolds CA et al. Perceptions of quality of life and priorities of owners of cats with heart disease. J Vet Intern Med 2010; 24:1421-1426.

Stella J, et al. Effects of stressors on the behavior and physiology of domestic cats. Appl Anim Behav Sci 2013; 143:157-163.

Feline Nutrition Basics from a Junk Food Junkie

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The veterinary profession is undergoing a subtle but important shift in terminology. Whereas previously a diagnosis of "Inflammatory Bowel Disease" or IBD was often given to any cat with diarrhea when time, patience, or finances precluded an actual diagnosis, we now tend to start with the term "Chronic Enteropathy". From there we move forward diagnostically and therapeutically in an organized manner that allows us to add important qualifiers, such as Chronic Enteropathy – Food Responsive Diarrhea. Only when we have exhausted the differential list and procured histopathology do we settle for a diagnosis of IBD (NOTE: the real name is *idiopathic* inflammatory bowel disease and it is a histopathologic diagnosis). One consequence of this shift in vocabulary is a shift in our choice of trial therapies, moving away from early intervention with glucocorticoids (IBD) to a renewed appreciation for the power and importance of dietary therapy.

History

"Pharmaceutical agents are often given inappropriate precedence in the treatment of gastrointestinal tract diseases. Nutrients have marked influences on the gastrointestinal tract and manipulation of the diet provides clinicians with a powerful therapeutic strategy to be used alone or concurrently with drug therapy"

W. Grant Guilford, J Nutrition, 1994

As early as 1994 Dr. Guilford recognized that different diseases of the GI tract were likely to respond to different dietary manipulations. Simply characterizing the clinical condition was an important first step towards deciding on the best fit amongst diet choices. For example, for chronic small bowel diarrhea Dr. Guilford recommended a "highly digestible, gluten-free, hypoallergenic, isosmolar, low in fat and low in lactose" diet. That should just about cover it!

We have long recognized the cat as an obligate carnivore but we continue to debate just exactly what impact that status should have on what we actually feed this species. Bear in mind that if left to their own devices, and assuming they more closely resembled a contestant on Hunger Games as opposed to the Couch Potato so many of us are accustomed to dealing with, cats would consume a diet high in protein, with low to moderate amounts of fat and minimal carbohydrate. A cat's obligate daily protein requirement (30% DMB) is over twice that of a dog (12%) and cats have specific requirements for particular proteins (ex. taurine) as well as a number of vitamins, arachidonic acid, carnitine, and vitamin D.

Acute gastroenteritis

Historically the first principle in the nutritional management of acute gastroenteritis has been no nutrition at all – "rest" the GI tract with a 24-48 hour fast. In addition to diarrhea, nausea and inappetence, the patient was often vomiting upon presentation, adding to the argument against putting anything (ie. food) down the pet's throat. The potential contribution of acute pancreatic inflammation and the concern over stimulating the pancreas with food also fuels the fasting paradigm. Following the period of fasting, small quantities of a "bland" diet are gradually introduced as we hold our breath hoping the offending etiology has passed. A somewhat more scientific justification for a period of fasting would be the concern over antigen exposure in the gut during a period of inflammation, potentially creating a "food allergy" where previously there had been none. With cats this approach can be problematic. For one thing, a high protein/low carbohydrate diet does not fit the usual definition of a "bland" diet. The canine bland diet contains a small amount of highly digestible protein, a low fat content, and moderate to large amounts of highly digestible carbohydrate (ie. white rice). In addition, cats frequently can be anorectic for several days before their owner's realize what's (not) happening and present them to the veterinarian, and anorexia in a cat can have much more severe consequences than anorexia in a Labrador retriever. Not feeding a cat for 24 hours is still considered a viable way to "rest" the GI tract in cases of acute gastroenteritis, but the clinician must be aware of the likelihood that the clock on that 24-hour window may well have already run out by the time the patient is in your office.

Several recent pharmaceutical advances are of tremendous benefit to the cat with acute gastroenteritis, and the clinician attempting to care for that patient. Metoclopramide still may have a place as a pro-motility agent in the cat, but it has largely been replaced by cisapride (5mg per cat, two to three times daily) for that function. The pharmacology of the cat's emetic center is simply not amenable to metoclopramide as an effective feline anti-emetic. Fortunately, ondansetron (0.5 mg/kg IV or PO once daily) and maropitant (1mg/kg daily, subcutaneously or orally – $1/4^{th}$ of a 16mg tablet) appear to be very effective anti-emetics in the cat. So if needed, we can stop the cat with acute gastritis from vomiting. What about getting them to eat? Cyproheptadine (2-4mg per cat, once or twice daily) has long been used as an appetite stimulant in cats, with variable success. More recently, mirtazapine ($1/4^{th}$ of a 16mg tablet once daily, reduce the dose in cats with chronic kidney disease) has been shown to be an effective appetite stimulant in many cats, and may have some anti-emetic properties as well. Contrary to the original dosing information (every 3 days), research by Dr. Quimby at Colorado State University has shown that the pharmacokinetics of mirtazapine in cats would require daily administration of the drug

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Finally, if a feline patient at CSU is approaching 48 hours without having been convinced to take on nutrition voluntarily (or with the help of pharmaceutical intervention), we will move relatively quickly towards "assisted feeding" through either a nasoesophageal feeding tube (liquid diet such as CliniCare at 1 kcal/ml, or the human product Ensure, also 1 kcal/ml), or quite frequently, an esophageal feeding tube (E-tube) with a blenderized diet, particularly if we are trying to get the cat out of the hospital.

Dietary intervention for acute gastritis in cats:

- High quality protein
- Highly digestible diet (>90%), single ingredients, no additives or flavorings
- Moderate energy density, small amounts of highly digestible carbohydrate
- High moisture content
- Fat for palatability
- 3-4 meals/day

The quality of the protein source in the diet is perhaps the single key ingredient for the successful passage and placation of an inflamed feline GI tract. Any poor-quality, undigested protein enters the colon as food for the bacterial microbiota that residue there. This may result in a change in the quantity and quality of the colonic bacterial population ("there goes the neighborhood"), stimulates the secretion of water into the GI lumen, and increases the amount of ammonia produced and thereby further damages an already diseased GI mucosa. In short, exacerbates both the feel (softer) and smell (bad) of the problem (diarrhea).

Food responsive diarrhea, a chronic enteropathy of cats

The veterinary profession (with the persistent prodding of pet food companies) is expanding the clinical definition (a bit faster than our basic understanding) of the impact diet has on gastrointestinal disease. Even the language is evolving to acknowledge the fact that diet plays a role in GI health well beyond the simple classification of allergy or intolerance. Cataloging dietary components as a cause or contributor to GI disease has evolved from "It's the beef" to looking at the potential role of grains, gluten, preservatives and preparation. Prescribing dietary intervention as a contributor to the cure for GI disease has evolved from single-source Lamb & Rice to diets incorporating most any creature on the planet, exotic vegetables, prebiotics, probiotics, a spectrum of digestibility, combinations of fibers and various volumes of fat, essential ingredients as well as essentially eliminated ingredients.

Dr. Guilford and many others have continued to contribute strong research evidence for the impact of diet as both the cause and potential cure for GI conditions. Several key take-home points from this effort are:

- A significant percentage of cats with GI disease will respond favorably, if not completely, to dietary intervention
- A diet trial for a gastroenterologist lasts about 2-weeks, compared to the 8-12 week effort for a dermatologist
- The standard dietary intervention remains the hypoallergenic/hydrolyzed diet
- A much more diverse array of dietary options should be considered
- Sometimes it is a matter of matching a specific diet with a particular patient, especially with cats

Fiber

- Non-digestible plant carbohydrate

Soluble, fermentable fiber (ex. beet pulp) is easily broken down by GI bacteria into short-chain fatty acids (SCFA), an essential nutrient for repairing and maintaining a healthy GI mucosa. Soluble fiber will also slow down digestion, delay gastric emptying, inhibit absorption of nutrients and cholesterol, slow GI transit time, increase fecal water content, and shift the microbial balance towards "healthy" bacterial species (*Lactobacilli* and *Bifidobacter*) from unhealthy species (*Clostridium* and *E coli*).

- Oatmeal, oat cereal, lentils, apples, oranges, pears, oat bran, strawberries, nuts, flaxseeds, beans, psyllium, carrots
- Metamucil: psyllium, $1/8^{th}$ – $1/4^{th}$ teaspoon twice a day

Insoluble, poorly fermentable fiber (ex. cellulose) adds bulk to the stool, and may help normalize motility and act as a laxative. Colitis is the GI condition that appears to be most responsive to this action, hence the proliferation of "fiber-responsive" diets. Fiber-responsive diets high in insoluble fiber should be avoided in cats prone to constipation (chronic kidney disease) or obstipation (megacolon).

- Whole wheat, whole grains, wheat bran, seeds, nuts, barley, brown rice, zucchini, broccoli, carrots, green beans, root vegetable skins
- Canned pumpkin: 90% water, 3% fiber, 1-2 teaspoons per meal

Summary

- Dietary intervention may not be the only therapy, but it must be a part of an effective plan
- It takes 3 strikes before a cat is out; even a different version of a diet-type may hit the mark
- 2 weeks, not 12, or "Thank Heaven I'm not a Dermatologist!", for a GI diet-trial

- Expand the definition of Dietary Intervention beyond Diets

References

Zoran DL. Nutritional management of feline gastrointestinal diseases. Top Companion Anim Med 23:200-206, 2008.
Guilford WG, Jones BR, Markwell PJ, et al. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. J Vet Int Med 15:7-13, 2001.

Crappy Cat Cases:
A Look at Cat Crap

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Following a complete History and Physical Examination, often the first step in the diagnostic work-up of feline diarrhea in an otherwise seemingly healthy cat is to stop looking at the cat for a moment and start looking at what is coming out of the cat. With technological advances, the "fecal exam" has evolved from a quick smear on a glass slide +/- a drop of saline and a high school chemistry microscope, to entire laboratories devoted to the PCR detection of a single organism. One result of this technology appears to be that you can find almost any infectious organism you want to find in the feces of almost any cat. Ironically, this explosion of technical diagnostic ability has actually highlighted the importance of our non-technical skill set, the History and Physical Examination, when deciding just which infectious organism we should be most interested in setting out to find in the feces of a particular patient.

Feline panleukopenia

Feline "Panleuk" is a viral infection of non-vaccinated cats (and therefore kittens are particularly susceptible) caused by feline parvovirus that results in an acute presentation of predominantly gastrointestinal signs: vomiting, diarrhea, anorexia, dehydration and lethargy. This condition is often terminal. Like Parvo in puppies, the virus attacks the rapidly dividing cells of the GI mucosa, destroying the normal architecture and function of the villi and crypts. The CNS and retina can be affected, and the disease derives its name from the panleukopenia seen on CBC.

The virus is very stable in the environment and extremely contagious, although the disease is extremely unlikely in well-vaccinated cats. Hence the classic "at-risk" population is young kittens (< 6 months of age) in a shelter environment, often with an unknown or inadequate vaccination history.

The panleuk posture is one of severe dehydration, weakness and lethargy, with the head flat on the floor or hanging into a water bowl, similar to the hypokalemic cat. Abdominal palpation may elicit discomfort and reveal intestines that are too firm or too soft, but either way, just not right. As with many acute and severely ill cats, body temperature is more likely to drop than register as a febrile as the condition progresses. It the kitten was infected very early on the presentation may include cerebellar signs such as hypermetria and a wide-based stance. A fundic exam should be performed to look for retinal dysplasia. The viral destruction of leukocytes makes these kittens susceptible to secondary infection and some number of them are likely to present with concurrent respiratory signs – the triad of a distemper dog: GI, respiratory, and CNS.

Severe panleukopenia is present on the CBC of these kittens and the biochemical profile may reflect the patient's dehydration and GI signs. The fecal CPV antigen immunoassay, a canine parvovirus assay, detects the feline panleukopenia virus in feces. Paired serum samples would demonstrate a rising antibody titer over a 2-3 week period. Viral isolation and electron microscopy are used less frequently.

Treatment is largely supportive:

- Hydration – often severely dehydrated
- Electrolytes – abnormal secondary to diarrhea and vomiting
- Nutrition – patients are often anorectic, consider nasogastric tube for support
- Transfusion – sometimes used for oncotic support
- Secondary bacterial infections – broad spectrum antibiotic

The persistence of the virus in the environment is problematic and requires significant attention to all areas of potential shedding, using a 1:32 dilution of household bleach. The KEY to control is vaccination of all cats (those that survive the infection appear to be protected for life). There are a variety of products available, and the last "kitten" vaccine should be administered at 16-20 weeks of age (see AAFP Guidelines and Disease Information Fact Sheet (Dr. Margie Scherk), www.catvets.com).

FeLV

Feline leukemia virus (FeLV) is a retrovirus that infects the intestinal crypt epithelial cells, although most famous its effect on cells of the bone marrow and immune system. Young cats and kittens appear particularly susceptible, especially if they spend time outdoors or are from a multi-cat household. Grooming, biting, and sharing life (or more specifically, saliva) with other cats increases the likelihood of transmission. FeLV is a differential for persistent diarrhea in a young cat, particularly if accompanied by concurrent infections. Lymphoma is also common in young FeLV-positive cats.

The CBC often reflects the hemolymphatic aspects of infection, resulting in anemia, abnormal lymphocyte counts, neutropenia, and thrombocytopenia. Biochemical changes are non-specific. The IFA assay will identify an FeLV antigen, although may not detect the virus for up to 12 weeks post-infection. The ELISA assay may detect the same viral antigen earlier in the disease progression.

Treatment is again largely supportive (as above) although these patients are more likely to require blood transfusions for their anemia. More specific drugs to consider for the treatment of these kittens include:

Zidovudine	5-15 mg/kg PO BID
alpha-interferon	30 U/day PO for 7 days every other week
Propionibacterium acnes	0.5 mL/cat IV once or twice weekly
acemannan	100mg/cat/day
Oxytetracycline (*Mycoplasma haemofelis)*	15 mg/kg PO TID
Doxycycline (*Mycoplasma haemofelis)*	5 mg/kg PO BID
Erythropoietin	35-100 IU/kg SC q48 hours
rhG-CSF	5 ug/kg SQ q24 hours

For FeLV vaccination at CSU we use the canarypox-FeLV recombinant vaccine, always testing the cat for FeLV status prior to vaccination. Decreasing exposure to other cats is another strategy. (see AAFP feline retrovirus management guidelines).

FIP

Another viral disease of high mortality in young cats, FIP, a mutated coronavirus, does most of its damage through an immune-mediated process where one of the body's defenses, macrophages, actually help spread and perpetuate the disease, which is classically pyogranulomatous in nature. Anorexia, weight-loss, and diarrhea are clinical signs associated with GI involvement, but usually the other effected tissues result in the clinical signs that are most suggestive of the diagnosis. Panleukopenia is actually another differential to consider in these young cats and kittens as they may have neurological and ocular signs, but FIP cats also often have swollen bellies full of fluid and granulomatous masses, and are frequently icteric. Elevated globulins and a viscous, straw-colored abdominal fluid are highly suggestive of the disease, although histopathology (intestines, liver, kidney) is the gold standard.

Treatment is supportive, but FIP is almost invariably a terminal disease. Vaccination is not generally recommended by the American Association of Feline Practitioners, and prevention is best done through the reduction of possible exposure.

Tritrichomonas

"Good news Mrs. Smith, your cat's diarrhea is likely to resolve all on its own in just 6 months to 2 years!"

Tritrichomonas foetus is a motile flagellated protozoal cause of diarrhea, predominantly in young cats, but reported in older cats as well. One of its best friends appears to be *Giardia,* as they are commonly found hanging out together. Both are most often transmitted by the fecal-oral route. The clinical presentation is usually one of persistent or recurrent large bowel diarrhea with few other problems besides a very sore bum, maybe even rectal prolapse. Although rare, some cats can present in much worse shape, with anorexia, weight-loss, fever, fecal incontinence and abdominal pain. Another common aspect of the presentation is that a battery of dewormers has failed to have the desired effect. The classic history includes an environment of exposure; shelters, cat shows, breeders, or catteries.

Diagnosis starts with an index of suspicion based on the clinical presentation. A wet mount of fresh feces (the fresher the better, no refrigeration, use 40x magnification) may reveal the organism – the classic distinction between *Tritrich* and *Giardia* is based on motion: *Tritrichomonas* appears to have a jerky movement and spindle-shaped undulating membranes, *Giardia* with a spiral motion and a concave ventral disc. Direct examination is, however, low yield. Fecal culture for protozoal organisms is available (InPouch TF), one advantage being that Giardia organisms do not grow in the pouches (incubated at 37^{o}C for 48 hours or room temperature for 12 days, examine daily) while at CSU we frequently use PCR to identify the presence of the organism (the Colorado Diagnostic Laboratory offers a duel PCR assay for both Tritrich and Giardia, again emphasizing that the 2 are often found in the same cat). Again, we start with a clinical diagnosis, since we have found adult cats PCR positive for *Tritrichomonas* where the organism very likely has nothing to do with the cat's diarrhea. Testing all cats in a household does help to identify carriers.

There are a lot of drugs that won't treat *Tritrichomonas*; the one that seems to have the most success is Ronidazole (30 mg/kg/day for 14 days), although recent work by Dr. Jody Gookin (who first identified this organism as a cause of diarrhea in young cats) suggests that some degree of resistance to Ronidazole is emerging in this population of bugs, much as there is an increase in resistance of *Giardia* to metronidazole. Like metronidazole, adverse side-effects of ronidazole include neurotoxicity (ataxia and seizures). T. foetus is easily killed in the environment with most disinfectants, so regular cleaning of "infected" households is important – asymptomatic carriers are common. This is one reason for therapeutic failure, in addition to inappropriate dosing of ronidazole or emerging resistance of the organism to this treatment. Some practitioners will use a high fiber diet in these patients because of the large bowel aspect of the disease. Probiotics are frequently recommended, and a recent prospective, double-blinded, placebo-controlled study found that adding probiotics (*Enterococcus faecium*) to Ronidazole for the treatment of *Tritrichomonas* significantly reduced the likelihood of relapse following treatment, compared to treatment with Ronidazole alone (Lalor & Gunn-Moore, International Society of Feline Medicine abstract, 2012). There is some question regarding the safety of Ronidazole in kittens and it is generally not recommended for use in kittens less than 12 weeks of age, but in this abstract the range of the treated patients started at 2 months of age and no adverse side-effects were reported. Capsules are stored in the freezer and owners should use precautions when handling the drug (use gloves, do not open or crush capsules) as it is considered a carcinogen.

Giardia

Giardia is a flagellate protozoan parasite that most often causes acute, small bowel diarrhea, but should also be a differential for acute or chronic large, small, or mixed bowel diarrhea – in other words, diarrhea (oh, and occasionally pets will vomit). Young cats are more likely to be clinically effected than older cats, and the condition may be severe in kittens.

As with *Tritrichomonas*, kittens from population-dense environments (kennels, catteries, and cat shows) are at increased risk, a number of dewormers appear ineffective against *Giardia*, and resistance to metronidazole also appears to be an emerging problem.

Trophozoites can be found in fresh feces where the "falling leaf" motility and concave surface distinguishes them from the "herky-jerky" movement of *Tritrichomonas*. Cysts are shed intermittently but can be revealed through zinc sulfate and centrifugal flotation of fresh feces (3 samples, 2 grams of feces mixed with 15 ml of a 33% zinc sulfate soluition, strained, filled with additional zinc sulfate, and centrifuged for 3-5 minutes at 1500 rpm with the tube coverd with a coverslip; Lugol's iodine may be added to the centrifuge tube to make identification easier). Various fecal ELISA assays are available, and at CSU we often employ PCR.

Therapy can be attempted with:

Fenbendazole	50 mg/kg PO q24 hours for 5 days
Pyrantel, praziquantel, febantel	56 mg/kg (febantel) q24 for 5 days
Furazolidone suspension	4 mg/kg BID for 7-10 days
Metronidazole benzoate	10-25 mg/kg PO BID for 5-7 days
Tinidazole	30 mg/kg PO q24 hours for 3 days
Quinacrine	11 mg/kg PO, q 24 hours, 12 days

Therapeutic failure and relapse is common, suggesting misdiagnosis, inappropriate dosing, lack of client compliance, reinfection, or concurrent disease.

Cryptosporidium parvum

Cryptosporidium is a coccidian parasite that can cause anything from nothing to transient to life-threatening disease. Diagnosis is made with a fecal ELISA or IFA, although be aware that like Giardia, Cryptosporidium is shed intermittently. There are very few treatment options available in cats; azithromycin (5-10 mg/kg PO q 24 hours for 14 days) has been successful in anecdotal reports.

Summary

- A number of viral causes of kitten diarrhea have not been covered (calicivirus, rotavirus, astrovirus, enteric coronavirus; definitive diagnosis is difficult and treatment is largely supportive care
- A number of bacterial causes of kitten diarrhea have not been covered (salmonella, campylobacter, clostridium, colibacillosis; definitive diagnosis is difficult and treatment is largely supportive care
- Kittens are particularly susceptible to the effects of dehydration, lack of nutrition, and thermoregulation; once again highlighting the importance of all aspects of supportive in these small patients.

References

Truyen U, Addie D, Belák S, et al. Feline panleukopenia: ABCD guidelines on prevention and management. J Feline Med Surg 11:538-546, 2009.
Levy J, Crawford C, Hartmann K, et al. AAFP feline retrovirus management guidelines. J Feline Med Surg 10:300-316, 2008.
Pederson MC. A review of feline infectious peritonitis virus infection: 1963-2008. J Feline Med Surg 11:225-258, 2009.
Marks SL, Willard MD. Diarrhea in kittens. In, August, JR (Ed), Consultations in Feline Internal Medicine, vol 5. Elsevier, St. Louis, MO., p 133, 2006.
Tritrichomonas information found at http://www.cvm.ncsu.edu/docs/personnel/gookin_jody.html

Novel Therapies for Feline Chronic Enteropathy

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Whether it is from internet research, social media, TV advertising, or personal experience, our clients are becoming increasingly aware of therapies beyond those traditionally utilized in our treatment of gastrointestinal disease. Hence, we must make every effort to stay at least one step ahead of our clientele, and take that step using as much evidence-based medicine as possible to support our commentary and our recommendations. This is not an easy task, but it is an important one if we hope to maximize the effectiveness, both therapeutic- and cost-, of our treatment regimens.

Probiotics

Our knowledge of the GI microbiome is still incomplete. We know there are normal inhabitants, such as Firmicutes, Bacteroidetes, Fusobacteria, etc.; we know there are pathogens including various Clostridium, Campylobacter, Salmonella, and Escherichia spp; and we know that "dysbiosis" is a common finding in dogs with chronic diarrhea as a result of GI disease.

What we know about the use of probiotics in GI disease is even more incomplete. We know that to have any chance of being beneficial, the probiotic supplement must 1) contain a lot of organisms – current human trials are often using orders of magnitude higher doses than those found in veterinary studies; 2) those organisms must be alive; 3) probiotic effects are likely to be rapid onset with minimal staying power once discontinued; 4) probiotics are assumed to work by changing the make-up of the intestinal microbiota, but may in fact exert effects in other ways; 5) fortunately, like cobalamin, probiotics seem to belong on the same "do no harm" poster, with very few and very extra-ordinary exceptions.

Probiotics in the Feline Veterinary Literature

Citation	Population (n)	Key	Reported Effect
Marshall et al AJVR 2006	Healthy adult cats (12)	2	↑ Lactobacillus, ↓ Clostridium & Enterococcus
Veir et al Vet Ther 2007	Kittens (9)	1	↑ CD4+ cells
Lappin et al JFMS 2009	Chronic FHV-1 cats (12)	1	lessened morbidity
Rishniw et al JFMS 2011	CKD cats (10)	3	Failed to reduce azotemia sprinkled on food
Garcia et al FEMS 2011	Healthy cats & dogs (12/12)	4	↑ abundance of probiotic bacteria in feces
Bybee et al JVIM 2011	Shelter dogs & cats (> 100)	1	Cats sig fewer episodes ≥ 2 days
Hart et al JFMS 2012	Feline chronic diarrhea (53)	4	70% perceived improvement in diarrhea
Lalor & Gunn-Moore ISFM 2012	Tritrichomonas (Abstract)	1	Concurrent Rx reduces recurrence

1 Enterococcus faecium SF68 (FortiFlora); 2 Lactobacillus acidophilus; 3 Azodyl; 4 Proviable-DC (Nutramax)

Cobalamin

As we race to give the injection of our current "do no harm" poster child, vitamin B12, do not lose sight of the fact that cobalamin levels can be used as a diagnostic tool. Many cats with chronic gastrointestinal signs receive cobalamin supplementation regardless of their endogenous level, and so that level is often left unmeasured. But research suggests that the lowest cobalamin levels are frequently found in cats with GI lymphoma, and gastroenterologist are forever struggling with the important distinction between IBD and GI lymphoma. Of course it is not that easy – cats with IBD can have very low cobalamin levels, and cats with GI lymphoma can have normal cobalamin levels, but we start with a clinical diagnosis and test to support or refute that diagnosis. In that capacity, the initial cobalamin concentration could be an important clue.

It was the Ruaux et al. study of 2005 (JVIM) that alerted the profession to the importance and impact of cobalamin supplementation (250 micrograms SQ once weekly) in cats with GI disease and marked hypocobalaminemia (≤ 100 ng/L). Since that seminal study cobalamin levels are being measured in cats with a wide variety of non-GI diseases and hypocobalaminemia may be a significant contributor to a number of conditions. In 2007 Allenspach et al. (JVIM) identified hypocobalaminemia (≤ 200 ng/L) as a significant risk factor for a negative outcome for dogs with chronic enteropathies, and a cobalamin less than 150 ng/L is suggestive of GI lymphoma in cats.

Stem cells

The most commonly diagnosed Feline Chronic Enteropathy is inflammatory bowel disease. IBD in cats is not subdivided into ulcerative colitis and Crohn's disease, as IBD is in human patients. The cytokine profile in cats with IBD compared to cats with non-IBD GI disease shows an increase in both immunomodulatory cytokines IL-10 and TNF-β as well as the proinflammatory cytokines IL-6, IL-18, TNF-α, and Il-12p40. In a separate study the proinflammatory cytokines IL-1, IL-8, and IL-12 were increased in cats with IBD. Clearly there is significant immune dysregulation in feline IBD, and although the cytokine profile is complex and incompletely understood, it appears consistent with a Th1 response, as seen in humans with Crohn's disease. The trophic properties along with the

anti-inflammatory and immunomodulatory effects of MSC administration make it a theoretically beneficial therapeutic modality for the treatment of feline IBD. The early success reported in animal models and clinical trials with human patients suffering from Crohn's disease further suggest that the use of MSC therapy in feline IBD warrants further investigation. Our laboratory has shown that feline adipose-derived MSC (fMSC) can be generated in large quantities to allow for clinical use, and that these fMSC are plastic-adherent, spindle-shaped cells that possess tri-lineage differentiation capabilities and suppress T-cell proliferation in vitro. Allogeneic fMSC have been safely and repeatedly administered to healthy and diseased cats with no notable side effects. We are currently conducting a blinded placebo control study to evaluate the safety, feasibility, and clinical effect of allogeneic fMSC as a treatment for feline IBD.

What's all this have to do with my clients and their cats?

Adipose-derived feline mesenchymal stem cells ARE NOT embryonic stem cells, and so a significant barrier to their use (those based on philosophical, religious, and ethical beliefs) has been removed. Any client with a keyboard can quickly immerse themselves in the internet enthusiasm for the "silver bullet" potential of stem cell therapy – and then they come to see you! As summed up by Dr. Dori Borjesson, (Cyranoski 2013), many veterinarians offer stem cell therapies to satisfy demanding customers, so "Clinicians are sucked into giving treatment" even in the absence of research to support such treatment.

It appears that currently there are 2 veterinary companies vying for your stem cell business; Vet-Stem (www.vet-stem.com) which offers Vet-Stem® Regenerative Cell Therapy® and MediVet America, LLC, (www.medivet-america.com) which offers an in-house kit. In either case, the majority of these commercial treatments involve patients with orthopedic and musculoskeletal problems: chronic osteoarthritis, soft tissue injuries of the joints, tendons and ligaments, and fractures, although feline gingivitis, kidney disease, IBD, and pulmonary fibrosis are also reported as targets. Neither website provides any references or cites any research on the use of their product in cats with chronic enteropathies, including IBD.

In both cases the process begins with the harvesting of adipose tissue from the patient to be treated (autologous treatment). Vet-Stem has you ship that adipose tissue to their facility for processing, the company returns the injection-ready product (Vet-Stem® Regernerative Cell Therapy®) within 24 hours, at a cost of approximately $2,000 - $3,500, and with the requirement that the veterinarian has completed the company's accreditation course. MediVet America provides a kit for the in-house processing of adipose tissue, producing an injection-ready product in approximately 4 hours, at cost of about $1,800. Both companies claim to have serviced thousands of pets, although neither provides a specific number for the cats that have received treatment.

MediVet America states that "Adult stem cells are highly concentrated in the fat tissue. At this concentration, it is no longer necessary to culture the stem cells to acquire the necessary cell numbers to make a healing impact. The stem cells are contained within a pool of cells in the fat termed the Stromal Vascular Fraction (SVF). The SVF may impart anti-inflammatory effects, add bioactive peptides, and contribute to reformation and architectural organization. These are benefits lost once stem cells are cultured." The company provides a enzyme system to break down the adipose tissue and a filter and antibiotic wash for sterility of the resultant stromal vascular fraction. A key step appears to be the LED light activation of proliferation, differentiation, and induction prior to the reintroduction into the patient. MediVet claims that "we have seen positive clinical improvement in 95% of the arthritic cases performed nationwide."

Vet-Stem processes the adipose tissue within their own facility and returns injection-ready Vet-Stem Regerative Cells (VSRC™) within 24 hours, "a functionally diverse cell population able to communicate with other cells in their local environment." Bob Harman, Vet-Stem, Inc. CEO is quoted as saying there is "an 80% success rate in imp;rovement of quality of life." (Smith 2013). Again, there are no references or cited research on the use of this therapy in cats with chronic enteropathies, including IBD. The website states that Vet-Stem is currently evaluating the use of stem cells for the treatment of IBD, feline CKD, liver disease, immune-mediated diseases, and heart disease. Their website states that cancer, systemic infection, neurologic disorders (including spinal cord injuries), uncontrolled diabetes mellitus, and any organ disease disqualifies a pet for Vet-Stem therapy.

Stem cells - conclusion

- Stem cell therapy is not currently regulated by the FDA.
- "Stem cell therapy" is actually the injection of a heterogenous population of cells, including mesenchymal stem cells, endothelial progenitor cells, fibroblasts, haematopoietic and immune cells, and others.
- A search of PubMed for studies on MSC therapy in clinical cases of feline diseases produces a single pilot study looking at their use in cats with CKD (Quimby 2011).
- Stem cells have become the latest in a long line of therapies in veterinary medicine where our use is fast and far out-pacing our understanding.
- Proceed with optimism and hope, but significant contemplation and caution.

Summary

- Dietary intervention may not be the only therapy, but it must be a part of an effective plan
- It takes 3 strikes before a cat is out; even a different version of a diet-type may hit the mark
- 2 weeks, not 12, or “Thank Heaven I’m not a Dermatologist!”, for a GI diet-trial
- Expand the definition of Dietary Intervention beyond Diets

Acknowledgments

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References

W. Grant Guilford. Nutritional management of gastrointestinal tract diseases of dogs and cats. J Nutr 124:2663S-2669S, 1994.
Zoran DL. Nutritional management of feline gastrointestinal diseases. Top Companion Anim Med 23:200-206, 2008.
Guilford WG, Jones BR, Markwell PJ, et al. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. J Vet Int Med 15:7-13, 2001.
Burns K. Stem cells in theory & practice. *J Am Vet Assoc* 2011: 238:396-399.
Cyranoski, D. Stem cells boom in vet clinics. *Nature* 2013: 496:148-149.
Lopez, MJ. Stem cell therapies: reality in the making. *Clinician’s Brief* June 2013: 69-71.
Smith, K. Silver bullet or flash in the pan? *Trends* (trends.aahanet.org) Aug 2013: 20-25.
Trepanier L. Idiopathic inflammatory bowel disease in cats. Rational treatment selection. *J Fel Med Surg* 2009: 11:32-38.

The Philosophy Behind Feline Triaditis

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Occam's Razor has been at the foundation of medical education since the dawn of time. Dr. Hickam first challenged Occam's Razor while on staff at Indiana University Medical School. Although at one level this debate is one of philosophy, for those of us working with cats, the distinction between these two philosophies has a potentially major impact on the clinic floor. Feline "triaditis" serves as an excellent example.

Definitions

Occam's Razor, expressed in Latin as the lex parsimoniae (law of parsimony), is a principle that generally recommends selecting the competing hypothesis that makes the fewest new assumptions, when the hypotheses are equal in other respects. When discussing Occam's razor in contemporary medicine, physicians speak of diagnostic parsimony. Diagnostic parsimony advocates that when diagnosing a given injury, ailment, illness, or disease a doctor should strive to look for the fewest possible causes that will account for all the symptoms. Hickam's dictum states that it is often statistically more likely that a patient has several common diseases, rather than having a single rarer disease which explains their myriad symptoms. Also, independently of statistical likelihood, some patients do in fact turn out to have multiple diseases, which by common sense nullifies the approach of trying to explain any given collection of symptoms with one disease. The classic examples in Feline Medicine are Chronic Kidney Disease (Occam's Razor) and Diabetic Ketoacidosis (Hickam's Dictum).

Feline triaditis – Hicam's Dictum or Occam's Razor applied to the cat

The origin of the term "triaditis" in feline medicine appears to have been the publication by Weiss DJ et al. (JAVMA 1996) "Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis, and nephritis in cats." In that report we find the following statement:

"The prevalence of IBD (83%) and pancreatitis (50%) was greater for cats with cholangiohepatitis, compared with cats without inflammatory hepatic disease. Thirty-nine percent of cats with cholangiohepatitis had IBD and pancreatitis. Evidence of IBD in association with cholangiohepatitis was characterized by infiltration of lymphocytes and plasma cells into the lamina propria; however, neutrophilic infiltrates also were found in 40% of cats with cholangiohepatitis." For the authors the clinical implication of this finding was that cats with a diagnosis of cholangiohepatitis should be evaluated for IBD and pancreatitis.

Unfortunately, our understanding of the term 15 years later remains rudimentary and speculative, as highlighted in the publication by Clark JEC et al. (JFMS 2011) "Feline cholangitis: a necropsy study of 44 cats (1986-2008)."

"… it is clear that concurrent pancreatitis and IBD occurs in cats with all forms of cholangitis (30%) and that some cats with cholangitis do not have pancreatitis or IBD. It is unknown whether a single pathogenesis relating inflammatory disease of these three organs occurs in cats with all forms of cholangitis. Bacterial and immune-mediated etiologies have been proposed for the various forms of cholangitis. Information regarding etiology of, and predisposing factors for, concurrent cholangitis, pancreatitis and IBD could not be determined in this study. Further investigation is required to better understand the etiopathogenesis of this condition."

Triaditis can be broken down into the component parts; in the original research it was felt that the predominant signs of triaditis were the result of the cholangitis, with pancreatitis and IBD being secondary complications. More recently, with an increased awareness of pancreatitis in cats, and the long-standing popularity of the diagnosis of IBD, rank-ordering the importance of the individual diseases or determining the actual prevalence of the various possible combinations has become problematic.

Feline cholangitis

Cholangitis is the most common primary hepatic disease of cats (hepatic lipidosis is more common, but secondary to another concurrent condition and anorexia in the vast majority of cases). There are 3 distinct forms of cholangitis in cats: Neutrophilic (bacterial), Lymphocytic, and Chronic cholangitis associated with liver fluke infection.

Although clinical signs can be non-specific (anorexia, weight loss, lethargy, vomiting, diarrhea, fever), variable, and overlap extensively, Table 1 attempts to summarize the nomenclature and clinical characteristics of Neutrophilic and Lymphocytic cholangitis.

Neutrophilic (N) acute and chronic	**Lymphocytic (L)**
Younger males	Older, chronic, progressive (European breeds)
Acute, febrile, icteric, lethargic, abd pain	Variable appetite, vomiting, weight loss
+/- Vomiting or Diarrhea	Icteric, ascites
Extra-hepatic biliary obstruction, lipidosis	↑Globulins
↑ALT (although can be normal)	Total bilirubin, ALT, ALP, GGT are all variable
total bilirubin, ALP, GGT are all variable	Bile duct distention, hepatomegaly, mixed echogenicity

CBC shows left shift w/toxic neutrophils	Bile cytology (toxoplasmosis, *Helicobacter*)*
US reveals thickened GB wall	Bile culture (E.coli, other enterics)
Bile cytology (toxoplasmosis, *Helicobacter*)*	Liver touch-prep cytology for bacteria
Bile culture (E.coli, other enterics)	Histopathology for definitive diagnosis

Abd = abdominal; GB = gallbladder; CBC = complete blood count; US = ultrasound

* 22 gauge 1.5 inch spinal needle in a trans-hepatic approach (decreased leakage)

Table 2 summarizes the treatment options for feline cholangitis.

Treatment	Information	Dose
Fluids & Electrolytes	Oral (voluntary), IV, subQ	40-60 Kcal/kg/day
Nutrition	Oral (voluntary), E-tube	40-60 Kcal/kg/day
Cobalamin (vit B_{12})	Taper after 6 weeks	250–500 µg SC once per week
Pain management	As covered under Pancreatitis	
(N) Antibiotics	Ampicillin, Cephalexin, Clavimox*	3-6 months
(L&N) Metronidazole	Immunomodulatory & Antibiotic	7.5 mg/kg BID
(L) Prednisolone	Immunomodulation	1-4 mg/kg/day, taper q2wks
(L) Chlorambucil		
Ursodiol	Choleretic, "silver bullet"	10-15 mg/kg q24hr, long term
SAMe	Liver protectant, antioxidant	200 mg q24hr
vit K_1	Dose prior to E-tube placement	5 mg/cat q1-2 days SQ
Lactulose	HE, ptyalism	0.5-1.0 ml/kg PO TID
Neomycin	HE, act within GI tract	20 mg/kg q8–12hr PO
Methotrexate	Confirmed cases of bringing fibrosis	0.4 mg/day divided, q7-10 days

E-tube = esophagostomy feeding tube; cobalamin = DOSE; BID = twice daily; TID = 3 times daily; HE = hepatic encephalopathy

*May combine with baytril; Avoid chloramphenicol, clindamycin, erythromycin, lincomycin, streptomycin, sulfonamides, trimethoprim- sulfas, tetracyclines

Pancreatitis

Feline pancreatitis may occur as one of two forms, or an overlap of the two: Acute Necrotizing (ANP) is the more rare presentation, with acute or chronic Lymphoplasmacytic appearing to be more common. There is no age, sex, or breed predisposition, although some reports find Siamese to be over-represented. The clinical signs can be indistinguishable and include lethargy, anorexia, and dehydration, with icterus, abdominal pain, and hypothermia appearing in the more severe ANP form. Abnormalities on the biochemical profile can include elevations in liver enzyme activity, total bilirubin, and blood glucose. The cats are often azotemic with electrolyte abnormalities, including hypokalemia. Low ionized calcium is a poor prognostic indicator. CBC can reveal a nonregenerative anemia and a leukocytosis is more common than leukopenia. The feline PLI (Texas AM GI Lab) or the SpecfPL (IDEXX), run on a serum sample from a fasted cat, are excellent blood tests for the ANP form (100% sensitivity), while they perform with a bit less sensitivity in cases of mild or chronic feline pancreatitis (60-85% sensitivity). At CSU we have removed amylase and lipase from our biochemical profiles entirely. Abdominal radiographs could be normal or show a loss of serosal detail, a mass effect, or dilated fluid or gas-filled duodenum. Abdominal ultrasound could also be normal, or reveal a hypoechoic pancreas, hyperechoic surrounding mesentery, a mass effect, or dilated common bile duct. Definitive diagnosis is histopathology, obtained either through laparotomy or laparoscopy, but with the caveat that pancreatic disease can be focal and non-uniform.

The cause of either form of pancreatitis in cats is unknown or undetermined in the majority of cases. Differentials to consider include parasites (*Toxoplasmosis, Amphimerus pseudofelineus*), viruses (Herpes and FIP), trauma, hypoperfusion and ischemia, and concurrent disease. It seems unlikely that glucocorticoids, obesity, or high fat intake are causes of pancreatitis in cats.

Table 3 summarizes treatment options for the various forms of pancreatitis seen in the cat.

Acute Necrotizing Pancreatitis (ANP)		
Fluids	Crystalloids & Colloids	Consider Hetastarch, Dextran
Nutrition	NE-tube, E-tube	Crucial for the Cat
Antiemetics	Maropitant	1.0 mg/kg q24 hours
	Ondansetron	0.1-1.0 mg/kg q12-24 hours
Pain management	Buprenorphine	0.005–0.01 mg/kg lingual q 4–8 hours
	Meperidine	1–2 mg/kg IM q 2–4 hours
	Butorphanol	0.2–0.4 mg/kg IM q2–4 hours
	Ketamine or Lidocaine	CRI
Acidity	H2 Blockers, Pantoprazole	0.5–1 mg/kg IV over 15 minutes q24h
Antibiotics	Controversial, Cefotaxime	50 mg/kg IM q8 hours

Plasma	Controversial	20 ml/kg IV
Chronic Pancreatitis		
Fluid support	Oral, subQ, E-tube	Hydration
Nutrition	Highly digestible	Feed the Beast
Cobalamin (vit B_{12})	Taper after 6 weeks	250–500 µg SC once per week
Pain management	Buprenorphine	0.005–0.01 mg/kg lingual q4–8 hours
Antiemetic	Maropitant	1.0 mg/kg q24 hours
Choloretic	Ursodiol	10 - 15 mg/kg q24hours
Antioxidant	SAMe	200 mg/day
Probiotic	Proviable, FortiFlora	As directed by the package insert
Omega-3 FA	Various formulas	2000 mg/day
Steroids	Human Autoimmune disease	5 mg/cat/day
Antibiotics	Broad spectrum	Cover *E. coli*

Feline inflammatory bowel disease

Feline Inflammatory Bowel disease (IBD) is a histopathologic diagnosis for a chronic enteropathy that occurs most commonly in middle-age to older cats. Clinical signs include chronic diarrhea, vomiting, variable appetite, and weight-loss. These signs may be intermittent or persistent, and of variable severity. In addition to histopathology of the small intestine and colon, additional information can be obtained from more recently available advanced diagnostics, such as immunohistochemistry, flow cytometry, and PCR. Although it is suspected that the luminal bacteria (normal microbiota and/or pathogens) play an important role our lack of understanding of the pathogenesis of IBD often renders current treatments non-specific and unsatisfactory. It is especially important to rule-out as many clinically plausible differentials as possible before settling for a diagnosis of IBD, which, after all, is more correctly termed *idiopathic* IBD. Research has repeatedly demonstrated that an number of cats with chronic enteropathies respond very well, in not completely, to dietary intervention alone, an option which may not be considered if the initial diagnosis is IBD.

Table 4 summarizes the treatments used most frequently in cats with IBD.

Treatment	**Information**	**Dose**
Dietary – decrease antigens	Hypoallergenic, hydrolyzed	Various Brands available
Dietary – increase fiber	Large bowel, Fiber-responsive	
Dietary – avoid high fat	Osmotic diarrhea	
Prednisolone	Anti-inflammatory, immunomodulation	1-2mg/kg BID, taper
Budesonide	Local activity, High first-pass metabolism	1 mg/cat/day, taper
Chlorambucil	Low grade lymphoma	Various schedules
Probiotics	Intestinal microbiota	Beware of “false” advertising

Summary

- Feline patients frequently carry more than one significant disease
- Concurrent diseases may be distinct entities or share a common etiology
- Failure to recognize and address concurrent disease often precludes therapeutic success
- Feline cholangitis, pancreatitis, and IBD may be housed within the same cat
- Histopathology remains the gold standard for diagnosis; gallbladder aspiration is an important adjunct

Failed Therapy for GI Problems: Adversity or Opportunity

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If our patients read textbooks our job would be much easier. If our patients came to us with Presenting Complaints such as "lymphangiectasia", or "low-grade alimentary lymphoma" our job would be much easier. If our patients restricted themselves to one disease at a time, our job would be much easier. If our patients segregated themselves such that the positive predictive value of our diagnostic tests were through the roof, our job would be much easier. And if our prescribed therapy never failed, our job would be much easier. Our job is not very easy. I have learned (or been forced) to embrace the importance of diagnostic dilemmas and developing some form of organized approach to evaluating my therapeutic failures. If nothing else, I have gained a deep appreciation for the connection between diagnostic dilemmas and failed therapy.

The appointment

When a client pays for an appointment they are paying for the clinical expertise of the veterinarian (well, that and the electricity, the receptionist's salary, the mortgage on the building, etc.). The clinical expertise of the veterinarian has a profound impact on how much more the client will pay on diagnostic testing, how effectively and efficiently a diagnosis is identified, and the likelihood the patient leaves the appointment with the correct diagnosis and the appropriate treatment. But even the best clinicians encounter diagnostic dilemmas where the presenting complaint or the clinical signs scream for one diagnosis while much softer signs suggest an alternative interpretation. The gastrointestinal tract offers a number of interesting examples to consider. The gastrointestinal tract also highlights the concept that failed therapy does not mean failure. Instead, failed therapy often represents an important diagnostic clue and if considered thoughtfully, will likely have a significant and beneficial impact on case management.

Basic principles

- Know your drugs before you use them
- Diagnostic tests; Only as good as you are
- Define the Problem: Verify

Failed therapy

- Wrong diagnosis
- Right diagnosis, wrong treatment
- Right diagnosis & treatment, owner?
- Concurrent disease, new disease, progression
- Effective therapy unknown
- Failed therapy a clue to Diagnostic Dilemma

Diagnostic testing

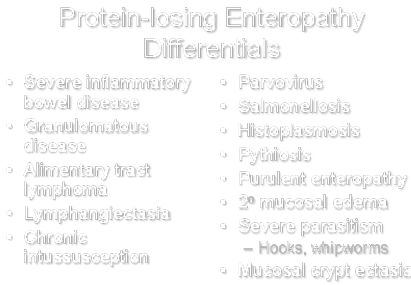
Sensitivity – the proportion of true positives that are correctly identified by the test
Specificity – the proportion of true negatives that are correctly identified by the test

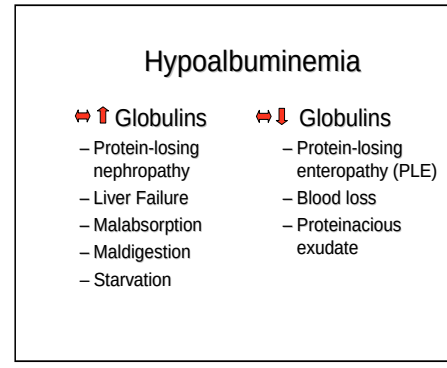
- True positive: Sick pets correctly diagnosed as sick
- False positive: Healthy pets wrongly identified as sick
- True negative: Healthy pets correctly identified as healthy
- False negative: Sick pets wrongly identified as healthy

Positive Predictive Value (PPV) - The ratio of true positives to combined true & false positives; the proportion of pets with positive test results who are correctly diagnosed. It is the most important measure of a diagnostic method as it reflects the probability that a positive test reflects the underlying condition being tested for. Its value depends on the prevalence of the disease.

Case examples

Hypoalbuminemia and protein-losing enteropathies





Although the combination of hypoalbuminemia and hypoglobulinemia is "textbook" for a protein-losing enteropathy (PLE) – assuming the dog is not bleeding out in front of you or has presented with 3rd degree burns over most of its body – it should be noted that a normal, or even elevated globulin level should never be the only reason to take PLE off a list of differentials that was generated by a History and Physical Examination. It should also be noted that PLE is not really a diagnosis at all, but simply a description of the consequences of the severity or chronicity of the actual underlying problem. The diagnostic work-up can begin by adjusting the above list of PLE differentials based on the breed and age of the dog, with IBD being more common in older animals, lymphosarcoma being less particular, and lymphangiectasia preferring certain breeds. Parvovirus and intussusception often occur together in young dogs as does heavy GI parasitism, while histoplasmosis has a geographical distribution.

Once hypoalbuminemia is noted on the biochemical profile and globulins are assessed the clinician needs to confirm that there is no significant loss of protein in the urine (urine protein:creatinine ratio) and the liver is cable of producing adequate protein (other biochemical indicators of liver function followed by a bile acids test if necessary). Other common laboratory abnormalities consistent with PLE include lymphopenia, hypocholesterolemia, hypomagnesemia, and hypocalcemia. It would be unusual for an animal with a PLE not to present with diarrhea, and a thorough fecal examination is an essential part of that diagnostic work-up. In addition, feces can be submitted (Texas A&M GI Laboratory) for measurement of fecal α1-protease inhibitor enzyme quantification, a molecule that is of similar size to albumen but is not degraded in its journey through the GI tract, and hence, and indirect marker of albumen loss and a relatively sensitive (more sensitive than serum albumen?) marker of protein-loss through the GI tract. Be aware of possible significant and clinically relevant electrolyte abnormalities in Ca^{++} and/or Mg^{++}, as well as either Secondary Hyper- or Hypoparathyroidism.

The most direct route to a diagnosis in cases of PLE is histopathology. The advantages and pitfalls of the various techniques available (endoscopy, laparoscopy, and exploratory surgery) is beyond the scope of these notes. It is common for lesions suggestive of lymphangiectasia AND inflammatory bowel disease to be present within the same biopsy sample – the bursting of lacteals and release of their contents is likely to set up an inflammatory response, and the crowding of the interstitial space with cells of the immune system is likely to impede normal lymphatic flow. This makes the site (duodenum versus ileum), depth (mucosal versus full-thickness), and quality of the biopsy of significant importance in final interpretation. The potential diagnostic yield provided by abdominal ultrasound prior to any of the above-listed techniques is also beyond the scope of this discussion, as the literature continues to debate the significance and sensitivity of certain ultrasonographic abnormalities, such as a loss of normal intestinal wall architecture, intra-mural "speckles", or enlarged mesenteric lymph nodes.

Lymphangiectasia

Breed predisposition: Yorkshire terriers and Soft-Coated Wheaten terriers.

NOTE: If endoscopy is planned and lymphangiectasia is a primary differential, administration of corn oil one hour prior to the biopsy procedure may increase the likelihood of documenting dilated lacteals (Drs. Willard and Zoran, Texas A&M).

Treatment Options for Lymphangiectasia	
TPN or PPN	Critical Care setting
Low-fat Diet	Royal Canin, Purina, Iams, Science Diet, etc.
Medium chain triglyceride oil (MCT)	Controversial
Corticosteroids	1-2 mg/kg SID (caution: catabolic hormone)
Oncotic Pressure	Colloids, Plasma, Human Albumen
Rutin	50 mg/kg TID (anecdotal)

Feline hypereosinophilic syndrome

A syndrome that appears to be unique to the Feline, eosinophilic infiltrates are found in the intestinal tract, and the diagnosis may stop there, being deemed Eosinophilic Gastroenteritis. But in this syndrome the GI tract is just part of the pathologic picture, and eosinophils are found to be invading a number of other parencymal organs, particularly the spleen. Cats with this syndrome are usually > 7 years old and most frequently present with diarrhea (often bloody) and weight-loss. Physical examination reveals thickened small intestines, again leading the clinician to conclude that this is only a disease of the tube itself, not the rest of the animal. Peripheral eosinophilia can be seen, sometimes to a minor degree (2,000 cells/μl) and sometimes to an astonishing degree (60,000 cells/μl). The biggest dilemma is the difference in prognosis: garden-variety eosinophilic gastroenteritis should usually respond quite favorably to standard IBD treatment, while Hypereosinophilic Syndrome responds poorly to a similar protocol, and in fact, to most any protocols attempted, ie. the prognosis is quite poor for these patients.

Motility disorders

Motility disorders may be famous enough to warrant their own name, as in Feline Megacolon, but otherwise are often a secondary complication of the more standard enteropathies, or even non-GI systemic disease. Barium and BIPS are messy and variable, leaving us with few diagnostic options when trying to identify motility disorders. Our therapeutic options are also limited, often non-specific,

and all too frequently, quite non-satisfactory. It is important to remember that likely the ideal way to induce normal gastric motility in an abnormal animal (diseased or recovering) is eating!

Drug	Dose	Comment
Metoclopramide	0.2-0.2 mg/kg TID-QID	Efficacy in Question
Cisapride	1.25 – 5.0 mg/cat TID	Compounding Pharmacy
Ranitidine	1-2 mg/kg PO BID-TID	Stim feline colonic activity
Lactulose	2-3 ml PO TID	
Psyllium	1-4 tsp q12-24hr	
Canned Pumpkin	1 tbsp BID	Not Pumpkin Pie filling
Kristalose	¼ to 1 tsp BID	Powdered lactulose
Miralax granules	¼ tsp BID	GoLytely minus electrolytes
Misoprostol	25-50 μg/day	PGE1 stim intestinal motility

Dysautonomia

Clinical signs consistent with a diagnosis of dysautonomia include poor body condition, lethargy, constipation and/or diarrhea (rarely to the point of fecal incontinence), regurgitation and/or vomiting, and anorexia. Signs of urinary dysfunction (i.e. incontinence) can also occur. In addition to overall poor body condition (although at CSU we've also seen dogs that look quite healthy on the outside) physical examination often reveals dry mucus membranes, dilated pupils and raised 3rd eyelids, slow or absent papillary light reflexes, an inappropriately low heart rate, and poor anal tone.

Baseline blood work shows non-specific changes consistent with vomiting, malnutrition, or muscle wasting. Plain thoracic films will often reveal megaesophagus, or fluoroscopy/barium contrast shows esophageal hypomotility. Abdominal films can be particularly striking. The bladder is often large (and flaccid) and the stomach maybe chalked full of food hours after the last meal. The appearance of the intestinal track is frequently interpreted as consistent with a GI obstruction, or in their most extreme state, a mesenteric torsion. This explains why one of the more frequent "diagnostic tests" in cases of dysautonomia is a negative abdominal exploratory surgery.

Once dysautonomia makes it on to the list of differentials there are a number of ancillary diagnostics to perform while resisting the urge to open the animal's abdomen. A Shirmer tear test may reveal "dry eyes", the dog's bradycardia is minimally responsive to atropine, intra-dermal histamine (compared to saline control) fails to elicit a wheal or flare, and dilute pilocarpine (compared to the non-dysautonomic dog in the next cage) leads to an extremely mitotic pupil (denervation hypersensitivity). The simplistic nature of this battery of tests makes us uncomfortable, but if we're lucky, the combination of bizarre results makes us confident in our diagnosis, there just aren't many other conditions that fit. The problem arises if we fail to consider dysautonomia in the first place.

Supportive care (e.g., artificial tears, elevated feedings, expressing the urinary bladder, antibiotics, etc.) is the basis of therapy, as well as parasympathomimetic drugs such as bethanechol and metoclopramide. A low-profile gastrostomy feeding tube can be placed to help the owner provide adequate nutritional support if the patient's megaesophagus precludes effective oral intake. The prognosis for dysautonomic pets is grave and the owner must be committed to providing extensive nursing and supportive care. Even with partial recovery of some faculties, complete recovery is highly unlikely.

Summary

- Diagnostic tests are only as good (Positive Predictive Value) as you are (clinical decisions impacting Prevalence of the Disease in the population being tested)
- Dogs and Cats do not read veterinary textbooks
- Exceptions, incongruities, subtle signs, and things that don't make sense are important
- Therapeutic failure is not failure, but opportunity

Medicine's Cutting Edge: What's New in Gastroenterology (Parts 1 and 2)

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Fecal transplants for refractory diarrhea

There is a controversy as to how much of a pathogen C. perfringens actually represents, however it does appear to cause issues in some dogs. In the study presented 8 dogs with antibiotic refractory diarrhea and persistent C. perfringens PCR tests were examined. All dogs had failed treatment with metronidazole and amoxicillin/clavulanic acid. The dogs were given an enema that contained feces from a healthy donor dog that had been blenderized with sterile saline. This was repeated between one and three times in various dogs. All eight dogs responded extemely well with complete resolution of diarrhea. In 6 dogs the C. perfringens alpha toxin gene expression could no longer be detected.

These results are certainly of interest. Although this study focused on the ability to suppress C. perfringens it is important to remember that all dogs improved, even though 2 still had the organism. It may be better to consider this as a treatment in dogs with non-antibiotic responsive diarrhea. There certainly is a lot of interest in this area in humans where it has been found to be very helpful in the treatment of C. difficile associated diarrhea (resolution of around 90%). The technique is old with some mention of it in the 1940's and 50's, however as the arsenal of antibiotics increased, these treatments lost favor. There has however been the development of antibiotic resistant strains that once again has led to fecal transplant research.

Oral cobalamin supplementation in dogs with chronic enteropathy and hypocobalaminemia

Low cobalamin concentration can be found in dogs and cats with a variety of disorders. Almost all dogs and cats diagnosed with EPI have low cobalamin concentration as do many dogs with chronic enteropathies. The low cobalamin has been associated with continued signs of enteropathy unless corrected. This generally has been done using weekly injections which is of course not necessarily a desirable way to treat a patient. Researchers from Sweden carried out a retrospective study in dogs diagnosed with a low cobalmin and signs of a chronic enteropathy that were treated with oral cobalamin. Supplementation was somewhat empiric with dogs <20 kg getting 1/4 of a 1 mg tablet per 10 kg of body weight and dogs >20 kg getting 1 mg daily. Serum cobalamin concentration had to be less than 200 pmol/L to be included in the study.

A total of 39 dogs were included in the study. At onset median cobalamin concentration was 178 (range 117-199 pmol/L).The median follow up increase in cobalamin concentration (20-195 days after starting supplementation) was 534 pmol/L (range 54 to 1305 pmol/L). This difference was statistically significant.

This study is quite interesting as it does suggest that oral supplementation with cobalamin may be a viable alternative to injections to normalize cobalmin concentration. The statistics do show that response is quite variable however and it would certainly be indicated to monitor cobalmin concentrations to see if there is a significant increase in cobalamin concentration if oral supplementation is used. In those patients that fail to have a significant rise in concentration it may be advisable to use injections. What is unanswered is if there is a difference in the clinical response to oral vs. injection for cobalmin supplementation. It would also be interesting to see if this helps with EPI.

References

ORAL COBALAMIN SUPPLEMENTATION IN DOGS WITH CHRONIC ENTEROPATHIES AND HYPOCOBALAMINEMIA. L. Toresson, J.M. Steiner, J.S. Suchodolski, T. Spillmann. J Vet Int Med 2014:28;1044

USE OF FECAL TRANSPLANT IN EIGHT DOGS WITH REFRACTORY CLOSTRIDIUM PERFRINGENS ASSOCIATED DIARRHEA. T. Murphy, J. Chaitman, E. Han. J Vet Int Med 2014:28;1047

Pancreatitis in Cats

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Pancreatitis is a common problem in cats and as with most things, cats are not small dogs. Clinical signs and outcomes tend to be different between the two species. As with dogs, pancreatitis needs to be on the differential list for most cats with signs of gastroenteritis. Diagnosis is not always straightforward, though this generally does not have a major impact on therapy as therapy for gastroenteritis and pancreatitis are very similar in cats.

Signalment and risk factors for pancreatitis

Most cats with pancreatitis are middle age or older. There is an association between GI disease, hepatic disease and pancreatic disease that is termed "triaditis" by some authors. This is based on a research paper that found an association with these diseases, however it was very specific forms of disease. Making a global association between these various diseases is not supported by scientific evidence.

Clinical signs

Clinical signs are variable, though generally less severe than in dogs. Anorexia is common as is lethargy. Pancreatitis is a common cause of hepatic lipidosis, so that the signs of HL may predominate. Pain on abdominal palpation is also much rarer. With chronicity, weight loss can occur. In cats necrotizing pancreatitis can also have a very rapidly fatal course, though clinical signs also tend to not be very specific.

Diagnosis

There is no test that says a patient does or does not have pancreatitis. This is especially true since many other diseases can have pancreatic involvement without pancreatitis being the major issue (i.e. foreign body).

Imaging

Radiographs can show non-specific changes. Ultrasound is better, but sensitivity and specificity can be quite variable (usually severe cases can be diagnosed, but with mild cases common degenerative changes to the pancreas can mimic pancreatitis).

Laboratory testing

The results of routine blood and urine analysis are not diagnostic, though at times they can help to assess severity (especially the CBC) and if concurrent issues such as diabetes are present. There may also be indications of cholestasis present. In cats hypocalcemia can be a clue to pancreatitis.

Amylase and lipase

Sensitivity and specificity are very poor in cats and as such these analytes are of no value in the diagnosis of pancreatitis.

TLI

The TLI assay is not sufficiently useful to rely upon to rule pancreatitis in or out.

fPLI/fPL

This test can be useful in diagnosing pancreatic disease, however the test is not specific nor necessarily sensitive (depending on cut off around 60 to 80% for sensitivity and specificity). It is also important that a positive test not be interpreted in a way that stops the clinician from looking for other reasons for the clinical signs present (i.e GI foreign body) as this could result in major issues not being diagnosed.

Treatment

There is no specific therapy for pancreatitis, the therapy that is needed is extremely good supportive care. Fluid therapy is a major part of therapy for pancreatitis. By providing fluids, acidosis and hypoperfusion are limited which can contribute to progression of disease. Buffered crystalloids are generally preferred over other crystalloids. A fluid therapy plan should of course address any dehydration present to minimize the impact of hypoperfusion, especially to organs sensitive to this such as the kidney and GI tract. In those patients where peripheral edema becomes an issue or where blood pressure cannot be maintained with crystalloids, colloids such as Pentaspan or Hetastarch can be used.

Anti-emetic therapy is important in those cases where ongoing vomiting or nausea are major issues, though this is rarer in cats.

Analgesia is an important part of treating pancreatitis in cats that show signs of pain. Pain severity will be variable and as such analgesic protocols should be adjusted. Buprenorphine is a good choice in many cases.

The use of prophylactic antibiotics in humans and dogs with pancreatitis is controversial. In cats there is little indication for their use unless an infection is diagnosed (i.e. aspiration pneumomia).

Nutrition is vital in cats with pancreatitis as they can not infrequently develop hepatic lipidosis if anorexic. Appetite stimulants rarely are efficacious enough to consider them as a viable option. Feeding tubes are generally the preferred way to provide nutrition. Given that cats can be quite unstable initially, placement of a naso-esophageal feeding tube is often the first step to meeting the

nutritional needs of cats with pancreatitis. This allows feeding of a liquid diet. CRI administration is better than bolus administration as it seems that tolerance to feeding is bettter (less nausea and vomiting). In many cases this is adequate to allow the cats to stabilize and start to eat on their own. If signs are persistent, placement of an esophageal or gastrotomy tube can be considered for longer term therapy, especially if the patient is to be discharged from the hospital.

References; Available on request from the author

Pancreatitis in Dogs

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Pancreatitis is a common problem in dogs and needs to be on the differential list for most adult dogs with signs of gastroenteritis. Diagnosis is not always straightforward, though this generally does not have a major impact on therapy.

Signalment and risk factors for pancreatitis

Most dogs are middle age or older. Miniature Schnauzers, Poodles and Yorkshire Terriers appear to be predisposed, though the evidence for this is limited.

Other concurrent disease processes may predispose patients to developing pancreatitis. Diabetes mellitus, hyperadrenocorticism and hypothyroidism may all increase the risk of pancreatitis as may the history of prior GI disease.

Medications have been associated with an increased risk of pancreatitis. Agents implicated include, potassium bromide, phenobarbital, azathioprine and furosemide to name a few.

A risk factor that is often discussed is dietary indiscretion. Dogs that consume unusual foods (i.e. get into table scraps or the garbage) have a higher incidence of pancreatitis.

Acute pancreatitis may develop from decreased perfusion to the pancreatitis. This can be seen with shock, general anesthesia and other causes of hypotension and hypoperfusion.

Clinical signs

Clinical signs are variable, from mild anorexia and mild GI signs to rapidly progressive shock and death. No changes are present that are specific enough to rule pancreatitis in or out. Common clinical signs are anorexia, vomiting and cranial abdominal pain. Depending on how severe the pancreatitis is, other signs such as fever, dehydration, hypothermia, or hypotension can be present. If the pancreatic inflammation has been present for several days, icterus may become visible, generally secondary to obstruction of the common bile duct.

Diagnosis

There is no test that says this patient does or does not have pancreatitis. This is especially true since many other diseases can have pancreatic involvement without pancreatitis being the major issue (i.e. foreign body).

Imaging

Radiographs can show non-specific changes. Ultrasound is better, but sensitivity and specificity can be quite variable (usually severe cases can be diagnosed, but with mild cases common degenerative changes to the pancreas can mimic pancreatitis).

Laboratory testing

The results of routine blood and urine analysis are not diagnostic, though at times they can help to assess severity (especially the CBC) and if concurrent issues such as diabetes are present. There may also be indications of cholestasis present.

Amylase and lipase

Sensitivity and specificity are poor. Concurrent gastrointestinal disease or poor renal excretion can increase amylase and lipase.

TLI

The TLI assay is not sufficiently useful to rely upon to rule pancreatitis in or out.

cPLI/spec cPL

This test can be useful in diagnosing pancreatic disease, however the test is not specific nor necessarily sensitive. Prevailing opinion was that it was sensitive (good to rule out pancreatitis) but not very specific (too many false positives). One study that looked at histopathology as the gold standard however showed that specificity was good at the >400 ug/L (90%) but sensitivity was poor (33% at the same cut off). Another major concern was that although it was specific, few of the dogs with pancreatitis had this as the major reason for their clinical signs. This lab test is also commonly elevated with Cushings disease and hyperlipidemia without signs of pancreatitis. It is also important that a positive test not be interpreted in a way that stops the clinician from looking for other reasons for the clinical signs present (i.e GI foreign body) as this could result in major issues not being diagnosed.

Treatment

There is no specific therapy for pancreatitis, the therapy that is needed is extremely good supportive care. Fluid therapy is a major part of therapy for pancreatitis. By providing fluids, acidosis and hypoperfusion are limited which can contribute to progression of disease. Buffered crystalloids are generally preferred over other crystalloids. A fluid therapy plan should of course address any dehydration present to minimize the impact of hypoperfusion, especially to organs sensitive to this such as the kidney and GI tract. In those patients where peripheral edema becomes an issue or where blood pressure cannot be maintained with crystalloids, colloids such as Pentaspan or Hetastarch can be used. Plasma has been anecdotally suggested to be useful for pancreatitis, however studies in dogs and

humans have not shown any clinical benefit. The beneficial effect was attributed to providing substances such as coagulation factors, alpha 2 macroglobulin, and others that are depleted in the course of pancreatitis. Of course, plasma is an excellent colloid. They can be considered in those patients with DIC, though even in these cases it is unclear if there is any benefit.

Anti-emetic therapy is important in those cases where ongoing vomiting or nausea are major issues. A wide variety of products can be used and response will be variable. Maropitant (Cerinia©), metoclopramide, ondansetron/dolasetron and chlorpromazine are all options. Generally I avoid use of metoclopramide as it may in theory limit pancreatic perfusion and in my hands is at best a poor anti-emetic.

Analgesia is an important part of treating pancreatitis in dogs. Pain severity will be variable and as such analgesic protocols should be adjusted. In most patients opiods will be needs. The more potent of these preparations can however also lead to clinical issues such as vomting, regurgitation and anorexia. This can be minimized by using CRIs over bolus administration. Buprenorphine is a good choice in mild cases, in cases with more signs of pain use of hydromorphone, ketamine and possibly lidocaine need to be considered.

The use of prophylactic antibiotics in humans with pancreatitis is controversial. In dogs there is little evidence that bacteria play a role with acute pancreatitis. As such their routine use is not advisable. They can be considered in those patients where there is a suspicion of bacterial infection (i.e. aspiration pneumonia) or where the CBC and other clinical data suggest that sepsis, GI necrosis or pancreatic necrosis are present.

References; Available on request from the author

GI Formulary: More is not Better

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Gastric ulceration

Prevention is always preferable to treatment. The same applies for gastric ulcers/erosions. In most cases this is of course not possible. One exception is ulceration associated with NSAID administration. The prostaglandin analogue misoprostol (3 to 5 µg/kg q 8h) has been shown to prevent ulcers in humans treated with NSAIDs. Proton pump inhibitors also show promise with this, whereas H2 blockers are not considered efficacious.

A variety of medications are available for treating erosions/ulcers, the majority work by suppressing stomach acid secretion. Both H_2 receptor antagonists and proton pump inhibitors have been used in dogs and cats. It is not uncommon to see gastric acid suppressing agents being combined with sucralfate for the treatment of erosions/ulcers. This does not appear justified since in humans the combination is no more effective than using a single agent.

The H_2 blockers bind to receptors on the acid producing parietal cells. This renders the cells less likely to respond to histamine, gastrin or acetylcholine. Commonly used H_2 blockers used include cimetidine, famotidine and ranitidine. Ranitidine also has prokinetic effects in the GI tract that make it an antiemetic as well. Studies in dogs suggest that these agents do not suppress stomach acid production adequately. Proton pump inhibitors are more effective at significantly decreasing gastric acid secretion since the binding of the drug to the parietal cell is irreversible and inhibits stomach acid secretion. Omeprazole (0.2 to 0.7 mg/kg daily) has been used in dogs and is highly effective.

Sucralfate is a mucosal protectant that is often used with GI erosions/ulceration. It binds to defects in the mucosa, protecting the damaged area. Production of prostaglandins is also increased which results in increased mucous and bicarbonate production. Many additional effects have been documented as well.

Promotility agents

A variety of purported prokinetic medications are available, though evidence that they work in a clinical patient are limited. Metoclopramide (0.2-0.4 mg/kg q 8h) can be used and has been shown to be a prokinetic in healthy dogs. It has central antiemetic effects as well as speeding gastric emptying. A more potent effect with regard to gastric emptying can be achieved with cisapride (0.1 to 1.0 mg/kg q 8-12h). Erythromycin at low dosages will also promote gastric emptying by stimulating motilin receptors in the GI tract (0.5 to 1.0 mg/kg q 8h). Oral ranitidine and nizatidine also have prokinetic effects because they inhibit acetylcholinesterase activity thereby increasing parasympathetic tone.

Antiemetics

Antiemetics are commonly used in veterinary practice. By reducing nausea they improve the condition of the patient. They also reduce loss of fluids and electrolytes caused by persistent vomiting. Antiemetics can act at various receptors. Some are specific to individual receptors whereas others may influence multiple receptors. In patients response to a specific antiemetic can be variable so that various agents or combinations may be needed to achieve the desired therapeutic benefit.

Metoclopramide is a commonly used antiemetic. It can be given via intermittent subcutaneous injections (0.2 –0.4 mg/kg q 6 h, SQ, IM) or via a constant rate intravenous infusion (1-2 mg/kg/day). The latter appears to be more efficacious. This medication predominantly affects the D_2 dopaminergic receptors in the CRTZ and gut. It also affects the 5-HT_3 serotonergic receptors in the CRTZ.

Phenothiazines such as chlorpromazine (0.2 – 0.4 mg/kg q 8h SQ) or prochlorperazine (0.5 mg/kg q 8h SQ or IM) are broad spectrum antiemetics with activity at the α_2-adrenergic, D_2-dopaminergic, histaminergic, and cholinergic receptors. These medications are a good choice in those patients that fail to respond to metoclopramide, it is possible to use both agents concurrently. They can cause hypotension and this should be monitored for. Sedation is also usually quite pronounced.

A limited number of medications are specific to the 5-HT_3 serotonergic receptors. Ondansetron (0.5 – 1.0 mg/kg q 12 to 24h PO) can be helpful in some cases of vomiting associated with stimulation of the CRTZ.

H_1-histaminergic receptor antagonists include diphenhydramine (2 – 4 mg/kg q 8h PO) and dimenhydrinate (4 – 8 mg/kg q 8h PO). These can be used for the treatment of motion sickness or vestibular disease.

Erythromycin at low dosages (0.5 – 1.0 mg/kg q 8h) can also be an antiemetic by stimulation of the motilin receptors that increase GI motility and promote gastric emptying.

Maropitant is a veterinary specific antiemetic that is widely used. It is a NK 1 receptor antagonist. It is approved for use in dogs older than 8 weeks of age and for 5 consecutive days. Efficacy is good, probably as good as most other antiemetics.

References; available upon request from the author

Constipation in Cats

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Constipation is a frequent complaint middle aged to older cats. In some cases the disease becomes refractory enough to treatment that either subtotal colectomy or euthanasia have to be considered. The problem is thought to be caused by underlying metabolic problems in some patients such as kidney disease or other issues that generally result in dehydration. These are however relatively rare and do not generally cause clinical signs. Most clinical cases of recurrent constipation/obstipation are idiopathic in nature. Pelvic abnormalities and strictures represent some of the occasional causes of this problem that can be identified with work up as is nerve trauma to the sacral region. Megacolon represents the extreme manifestation of obstipation/constipation. In cats with megacolon abnormal smooth muscle cell function of the colon has been detected though this was in cats with advanced disease so it is uncertain if this was truly the cause or a manifestation of chronic constipation.

The consequences of constipation/obstipation usually are metabolic derangements. With prolonged problems endotoxemia and even death can occur. Long term this can also lead to megacolon, though in many cases megacolon can occur without a clear history of constipation/obstipation.

Treatment

A variety of treatments have been recommended for the constipated/obstipated cat as well as the cat with megacolon.

Initial management

When initially presented relieving the constipation is indicated. This can be done with a variety of ways, whereby manual disimpaction is the least “nice” of the options and should be reserved for refractory cases. Enemas can often be helpful to help to moisten dried out feces. In general 5 to 10 ml/kg of warm water can be given as an enema. Alternatively smaller volumes of DSS (5 to 10 ml total dose) can be given, though this is more irritating. This can be supplemented with oral lactulose and fluid therapy to maximize efficacy.

Recently we have adapted the use of PEG solutions administered via NE tube to help relieve obstipated/constipated cats. This is similar to methods used in humans. We give PEG solution as a slow trickle via NE tube (4 to 18 hours). This generally results in defecation within 6 to 12 hours. Obviously before embarking on this therapy it is wise to rule out obstructions of the GI tract that would make passing feces difficult or impossible. To date we have not had any significant adverse side effects and have not had to resort to manual disimpaction. In some cases enemas were given concurrently, thought this does not appear to be necessary.

Long term management

Ultimately in those cats where the problem constantly recurs, surgical intervention may be needed. Medical therapy (life-time) can in many cases avert the need for surgery or significantly delay the need for surgery.

Diet is an important part of management and it is difficult to be sure which diet is best in each individual case. Increased fiber and low residue diets are the most popular.

Fiber has been recommended for many years. This can be a psyllium product (Metamucil 1-4 tsp per meal), pumpkin pie filling or wheat bran. Fiber has been shown in humans to be only moderately effective as a laxative.

Lactulose is also a very good option for maintaining soft stools. The dosage is 0.5 ml/kg two to three times daily. Dosage is adjusted to obtain the stool quality desired. In humans this product is known to cause flatulence and GI cramping. A powder form is available that may be better tolerated in cats. Recently PEG containing laxatives (Miralax) have been recommended for use in cats. In humans PEG laxatives have been shown to be safe and effective with few adverse side effects. These products have been recommended in cats though there is no published data showing efficacy or safety. We did carry out a study in 6 cats and did not see any clinically significant adverse effects. Dosage was quite variable, so individual dose titration is recommended. Starting at ½ to ¼ of a teaspoon twice daily is a good starting point.

Prokinetic medications are vital to managing the chronically impacted cat. Cisapride (2.5 to 5 mg/cat q8 to 12 hours) has helped many cats avoid surgery for megacolon. It can be obtained from many compounding pharmacies. Other medications are available as well, however in most cases Cisapride is adequate.

References

Candy DCA, Edwards D, Geraint M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PGE + E) followed by double-blind comparison of PEG + E versus lactulose as maintenance therapy. Journal Pediatric Gastroenterology and Nutrition 2001; 43:65.

Ramkumar D, Rao SSC. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastrorenterol 2005;100:936.

Washabau RJ, Holt DE. Diseases of the large intestine. In Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine, 6th ed. St. Louis, Elsevier, 2005.

EPI:
Not Such a Zebra

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EPI in dogs

What is exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency (EPI) is a condition where the pancreas no longer produces adequate amounts of digestive enzymes. Clinical signs usually will not occur until over 90% of the exocrine pancreas has become non-functional. The majority of cases in dogs are caused by pancreatic acinar atrophy, though some may also develop because of chronic pancreatitis. Clinical signs develop because digestion no longer occurs properly leading to malabsorption with weight loss and diarrhea. Maldigestion and malabsorption does not just result from the enzyme deficiency. The disease also leads to changes in small intestinal digestive processes. Small intestinal bacterial overgrowth (SIBO) is also frequently seen and can contribute to the diarrhea seen. Low cobalamin levels are also seen which may play a role with small intestinal disease in these dogs.

What is pancreatic acinar atrophy

Pancreatic acinar atrophy (PAA) is a condition where a normal pancreas undergoes atrophy. A familial predisposition in German Shepherds and rough-coated collies has been established. It can however occur in any breed with large breed dogs being more commonly affected.

What is a typical signalment for EPI

Since PAA is the most common cause of EPI many of the patients are German Shepherds. They tend to be young animals, usually under 2 years of age.

What are the clinical signs of EPI

Signs of EPI are relatively typical, though they can be caused by other diseases as well. Dogs with EPI can have profuse diarrhea. The bowel movements are often malodorous. Borborygmus and flatulence are common. These patients will have a ravenous appetite yet continue to lose weight. Poor hair coat is common because of the malnourishment present. On occasion other signs such as vomiting, coprophagia, pica and anorexia can be seen.

Routine clinical pathologic tests rarely document abnormalities. Folate levels may be elevated and cobalamin concentration decreased in dogs with EPI. This may be from SIBO, however the cobalamin deficiency may also occur because the pancreas produces a factor needed for cobalamin absorption that can be lacking in dogs with EPI.

How is EPI diagnosed

EPI is generally diagnosed with pancreatic function tests. Canine TLI is currently the preferred test for EPI. The animal should be fasted 12 hours to collecting serum for analysis. Low TLI concentration in patients with typical clinical signs are considered highly diagnostic. Low TLI values can be found in dogs without clinical signs. Many other tests have been tried but none are superior to TLI.

How is EPI treated

Treatment of EPI hinges on enzyme replacement and nutritional intervention. Powdered pancreatic enzymes work best and are used at 1 to 2 teaspoons per meal. There is no need to pre-incubate the food. Alternatively fresh pancreas (50-100g/meal) can be used. The majority of the enzymes are destroyed in the stomach so some dose titration may be needed. Although raw pancreas results in higher GI lipase activity, response rates between powdered enzymes and raw pancreas were comparable.

In these patients it is vital to manage their diet carefully. Initial management can be with a high quality maintenance diet. Fat restriction should not be attempted initially, in fact fat supplemented diets may be a consideration if body condition cannot be improved. If this results in persistent diarrhea, a fat restricted, highly digestible diet should be tried. Cobalamin injections can be given (250-500 µg, repeat as indicated by serum levels), especially to those patients that are responding poorly to therapy. Cobalamin concentration can be determined via a blood test. Vitamin absorption may generally be inadequate in these patients so that use of vitamin supplements is prudent. Antibiotics are indicated if SIBO is suspected to be contributing to poor therapeutic response. Metronidazole, tylosin and tetracyclines are all good options for this. Tylosin may be preferable as it seems to be very good at treating chronic diarrhea in dogs.

What is the prognosis for EPI

Generally the prognosis is good, especially if the initial response to therapy is good. Around 60% of dogs will do very well, 10% get better and 20% do poorly. With a poor initial response overall survival seems shortened. Cobalamin deficiency has been the only factor that seemed to correlate with how well the initial response was. Factors that did not have an effect were the type of supplement used, additional drugs used or diet used.

EPI in cats

The diagnosis of EPI in dogs and cats has become more common as the assay for feline trypsin-like immunoreactivity (fTLI) became available. The test is considered diagnostic for EPI if a concentration of < 8 µg/L is found. Previous to this diagnosis was complicated based upon clinical signs and a variety of fecal digestion assays. There is relatively little information on EPI in cats that has been published. There have been individual case reports as well as 3 case series that included 41 cases.[1-3] These case series showed that weight loss was the most common clinical sign of EPI in cats. Diarrhea was common, but not present in all cats and often not like the "typical" feces noted in dogs (voluminous, malodorous, steatorrhea). Polyphagia was uncommon. Age range was quite broad from 3 months to 16 years with the majority being middle aged. Although these case series are interesting they only provide information on a small number of patients, considering that in 2010 there 775 samples submitted to the Gastrointestinal Laboratory at Texas A&M University with fTLI concentrations consistent with a diagnosis of feline EPI.[4]

At the 2011 ACVIM Forum in New Orleans a research abstract was presented by researchers from the GI Laboratory and Department of Clinical Sciences at Texas A&M.[5] The researchers searched their database for cats with a TLI concentration below 8 µg/L found over a 15 month period. Questionnaires were sent to the veterinarians that had submitted the samples, with 150 surveys being returned. There were many breeds involved and it did not seem that there was a clear breed predilection, though this could not be definitively determined with this type of study. Mean age of the cats was 8.1 years ± 4 with 41% being female and 59% male. Body condition was poor with a median of

3/9. Of the cats that had cobalamin determined, 77% were deficient with many of them having undetectable concentrations. Folate was increased in 47% of the cats where it was determined.

The most common clinical sign in this study was weight loss which was seen in 91% of the cats. The amount of weight loss varied widely from 40 grams to 6.82 kg with a median of 1.4 kg. Loose stools were seen in only 62% of the affected cats. Other clinical signs included poor haircoat (50%), anorexia (45%), increased appetite (42%), depression (40%), watery diarrhea (28%), and vomiting (19%). Concurrent diseases were also quite commonly reported (58%). The most common ones were inflammatory bowel disease (IBD, 21%), diabetes (14%), pancreatitis (11%) and hepatic lipidosis (6%). Of the affected cats 68% were treated with pancreatic enzyme supplementation with a good response in 66%, partial response in 24% and poor response in 10%.

This study is interesting on many levels. It is the largest study to date so the clinical information is very valuable. There are of course potential methodological issues with survey studies that introduce bias depending on high the response rate, though in this case they do not detract from the clinical relevance of the data. EPI in cats is certainly not as rare as we once thought it was. The clinical presentation deviates significantly from the typical presentation in a dog. Weight loss is certainly common in both dogs and cats and can be quite pronounced, however in cats diarrhea is clearly not a consistent finding. The diarrhea also appears to be much less severe when it is seen and often does not have the characteristics we expect to see such as large volume, highly fluid and greasy appearing stools. Polyphagia does occur in some cats, however almost half the cats were reported to have a decreased appetite.

A variety of concurrent diseases were found, most of them are not surprising. The etiology of EPI in cats in most cases probably relates to chronic pancreatitis and easily explains the 11% of cats that were thought to have pancreatitis in this study.[1-4] In dogs it usually is related to pancreatic acinar atrophy which may also be the cause of EPI in very young cats.[4] With chronic pancreatitis you can also see the development of endocrine pancreatic insufficiency, e.g. diabetes. Hepatic lipidosis has also been linked with pancreatitis. IBD was reported in 21% of the cats with EPI which may well have to do with what is termed triad disease or triaditis. In cats it has been shown that there is a statistical association between IBD, pancreatitis and cholangiohepatitis.

Treatment for EPI with pancreatic enzyme supplementation was successful in a significant percentage of the cases. The cats with EPI also had other issues that might have impacted management. Most of the cats had low cobalamin concentrations. It has been previously shown that in cats with hypocobalaminemia supplementation of parenteral cobalamin is often needed to resolve GI signs (250 µg subcutaneously weekly for 6 weeks, then once monthly with periodic checks of serum concentration). In addition the presence of EPI may be associated with small intestinal dysbiosis (formerly termed small intestinal bacterial overgrowth). The low cobalamin and high folate would certainly point toward this diagnosis. If pancreatic enzyme supplementation and cobalamine injection do not resolve signs, consideration should be given to antibiotic therapy. Dietary therapy is also very important, though to date there are no studies that tell us which diets to preferentially use.

This study does point out that EPI is not as rare as we thought and it would seem prudent to test for fTLI concentration in cats with unexplained weight loss or chronic diarrhea, even if they are very young. The presence of hypocobalaminemia should also increase the suspicion that EPI is present. It should also be considered in those cats with diabetes that appear to have good glycemic control but consistent weight loss or diarrhea. In the unexplained weight loss cases where blood work, T4, thoracic radiographs and abdominal ultrasound did not establish a diagnosis, I would often perform endoscopy to determine if occult neoplasia or some form of IBD was present. Based on this study, I will certainly have fTLI, cobalamin and folate determined prior to this more expensive and invasive diagnostic procedure.

References

1. Steiner JM, Williams DA. Serum feline trypsin-like immunoreactivity in cats with exocrine pancreatic insufficiency. J Vet Intern Med 2000;14:627-629

2. Kook PH, Zerbe P, Reusch CE. Exokrine Pankreasinsuffizienz bei der Katze. Schweiz Arch Tierheilk 2011;153:19-25.

3. Thompson KA, Parnell NK, et al. Feline exocrine pancreatic insufficiency: 16 cases (1992-2007). J Feline Med Surg 2009;11:935-940.

4. Steiner JM. Exocrine pancreatic insufficiency in the cat. Topics in Compan An Med 2012;27:113-116.

5. Xenoulis PG, Wooff P, et al. Feline exocrine pancreatic insufficiency: 150 cases. J Vet Intern Med 2012;26:765.

Zoonotic GI Diseases: What You Don't Know Can Hurt You

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Zoonotic disease has always been an area where veterinarians have been involved. Zoonotic infections can be viral, bacterial, fungal and parasitic in origin. The veterinary profession has helped protect people from potentially lethal zoonotic infections, for example by widespread vaccination of domestic animals against rabies. Complacency over infectious diseases had increased in industrialized countries with the advent of antibiotics and vaccinations to the point where infectious disease was an issue apparently of little importance. Recent times have shown this assessment to be incorrect with new players such as HIV and more recently SARS. There are however still plenty of old players around that have not went away just because they were ignored, some of them are zoonotic. It is our duty as veterinarians to protect the general public from these threats as best as possible. It is also vital to have an understanding of zoonotic disease to prevent infection of those people routinely involved with large numbers of animals, namely the veterinary health care team including veterinarians. Fortunately many of the zoonotic diseases of concern are preventable or the chances of transmission to humans can be significantly reduced by proper education and management techniques. This article will review some of the diseases to be concerned about, though obviously it is not an all-inclusive list of all zoonotic diseases.

Bacterial zoonoses

Many zoonotic diseases are bacterial in origin. Many of these bacteria are enteric organisms, as a result feces is a major way to spread these infections. Others can be transmitted via bites or scratches such as Bartonella. Especially with enteric bacteria it is important to remember that clinically healthy animals can still harbor pathogenic bacteria. Elimination of these bacteria is often not possible so it is very important that measures are put into place in practices to minimize the risk to other patients, staff and the general public. It is also very important to educate clients to the potential risks, especially if the household has members that are not fully immunocompetent.

Salmonellosis

Salmonellosis has received public attention on occasion. Most cases of this disease are acquired as a result of ingestion of contaminated food. Raw chicken and uncooked eggs are generally recognized as common sources of salmonella infections in man. The risks of exotic pets, especially in regard to turtles have also been widely publicized. Another area that has received some media attention is rawhide chews which can be contaminated with salmonella. Depending upon the source, a large percentage of rawhides and pig ears can harbor salmonella. In one outbreak it was shown that contact with the treats or pets that consumed them was responsible for human salmonellosis.[1] Of 94 pig ear samples from retail outlets 51% were harboring Salmonella. Salmonella was also found in other treats including beef hoof, braided chews and similar products. Of great concern were outbreaks of multidrug resistant Salmonella typhimurium in small animal facilities including an animal shelter and 2 small animal clinics in 1999.[2] In one veterinary clinic the likely source of the infection was a kitten with diarrhea, 10 of 20 employees developed clinical signs. In another instance one affected person was an employee and 2 were clients that had brought their cats to the clinic for treatment. After discharge the cats developed diarrhea and the owners subsequently became ill. This obviously raises the specter of liability for the pet and owner's illness.

It certainly is not surprising that dogs can also harbor Salmonella species. Most recent studies have shown a prevalence of around 1 to 2 % in normal dogs and cats.[3,4] Percentages may be higher in animals with diarrhea. Very high prevalence had been found in racing sled dogs, where 69% of dogs without diarrhea were shedding salmonella.[5] In Greyhounds with diarrhea 61% were positive for Salmonella, in non-diarrheic dogs the percentage was 11%.[6] The increased proportion of Salmonella positive animals in these dogs may relate to the stress of athletic performance or to their diets.

Raw meat can be a source of salmonella infection in dogs. This has been shown in a variety of studies looking at athletic dogs such as Greyhounds and sled dogs that routinely receive uncooked meat as part of their diet.[6] Recently there has been considerable interest in raw diets for pet dogs, the most popular called BARF (biologically appropriate raw food). The internet is replete with sites that popularize this type of diet and it's supposed health benefits. It does however mean that owners are routinely contaminating their environment with potentially infectious materials such as raw chicken. Dogs are not known to be especially clean eaters and it is highly likely that infectious organisms are disseminated throughout the home. In a recent study on a small number of dogs, 30% of dogs fed a BARF diet were shedding Salmonella, 80% of the food samples were positive.[7] This has also been my personal experience where dogs fed BARF diets are positive for Salmonella (2 of 3 tested) even without clinical signs of diarrhea.

Campylobacter

The prevalence of campylobacter closely parallels that of Salmonella in cats, with approximately 1% harboring this infection.[4] The prevalence in dogs is considerably higher in some studies where up to 28% of dogs are infected.[3] Other studies however show the prevalence to also be around 1%.[8] The majority of human cases are acquired by ingestion of contaminated food. The percentage of

poultry with campylobacter is higher than the percentage with salmonella. There is the possibility of spread from dog or cat to man. The majority of dogs will not show clinical signs if infected.

Prevention

Some very simple management techniques can prevent bacterial infections from being transmitted. Hand washing is vital; it should be done between each patient and certainly before eating. Food should also remain out of the area where animals are handled. In those cases with diarrhea or proven infections gloves should be worn when handling the patient and hands washed after removing the gloves. Patients with diarrhea, confirmed or suspected zoonotic infections should also be isolated from other animals, especially those that are very susceptible to infections such as those with major trauma, surgeries or on immune suppressive therapy. Animals fed raw meat diets should be considered carriers of pathogens until proven otherwise. Antibiotics should obviously be used wisely to limit the emergence of resistance strains. Dogs diagnosed with renal failure that do not have an obvious cause, i.e. ethylene glycol intoxication, should be tested for leptospirosis. Even after exposure a short course of antibiotics can prevent clinical disease in humans.

Parasitic zoonoses

Unlike bacterial infections, parasites are much easier to prevent. There are a wide variety of effective deworming medications that can eliminate or at least significantly decrease the chances of contracting parasites. Unfortunately, the indications are that we as veterinarians do a relatively poor job of this. In 1991 a survey of veterinarians showed that recommendations in regard to parasite control were inadequate.[9] Only approximately 1/3 of veterinarians routinely discussed the zoonotic risk of parasites with owners. Almost 2/3 of the veterinarians incorrectly recommended treating intestinal parasites beginning at an age over 4 weeks. Less than half gave preventive anthelmintics to pups and dogs and about 1/3 did not recommend routine testing and treatment of nursing dogs. Approximately three fourths of the veterinarians tested for helminths in pubs. Unfortunately, over half of the respondents did not initiate therapy unless there was a positive fecal test. This is not appropriate since fecals can be negative even when the dogs are harboring adult parasites. Even more shocking was that almost half of the veterinarians surveyed considered roundworms or hookworms of little or no concern as a zoonosis. The majority of veterinarians in this survey did not even come close to properly addressing parasite burdens. More recently a survey was carried out of Connecticut pediatricians and veterinarians.[10] The only comfort we can get from this study is that veterinarians seem to do a better job of discussing zoonosis than physicians. Interestingly veterinarians thought physicians or public health departments were responsible for public education whereas physicians thought it should be public health departments or veterinarians, which means both groups did not feel they had ultimate responsibility in this regard. Considering that ten years had elapsed between studies there was little indication that prevention strategies had improved. Only about 12% of veterinarians began deworming puppies at 2 to 3 weeks of age. The greatest majority (78%) didn't begin treatment till the puppies were over 6 to 7 weeks of age. Slightly more than 50% of veterinarians carry out prophylactic deworming of puppies and kittens, unfortunately almost half of them use an interval greater than 2 weeks as recommended by the Centers for Disease Control. Parasite control is an area where small animal practitioners need to do a much better job in the interest of the pets and the general public.

Roundworms

Roundworms are still of major zoonotic concern. Prevalences vary from 3%[8] to 33%[11]. Prevalences tend to be higher in kittens and puppies, though this may be misleading in that shedding is more intermittent in adults. Zoonotic transmission to humans does occur, with children being especially susceptible to the negative affects. Visceral larva migrans can be a devastating disease. In Connecticut 10.2 to 27.9% of children were seropositive for exposure to roundworms.[10] Thousands of cases are diagnosed each year. Pups acquire Toxocara canis in utero, transmammary or fecal-oral. The adults can become patent and begin shedding eggs at 3 weeks of age. In cats in utero infection does not appear to occur, infection is transmammary or fecal-oral. The eggs are very resistant and can persist for years in the environment.

Prevention

In dogs and cats it is inappropriate to test for intestinal parasites and then not treat because of a negative fecal. Shedding is intermittent and can be low grade. Routine prophylactic deworming is ideal in all patients; the current dewormers available are highly efficacious with a low incidence of side effects. Puppies should be started at 2 weeks of age and should be dewormed every 2 weeks thereafter until 8 weeks old. Kittens can be started at 6 weeks and repeated at 8 and 10 weeks. Four to 6 weeks after anthelminthic therapy is completed it would be advisable to perform a fecal exam to make sure the parasites have been eradicated. Treating the nursing dam is also indicated, as they will often begin to shed heavily around the time of parturition. Many heartworm preventives can also aid in reducing parasite burdens in adult dogs, although the 4 week interval will allow shedding and may not be adequate for heavily exposed dogs. If one of these heartworm preventives is not used then at least annual deworming is recommended, more frequently if indicated by exposure risk (puppies, kennel, etc.). Extensive recommendations for prevention of zoonotic transmission of intestinal parasites from pets to humans can be found on the CDC website at http://www.cdc.gov/ncidod/dpd/parasites/ascaris/prevention.htm. Another part of the CDC website that is well worth surfing is http://www.cdc.gov/ncidod/dpd/parasiticpathways/animals.htm as there are great handouts available that explain about the parasites that can be very informative for clients.

Hookworms

Hookworms can be found in many areas of the country though the southeast appears to have a greater prevalence of Ancylostoma than other regions. Hookworm larvae can penetrate the skin of humans leading to cutaneous larva migrans. More severe manifestations are also possible with skeletal muscle involvement, visceral migrans and human intestinal involvement. Prevention programs are the same as for roundworms.

Tapeworms

The most common tapeworm in dogs and cats, Dipylidium caninum, is not zoonotic. There is increasing concern however about Echinococcus multilocularis. Originally limited to Alaska it is now enzootic to northcentral US and southcentral Canada, though it has been identified in Wyoming, Nebraska, Iowa, Ohio, Indiana and Illinois.[12] The main reservoirs are foxes and coyotes. Ingestion of eggs from this parasite by a human lead to alveolar hydatid disease, a potentially fatal occurrence. The liver and other organs are usually affected, surgery is often not curative. To date only a few people have been diagnosed with this disease, given its spread it is likely this will increase. Since this is a highly fatal disease preventive measures should be instituted. In areas where E. multilocularis is known to be dogs and cats that are predatory should routinely be dewormed with a medication that eliminates tapeworms as well as the other common intestinal parasites.

Given the central role veterinarians play in the healthcare of pets we have a vital role in minimizing the risk of zoonotic disease. We also need to be especially vigilant with these diseases as they can spread to other animals we are caring for or potentially to us or the people that work for us. The surveys that have been done to date do not suggest that we are doing the best that we could. Recognizing the importance of zoonotic disease and providing educational information to pet owners will increase the quality of medicine we practice and good medicine is always good for a practice.

References

Clark C, Cunningham J, et al. Characterization of Salmonella associated with pig ear dog treats in Canada. J Clin Microbiol 2001;39:3962-3968.

Anonymous. Outbreaks of multidrug-resistant Salmonella typhimurium associated with veterinary facilities – Idaho, Minnesota, and Washington, 1999. Morbidity and Mortality Weekly 2001; 50:701-704.

Cave NJ, Marks SL, et al. Evaluation of a routine diagnostic fecal panel for dogs with diarrhea. JAVMA 2002; 221:52-59.

Hill SL, Cheney JM, et al. Prevalence of enteric zoonotic organisms in cats. JAVMA 2000; 216:687-692.

Cantor GH, Nelson S, et al. Salmonella shedding in racing sled dogs. J Vet Diagn Invest 1997; 9:447-448.

Stone GG, Chengappa MM, et al. Application of polymerase chain reaction for the correlation of Salmonella serovars recovered from greyhound feces with their diet. J Vet Diagn Invest 1993; 5:378-385.

Joffe DJ, Schlesinger DP. Preliminary assessment of the risk of Salmonella infection in dogs fed raw chicken diets. Can Vet J 2002; 43:441-442.

Hackett T, Lappin MR. Prevalence of enteric pathogens in dogs of North-Central Colorado. JAAHA 2003;39:52-56.

Harvey JB, Roberts JM, Schantz PM. Survey of veterinarians' recommendations for treatment and control of intestinal parasites in dogs: public health implications. JAVMA 1991; 199:702-707.

Gauthier JL, Richardson DJ. Knowledge and attitudes about zoonotic helminths : a survey of Connecticut pediatricians and veterinarians. Compend Contin Educ Pract Vet 2002; 24 (supplement):4-9.

Spain CV, Scalett JM, et al. Prevalence of enteric zoonotic agents in cats less than 1 year old in central New York state. J Vet Intern Med 2001; 15:33-38.

Hildreth MB, Johnson MD, Kazacos KR. Echinococcus multilocularis: a zoonosis of increasing concern in the United States. Compend Contin Educ Pract Vet 1991; 13:727-740.

Those Troublesome Chronic Diarrhea Cases

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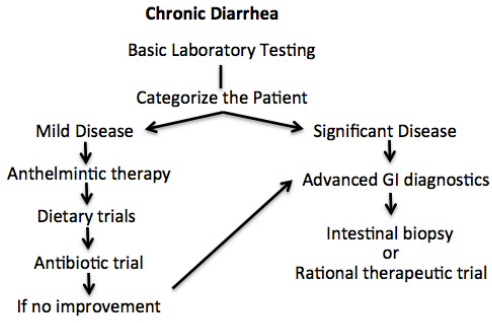
Chronic diarrhea is a common complaint, and the potential etiologies are extensive. Parasites, dietary intolerances, metabolic disease, pancreatic disease, bacterial causes, and inflammatory bowel disease are but a few etiologies of chronic diarrhea. Inflammatory bowel disease (IBD) is a common condition diagnosed in dogs and cats; however, it is not a specific disease but rather a term that describes animals having gastrointestinal (GI) signs with histologic evidence of inflammation within the intestine. IBD does not however describe the etiology, nor does the extent of inflammatory cells parallel the severity of clinical signs. Before beginning extensive diagnostics or obtaining an intestinal biopsy specimen from a patient with chronic diarrhea, there are a few diagnostic tests or trial therapies to consider. Obviously the course of action is predicated in part on a good clinical evaluation and based on the severity of the clinical disease.

Every patient with chronic GI signs should have a thorough history, physical examination, complete blood count, biochemical profile, urinalysis, and fecal examination. In many cases, this initial evaluation will determine if the etiology of the diarrhea is primary GI disease or secondary to other systemic or metabolic disease or if the diarrhea is predominately of small bowel or large bowel origin. For example, Addison's disease, liver disease, and renal disease can all be associated with secondary GI involvement. If the initial workup fails to provide a clue as to the etiology, then begin a specific GI evaluation. The fecal examination should include standard fecal flotation, wet mount preparation, and stained cytology. A stained Diff-Quick cytology may reveal such things as neutrophils, eosinophils, fungal organisms, or clostridial spores and may provide clues about the etiology. This is also the time to classify the patient based on the severity of disease: minimal signs and debilitation or those cases having severe disease obviously requiring an in-depth GI workup. For the animal with relatively mild diarrhea without weight loss or debilitation, I prefer to use trial therapy as part of the clinical evaluation. Trial therapy involves antiparasitic therapy, dietary food trials, and antibiotic therapy. If these trial therapies fail to resolve the diarrhea, further GI evaluation is indicated. Additional diagnostic testing may include imaging studies (ultrasonography is preferred as barium studies are rarely helpful), serology trypsin-like immunoreactivity, folate, cobalamin), and endoscopy or surgery for intestinal biopsies.



Always rule out parasites

Parasites must always be considered in any dog experiencing chronic GI signs.[1] *Giardia* and common nematodes are usually diagnosed using proper fecal examination techniques. Often it is difficult to find *Giardia* cysts on flotation, hence a more accurate way to diagnose *Giardia* is through fecal ELISA, which is highly sensitive and specific. It is important to know that *Giardia* also have antimicrobial sensitivity patterns like bacteria. Therefore, it is currently impossible to predict which anti-*Giardia* drug will be effective in an individual dog or cat. The treatment of choice for years has been metronidazole. Currently, metronidazole at a dose of 25 mg/kg orally twice daily for seven days is preferred; however, there are many different doses and durations of therapy reported (*Table***)**. Neurologic signs associated with toxicity occur at higher doses.

Other suggested *Giardia* therapies include febendazole or febantel for five days.[1] High-fiber diets may help lessen re-infection when given during the therapy. With treatment failure, one should make sure that *Giardia* is truly the problem and also that subsequent recontamination is not occurring. Infection with *Giardia* does not confer immunity. In resistant cases, combined febendazole and metronidazole therapy has been suggested. In difficult cases, bathing the animal before therapy and decontaminating the environment using quaternary ammonium compounds is also recommended. It is controversial whether to treat healthy dogs and cats that test positive for *Giardia* because *Giardia* is generally not considered a significant human health risk. I recommend treating the asymptomatic, positive dog and if on recheck evaluation the patient is still positive but subclinical, I will repeat therapy using a different agent. If the animal remains positive after two therapies, I simply recheck the patient again at the next yearly health evaluation. Some animals are chronic asymptomatic carriers and are very difficult to clear. It is a more significant concern when infected dogs live with immunocompromised individuals or young children.

Young cats with diarrhea

The organism *Tritrichomonas foetus* (TTF) has been identified as a cause of chronic diarrhea in young cats.[2] This organism appears to be genetically similar to that associated with bovine venereal disease. Most of the affected cats are under 1 year of age and are

reported to have a watery to sometimes mucoid diarrhea. It is most often observed in cats from humane shelters or catteries, and Abyssinians and Bengal cats appear to be over-represented or to have a more resistant disease. There are several ways to diagnose TTF. In some cases, a diagnosis can be made by performing a wet mount fecal prep and identifying the organism. A small amount of stool is thinned with warm saline solution, a coverslip applied, and the feces examined at 40X. It is important that the stool is fresh for examination. A colonic flush of saline can also be used to obtain fecal material for cytology and culture. TTF is identified by its progressive forward motion. (In contrast, *Giardia* has a falling leaf motion.) Feces can also be cultured in your practice using the bovine TTF culture technique employing an In Pouch TF™ culture method (Biomed Diagnostic Labs) (*Figure 3*). With these pouches, a very small amount of stool is placed in the broth and cultured at room temperature. The bag is then examined under a microscope 24 to 72 hours later for evidence of motile organisms. Fecal PCR for TTF is offered by many commercial labs and is considered the test of choice for confirming the infection. Ronidazole is the only antimicrobial shown to have efficacy in treating TTF infection.[3] Ronidazole is given at 30 mg/kg q24h PO for up to 14 days. Ronidazole has a very narrow therapeutic range; higher doses or a longer duration can result in neurotoxicity. Ronidazole is not approved for use in the United States and must be obtained through a reliable 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 because a negative PCR result means TTF is a less likely cause of the diarrhea. When left untreated many cats eventually become normal, especially young cats under 1 year of age. In one study, 88% cats with TTF infection were reported to undergo spontaneous resolution of diarrhea within two years of a diagnosis; however, most remained infected based on PCR results when retested as long as two to five years after the initial diagnosis.[4] The role of these asymptomatic carriers in disease transmission remains unclear.

When the diet works

Over the years, I have become more and more impressed to see GI signs resolve simply by changing a patient's diet. It is my impression, which is supported by a number of clinical studies, that possibly 30% to 50% of dogs and cats with nonspecific GI disease may respond to diet alone.[5-7] A positive response to a diet trial is referred to as a food-responsive diarrhea (FRD). FRDs include both true dietary allergies and dietary intolerances. Allergies result from a reaction with a protein antigen, whereas intolerances occur in response to some substance in the diet, such as a preservative or food coloring. Dietary trials using a test diet generally require two weeks or less to appreciate a response; the GI signs seem to respond much faster than dermatologic signs, which that may take eight weeks or more to improve. There is no ideal diet that will consistently resolve diarrhea. My personal favorite is the use of a hydrolyzed diet, such as Purina HA®. Hydrolyzed diets are single-protein sources (usually soy-, rice-, or potato-based) and have undergone digestion, producing low-molecular-weight protein derivatives that are thought to be highly digestible with low antigenic potential. Their benefit might actually be because they are pure and contain little else that might contribute to a dietary intolerance. These diets have now become the ideal initial trial diet. If a positive response is observed, then the patient's GI signs can be controlled with a diet. The patient can either continue on the test diet or you can attempt to find another long-term diet that works well for both the client and patient. Some clinicians recommend if there is a diet response that the patient to be fed that diet exclusively for at least three months, at which time the diet can be changed or even the original diet reintroduced. Only a small percentage of dogs with GI signs (~8%) relapse on challenge and are thus truly food allergic.[7] Feeding novel-protein diets with a single protein antigen would be an alternative approach. If using the novel antigen diets, one should prescribe only veterinary diets because many over-the-counter novel-protein diets are not all that novel and have been shown to contain many other antigens not listed on the label.[8] Highly digestible gastrointestinal diets such as Purina EN® may improve assimilation, promote gastrointestinal health, and modify the microbiota. Diets containing highly fermentable fibers such as those containing fructooligosaccharides (also referred to as prebiotics diets) are often useful for colonic disease because fermentation products are shown to benefit mucosal function and modify enteric microbiota, promoting "good" bacteria and inhibiting certain pathogenic bacteria.[9] If a diet trial is unsuccessful, with no improvement in clinical signs after 10 to 14 days, the next step is to institute an antibiotic trial.

GI drugs and bugs

There are many dogs with chronic large or small bowel disease that have an antibiotic-responsive diarrhea (ARD). An old term for ARD is *small intestinal bacterial overgrowth (SIBO).* However, SIBO is a poorly defined syndrome in dogs, and we currently have no way to adequately and convincingly diagnose bacterial overgrowth or to know in which cases antibiotics would be beneficial short of a therapeutic trial. More recently the term *gastrointestinal dysbiosis* has been given to conditions associated with an abnormal GI bacterial ecosystem.[10] In simple terms, GI dysbiosis refers to an imbalance in GI bacteria with the loss of the "good bacteria" coupled with an increase in the so-called "bad bacteria." For chronic diarrhea cases that do respond to antibiotic therapy, it is likely the antibiotics are not eliminating a specific pathogen but rather changing the overall bacterial ecosystem, promoting a more normal bacterial makeup. Some cats and dogs with gastrointestinal dysbiosis have decreased serum cobalamin (vitamin B_{12}) concentrations.[11] The cobalamin deficiency can be due to lack of intrinsic factor production, abnormal increased intestinal bacterial utilization, or ileal disease causing inadequate cobalamin absorption. Serum folate concentrations are usually variable in cases having dysbiosis.

Metronidazole is frequently used in GI cases but long-term administration and potential side effects make it less desirable than other options. Metronidazole has been shown to cause DNA damage to feline lymphocytes in vitro. There is also evidence in laboratory animals that it has some carcinogenic potential.[12] A suggested GI dosage for metronidazole in cats and dogs is 7.5 to 10 mg/kg given orally twice daily. A commonly used alternative, and my first choice, is tylosin. Tylosin was first reported to be useful for chronic diarrhea in the early 1970s and there has been a recent resurgence in interest and use of the antibiotic. Tylosin is a macrolide, bacteriostatic antibiotic that is currently marketed over the counter for the treatment of respiratory disease in chickens. Tylosin has activity against most gram-positive and gram-negative cocci, gram-positive rods, and *Mycoplasma*; however, the gram-negative bacteria *Escherichia coli* and *Salmonella* species are intrinsically tylosin-resistant.[13] Tylosin works by transiently changing the GI enteric bacterial population, probably by promoting the growth of beneficial commensal bacteria while suppressing deleterious bacteria. Once tylosin is discontinued, the original bacterial population often returns to its pretreatment state. There is also a suggestion that tylosin may have anti-inflammatory properties.[13] Tylosin appears to have almost no systemic or toxic side effects. The initial dose recommendation for tylosin in both dogs and cats is 15 mg/kg orally, twice a day, mixed with the food (has a bitter taste) or given via gelatin capsule. (Note: it comes as a powder and 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.[13] Tylosin is effective for most *Clostridium perfringes* and is considered by many to be the treatment of choice for suspected clostridial diarrhea.[14]

Probiotics

To date, there have been very few controlled clinical studies evaluating probiotic success. However, a large double-blinded placebo control study of shelter dogs and cats developing diarrhea found significantly fewer cats that received *Enterococcus faecium* (FortiFlora®, 2.1 x 10^9 cfu/day) developed diarrhea for greater than a two-day duration.[16] Probiotics exert their effects as long as they are being given but once stopped the GI flora generally returns to the pretreatment state. It may seem counterintuitive to give antibiotics with probiotics, but clinical improvement is often seen when they are given in combination. Probiotics are considered a safe adjunctive therapy and are commonly used for both acute and chronic diarrhea in dogs and cats as well as for the prevention of stress induced diarrhea.[15-17] Recommendations for the ideal probiotic, containing an adequate type and number of viable organisms for specific GI disorders, become difficult to make. Some over-the-counter preparations have been found not to contain the label claims.[18] My recommendation is to use a product produced by a reputable veterinary company that has done research on their product.

German shepherds with chronic diarrhea

A clinical syndrome frequently encountered in German shepherd dogs is chronic GI signs and weight loss. Exocrine pancreatic insufficiency is common in the breed, requiring pancreatic enzyme supplementation, and it must first be ruled out. The diagnosis is made by documenting a subnormal trypsin-like immunoreactivity (TLI) concentration followed by improvement with pancreatic enzyme replacement. A second group of German shepherd dogs with similar clinical signs have normal TLI concentrations. Many of these dogs turn out to have an antibiotic-responsive diarrhea due to GI dysbiosis. Testing should include measurement of folate and cobalamin (serum B_{12}) concentrations. Low cobalamin and high folate levels are characteristic of both exocrine pancreatic insufficiency and GI dysbiosis. Dogs with subnormal cobalamin concentrations will require parenteral supplementation (initially, about 500 µcg subcutaneously weekly) as part of the therapy. The cause of the GI dysbiosis in German shepherds is unknown. Researchers have investigated IgA concentrations, suggesting the possibility of an inherent deficiency leading to altered GI immunity. More recently researchers have measured toll-like receptors (TLR) in the GI tract of these dogs with a documented abnormal expression of the receptors. Using candidate gene analysis, polymorphisms in TLR4 and TLR5 were recently shown to be significantly associated with IBD in German shepherds.[19] Furthermore, the same polymorphisms in TLR5 were also associated with IBD in a heterogeneous population of dogs consisting of 38 different breeds.[19] These mutations could well play an important role in the pathogenesis of IBD in dogs, as a mutated receptor will lead to misrepresentation of commensal bacteria as pathogens, therefore signaling “danger” to the host and initiating the characteristic inflammatory response seen in this disease. Management of affected German shepherds involves diet, antibiotics, and cobalamin supplementation. Prebiotics and probiotics are also often given as additional adjunctive therapy. This condition tends to require life-long management.

When is it inflammatory bowel disease?

A diagnosis of IBD requires a complete laboratory evaluation to rule out other diseases. A complete blood count, biochemical profile, urinalysis, fecal cytology, and parasite evaluation are required in all cases. An eosinophilia or hypoproteinemia may provide clues to IBD. Abdominal radiographs or ultrasonography may be helpful. However, ultrasound images showing increased wall thickness are neither specific nor sensitive for the diagnosis of IBD.[20] Specific testing may include measurement of serum folate and cobalamin concentrations. Cobalamin deficiency is a common complication of feline GI disorders, and complete improvement in GI function is not possible until cobalamin deficiency is corrected.[11]

An overall impression is that most cases of IBD can be managed; however, unless the underlying etiology can be identified and removed, it can become a long-term proposition. A retrospective study demonstrated that only 26% of canine IBD cases progressed to complete remission, with intermittent clinical signs remaining in about half of the cases, 4% being completely uncontrolled, and 13% resulting in euthanasia because of poor response to treatment.[21] Another study found 18% of the dogs were euthanized because of their disease.[6] Poor prognostic indicators are hypoalbuminemia and hypocobalaminemia.[6]

Treatment of IBD

Patients that do not respond to a diet or an antibiotic trial are usually administered glucocorticoids. It is estimated that about 30% of the dogs that fail to respond to a change of diet and antibiotics will respond to corticosteroids. Generally oral prednisolone is given to dogs and cats once daily at a starting dose of 1 to 2 mg/kg, and then the dose is tapered over an eight-week period. However, the side effects of glucocorticoids can be marked, and I try never to exceed a total of 40 mg per day in large-breed dogs. Budesonide is a novel glucocorticoid that is reported to have high first-pass hepatic metabolism and exerts a “local effect” on the intestine with minimal systemic effects. An enteric-coated formulation is used for people with IBD but a non-enteric coated formulation made by a compounding pharmacy should be used. Despite apparent efficacy of budesonide in dogs and cats, the systemic steroid effects are present and consequently, its use may have no benefit over traditional corticosteroid therapy in most cases. The recommended dose is 1 mg once daily in cats and toy breeds and up to 2 mg once daily for large-breed dogs.

If there is poor response to glucocorticoids in dogs after the first three to four weeks or if the side effects are severe, then I recommend oral cyclosporine at 5 to 10 mg/kg once daily for at least two months. Many dogs with IBD that are steroid refractive are reported to respond to cyclosporine.[22] In cats, the use of chlorambucil (2 to 6 mg/m^2, q24h, PO, or 2 mg/cat three times a week) with prednisolone is preferable, if there is inadequate response to glucocorticoid treatment alone. If chlorambucil is used, hematologic parameters should be monitored regularly. Cyclosporine blood concentrations do not need to be monitored regularly, unless side effects induced by the cyclosporine treatment are suspected or an inadequate response to treatment is observed. If measuring cyclosporine serum concentrations, it is recommended to take blood samples one to two hours after giving the medication to ensure that peak concentrations are measured. If the cyclosporine serum concentration is above 700 ng/ml at peak level, then halving the dosage for the first two weeks can reduce the side effects.[22] If the patient responds to cyclosporine, then the medication can either be tapered slowly or stopped after 10 weeks. Sulfasalazine (20 to 50 mg/kg orally three times daily for three to six weeks) and related drugs are often used in dogs when IBD is limited to the large intestine. However, side effects include keratoconjunctivitis sicca, so tear production should be monitored regularly when using these drugs. I rarely prescribe sulfasalazine for large bowel disease because, in my experience, most patients get better with diet and antibiotics. Other novel or adjunctive therapies could include omega 3 fatty acids for anti-inflammatory effects and various antioxidants. Probiotics have also been suggested to be beneficial for treating IBD due to the multiple mechanisms described above.

References upon request

Abnormal Liver Enzymes: A Clinical Approach

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The identification of abnormal liver enzymes usually indicates liver damage but rarely provides a diagnosis or etiology. Abnormal liver enzymes are common and in a study of 1,022 blood samples taken from both healthy and sick dogs and cats, one diagnostic laboratory found 39% had ALP increases and 17% had ALT increases. When presented with a patient having abnormal liver enzymes it is important to recognize that the patient could have primary liver disease but more likely the patient has other primary non-hepatic condition resulting in secondary liver involvement. It is therefore important to perform a complete review of all other body systems.

It is also important to understand the reason for increased liver enzyme activity and the following sections will deal with liver specific tests.

Tests of heptocellular necrosis or degeneration

Increases in either alanine aminotransferase (ALT) or aspartate aminotransferase activity (AST) indicate hepatocellular membrane damage and leakage of the enzymes. This could be due to death of the hepatocyte or from hepatocyte degeneration where the membrane just has increased permeability. Conceptually ALT and AST should be thought of as hepatocellular "leakage" enzymes. Subsequent to an acute and diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. The plasma half-life of ALT activity is about 2.5 days (60 hours) in dogs however concentrations may take days to weeks to decrease following an acute insult based on models of acute hepatic injury. Persistent increased ALT and AST enzyme activity over weeks is characteristic of chronic hepatitis in the dog. As a general rule, ALT increases should be investigated when they are greater than twice normal or persistently abnormal over weeks to months. Hepatic AST is located predominately in hepatocyte mitochondria (80%) but is also soluble in the cytoplasm. Because of the mitochondrial location, AST elevations are more sensitive for liver disease than ALT and reflect more significant cell damage. On the other hand, AST is less specific than ALT because of the presence in other tissues (i.e., muscle so always check CK). Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST concentrations, due to their difference in plasma half-life, the serum AST will return to normal more rapidly (hours to days) than the serum ALT (days).

Tests of cholestasis and drug-induction

Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become increased in the serum subsequent to increased enzyme production stimulated by either impaired bile flow or drug-induction. These enzymes have a membrane bound location at the canalicular surface; ALP associated more with the canalicular membrane and GGT associated more with epithelial cells comprising the bile ductular system. With cholestasis, surface tension in the canuliculi and bile ductules increases and production of these surface enzymes is then up-regulated. An increase in the serum ALP and GGT activity can be the result of induction by endogenous, topical or systemic glucocorticoids, anticonvulsant medications (ALP only) and possibly other drugs or herbs. The plasma half-life for hepatic ALP in the dog is 66 hours in contrast to 6 hours for the cat and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than the cat. Bone source arises from osteoblastic activity and is elevated in young growing dogs before their epiphysial plates close or in some dogs with bone tumors or lytic lesions. One study identified that increased ALP concentrations in some dogs with osteogenic bone tumors tended to indicate a poorer prognosis, probably from diffuse bone metastasis. In the adult without bone disease, an increased serum ALP activity is usually of hepatobiliary origin. Hepatic GGT is located predominately on the canalicular membrane and bile ducts. Chronic elevations in GGT tend to better reflect hepatobiliary tract disease, with he most marked elevations resulting from diseases of the biliary epithelium such as bile duct obstruction, cholangiohepatitis, cholecystitis or neoplasia. In dogs, GGT has a lower sensitivity (50%) but higher specificity (87%) for hepatobiliary disease than total ALP. If ALP is elevated with a concurrent increase in serum GGT, specificity for liver disease increases to 94%. Bone does not contain GGT and the administration of anticonvulsant medications to dogs does not cause an increase in the serum GGT activity.

Evaluation of liver function

On a routine biochemical profile it is important to note the liver function tests (or tests that involve liver function) including bilirubin, albumin, glucose, BUN, and cholesterol. Bilirubin elevations can occur from hemolysis, hepatic dysfunction or extrahepatic cholestasis. Measuring the percent conjugated to unconjugated bilirubin to determine location is not useful in the dog. Albumin is exclusively made in the liver and if albumin is not lost, sequestered or diluted, a low concentration would suggest significant hepatic dysfunction. It may take greater than 60% hepatic dysfunction for albumin concentrations to decline. Cholesterol can be variable and

increased in cholestatic conditions and decreased in portosystemic shunts. When glucose and BUN activity is low from liver dysfunction suggests significant hepatic disease and a guarded prognosis.

Bile acids

Measurement of serum bile acids is thought to be the most sensitive function test that is readily available in small animal practice. Bile acids are synthesized from cholesterol in the liver and then conjugated and excreted into the bile. Bile acids are transported to the gallbladder and following a meal are excreted into the intestine where they emulsify fat for absorption. In the distal small intestine bile acids are actively resorbed and return to the liver where they are efficiently extracted by the hepatocytes and then re-circulated back into the bile. Only a small fraction of the total bile acid pool ever escapes into the systemic circulation. Thus, the enterohepatic circulation of bile acids occurs with a 95-98% rate of efficiency. The current suggestion for performing bile acid levels is to differentiate between congenital portal vascular anomalies and liver insufficiency, prior to the development of jaundice. The determination of total bile acids can contribute to the decision to obtain histological support for a definitive diagnosis. The fasting total serum bile acid concentration (FSBA) is a reflection of the efficiency and integrity of enterohepatic circulation. Pathology of the hepatobiliary system or the portal circulation results in an increased FSBA prior to the development of hyperbilirubinemia, therefore, bile acid measurement is not useful in the icteric patient. An increase is not specific for a particular type of pathologic process but is associated with a variety of hepatic insults or abnormalities of the portal circulation. Bile acids should be used to screen patients with persistently abnormal liver enzymes, to determine if there could be loss of hepatic function, which adds further diagnostic support during investigation of the case. It is also helpful to measure bile acids to determine level of hepatic dysfunction in animals with PSS or portal vein hypoplasia (PVH), also known as microvascular dysplasa. When the fasting value is greater than 25 µmol/L for the dog and cat, there is a high probability that the histology findings will define a lesion.

When the total fasted bile acid concentration is normal or in the “gray zone” the FSBA should be followed by a 2-hour postprandial serum total bile acid (PPSBA) looking for an increase of greater than 25 µmol/L. The diagnostic value of determining PPSBA concentration is increased sensitivity for the detection of hepatic disease and congenital portal vascular anomalies. In dogs, the specificity of fasting and postprandial bile acids for hepatobiliary disease is 95% and 100% when cutoff values greater than 15 µmol/L and 25 µmol/L are used, respectively. When using these guidelines it is prudent to recognize that a small number of apparently healthy dogs have been reported with PPSBA values above 25 umol/L or these may actually represent dogs that have PVH. Occasionally the FSBA value is greater than the PPSBA value. The reason for this non sequitur is probably multifactorial. It has been shown that (1) the peak PPSBA concentration for individual dogs is variable, (2) fasted dogs store about 40% of the newly produced bile in the gallbladder and (3) a meal stimulates the release of only between 5 to 65% gallbladder bile. Undoubtedly these physiologic variables in addition to physiological variation in intestinal transit time and concurrent underlying intestinal disease contribute to the dichotomy.

Recently, urinary bile acids have become available as a diagnostic tool. Identifying increased urinary bile acids provides similar information to what is obtained from serum bile acids and neither test appears to be better than the other. The advantage of urinary bile acid measurements would be for the screening of litters of young puppies for suspected inherited vascular anomalies where urine collection is simpler than paired serum samples.

Coagulation panels

Major clotting factors are synthesized in the liver (except factor 8) and therefore prolonged clotting time may suggest significant hepatic dysfunction or factor consumption. Because coagulation abilities may not be normal in patients with liver disease, it is advisable to check clotting times prior to performing liver biopsy.

Ammonia

High ammonia levels reflects abnormal hepatic portal shunting (acquired or congenital shunts) or significant hepatocellular dysfunction of greater than 70%. The liver detoxifies ammonia that primarily arises from the gastrointestinal tract by conversion to urea. Elevated fasting blood ammonia levels have been shown to be a sensitive (98%) and specific (89%) test for the detection of congenital or acquired portosystemic shunting in dogs. Due to problematic requirements for sample handling and submission, blood ammonia or the ammonia tolerance test is infrequently performed by some clinical practices. However, recent availability of blood ammonia for in-clinic analyzers, has helped make the test more feasible.

Diagnostic strategies.

In the asymptomatic patient with an increased liver biochemical test(s) the increased value should be confirmed. If no likely explanation for the laboratory abnormalities can be found there are two courses of action that one can take; either begin a diagnostic evaluation of the patient starting with bile acid determinations, or re-evaluate the patient’s liver enzymes at a later date. The diagram below depicts a general algorithm for the work-up of dogs that have abnormal liver enzymes. The identification of abnormal liver enzymes may occur when the sick patient is presented for evaluation or during a routine health screen in the healthy patient. Abnormal liver enzymes in the sick patient could either be the result of primary liver disease/damage or secondary due to a multitude of other non-hepatic disorders. The most common cause of abnormal liver enzymes is in fact, not primary liver disease at all but rather the result of reactive hepatic changes occurring secondary to other non-hepatic causes. Generally, secondary hepatic changes are

reversible once the primarily disease is treated. Successful resolution of the non-hepatic disease and continued abnormal liver enzymes would be a strong indication for further investigation of the liver for a primary disease process.

Imaging

Routine abdominal radiographs are helpful in determining liver size and shape and for detection of other intra-abdominal disorders. Ultrasonography is noninvasive, readily available and is the most informative initial imaging modality for liver disease. Ultrasound can determine parenchymal changes, mass lesions and disorders of the biliary system. Ultrasound however is not accurate in differentiation of the major parenchymal changes.

Fine needle aspiration

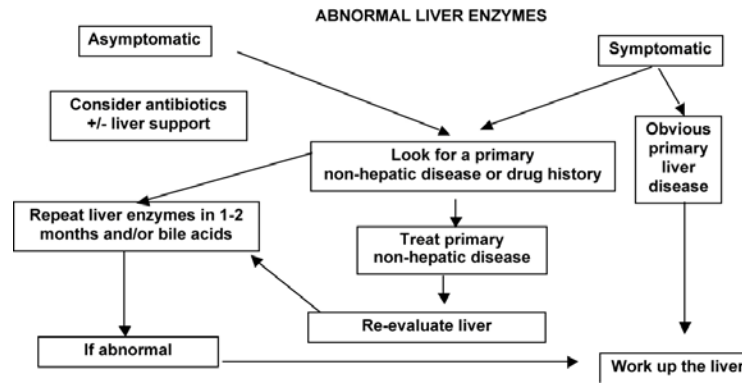
(FNA) for cytological evaluation is safe easily performed using ultrasound direction. One should be cautious in over interpretation of those results however. FNA is best for identification of vacuolar hepatopathies and neoplasia and is poor in detecting inflammatory hepatic changes. In one study we found FNA and cytology to only correlate in about 1/3 of the cases.

Liver biopsy

A biopsy is required for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The method for liver biopsy procurement may be surgery, ultrasound guided needle biopsy or laparoscopy. We believe if a needle biopsy is obtained that at least a 16g biopsy needle or larger be used and multiple liver lobes are biopsied. We generally take 3-4 biopsies with one split for culture and hepatic copper analysis and the remainder placed in formalin for histological evaluation

What you might find on a liver biopsy

When we evaluated 150 consecutive canine liver biopsies we identified the largest category to be secondary reactive hepatopathies (25%) followed then by chronic hepatitis (23%) and then neoplasia and vacuolar hepatopathies making up 69% of the biopsies performed. Smaller categories included vascular anomalies, acute liver damage and other miscellaneous conditions.



Reactive hepatopathies; a common diagnosis

The so-called “non-specific reactive hepatopathies” (NSRH) that occur secondary to non-hepatic disease can result in increased serum biochemical hepatic tests and histomorphologic abnormalities. Most of the NSRH cause increases in laboratory tests that evaluate hepatocellular integrity (ALT, AST) and tests of hepatic cholestasis (ALP, GGT). In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose, and BUN). Most of the animals with this type of secondary liver disease often retain normal hepatic function (albumin, serum bile acid concentrations), which again supports a concept that there is generally minimal loss of hepatocellular dysfunction. NSRH is often characterized by variable amount of hepatocellular degeneration or necrotic changes without evidence of significant chronic progressive inflammation. The reason the liver often undergoes these changes revolves from the fact that the liver is involved in so many metabolic and detoxification functions. Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release are all examples of conditions responsible for the majority of these changes. Gastrointestinal disease frequently results in secondary hepatic changes uptake of bacteria, toxins or nutrient abnormalities.

Histological findings associated with NSRH changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis or periportal hepatitis or variable random hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis. Whenever I observe these changes on histology I always begin a search for an underlying etiology.

A good example that helps explain this concept is inflammatory bowel disease in which it is not unusual to observe mild inflammatory changes around portal triads presumed to be the result of abnormal portal uptake of gastrointestinal “toxins”. Throughout the liver and closely associated with portal areas are Kupffer cells (fixed macrophages) that function to filter the blood of injurious toxins, inflammatory mediators and bacteria. When this macrophage system is abnormally insulted Kupffer cells release their own inflammatory mediators that in turn insult the hepatocytes.

In a review of consecutive liver biopsies at Colorado State University histology grouped as non-specific reactive changes made up the largest category of abnormalities (approximately 25%) In this group we were able to identify an associated disease in many that could explain the likely cause for the hepatic enzyme increases and histological changes observed. Concurrent diseases identified

included neoplasia, gastrointestinal, renal, autoimmune, dermatologic, dental, infectious and cardiac disease as a few examples. In some cases an underlying disease is not identified. The ALT values on the average are 1-2 X normal and the ALP values 1-3 X normal. It is interesting to note that in a series of 32 dogs having reactive hepatopathies, 8/8 cases in which serum bile acids were run, all were within the normal reference range again suggesting hepatic function tends to remain intact.

This category appears to be the most common histological change to occur in dogs and is by far the most common cause of elevated liver enzymes. Based on this fact, dogs presented with elevations in ALT and ALP should always have primary non-hepatic disease ruled out first. These changes are usually very reversible and no specific hepatic therapy is required short of treating the primary disease. The liver changes resolve once the primary etiology is successfully treated. Therapy providing good liver support such as antioxidants may be warranted.

Summary

Abnormal liver enzymes should not be ignored and should be investigated in a systematic manner as previously discussed. Asymptomatic animals with no evidence of significant or treatable disease or in situations where financial constraints limit further work up the patient should be fed a quality maintenance diet for the patient's stage of life and the possibility of instituting specific liver support therapy should be explored.

Acute Liver Disease

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Acute liver failure (ALF) is an uncommon condition that results in rapid deterioration of liver function occurring in a previously healthy animal. It is generally characterized by severe hepatocyte death due to aptoposis or cytolytic necrosis. The extent and location of the hepatocyte death depends on the etiology.

Etiology

Drugs are the most common known cause of ALF in dogs and cats. Drugs can affect the liver in one of two ways. First, they may have a direct toxicity to hepatocytes or becomes metabolized to a toxic compound that then causes damage. This first classification is referred to as a direct hepatotoxin and is dose related and reproducible. An example would be acetaminophen poisoning and CCNU therapy. More common however are drugs associated with an idiosyncratic drug reaction. Idiosyncratic drug reactions are unpredictable and not dose related but most often associated with abnormal or aberrant metabolism of the drug to a toxic compound. Listed below are some of the more common drug associated hepatotoxicities. It should be noted however any drug metabolized by the liver has the potential to be a hepatotoxin. The common incriminators causing an idiosyncratic reaction include the NSAIDs, trimethoprim-sulfa, lysodren, ketoconazole (and other antifungals), and diazepam (in cats) to name but a few. At Colorado State University we reported on a series of dogs developing acute liver toxicity associated with carprofen. The toxicity was idiosyncratic occurring in possibly 1 out of 10,000 dogs. We have also more recently identified toxicity associated with azathioprine. See table of common drug associated with liver disease. Some herding breed dogs lack p-glycoprotein that plays an important role in metabolism of many drugs. Thus it is not surprising that lack of P-glycoprotein, which occurs in many herding-breed dogs leads to increased susceptibility to drug toxicosis.

Other causes of acute liver failure include infectious agents such as Leptospirosis. Environmental toxins such as industrial solvents, plants, insects, chemicals, envenomation, sago palm seeds, heavy metals, Amanita phalloides (mushroom) and aflatoxin have been incriminated to cause liver disease. Several years ago there was a large outbreak of liver failure in many dogs in the Eastern part of the United States due to contaminated dog food with aflatoxin. In most cases aflotoxin is an isolated event. Xylitol an artificial sweetener found in chewing gum can result in a sudden drop in glucose due to increase insulin release and in some cases also causes acute liver disease as well.

Damage to the liver may range from mild to moderate hepatic necrosis resulting in minimal clinical signs. Signs may be associated with vomiting, lethargy and anorexia. Massive hepatic necrosis will result in ALF and produce significant clinical signs of liver failure and possibly death. The signs of ALF are variable but usually will always include anorexia, depression, lethargy and vomiting. Neurological signs from hepatic encephalopathy may progress to coma or seizures. Jaundice is invariably present. ALF can also result in evidence of hemorrhage either from lack of coagulation factors or from DIC. GI ulceration is common. Septicemia may occur from uptake of enteric bacteria. Hepatic pain may be observed on abdominal palpation.

Some drugs associated with liver toxicity

Acetaminophen	Arsenicals
Ketoconazole	Sulfonamides
Halothane	Carprofen (NSAIDs)
Griseofulvin	Itraconazole/ketoconazole
Mitotane (lysodren)	Trimethoprim-sulfa
Diazepam	Anabolic steroids
Anticonvulsant drugs	Antineoplastic drugs
Azathioprine	Tetracycline (doxycycline)
Amiodarone	CCNU

Clinical findings

Focal or mild to moderate hepatic necrosis is generally associated with clinical signs that are suggestive of liver disease. Acute massive necrosis however will produce clinical signs. The signs of acute hepatic necrosis are nonspecific but usually will include anorexia, depression, lethargy and vomiting. In hepatic failure hemorrhage and hepatic encephalopathy ensues this is then often followed by coma or seizures. Hepatic pain may be observed on abdominal palpation.

The clinicopathologic changes reflect the extent of necrosis and loss of hepatocyte numbers. The hepatic transaminases (ALT and AST) are released when the cell membrane is damaged and the cytosol enzymes leak out. A marked increase in AST to ALT ratio suggests more severe hepatocellular damage. Generally ALP and GGT increases are associated with hepatic necrosis and are only mild to moderately elevated. Hyperbilirubinemia is common when significant hepatic necrosis is present and frequently very high

when massive necrosis occurs. Changes in the liver function test will reflect the magnitude of hepatic damage. When the necrosis is massive and liver function is compromised these function changes will occur. Clotting factors decline and may contribute to hemorrhage. Hypoglycemia, low BUN, hypoalbuminemia, and increase in ammonia all reflect hepatic failure. It is important to note that with acute severe necrosis albumin concentrations may remain normal early in the disease due to the longer half-life of albumin (2 weeks) as compared to clotting factors being only (hours to days). Frequently platelet numbers and function are also compromised in massive liver failure and DIC is a common complication. With recovery the AST will decline prior to ALT and could be prognostically helpful.

Cerebral edema and associated increased intracranial pressure occurs with liver failure. The pathogenesis of the edema is unclear. It is thought that it is a combination of vasogenic and cytotoxic edema. Coagulopathy occurs from failure to produce clotting factors and platelet dysfunction. With secondary organ and vascular damage DIC is common in end stage liver failure. Hypotension from decreased peripheral resistance and cardiac dysfunction occurs. Hypokalemia, hyponatremia and respiratory alkalosis are reported in humans having hepatic failure. A metabolic (lactic) acidosis may also occur. Another serious complication of liver failure is renal dysfunction. The mechanism is complex and may be associated with acute tubular necrosis but also associated with vascular changes referred to as hepato-renal syndrome. Oliguric renal failure denotes a grave prognosis. Because of the failure to produce BUN in many cases it is prudent to follow serum creatinine that is not influenced by hepatic function.

The patient is also susceptible to infection and septicemia due to the transmigration of bacteria through the GI tract entering into the portal system. With hepatic dysfunction filtering of portal blood is impaired and systemic bacteremia results.

Management

When there is acute ingestion of a hepatotoxin toxin vomiting should be induced followed by administration of activated charcoal to prevent absorption of the toxin or drug absorption. In most cases the animal is clinical and too advanced for gastric lavage an charcoal to have any benefit.

The next step is to prevent further hepatocyte damage by providing an environment for optimal hepatic function. There is considerable evidence showing that free radicals are generated in acute liver damage and participate in the pathogenesis of liver injury. Free radicals are molecules with an unpaired electron that form by the injurious effects of certain drugs or various other toxic agents or events. Free radicals, if not inactivated, damage cellular macromolecules via lipid peroxidation and thus participate in cellular injury when produced in excess. Depletion of antioxidants primarily glutathione parallels hepatic damage. N-acetylcysteine (NAC, Mucomyst™) is thiol (SH) donor and promotes the production of glutathione. Glutathione is the most important detoxifier of toxic cellular xenobiotics. There is also evidence that NAC protects against hepatic ischemia-reperfusion damage possibly by inhibiting Kupffer cell function. Further NAC has beneficial effects on liver blood flow, oxygen extraction, and the formation of non-glutathione products that protect against cell injury. Experimentally NAC has protective effects against aflatoxin damage as well. The suggested dose for NAC is 140 mg/kg IV followed by 70 mg/kg IV bid or tid for one to three days. The injectable NAC should be diluted 1:4 in 5% dextrose and water and given slowly over 30 minutes to 1 hour. When vomiting has resolved NAC therapy can be switched to oral medications. Oral S-Adensosylmethionine (SAMe) also protects against liver damage in dogs and cats by increasing hepatocyte glutathione concentrations being a SH donor. It also acts as a methyl donor and enzyme activator for key reactions that maintain membrane structure and function. Reports show protection against acetaminophen toxicity in the dog and cat. SAMe is given orally at the dose of 20 mg/kg bid or daily. SAMe in combination with milk thistle products is commercially available and would be of benefit as well.

The use of other antioxidants is warranted in management of the liver disease including vitamin E and milk thistle or its by-products. Vitamin E, d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phopspholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. A suggested vitamin E dose is 50 to 400 IU a day. Other antioxidants that have been investigated but lack clinical experience in dogs and cats include allopurinol and desferoxamine.

Milk thistle has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. In a number of human clinical studies on patients having either acute or chronic liver disease has provided mounting evidence of the benefit of milk thistle. These studies must be interpreted with care because of the variable experimental design and limited number of cases. One canine study showed that dogs poisoned with amanita mushrooms that were treated with milk thistle had less clinical signs and complete survival while one-third of dogs in the untreated group died. Due to the lack of standardization of milk thistle preparations it is difficult to provide an appropriate dosage. Suggestions have included 50-250 mg/kg bid. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. It appears to have a synergistic effect with vitamin E.

Other therapy includes fluid therapy giving balanced electrolytes generally with potassium and glucose supplementation. Fresh whole blood or frozen plasma may be required to provide clotting factors. Stored blood should be avoided because ammonia

concentrations increase over time prom production of red blood cells. The use of hetastarch or dextrans may be required to maintain blood pressure. (Note low MW dextrans may worsen DIC). Generally an indwelling urinary catheter is placed to monitor urinary output and to detect oliguria. Fruosemide and dopamine may be used to induce a diuresis. Broad-spectrum intravenous antibiotic therapy is generally indicated to manage and possibly prevent septicemia. Antibiotic choice should be ones that are not hepatotoxic or require hepatic metabolism. Common antibiotics to avoid include trimethoprim-sulfa, tetracycline and metronidazole. Gastrointestinal ulceration is managed using the H2 blocker such as ranitidine (2-5 mg/kg BID/TID) and oral sucralfate (Carafate 1 mg tab/25 kg TID given 1 hour before ranitidine). Cimetidine is to be avoided in liver disease because it must be metabolized by the liver and alters hepatic metabolism (via cytochrome P450 system) of other drugs. The dose of H2 blockers should be reduced with renal dysfunction.

Conventional therapy for HE includes the use of enemas to clean the colon of both bacteria and protein substrates for ammonia production. Slightly acidic enemas will lower the pH of the colon thus ionizing ammonia and reducing its absorption. Povidone iodine (betadine) can safely be given by enema as a 10% solution (weak tea color) that will both acidify the colon and have an antiseptic action reducing bacterial numbers. Nonabsorbable intestinal antibiotics are used to alter bowel flora and suppress urease-producing organisms important in formation of factors causing hepatic encephalopathy. Antibiotic suggestions include oral ampicillin or aminoglycosides (neomycin, kanamycin or gentamicin). A nondigestible disaccharide lactulose (Cephulac or Chronulac) given orally acidifies the colon converting ammonia to ammonium which is poorly absorbable thus trapping ammonia in the colon. The fermentation products of lactulose will also act as an osmotic laxative reducing colonic bacteria and protein substrates. A dose of 1-10 ml orally TID is generally effective. Lactulose is not absorbed systemically and thus considered safe. The dose should be adjusted to cause 3 or 4 soft stools a day. If diarrhea develops the dose should be reduced. Lactulose can also be given by enema in treating the severe case of hepatic encephalopathy. Treatment of seizures with sedatives or barbiturates is generally contraindicated. One should make sure that the patient is not hypoglycemic and take measures to treat HE. In some cases worsening of the neurological status is associated with development of cerebral edema. Corticosteroids have however not been definitively shown to be effective in hepatic failure and edema. The combination of the synergistic effects of mannitol and furosemide is shown to be of some benefit in cerebral edema.

Prognosis

The prognosis of hepatic necrosis depends on the amount of damage and the secondary complications that occur. The prognosis for acute hepatic necrosis and hepatic failure depends on the extent of hepatic damage, metabolic complications and the ability to maintain the patient until hepatic regeneration is possible. Aggressive management and anticipation of potential complications will improve survival. With biochemical and clinical evidence of loss of hepatic function the prognosis becomes guarded. In humans artificial livers or liver transplant are used in severe cases. It has been stated that a prothrombin time greater than 100 seconds indicates a grave prognosis. It also appears the more peracute the liver failure the better the prognosis for recovery; the failures that are delayed in onset have a poorer prognosis. Also following acute hepatic necrosis either complete recovery or progression to cirrhosis or chronic hepatitis may occur. In general terms supportive care and management of metabolic complications is provided until hepatocyte regeneration returns the liver to normal function.

Copper-Associated Liver Disease: More Common than You Think

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There is increasing recognition that inflammatory liver disease in dogs is associated with abnormal hepatic copper (Cu) concentrations. Abnormal hepatic Cu accumulation results as either a primary metabolic defect in Cu metabolism unique to some breeds or as a secondary event associated with chronic hepatic cholestasis resulting in a decrease in biliary excretion of hepatic Cu. Abnormal hepatic copper can also accumulate in the liver secondary to increased dietary intake. Regardless of the cause at a certain concentration Cu contributes to hepatocellular damage.

Normal copper metabolim

Copper is an essential trace element required as a redox co-factor for many different enzymes. Copper enters the body through the diet and approximately 30% is absorbed by the upper small intestine with unabsorbed copper passing through the feces. Although the exact details of intestinal Cu absorption is not completely delineated it is clear that copper is taken up in the intestine through an active transport mechanism shared with zinc. Intestinal copper is quickly bound to the cytosolic protein metallothionein. Intestinal Cu is subsequently transported to the liver bound to albumin and transcuprein. The liver is responsible for the uptake and storage of copper, as well as the regulation of excretion of this metal into the bile. Hepatic copper is either complexed to ceruloplasmin, an acute phase reactant protein, and transported to peripheral tissues for utilization, or Cu is redistributed among the various metallothioneins in the liver. Metallothioneins are cysteine-rich, cytosolic proteins capable of binding several metal ions, including copper. Metallothioneins functions are to protect the hepatocyte against the toxicity from free Cu catalyzing oxygen free radicals and also to mediate Cu transport into the bile for removal from the body. The normal hepatic copper concentrations in dogs are maintained at approximately 200-400 µg/g dry weight liver.

Recently there has been characterization of the genetic regulation of copper excretion by the liver. A specific gene in humans ATP7b is a copper-transporting ATPase expressed within the secretory pathway of hepatocytes and plays a critical role in copper excretion and ceruloplasmin production. A second gene encoding COMMD1 (MURR1) is expressed in the liver suggesting that this protein also plays a role in hepatic copper transport and biliary copper excretion.[1] Wilson disease in humans is an inherited mutation in the gene encoding human ATP7b and results in hepatic copper overload and decreased Cu-ceruloplasmin production. Bedlington Terriers also have an inherited disorder of copper homeostasis. These animals have impaired copper excretion into bile but no abnormality in copper incorporation into ceruloplasmin suggesting that the defect occurs distal to the function of ATP7b in intracellular copper transport.[2] This disorder has recently been shown to result from deletion of a gene on dog chromosome 10 encoding a small cytosolic protein termed COMMD1 (MURR1).[3]

Copper hepatotoxicities in dogs

Bedlington terriers

Hepatic copper toxicity was first identified in Bedlington Terriers in 1975. It was subsequently shown that affected Bedlington Terriers have an inherited autosomal recessive defect, which results in reduced biliary excretion of copper with hepatic metallothionein sequestration of Cu in hepatic lysosomes. The pathogenesis of hepatic damage is thought to occur when the metallothionein sequestration ability for Cu becomes exceeded and free copper is released. The mitochondria appear to be the first organelle to become damaged resulting in mitochondrial electron leak initiating lipid membrane peroxidation and eventual cellular death.[4]

The excess hepatic copper is sequestered in lysosomes bound to metallothionein proteins. Routine stained histological sections may show abundant golden-brown refractile hepatocellular lysosomal granules that contain the sequestered Cu. These granules are nonspecific for copper, but may indicate abnormal copper accumulation. A more reliable semi-quantitative estimation involves histochemical staining for hepatic Cu. Reliable tissue bound copper stains include rhodanine and rubeanic acid. The copper tends to accumulate in a centrilobular location. A grading system of 1-4 estimating the quantity of Cu granules correlates roughly with quantitative determination of hepatic Cu when the values approach >750 µg/g dry liver weight.

Definitive determination of the amount of hepatic Cu requires a quantitative analysis of tissue Cu. Hepatic copper content is measured using atomic absorption spectroscopy and can be determined on a full 16 g needle biopsy sample, although larger samples provide better accuracy. Samples for analysis should be placed in a Cu free container (such as a serum blood tube) for analysis. Normal canine hepatic Cu concentrations are less than 400 µg/g dry weight liver. The concentration at which abnormal hepatic Cu contributes to hepatic damage is unknown. It is possible at least at my Diagnostic Laboratory, to take adequate size biopsy sample embedded in paraffin for histology and de-paraffinize the sample to obtain a quantitation of copper.

Morphologic evidence of inflammatory hepatic injury in Bedlington Terriers begins when concentrations reach approximately 2,000 µg/g dry weight although sub-cellular morphologic changes are found with lower Cu concentrations. Homozygous affected dogs have increased copper concentrations but should be older than one year of age prior to having a biopsy. This is because the heterozygous carrier dogs normally increase in copper concentrations out of the normal range until around 6-9 months of age before concentrations fall back into the normal range. Genetic testing (VetGen.com) is also available for Bedlington Terriers to determine if they are free of disease.[5] A liver biopsy is required to completely confirm if the dog is phenotypic affected.

Doberman pinscher

Doberman hepatitis is a form of chronic hepatitis. The incidence is unknown but may occur in as high as 4 to 6% of dogs. The high percent suggests a genetic predisposition.[6] Females seem to be over-represented. The disease begins in young dogs (1-3 years) with increased ALT concentrations and having sub-clinical hepatitis. Clinical evidence of liver disease usually begins around 4-7 years of age with chronic hepatitis and cirrhosis. Copper appears to be associated with the disease and recent studies suggest that copper is often increased prior to development of clinical hepatitis. Cu^{64} isotope studies demonstrate affected dogs have an impaired biliary excretion of copper.[7] Copper chelator therapy in sub-clinical dogs normalized copper concentrations with improvement in the grade of histological damage. In affected dogs the copper concentrations generally range from 1000-2000 µg/g DW liver. At this point no specific gene has been identified for this disease to determine the mode of genetic transmission. The above evidence suggests a primary defect in copper metabolism in the breed but awaits further conformation. An autoimmune mechanism is also suggested but this too requires further investigation. It appears that the hepatocyte may have abnormal MHC class II complex expression stimulating activation of CD4 T cells and an immune disease.

Dalmatians

A retrospective study summarizes 10 Dalmatians suspected of having hepatic copper toxicosis.[8] Two of the dogs were related and all presented for gastrointestinal clinical signs, had elevated liver enzymes and necroinflammatory hepatic changes associated with copper-laden hepatocytes most prominent in a centrilobular location. The mean hepatic copper concentration was 3,197µg/d dry weight liver. In 5 of these 9 dogs, hepatic copper concentrations exceeded 2,000 µg/d DW liver with several dogs having copper levels as high as those observed in Bedlington Terriers. These findings support the hypothesis that a primary metabolic defect in hepatic copper metabolism occurs in the Dalmatian breed. Some of these dogs also have renal glycosuria suggesting a Fanconi- like effect. The mechanism and genetic basis of this condition is under further study.

West Highland white terriers

The "Westie" breed has been associated with liver disease and hepatic copper accumulation. The clinical findings appear to be different than other breeds associated with copper accumulation. Dogs reported showed evidence of hepatitis or cirrhosis and had increased hepatic copper ranging from 1000-3000 µg/g dry weight liver. Twenty-four dogs described ranged from 3-7 years of age. Some dogs in this report had high copper concentrations but no evidence of liver disease while others did.[9] While the Bedlington Terrier tends to accumulate Cu with age it was not apparent in this group of dogs. Affected dogs that were bred produced offspring with elevated copper concentrations supporting a genetic defect. Several dogs were treated with zinc therapy and showed reduction in hepatic copper concentrations.

Labrador retrievers

Chronic hepatitis is reported to be common in this breed and there is evidence that copper accumulation is associated with some, but not all the cases. There has been extensive work on this syndrome in the Netherlands and they document it to be inherited and in fact, asymptomatic relatives of affected dogs also contain copper in their livers. We find females are more commonly affected and the diagnosis is generally made between 2 to 7 years of age. Hepatic copper concentrations generally range between 750 to 2000 µg/g dry weight liver. The histological location of the Cu being centrilobular suggests that Cu elevation is probably not secondary to cholestasis. It appears that copper chelation is beneficial in some dogs with hepatitis and copper accumulation.

Researchers demonstrated that the copper accumulation in these dogs is controlled using short-term penicillamine therapy followed by feeding a low copper diet. They further found dietary copper in commercially available dog food can influence hepatic copper concentrations and can be a risk factor for the development of copper-associated hepatitis in Labrador retrievers with a genetic susceptibility to copper.

Other breeds and cats

The Skye Terrier, Anatolian Shepherd, and possibly the Keeshond as well as other breeds have also been reported with liver disease and increased copper accumulation. The exact mechanism or extensive description in specific breeds is lacking. We will occasionally identify cats with increased copper and evidence of hepatitis and thus cats with evidence of inflammatory liver disease should be investigated for increase copper concentrations.

Treatment considerations

Regardless of the cause of hepatic Cu accumulation it has been shown that unbound Cu plays a role in hepatocellular damage. The treatment possibilities are threefold: (1) to decrease further absorption of copper from the gastrointestinal tract by feeding a Cu deficient diet or blocking dietary Cu uptake, (2) to enhance hepatic Cu removal using specific chelator therapy and/or (3) to protect the

liver from copper catalyzed oxidative damage using antioxidant agents. A specific therapeutic plan requires careful case evaluation and individual formulation.

We now speculate that a number of other dogs may have the inability to handle dietary copper resulting in hepatic copper accumulation. This theory comes about because the normal hepatic copper concentration for dogs has been increasing over the years and the fact that canine commercial diets are over supplementation with copper (if you compare that to copper requirements for humans). Further, in a study investigating feral dogs that were unlikely to have ever eaten commercial dog food were found to have significantly lower hepatic copper concentrations compared with normal control dogs eating a commercial diet. Consequently, we believe some dogs taking in excessive copper may have the inability to handle the high copper will develop copper associated hepatitis.

Diets low in copper are recommended for the dogs that have copper associated liver disease based on liver biopsy. However the restriction of dietary copper may do little to lower hepatic copper concentrations in diseased dogs having already large amounts of hepatic copper but diet will lessen further absorption of the metal. It is difficult to limit dietary copper because most commercial dog foods contain supplemental copper that likely exceeds the dog's actual dietary requirements. Most formulated "liver diets" have lower copper concentrations and are recommended. Homemade diets can also be prepared so that they do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron. The company www.BalanceIt.com makes a copper free dietary vitamin mineral supplement that can be used with homemade diets. They also have formulations for a homemade diet.

If the liver biopsy of a dog with chronic hepatitis indicates significant abnormal hepatic copper accumulation, a low copper diet and copper chelation or zinc therapy should be started. I believe hepatic copper levels of greater than 750 µcg/g dry weight (dw) liver (normal <400 µg/g dw) requires therapy to reduce copper concentrations. Animals having greater than 1,500 µcg/g dw should all have chelator therapy because that is a concentration considered to definitely be toxic to hepatocytes.

Zinc given orally as the acetate, sulfate, gluconate or other salt has been shown to be effective in preventing hepatic copper absorption from the GI tract in Wilson's disease patients that have been previously decoppered with penicillamine. Oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cell dies and is sloughed, the metallothionein bound copper becomes excreted through the stool. I will sometimes use zinc after a course of chelation therapy or as a primary therapy in a dog having modest hepatic copper accumulation or when the client can not afford penicillamine therapy. An initial induction dose of 5-10 mg/kg body weight divided BID of elemental zinc. Following one to 3 months of induction period the dose can be reduced in approximately half. The goal is to get serum zinc concentrations greater than 200µg/dl but less than 500 so I will often check serum zinc concentrations several times during a course of therapy. The zinc must be administered on an empty stomach and has the frequent side effect of vomiting. Zinc also has anti-fibrotic and hepatoprotective properties as well.

Chelator treatment using penicillamine is the primary therapy for copper associated liver disease. Penicillamine binds with copper and then promotes copper removal through the kidneys. Penicillamine is the most frequent copper chelator recommended for use in dogs. The dose is 10-15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting but can be managed by starting at a lower dose and then increasing the dose over time or by giving a small amount of food with the drug. Therapy using penicillamine is a slow and prolonged process taking months to cause a substantial reduction in hepatic copper concentrations. Penicillamine also has been shown to have a protective effect in the liver beyond chelation therapy. It is believed penicillamine induces a hepatic copper binding protein, metallothionein, thus binding and sequestering copper in a nontoxic form in the liver. The length of chelation therapy is variable but based on past experience some general recommendations can be made. Ideally repeat liver biopsies should be obtained to determine success of the chelation and to direct duration of therapy. The following is only a general recommendation; if copper is less than 1000 I will generally treat for 3-4 months, if 1000-2000 I treat for 4-6 months and if greater than 2000 6-8 months. I monitor ALT levels and if they become normal I often discontinue therapy, maintain on a low copper diet and will in some cases consider zinc supplementation as well. Ideally repeat liver biopsies with copper quantitation is the gold standard to direct therapy. Recently Cupramine has gone up in significant cost and therefore compounding formulations or DePen out of Canada is an option.

Antioxidant therapy is also indicated. Cu accumulation is thought to catalyze the formation of reactive free radicals causing membrane peroxidation. In another in vivo study using laboratory animals it was demonstrated that vitamin E therapy (d-alpha tocopherol) had protective properties against Cu hepatotoxicity. Vitamin E, a major membrane bound intracellular antioxidant, functions to quench membrane lipid peroxidation damage when free radicals are formed. Based on these preliminary studies it is suggested that vitamin E therapy may have a protective benefit in affected dogs with abnormal hepatic Cu concentrations and oxidative damage. A dose range of 100 to 400 IU of d-alpha tocopherol given daily is suggested. The supplement appears to be safe and free of side effects in this dose range. Other antioxidants or glutathione may also be beneficial however vitamin C has been shown to act as a pro-oxidant in the presence of increased concentrations of copper and should not be supplemented.

Summary

The abnormal accumulation of hepatic Cu can occur as a primary disease or secondary to cholestatic liver disease. Because of Cu's both direct and indirect effects on hepatocellular morphology and function, attempts should be directed at depleting abnormal hepatic Cu by either blocking Cu absorption or through chelation therapy.

References

[1]Sluis van de BJ, et.al. Hum Mol Genet 1999, 8:501. [2]Wijmenga C, et.al. Proc Nutr Soc 2004; 63:31. [3]van De Sluis B, et.al. Hum Mol Genet 2002; 11(2): 165. [4]Haywood S, et.al. Anal Cell Pathol 1996;10 (3):229. [5]Yuzbasiyan-Gurkan V, et.al. Am J Vet Res 1997; 58 (1): 23. [6]Speeti M, et.al. Vet Pathol 1998; 35:361. [7]Mandigers PJJ, et.al. J Vet Intern Med 2004; 18 (5): 647. [8]Webb CB, et. al. J Vet Intern Med 2002; 16 (6):665. [9]Thornburg LP, et.al. Vet Rec 1986;118(4);110. [10]Brewer GJ, et. al. J Am Vet Assoc. 1992; 201(4):564. [11]Twedt DC, et.al. J Am Vet Med Assoc 1988;192(1):52. [12]Spee B, et.al. Comp Hepatol 2005; 1:3. [13]Sokol RJ, et.al. Gastroenterology 1994; 107(6):1788.

Update on Liver Disease in Cats

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Laboratory testing

A sick cat may become icteric (jaundice) without having primary liver disease. This is because of the complexities of bilirubin metabolism combined with cat's weak ability to conjugate compounds. Normal hepatic bilirubin metabolism must go through several steps in the hepatocyte before excretion into the bile.[1] This metabolism can be affected by inflammatory cytokines or endotoxins and from nutritional alterations due to mobilization of free fatty acids delivered to the liver or from protein deficiencies resulting from catabolic conditions. Cats also have inherent low concentrations of glucuronyl transferase, an enzyme required to convert bilirubin to water-soluble form prior to hepatic excretion.[1] It is this complex pathway that can result in icterus without evidence of significant structural liver disease. We recently reviewed 180 cats having elevated bilirubin concentrations and cases were grouped them into those clinically icteric (bilirubin>3.0 mg/dl) or those with biochemical icterus (having only icteric serum with bilirubin ranging from 0.5 to 2.9 mg/dl). Cats with clinically icteric (bilirubin > 3.0 mg/dl) most often have primary hepatobiliary disease when hemolytic disease is ruled out. Cats having biochemical icterus (bilirubin < 3.0 mg/dl) do not always have primary hepatobiliary disease and many have other non-hepatic disorders with the liver being secondarily affected with what I refer to as a reactive hepatopathy.

A study evaluating the utility of liver biochemistries in the diagnosis of feline liver disease found the best predictive tests for primary liver disease includes ALP, GGT, total bilirubin and bile acids.[3] ALP increases with hepatic cholestatsis. ALP is unique in cats in that the half-life of the enzyme is short (6 hours compared to 72 hours in the dog) and the feline liver is reported to contain only one-third the concentrations found in dogs.[3] Consequently, increases in serum ALP with cholestasis are not expected to increase with the same magnitude as observed in dogs with similar diseases. ALP is also not induced by corticosteroids nor do they cause a steroid hepatopathy. Gamma-glutamyl transpeptidase (GGT) is a similar enzyme to ALP that increases with cholestasis and is more sensitive for feline inflammatory liver disease than ALP. Presumably this is because GGT is found in higher concentrations in the bile ducts than the hepatocyte where ALP predominates. Uniquely cats with idiopathic hepatic lipidosis usually have marked increases in ALP while GGT concentrations show only mild increases.[4] Cats with cholangitis usually have higher elevations in GGT than ALP. Bile acids in the cat are most useful in screening for portosystemic shunts.

Liver disease in cats

In an unpublished review of 175 consecutive liver biopsies performed on cats at Colorado State University several large categories were observed. Making up 87% of the liver biopsies were 4 groups: Lipidosis (both idiopathic and secondary, 26%), Cholangitis (25%), Neoplasia (20%) and Reactive hepatopathies (16%). Hepatic cysts are also an occasional finding in some cats but rarely cause problems. Lipidosis and cholangitis were the most common conditions and will be discussed below. Reactive hepatopathies refer to changes in the liver that occur secondary to a primary non-hepatic disorder such as inflammatory bowel disease, hyperthyroidism and cardiac disease as a few examples.

Hepatic lipidosis

Hepatic lipidosis can occur as either a primary idiopathic disease syndrome or secondary to a number of other primary disease conditions. Lipid accumulation in the liver is simply the result of nutritional, metabolic or toxic insults to the liver and the degree of lipid accumulation can be quite variable and the process is reversible.[5] For example, a common secondary disease associated with significant hepatic triglyceride accumulation is diabetes mellitus. This diagnosis is generally obvious (hyperglycemia and glycosuria) and the lipidosis resolves with appropriate therapy. Hepatic lipid accumulation can also result secondary to a number of other disease syndromes associated with anorexia and weight loss such as pancreatitis, inflammatory bowel disease or other major organ dysfunction. These secondary conditions generally have less severe lipidosis than the clinical syndrome associated with idiopathic hepatic lipidosis in which there is no identifiable etiologic factor. Lipid accumulation is more unique to cats than dogs, in other words cats get lipidosis easily from many conditions.

The etiology of idiopathic hepatic lipidosis is unknown and many theories have been put forward without substantial documentation. One proposal is that there is a defect in hepatic lipid mobilization and decreased ability for hepatic fat oxidation, decreased synthesis of apoproteins and decreased lipoprotein removal from the liver.[5] The cause for the rapid mobilization of peripheral fat however is as yet unknown. A second novel theory speculated by some is that the disease is a primary central anorexia disorder with resultant lipidosis. In any event it is important to investigate all possible secondary conditions leading to anorexia and initiating the typical cascade of hepatic lipidosis. One study reported on a number of cats with acute pancreatitis resembling the idiopathic form of hepatic lipidosis.

In the idiopathic form affected animals generally are older and obese cats that have undergone a stressful episode in the recent history followed by a period of complete anorexia. There does not appear to be a breed or sex predisposition. Cats will present with

an acute history of rapid weight loss (up to 40-60% body weight over 1-2 weeks), depression and icterus. The weight loss is significant with loss of muscle mass while abdominal and inguinal fat stores are often spared. Typical neurological signs commonly associated with hepatic encephalopathy in the dog are uncommon. Complete anorexia, lethargy and depression may however be in part the result of hepatic encephalopathy. These cats generally have a total aversion to any type of food.

The diagnosis of idiopathic hepatic lipidosis is supported by the clinical history and laboratory findings. Icterus and marked elevations in ALP are consistent findings. ALT (SGPT) levels are generally abnormal and quite variable in magnitude of elevation. GGT concentrations are only moderately increased in these cats. Icterus with a very high ALP and normal GGT should be a clue to probable idiopathic lipidosis given with appropriate clinical features. Hypercholesterolemia, hyperammoniemia and abnormal bile acid levels are characteristic. About 1/3 of the cats have a nonregenerative anemia, hypokalemia and clotting abnormalities and about 1/2 the cats demonstrate poikilocytes in the RBC's. Finding severe hypokalemia, anemia or other concurrent disease (ie pancreatitis) in lipidosis cats has a poor survival rate.[4]

The liver size may be normal or enlarged on palpation or radiographically. A definitive diagnosis requires a liver biopsy or hepatic cytology. A fine needle aspirate of the liver with cytological evidence of many vacuolated hepatocytes helps support a diagnosis. Be aware that cytological diagnosis does not always correlate with histology. A needle aspirate can be performed with the cat in dorsal recumbency and a 22 g needle on a syringe directed slightly cranial and lateral to the left from the left xyphoid space. The aspirate can be stained with Diff-quick or Sudan stain. A hepatic tissue biopsy confirms the diagnosis of lipidosis. Care should be taken when obtaining a liver biopsy as some cats may have coagulation abnormalities.

The therapy for idiopathic hepatic lipidosis requires aggressive management.[6] I believe up to an 80% or higher survival rate should be expected in cats given appropriate therapy and no underlying disease is present. Initial therapy requires rehydration with balanced electrolyte solutions. Replacement of potassium deficits is imperative as normokalemia improves survival.[4] Some cats may also require magnesium supplementation as well.[6] Administration of glucose containing solutions may actually cause marked hyperglycemia in these patients and result in a refeeding syndrome (see below). Cats also have a tendency to develop lactic acidosis and therefore lactate-containing fluids (i.e. Lactated Ringers) should be avoided. The practice of adding B-vitamins to the fluids should also be avoided because their prolonged exposure to light in the fluid bag will inactivate them. Parenteral administration is a better option.

Adequate nutrition then becomes the most important part of the therapy for hepatic lipidosis. Force-feeding or appetite stimulation is generally not adequate to meet caloric needs and tube feeding is the best way to administer adequate calories.[7] Nasogastric tubes can be used but due to the small size feeding is limited to liquid diets and they are less tolerated than larger tubes. I suggests placement of either an esophageal or gastrostomy feeding tube. In our practice we find that esophageal tubes to be well tolerated and having less complications than gastric tubes. One should refer to specific articles on tube placement techniques. We find the 20 French red rubber feeding tubes ideal for the esophagus.

The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and poorly documented. There is some evidence that L-carnitine supplementation in cats may protect against hepatic lipid accumulation (at least in weight reduction studies in cats) and consequently may be an appropriate dietary adjunct for cats with lipidosis.[8] Carnitine is required for transport of long chain fatty acids into the mitochondria for subsequent oxidation and energy production. A deficiency of carnitine may lead to impaired mitochondrial function. It appears that carnitine deficiency could result in chronic liver disease and that supplementation may help protect against encephalopathy, hypoglycemia, and subcellular damage. Studies have however have failed to show carnitine deficiency in cats with hepatic lipidosis.[9] Suggested dose is 250-300 mg/day. Supplementation is reported to be associated with better survival rates, however this is not well documented.

There is also new evidence to suggest many cats with hepatic lipidosis have or will develop cobalamin deficiency. Experimental cobalamin deficiency results in lethargy, anorexia and weight loss – the signs observed with lipidosis. Anecdotal reports suggest cats improve faster with high doses of cobalamin given 250 µg SQ weekly. Serum cobalamin levels should first be determined to document the presence of a deficiency.

Other therapies suggested include S-adensosylmethionine (SAMe) a nutraceutical that is a naturally occurring molecule found in all living organisms and is involved in the metabolism of glutathione (GSH). GSH participates in many metabolic processes and plays a critical role in detoxification mechanisms of the cell.[6] SAMe is also important in hepatocyte membrane integrity and function. The suggested dose is 100 mg/day. Another antioxidant hepatoprotectant is milk thistle or its extract silybin (available as a silybin-phosphatidylcholine combination, Marin™), is a safe hepatic support therapy.

The prognosis must be guarded however with aggressive nutritional therapy many if not most cats recover. Several complications that can occur with therapy include a re-feeding syndrome and vomiting. The re-feeding syndrome is associated with the development of an often life-threatening electrolyte disturbances that occurs within 24 to 48 hours of enteral feeding.[10] If vomiting occurs I will sometimes use maropitant (Cerenea™) or other antiemetics. Maropitant is metabolized by the liver and the dose I use in cats with hepatic lipidosis is lower (0.25- 0.5 mg/kg SO q 24 h) with my normal cat dose being 1.0 mg/kg SQ q 24 h. We have also used

mirtazapine (Remaron™) a tetracyclic antidepressant that has both antiemetic and appetite stimulant effects (approximate dose is 1/8 of a 15 mg tablet every 3 days) with encouraging preliminary success.

When the cat is consuming adequate calories without the need for tube supplementation the feeding tube can be removed. Tube feeding may extend for up to 4-6 weeks. A failure to respond to traditional hepatic lipidosis therapy should signal the need to investigate the likelihood of an underlying condition in the patient.

Inflammatory liver disease

Cholangitis is an inflammatory disorder of the hepatobiliary system. It is a disease complex that may be concurrently associated with duodenitis, pancreatitis, cholecystitis and/or cholelithiasis. The terminology is somewhat confusing and pathologists describe the condition differently. Based on the histological classification of the WSAVA Liver Standardization Group this complex has been separated into three histological groups; neutrophilic cholangitis, lymphocytic cholangitis and cholangitis associated with liver flukes.

Neutrophilic cholangitis

This classification has previously been referred to as suppurative or exudative cholangitis /cholangiohepatitis and is the most common type of biliary tract disease observed in cats in North America. Neutrophilic cholangitis is thought to be the result of biliary tract infection ascending from the gastrointestinal tract. In the acute neutrophilic form (ANF), the lesions are exclusively neutrophilic or suppurative but over time it is thought that cases may progress to a chronic neutrophilic form (CNF) having a mixed inflammatory pattern containing variable numbers of neutrophils, lymphocytes and plasma cells.

The ANF is thought to be the result of an ascending bacterial infection. Usually coliforms (E. coli) are cultured from the liver or bile. Inflammation can also extend into the hepatic parenchyma causing a cholangiohepatitis. Cats with this syndrome are usually young (~3-5 years) and present with acute illness usually a week or less in duration. They may have evidence of a fever, anorexia, vomiting or lethargy. A leukocytosis is generally identified on the CBC. The ALT and ALP are increased but variable and these cats are frequently icteric. Ultrasound should be performed to rule out pancreatitis and biliary obstruction. In some cases we will perform an ultrasound-guided cholecystocentesis for cytology and culture. An elevated feline PLI would support concurrent pancreatitis. A liver biopsy is required for histology and will confirm the diagnosis. The liver should always be cultured because of the relationship of bacteria and cholangitis. If obstruction is identified surgery becomes indicated to decompress and flush the biliary system. However, I always try to avoid surgical diversion surgery of the biliary system unless it becomes the last resort.

Therapy for these cats first includes fluid and electrolyte therapy if needed. Antibiotics are a critical part of the therapy as well. Ampicillin, ampicillin-clavulanic acid, cephalosporins and metronidazole have been suggested as effective antibiotics. Unless a culture and sensitivity says otherwise ampicillin or ampicillin-clavulanic acid are my choice because of the likelihood of E. coli and the fact that both are concentrated in the bile. It is recommended that cats be treated for at least 1 month or even longer with antibiotics. Short duration of therapy may result in reoccurrence of clinical signs. Ursodeoxycholic acid (Actigall 10-15 mg/kg/day) should be used as well. Abdominal discomfort and vomiting may be associated with hepatobiliary pain and buprenorphine (Buprenex™) should be administered.

There is also a direct relationship between chronic cholangitis and inflammatory bowel disease and chronic pancreatitis. One study found 83% of affected cats had inflammatory bowel disease and 50% had concurrent chronic pancreatitis. The association of the three together has been referred to as “feline triaditis”. Possibly the common channel theory where the pancreatic ducts and bile ducts join before entering the duodenum explain this triad of clinical signs. Ascending bacteria initiate the acute disease and then over time it becomes chronic. In a yet published study we have identified over 50% of affected cats to have evidence of bacteria in and around bile ducts of these cats suggesting that resident bacteria may be responsible for the chronic inflammation.

Affected cats are usually middle aged or older and have a long duration of signs being weeks to months. Presenting complaints are often vomiting, lethargy and anorexia. Signs may wax and wan and weight loss may be present. Physical findings identify jaundice in most, possibly hepatomegaly and rarely abdominal effusion.

The laboratory findings are variable. Most cats are icteric and there are variable increases in ALP/GGT or ALT/AST. Hyperglobulinemia is observed in over 50% if the cases. Ultrasound may reveal pancreatic, bile duct or gallbladder changes. The liver generally has a mixed echoegnicity pattern with prominent portal areas. Cats with concurrent pancreatitis may have increases feline pancreatic lipase immunoreactivity (fPLI). A liver biopsy confirms the diagnosis.

The primary treatment involves immunosuppressive therapy using prednisolone at 2-4 mg/kg daily and then slowly tappering over 6 to 8 weeks to 0.5-1 mg/kg given once or every other day. This therapy does not appear to resolve this chronic disease but generally slows the progression and may minimizes the clinical signs. A course of antibiotic therapy for several weeks is administered for the possibility of a bacterial component and in light of our yet unpublished study more aggressive antibiotic therapy may be indicated. Ursodeoxycholic acid is a nontoxic hydrophilic bile acid that when administered changes the bile acid milieu. Ursodeoxycholic acid (10-15 mg/kg/day) is nontoxic and suggested for these cats and in fact may be even more beneficial than corticosteroids. This drug is reported to increase bile flow (choleresis), change bile acid concentrations to less toxic concentrations, reduce inflammation and

fibrosis and improve liver enzymes. Liver support therapy such as SAMe, Silybin or other antioxidants may be of benefit in the long term management.

The disease is slow and progressive often scattered with periodic flair ups. Approximately 50% of the cases will have a prolonged survival. The final stage of this disease complex is biliary cirrhosis having extensive fibrosis and bile duct proliferation that may end with liver failure associated with ascites and hepatic encephalopathy.

Lymphocytic cholangitis

This is a condition (severe lymphocytic portal hepatitis, progressive lymphocytic cholangitis or nonsuppurative cholangitis) is described as a very chronic inflammatory biliary tract condition that is progressive over months and years. Some describe it as being acute or chronic in nature. This disorder appears to be more common in European cats than in cats in North America. The pathology of the liver is characterized by a consistent moderate to marked infiltration of small lymphocytes predominately restricted to the portal areas, often associated with variable portal fibrosis and biliary proliferation. The later stages result in considerable distortion of liver architecture. The bile ducts can also become irregular with dilation and fibrosis. In some cases lymphocytic infiltrates in the portal areas may be confused with well-differentiated lymphocytic lymphoma. It is postulated that lymphocytic cholangitis could be the result of immune mediated mechanisms based on preliminary immunologic studies while others have found DNA fragments of Helicobacter pylori in the bile of some cats suggesting bacterial involvement in the pathogenesis of the disease.[6] We have found bacteria to be less commonly associated with this condition using special fluorescent stains for enteric bacteria.

This syndrome as a slowly progressive chronic disease continuing over months and years. It is often first identified in cats under 4 years of age and Persian cats appear to be over-represented, suggesting a possible genetic predisposition.[5] The most common clinical features observed late in the disease include ascites, jaundice, and hypergammaglobulinemia (in almost all cases). In advanced cases, ultrasonographic examination often demonstrates dramatic changes intra and extra-hepatic bile ducts with marked segmental dilations and areas of stenosis that may lead the operator to believe there is an obstruction. Ascites and hepatic encephalopathy occur late in the disease as a result of acquired portal hypertension and hepatic dysfunction.

The treatment for the chronic lymphocytic cholangitis involves using anti-inflammatory or immunosuppressive therapy in addition to supportive therapy as described with neutrophilic cholangitis. Some report lymphocytic cholangitis had a better response when treated with ursodeoxycholic acid than with corticosteroids.[6] This finding may not be completely unexpected because ursodeoxycholic acid has been shown to have a positive treatment effect in humans having chronic primary biliary cirrhosis having a very similar histologic pattern to these chronic cases.

References

1. van den Ingh TSGAM, Cullen JM, Twedt DC, et al: Morphological classification of biliary disorders of the canine and feline liver. In: Rothuizen J, Bunch SE, Cullen JM, et al, eds. WSAVA standards for clinical and histological diagnosis of canine and feline liver diseases. Saunders/Elsevier: Edinburgh, 2006, p61.
2. Twedt DC, Armstrong PJ: Feline Inflammatory Liver Disease. In Bonagura JD, Twedt DC eds: Kirk's Current Veterinary Therapy XIV, St Louis, 2008, Saunders/Elsevier, p 576.
3. Gagne JM, Weiss DJ, Armstrong PJ: Histopathologic evaluation of feline inflammatory liver disease. Vet Pathol 33:521, 1996.
4. Weiss DJ, Armstrong PJ, Gagne J: Inflammatory liver disease. Semin Vet Med Surg (Small Anim) 12:22, 1997.
5. Lucke VM, Davies JD: Progressive lymphocytic cholangitis in the cat. J Small Anim Pract 25:249, 1984.
6. Rothuizen J: Cholangitis in cats-a review, Proceedings of the 31st World Small Animal Congress, Prague, Czech Republic, 2006, p 47.

Common Liver Diseases in Dogs

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Several hepatobiliary disorders have in the last few years come under increased recognition and interest in dogs. Understanding theses specific conditions is essential in the diagnosis and management of canine liver disease.

Vacuolar hepatopathies

Hepatic vacuolar change is a common histological diagnosis in dogs but not cats. When we reviewed 150 consecutive liver biopsies performed at Colorado State University approximately 12% of the cases had predominately a vacuolar hepatopathy (VH) as the major histological finding. By definition according to the WSAVA Liver Standardization Group VH refers to a reversible parenchymal change that is characterized by swollen hepatocytes with clear cytoplasm due to glycogen without displacement of the nucleus from the center. The distributionand the extent of the lesion can vary being either diffuse, zonal, or involve individual cells. VH is a relatively easy histological diagnosis to make however Periodic acid Schiff (PAS) staining with or without diastase can be used to demonstrate glycogen accumulation. Vacuolated hepatocytes can also result from fat accumulation secondary to abnormal fat metabolism and is referred to as hepatic steatosis or lipidosis. Hepatic steatosis is a distinct histological vacuolar classification associated with abnormal fat metabolism and will not be discussed in this chapter.

VH in dogs is most often associated with hyperadrenocorticism (HAC). The dog is particularly sensitive the effects of glucocorticoids that both induce serum alkaline phosphatase (ALP) steroid isoenzyme activity and causes hepatic glycogen accumulation. (see chapter Evaluation of Elevated Alkaline Phosphatase in Evolve). Congenital glycogen storage disorders, breed specific disorders, hepatic nodular hyperplasia and a variety of stress-associated secondary diseases are conditions that can cause this typical hepatic vacuolar changes. In a large study of 336 histological liver specimens having VH (defined as making up greater than 25% of the hepatocytes) were retrospectively reviewed for an underlying etiology (Hill et al., 2006). The authors report 55% of the cases were associated with either endogenous or exogenous glucocorticoids with the remaining 45% having no known glucocorticoid exposure. Most all of the dogs with no glucocorticoid exposure had other identifiable concurrent illness. Conditions such as renal, immune-mediated, cardiac, hepatic, gastrointestinal disease, or neoplasia accounted for many cases. The author's hypothesis was that stress-induced hypercortisolemia associated with acute or chronic illness likely contributed to the development of the VH. A second in vivo study showed that by experimentally inducing a chronic four to five-fold elevations in plasma cortisol concentrations to simulate a stress-like state in normal dogs inhibited non-hepatic glucose utilization and increased hepatic gluconeogenesis and glycogen formation through enhanced substrate delivery to the liver.

Idiopathic vacuolar hepatopathy

There is a subset of dogs having elevations in serum alkaline phosphatase and excessive hepatic glycogen accumulation that do not have evidence of either a stress induced illness, evidence of HAC based on cortisol testing, a history of recent glucocorticoid administration or have a specific hepatic disease. These dogs are referred to as having an idiopathic vacuolar hepatopathy (IVH). They generally have no clinical signs and are usually identified during investigation of unexplained elevations in serum alkaline phosphatase (ALP) found on a routine health screen. Several theories have been put forward as to the cause of IVH. Some believe adrenal progestagens; most likely increases in 17-hydroxyprogesterone and progesterone are responsible as these changes as they are frequently identified to be abnormal when a commercial adrenal steroid panel is performed. However, critical evaluation and validation of the adrenal steroid panel (17-hydroxyprogesterone, progesterone, estradiol, testosterone and androstenedione) is as yet still lacking and a direct association has not be made. Because the VH changes are typical of glucocorticoid excess it is entirely possible that a yet to be identified adrenal steroid could be responsible for the VH. Obviously future research is necessary to delineate this syndrome and the relationship to adrenal steroids.

Scottish terriers are also reported to have a breed-specific syndrome associated with a VH and elevated serum ALP. These affected dogs generally have no clinical signs. The authors found that the elevated ALP was predominately the corticosteroid isoform and following ACTH stimulation test in conjunction with an adrenal steroid panel found increases in one or more non-cortisol steroid hormones. The authors conclude that affected Scottish terriers have a type of hyperadrenocorticism on the basis of exaggerated adrenal hormone response. We have also observed similar non-cortisol steroid hormone increases in Scottish terriers but also in Scottish terriers without VH or increases in ALP adding more confusion to this syndrome. The reader should refer to Chapter 51, Occult hyperadrenocorticism: Is It Real? for further information concerning adrenal steroids.

Dogs with IVH generally have no clinical signs. They are usually identified serendipitously on a biochemical profile identifying elevations in serum ALP concentrations that subsequently initiates a diagnostic work-up. Most affected dogs are middle-aged or older at the time of diagnosis. There does not appear to be a breed or sex predisposition other than the syndrome described above in the Scottish terrier. A small percent of dogs may have reported polyuria and polydipsia (PU/PD) but the other signs typical of HAC are generally absent. The work up of the asymptomatic dog having an IVH usually begins after the identification of an elevation in serum

ALP. The ALP increases are often 5 to 10 times normal concentrations; the other liver enzymes are usually normal or there are occasional mild elevations in alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT). Marked elevations in liver enzymes other than ALP is not typical of this syndrome and if present other types of liver disease should be investigated. The work-up should first rule out common causes for an elevated ALP such as drug administration (including topical or systemic steroids, phenobarbital, or herbal medications), cholestatic liver disease, or bone disorders. Next adrenal testing (ACTH stimulation or low dose dexamethasone suppression) would be prudent to perform to eliminate possibility of HAC. Determining the percent of ALP steroid isoenzyme is generally not helpful. Dogs with IVH will have predominately a steroid-induced ALP isoenzyme but this is neither specific for HAC or IVH and other non-adrenal illness may also have similar increases in the steroid-induced ALP isoenzyme. Basic tests of liver function tend to be normal however the author has seen a few cases having very mild elevations in serum bile acids. Abdominal ultrasound of the liver is helpful to rule out hepatic nodular hyperplasia, occult hepatic neoplasia or cholestatic disorders that all could be differentials for an elevated ALP. Affected IVH dogs generally have an enlarged uniformly hyperechoic liver with rounded borders. Adrenal glands are generally normal. Fine needle aspiration of the liver with cytology supports a diffuse vacuolar change. A PAS stain of the cytology sample can help confirm the presence of hepatic glycogen. A liver biopsy confirms diffuse vacuolar change but is rarely necessary. I generally make the diagnosis of IVH based on the above diagnostic findings and after exclusion of HAC, drugs, hepatic nodular hyperplasia, hepatic neoplasia or cholestatic liver disease.

At this time I believe adrenal sex steroid panel testing for most cases is not necessary for two reasons; first, our inability to adequately interpret the tests results and second, most all IVH dogs are generally asymptomatic and information obtained from the testing offers little important diagnostic or therapeutic information. Several labs offer adrenal hormone analysis and currently the most extensive adrenal steroid hormone profile is offered by the Clinical Endocrinology Laboratory at the University of Tennessee. The protocol for running the test is identical to that for a standard ACTH stimulation test.

Both proteinuria or hypertension are occasionally identified in cases of IVH and the affected dos should be periodically monitored for these complications and if identified, managed appropriately. Dogs with IVH are also thought to have an increased risk for developing biliary mucoceles and there is also some anecdotal evidence to suggest that some Scottish terriers with VH are at an increased risk of development of hepatic neoplasia (hepatocellular adenoma or carcinoma). Consequently it would be prudent to monitor IVH dogs from time with an ultrasound of the liver and biliary system.

The management of IVH is controversial at best and there are no studies critically evaluating therapy for this syndrome. I believe that specific therapy is unnecessary unless complicating factors such as hypertension, proteinuria or significant PU/PD exist. Problem associated with therapy arise from the fact we do not know what the endpoint of therapy should be; is it normalization of adrenal hormones, return of ALP into the normal range or histological resolution of the VH? There are anecdotal reports of dogs with IVH being successfully treated using low doses of mitotane and monitoring clinical parameters and measuring adrenal steroid concentrations including cortisol to assure hypoadrenocorticism does not result. Trilostane often shows a similar clinical response however concentrations of 17-hydroxyprogesterone and progesterone are frequently higher following this therapy. Ancedotal reports of clinical improvement in dogs having IVH using either oftherapy does suggesting abnormal adrenal steroid production may be involved in the pathogenesis of this syndrome. However these treatments beg the question if therapy is warranted due to the expense of medication and monitoring and the potential complications associated with the therapy alone. Until more is known about this syndrome this author can't recommend specific adrenal therapy unless significant clinical findings would warrant a trial therapy.

Alternative therapies suggested include melatonin and flax seed products. Melatonin has been shown to decrease sex hormone concentrations in normal dogs. It is reported to be beneficial in some dogs with alopecia X syndrome, and has also been suggested for IVH. Doses of 3 mg/15 kg q 24h PO has been recommended however here is no published data showing effectiveness for dogs with IVH. Flaxseed hull products with lignans have also been suggested because they compete with estridiol production but again there is no reported evidence of benefit for IVH syndrome.

Liver support therapy using products such as s-adenosylmethionine (SAMe), the milk thistle products, or other antioxidants may have some beneficial effects. One study showed dogs given glucocorticoids and treated with SAMe failed to show a decrease in serum ALP or amount of VH but did have improvement in hepatocyte oxidative status through increased glutathione concentrations. The above products are generally safe for liver support but will unlikely have any effect in the resolution of IVH.

Hepatic nodular hyperplasia

This is a benign process causing an increase in hepatic values and histomorphologic changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. Grossly, the appearance may be suggestive of chronic hepatitis or neoplasia. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater than 10 years of age. Laboratory findings include an ALP increase (mean ALP ~ 600 IU/L), but some may have mild increases in ALT and AST concentrations as well. Ultrasound may be normal or may demonstrate larger nodules (many can be only microscopic and not observed on ultrasound). Biopsy confirms the diagnosis, however a wedge section is preferred. A needle aspirate or needle

biopsy may only demonstrate show a vacuolar hepatopathy There is no specific therapy and it does not progress to a neoplastic process.

Gallbladder mucocele

To date greater than 130 cases of gallbladder mucocele have been documented in the literature. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile stellate or finely striated patterns of mucoid material within the gallbladder lumen detected with ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the $ABCB_4$ hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing's disease) and idiopathic vacuolar hepatopathy, hyperlipidemia and dogs on high fat diets. Gallbladder mucoceles appear ultrasonographically as an immobile accumulation of anechoic-to-hypoechoic material characterized by the appearance of stellate or finely striated bile patterns (wagon wheel or kiwi fruit appearance). This should be differentiated from biliary sludge (bile sludge can be found in normal animals), by the absence of gravity dependent bile movement while the mucocele is non-movable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic or common bile duct may be normal size or dilated suggesting biliary obstruction. Gallbladder wall discontinuity on ultrasound indicates rupture whereas neither of the bile patterns predicted the likelihood of gallbladder rupture.

Cholecystectomy is the treatment of choice for biliary mucoceles. Following cholecystectomy and recovery of postoperative period the prognosis is excellent especially when the liver enzymes are normal. Mortality rates have been reported to be in the 20% range and some may persist in having liver disease with elevated liver enzymes. There are reports of resolution of some mucoceles using ursodeoxycholic acid (ursodiol) and a low fat diet but this should only be attempted in the healthy patient and with careful monitoring. Ursodeoxycholic acid is thought to up-regulate biliary excretion of phospholipids and increase bile salt dependent flow.

On histopathology the gallbladder demonstrates cystic mucinous hyperplasia. The pathophysiology of this condition is unknown. It is possible biliary stasis and abnormal bile composition or lack of solubility results in gallbladder mucosal irritation and subsequent mucinous hyperplasia. Infection does not appear to be a factor in this condition. A mucocele is reported the most common cause of a gallbladder perforation.

Portal vein hypoplasia

Portal vein hypoplasia (PVH), also referred to as microvascular dysplasia (MVD), is a common syndrome in the dog associated with abnormal microscopic hepatic portal circulation. It is thought that PVH is 15 to 30 times more common that a congenital portosystemic shunt (PSS). Hepatic PVH has been suggested as the terminology by the WSAVA Liver Standardization Group that may better reflect the etiology of this condition although MVD is ingrained in the veterinary liturature. It is believed that the primary defect in affected dogs is the result of hypoplastic small intrahepatic portal veins. This condition is thought to be a defect in embryologic development of the portal veins. With paucity in size or number of portal veins there is a resultant increased arterial blood flow in attempt to maintain hepatic sinusoidal blood flow. The hepatic arteries become torturous and abundant in the triad. Sinusoidal hypertension occurs under this high pressure system. Lymphatic dilation results and it is thought that this opens up of embryologic sinusoidal vessels to reduce pressure and thus acquired shunts develop to transport some (but not all) of the blood to the central vein thus by-passing the sinusoidal hepatocytes. This results in abnormal hepatic parenchymal perfusion and lack of normal trophic factors bathing the sinusoids causing hepatic atrophy. With portal shunting of blood increased iron uptake also occurs that results in hepatic iron granuloma formation. Ascites or portal hypertension generally do not occur in this condition.

Because similar histological changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary. The condition that was first described in Cairn terriers and now is felt to occur in other breeds of dogs. Yorkshire Terriers and Maltese may be over represented. Animals show no outward clinical signs and are usually identified because of elevated liver enzymes (ALT). All patients have abnormal serum bile acid concentrations (usually moderate elevations) but generally they are less than 100 µmole/L. It is reported PVH dogs have normal protein c concentrations while PSS dogs have concentrations less than 70% normal. There is no specific therapy. Some suggest antioxidants (i.e., SAMe, milk thistle etc.). The long-term prognosis is uncertain because of lack of experience with this relative new disease. There may be a small number of dogs developing portal hypertension over time.

Update on Chronic Hepatitis in Dogs

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The most important and most common primary liver disease in the dog is chronic hepatitis. Chronic hepatitis is not a single disease but rather the inflammatory changes can be due to many of etiologies. The therapy should be directed first at the cause of the inflammation. In most all cases a liver biopsy is required to confirm the diagnosis before effective therapy can be begun.

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change frequently secondary to intra-abdominal disorders like IBD I need the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatoencephalopathy. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

Etiology

The etiology of this chronic inflammatory condition is generally never determined. To date the best-described etiology of chronic hepatitis is the copper associated hepatitis of the Bedlington terrier (see below copper associated hepatitis). This breed and others are thought to have an inherited copper associated chronic hepatitis. Copper accumulates in hepatocyte from abnormal metabolism to a level that then becomes toxic causing hepatocyte death. There are also likely breeds that have difficulty in handling copper if taken in orally in excess amounts.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a viral etiology of hepatitis in the dog however has been unrewarding. The canine adenovirus type 1 given experimentally to partially immune dogs did caused hepatitis and fibrosis. Others identified a suspected acidophil cell hepatitis virus in dogs that were vaccinated with liver homogenates from dogs dying from chronic hepatitis. The vaccinated dogs developed fibrosis and inflammation in their livers. Subsequent further research or publications into viral etiologies are lacking. Chronic hepatitis has also been associated with leptospirosis with the authors describing "atypical leptopsires" in a colony of dogs having hepatitis. However we have examined over 50 dogs livers havng hepatitis using PCR for Leptospirosis and did not identify a single positive case. Other infectious agents suggested as a possible etiology include *Helicobacter sp*, Bartonella, and Leishmaniasis.

Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital will develop chronic hepatitis. We have also observed some dogs treated with NSAIDs to also have hepatitis which asks the question of NSAIDs being related to hepatitis. In man alpha-1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for ATT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage. The breed most often associated with AAT accumulation is thought to be the cocker spaniel.

Finally immune associated hepatitis may also occur in the dog. Autoimmune liver disease in humans is an important cause of chronic hepatitis and is associated with diagnostic circulating autoantibodies. It appears that autoantibodies (ANA, antimitochrondial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are markers of autoimmune hepatitis in humans. A number of studies have been performed in dogs looking for liver associated antibodies and cell-mediated responses to support autoimmune disease as an etiology. Findings so far suggest autoimmune liver disease exists but studies fail to conclusively prove its existence. The pathogenesis proposed is that an insulting agent damages the hepatocytes thus releasing liver antigens that initiate a secondary immune response perpetuating chronic hepatitis. Nonetheless, immune-mediated mechanisms are thought to occur in some cases of chronic hepatitis and this is further supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There are also a number of breeds that have an increased incidence of chronic hepatitis and are thought to be inherited. Some of these breeds have copper associated chronic hepatitis and are discussed below. Other breeds not yet associated with copper include the standard poodle, Cocker spaniel, Springer spaniel and Scottish terrier. The pathogenesis of the hepatitis is yet unknown. Cocker

spaniels both English and American tend to be more commonly males and ATT accumulation may play a role in their disease. More recently in Europe English Springer Spaniels have been reported to have a breed associated hepatitis. Standard poodles are more commonly females and tend to have prolonged survival with immunosuppressive therapy. We are currently studying the standard poodle at Colorado State University.

Clinical findings

The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation ranges from 4 to 10 years. It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older than 10 years of age. As a general rule old dogs (> 11 years of age) don't generally present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease.

The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of rise need not be marked however. One report found 75% of the cases with abnormal bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. One must work with the pathologist when making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present.

Prognosis

There is little information of the prognosis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck found mean survivals ranging from 6 to 16 months with therapy. This study also identified that dogs with hypoalbuminemia, hypoglycemia and coagulopathies have very guarded prognostic factors and many died within 1 week of diagnosis. A second study of 79 dogs found that dogs with cirrhosis had a survival of less than one month and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment.

Treatment

I have four general goals in therapy: 1) remove the etiology, 2) provide an adequate diet, 3) give specific therapy and 4) providing general liver support. First step in the therapy for chronic hepatitis and other liver diseases involves removing the primary etiology if it can be identified. Short of treating the primary etiology all other therapies suggested are unproven in the management of liver disease in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies.

Diet

Adjusting diet therapy should be considered in all cases however only general guidelines should be given. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about diet and liver disease that liver patients should be placed on a protein restricted diet. Protein restriction should only be instituted in the patient that has clinical evidence of protein intolerance (i.e. hepatic encephalopathy). Diets low in copper are recommended for the dogs that have copper associated liver disease based on biopsy. Most formulated "liver diets" have lower copper concentrations and are often supplemented with additional zinc. Homemade diets can also be prepared that do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron.

Antiinflammatory therapy

Decreasing inflammation as a specific therapy for chronic hepatitis in the dog or cholangitis in the cat is unproven although the author's clinical impression suggests anti-inflammatory therapy is beneficial in some cases. The treatment of chronic hepatitis is quite controversial and there are as yet no good controlled studies in animals to support corticosteroids use in every case. Antiinflammatory therapy is indicated in suspected immune mediated chronic hepatitis. A suggested dose of 1 to 2 mg/kg/day using prednisolone

(prednisone requires hepatic biotransformation) should be instituted. When clinical improvement is suspected or after several weeks the dose is then gradually tapered eventually to a dose of 0.5 mg/kg/day or every other day. The only accurate way to evaluate a response to any therapy is to re-biopsy the patient in 6 months to 1 year because the patient will develop a concurrent steroid hepatopathy with increased liver enzymes making laboratory determination of any improvement impossible. Alternatively one could stop steroids and recheck enzymes in 1 to 2 months. We have more recently been using cyclosporine in many cases with a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to Neoral™ (also sold as modified generic cyclosporine) that ensures more consistent bioavailability. With evidence of clinical response at 5 mg/kg bid I will often decrease to once a day therapy. Using cyclosporine alone one can follow the liver enzymes making the need for a liver biopsy less frequently required.

Antifibrotic drugs

Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has limited success I chronic hepatitis. Recently it was found that angiotensin II inhibitor Losartan (Zestril™, 0.25-0.5 mg/kg/Day) has effects in reducing or preventing fibrosis in humans by effecting function of stellate (fibrosis producing) cells.

Choleretic drugs

Decreasing cholestasis has been shown to be of benefit in humans and animals having cholestatic hepatobiliary disease. As serum bile concentrations increase (these are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol -Actigall™- 300 mg caps) is a choleretic agent developed to dissolve gallstones but later fond to have positive effects in patients with chronic hepatitis. This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophylic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics makes one believe ursodeoxycholic acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Although with obstruction surgery is indicated ursodeoxycholic acid is not a prokinetic and will not cause a rupture. In fact in experimental bile duct obstructions there was less secondary "toxic" changes in the liver in rats given ursodiol than placebo.

Antibiotics

Antibiotics are indicated for primary hepatic infections. There however may be evidence that bacterial colonization may take place in a diseased liver. Kupffer cell dysfunction could be a reason for secondary bacterial infections. It may be prudent for antibiotic therapy or trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole are suggested. Metronidazole may have some immunosuppressive properties as well as antibacterial mechanisms. For liver disease I would use 7.5-10 mg/kg bid a much lower dose used for other bacterial infections because of hepatic metabolism of the drug.

Antioxidants

There has been recent interest in the management of certain types of liver disease using antioxidants. Antioxidants in general provide liver support to promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats.

Vitamin E, d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phopspholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. In a small study of dogs having chronic hepatitis we found all dogs had evidence of oxidative damage. In a three-month placebo controlled study treating only with vitamin E there was evidence improvement in the oxidant status of the treated dogs however we did not identify changes in clinical, laboratory or histology during this short treatment period. A suggested vitamin E dose is 50 to 400 IU a day. The d-alpha tocopheryl formulation is much more potent than the most common commercial form (dL-alpha tocopheryl). Since bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is suggested. For a water soluble form I use Twin labs Liqui-E. The vitamin E is derived from TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) and has a rapid absorption. Because of the potential benefits of vitamin E, the lack of side effects and since the drug is inexpensive I place most all my liver patients on E therapy.

S-Adensosylmethionine (SAMe) is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Research has demonstrated that the exogenous administration of SAMe to have potential beneficial effects for a number of types of liver damage. In one study giving acetaminophen to cats at a sub-lethal dose we observed protective effects of SAMe when measuring markers of hepatic oxidative damage and RBC fragility. Studies investigating naturally occurring liver disease in animals are required to determine the benefit of SAMe administration in liver disease.

I will routinely prescribe SAMe (Denosyl™) in patients having acute liver toxicity and in many cases having chronic liver disease or other liver disorders. A recommended dose range is 20 mg/kg/day. It should be given on an empty stomach and the tablets not broken. There are numerous commercial sources of SAMe each having variable concentration or purity of the compound. Foil wrapped tablets produced by a company that provides reliable purity and potency is recommended.

Milk thistle has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Clinical trials are limited in small animals and reported success is only anecdotal. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. To date there is only one published clinical study evaluating the efficacy of silymarin in the treatment of liver disease in dogs. In this placebo controlled experimental study dogs were poisoned with the *Amanita phalloides* mushroom. Researchers showed silymarin to have a significant effect on liver enzymes, the extent of histological liver damage and survival outcome. Based on this canine study and several clinical reports in humans poisoned with *Amanita* and treated with silymarin having a favorable outcome many physicians in Europe now accept silymarin as part of the standard protocol for mushroom poisoning.

General support therapy

The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.

Diagnostic Laparoscopy: Overview of What You Can Do and How to Charge for It

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Laparoscopy is a minimally invasive procedure for examination, biopsy or performing surgical techniques within the abdominal cavity. The technique involves distention of the abdominal cavity with gas followed by placement of a rigid telescope through a portal in the abdominal wall to examine the contents of the peritoneal cavity. Biopsy forceps or other instruments are then passed into the abdomen through adjacent portals to perform various diagnostic or surgical procedures. The limited degree of invasiveness, diagnostic accuracy, and rapid patient recovery make laparoscopy an ideal technique for tissue biopsy or to perform selected surgical procedures. Laparoscopy is easy to perform once the basic indications and the technique is learned. Thoracoscopy is the examination of the chest cavity and can be performed with the same instrumentation as used with laparoscopy but requires specific anesthesia considerations.

Should laparoscopy be incorporated in your practice? The answer is yes, if you have a busy practice and want to include cutting edge minimally invasive diagnostics and surgical techniques to your patients. The capital investment of the laparoscopic equipment should easily pay for it's self if basic indications are applied to your clinical cases. One should always ask "Can I do this with the laparoscope?". Laparoscopy has an easy learning curve when compared to that of flexible GI endoscopy or ultrasonography. A routine diagnostic laparoscopic procedure can often be performed within 15-20 minutes and many of the diagnostic procedures I perform are done on an outpatient basis. Because of the minimal invasiveness of laparoscopy there is considerable client acceptance and willingness to have laparoscopy as an option.

Indications

Common indications for diagnostic laparoscopy includes examination and biopsy the abdominal organs or masses. Laparoscopy is frequently used as a method for obtaining liver, pancreas, kidney, splenic, and intestinal biopsies. Laparoscopy is also used to diagnose and to stage the extent of neoplastic conditions of the abdominal cavity or to determine the cause of an unexplained abdominal effusion. Other ancillary diagnostic techniques using laparoscopic guidance include gallbladder aspiration (choleocystocentesis), and splenoportography. Surgical laparoscopy in small animals is still in its infancy and techniques and procedures are being developed. One's imagination and available surgical instruments limit surgical laparoscopy. Surgical procedures that have been performed on small animal clinical cases include: gastrostomy and jejunostomy feeding tube placement, adrenalectomy, gastropexy, ovariohysterectomy, cryptorchid removal, transabdominal cystoscopy with cystic calculi removal to name but only a few techniques performed. See table 1 for common diagnostic and surgical procedures performed with laparoscopy.

The advantages of laparoscopy over a conventional surgical laparotomy include improved patient recovery because of smaller surgical sites, lower postoperative morbidity, and decreased infection rate, postoperative pain, and hospitalization time. Other less obvious benefits of laparoscopy are related to fewer stress mediated factors than do occur with surgery.

Due to the limited degree of invasiveness of this procedure there are few contraindications of laparoscopy. Often, the high-risk patients become good candidates for the less invasive laparoscopic procedure than a full surgical exploratory. Abdominal effusion, abnormal clotting times, and poor patient condition are only relative contraindications. Fluid can be removed prior to or during a laparoscopic procedure and has little influence over the success rate of the procedure. Abnormal clotting times may also not definitively preclude the use of laparoscopy. Abnormal coagulation from liver disease does not always correlate with excessive bleeding at the biopsy site. Laparoscopy further makes it possible to visually select areas that appear to be less vascular and to monitor the extent of bleeding following the collection of a biopsy. If bleeding is considered excessive various laparoscopic techniques can be used to control the hemorrhage. Absolute contraindications for laparoscopy include septic peritonitis or conditions for which surgical intervention is clearly indicated. Relative contraindications include the patient condition, small body size, or obesity. The procedure becomes difficult in extremely small (<2 kg body weight) or obese patients.

Basic equipment

The basic equipment required for diagnostic laparoscopy includes the telescope, corresponding trocar-cannula, light source, gas insufflator, veress needle (for insufflation), and various forceps and ancillary instruments. Telescopes most frequently used in small animal laparoscopy generally range in diameters from 2.7 to 10 mm. The author recommends and uses a 5-mm diameter 0-degree field of view telescope for routine diagnostic laparoscopy. The 0-degree designation means that the telescope views the visual field directly

in front of the telescope in a 180-degree circumference. Angled viewing scopes enable the operator to look over the top of organs and see into small areas but the angulation also makes the orientation more difficult for the inexperienced operator.

The telescope is connected to a light source using a light guide cable. It is generally recommended that a high-intensity light source such as a xenon light source be used for laparoscopy. Light sources used for gastrointestinal endoscopy are generally sufficient for laparoscopy. A video camera attached to the telescope allows the image to be viewed on a video screen. Video-assisted laparoscopy is imperative when performing surgical procedures.

A veress needle is used for initial insufflation of the abdominal cavity. The needle consists of an outer cutting tip and, contained within the needle, a spring-loaded obturator that retracts into the needle shaft as it traverses the abdominal wall. Once in the abdominal cavity the obturator is once again advanced beyond the sharp tip and prevents needle injury to internal abdominal organs. The needle is then connected to the automatic gas insufflator. Most automatic insufflators are similar and function to dispense gas at a prescribed rate while maintaining a predetermined intra-abdominal pressure. Carbon dioxide is the gas most often used in order to prevent air emboli and spark ignition during cauterization.

The trocar cannula units are required to enter the abdominal cavity and are of a corresponding size to receive either the telescope or the biopsy instruments. It consists of a sharp trocar housed in an outer cannula. Together they are used to penetrate the abdominal wall. Once in the abdomen the trocar is removed while the cannula remains in place traversing the abdominal wall and becomes a portal for introduction of the telescope or instruments into the abdominal cavity while maintaining the pneumoperitoneum.

Common accessory instruments include a palpation probe used to move and palpate abdominal organs and biopsy forceps. The author prefers a 5 mm diameter biopsy forceps with oval biopsy cups to obtain liver, spleen, abdominal mass, and lymph node biopsies. A variety of other biopsy forceps, tissue graspers, and aspiration needles are also available for diagnostic laparoscopy. A “true-cut” type or similar biopsy needle is required for both kidney and deep tissue biopsies. This type of biopsy needle is passed directly through the abdominal wall and guided to the area to be sampled without the need for a cannula.

Procedural considerations

The patient should be fasted for at least 12 hours before the procedure and the urinary bladder should be evacuated. Laparoscopy is commonly performed using general gas anesthesia and most patients tolerate the anesthesia and laparoscopy well. In some situations the author will perform diagnostic laparoscopy using only heavy sedation in conjunction with local anesthesia at the entry sites. In order to select the appropriate cannula portal placement sites one must first determine the objectives of the laparoscopic procedure. The two most common approaches are a right lateral and a midline approach. The right lateral approach is recommended for diagnostic evaluation of the liver, gallbladder, right limb of the pancreas, duodenum, right kidney, and the right adrenal gland. A ventral approach is useful for many operative procedures, and offers good visualization of the liver, gallbladder, pancreas, stomach, intestines, reproductive system, urinary bladder, and spleen. With the ventral approach visualization is sometimes hindered by the location of the falciform ligament. A complete description of a step-by-step technique of the laparoscopy procedure is beyond the scope of this paper and has been previously described.

Liver biopsy

A major indication for diagnostic laparoscopy is for visualization and biopsy of the liver. I generally use a right lateral approach however a ventral or left lateral entry site can also be used. The entry sight is determined based on what one desires to view. For a liver biopsy I believe that a 5 mm oval cup shaped forceps provides excellent biopsy samples. The forceps are visually directed to the area of the liver to be samplaed. A 3x5 mm biopsy sample is obtained using this technique. Either the edge or flat surface of the liver can be sampled using this method. Once the liver tissue is grasp the forceps are held closed for 15-30 seconds and then the sample is pulled away from the liver. Generally multiple liver samples are taken. The size of the sample is adequate for most all liver evaluations including quantitative hepatic metal analysis. Following liver biopsy the site is examined to assure adequate clotting. Normally only several milliliters of blood is lost from the biopsy site; however due to the magnification it often seems like a larger volume of blood. A palpation probe should be used to examine the site for excessive bleeding. The probe can also be used to apply local pressure over the bleeding area if necessary. Although infrequently required, excessive bleeding can be managed by placing a small piece of Gel Foam™ over the bleeding area using endoscopic grasping forceps. Electrocoagulation can also be performed at the bleeding area however this is rarely necessary. A recent report found that laparoscopic directed forceps liver biopsies had better diagnostic yield than two 18-gauge biopsy needle samples. The major difference being the sample size obtained with the two techniques.

Pancreatic biopsy

The pancreas is best evaluated with a right or ventral abdominal approach. Often the diagnosis of acute or chronic pancreatitis can be made based on visual inspection alone. Viewing the pancreas in acute pancreatitis is sometimes difficult when there is considerable inflammation and adhesions around the organ. Pancreatic samples are generally always taken using a punch type biopsy forceps. The samples should be obtained from an edge of the organ away from the pancreatic ducts that traverse the center of the gland.

Complications from laparoscopic pancreatic biopsies are rare and the incidence of postoperative pancreatitis in our experience and in one experimental study was non-existent. We have also used laparoscopy to locally lavage the pancreatic area.

Renal biopsy

Renal biopsies are generally obtained using a standard biopsy needle. The right kidney is preferred for renal biopsies, because it is less movable than the left kidney. A right lateral approach is most often used. The abdominal entry site for the biopsy needle is determined during laparoscopy. A small skin incision is made at the needle entry site and the biopsy needle is passed directly through the abdominal wall and advanced toward the kidney. The biopsy needle is visually directed to obtain renal cortex, avoiding the large vessels at the cortico-medullary junction. Following the kidney biopsy there are usually several milliliters of blood lost at the biopsy site. If bleeding from the kidney biopsy is excessive, the palpation probe can be directed to the area and pressure applied at the site until the bleeding has stopped.

Intestinal biopsy

The small intestine can also be biopsied using laparoscopy by a technique of exteriorizing a piece of intestine through the abdominal wall using the accessory trochar cannula entry site. A 5 mm grasping forceps with multiple teeth is used to grasp the intestine. The antimesenteric boarder of the intestine is firmly grasped and the intestine is then pulled to the cannula. Once the forceps with intestine are firmly approximated to the cannula, the cannula wall incision is elongated to exteriorize a small loop of the bowel. Stay sutures are placed in the intestine to prevent it from falling back into the abdomen. A small full thickness piece of intestine is obtained using the same technique as one would use for an open surgical procedure. The intestine is closed and returned to the abdominal cavity. If further diagnostics or more biopsies are to be obtained a pneumoperitoneum must be established and the trochar cannula reintroduced. A similar technique can be used for exteriorizing the jejunum or stomach for surgical placement of a jejunostomy or gastrostomy feeding tube. Laparoscopic tube placement requires a pexy of the bowel to the abdominal wall.

Surgical procedures

There are also a number of surgical procedures that can also be performed which are beyond the scope of this lecture but include gastropexy, jejunostomy tube placement, laparoscopic assisted cystotomy, adrenalectomy, cholecystectomy are but a few of the procedures

Complications

The complication rate of laparoscopy is low. In a review by the author of a series of cases involving diagnostic laparoscopy the complication rate was less than 1%. Serious complications include anesthetic or cardiovascular related death, bleeding, or air embolism. Minor complications are generally operative and are associated with inexperience or failure to understand the limitations and potential complications.

Congenital Heart Disease: What Can I Tell from Radiographs?

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General principles of cardiac radiography

Radiographs are essential for the evaluation of cardiac disease. They are easy to perform and useful for evaluation of the cardiac silhouette, pulmonary vessels, and pulmonary parenchyma. Proper positioning and technique are essential for evaluation of the cardiac silhouette and pulmonary vessels. This includes at least two orthogonal views (lateral and ventrodorsal or dorsoventral). Often the dorsoventral is preferred for cardiac evaluation and better visualization of the caudal lobar vasculature. The underlying cause of the cardiac disease may not always be evident on radiographs; therefore, echocardiography may be necessary to determine the etiology or further define congenital cardiac diseases.

Cardiac anatomy

There is a wide range of normal size and shape of the cardiac silhouette in dogs. In breeds with a deep chest the trachea will diverge from the spine acutely, while in brachycephalic breeds the trachea may parallel the spine. A line drawn from the carina to the apex of the heart on the lateral view should divide the heart into approximately 3/5 on the cranial side (right heart) and 2/5 on the caudal side (left heart). On the lateral view the cardiac silhouette should be 2.5-3.5 intercostal spaces at the widest dimension. These are not absolute values and are highly variable between breeds. In a brachycephalic dog 3.5 intercostal spaces would be normal, while in a very deep-chested dog 3.0 intercostal spaces may signify enlargement.

A cranial and caudal cardiac waist may be (but is not always) visible in normal dogs on the lateral view. The degree of cardiosternal and cardiophrenic contact is highly variable and subjective. On the ventrodorsal view the widest width of the cardiac silhouette should be < 50-66% of the widest width of the thorax. The vertebral heart score (VHS) provides a useful objective measurement of cardiac size. In the dog the VHS is < 10.5, with slight variations based on breed.

The cat heart should be very petite on both views. There is usually 1 intercostal space between the apex of the heart and diaphragm. The normal VHS is < 7.8 in the cat.

The clock face anatomy applied to the cardiac silhouette is very helpful in evaluating specific chamber and vascular anatomy abnormalities. Don't forget to evaluate the diameter of the caudal vena cava (CVC), which should be less than the diameter of the aorta. Evaluation of the pulmonary arteries and veins is an essential part of the overall assessment. A general rule of thumb for dogs is the cranial lobar vessels (evaluated on the lateral view) should be less in diameter, where they cross the 4th rib, than the proximal third of that same rib. On the ventrodorsal view the caudal lobar vessels are evaluated at the level of the 9th rib and should be less in width than the rib width.

Radiographic abnormalities associated with patent ductus arteriosis (PDA)

The abnormal communication between the proximal descending aorta and pulmonary artery leads to left to right shunting and radiographic changes depend on the severity/size of the shunt and patient age. A focal bulge in the descending aorta is considered pathopneumonic for PDA. Additional changes that are often seen are left atrial/auricular and left ventricular enlargement, main pulmonary artery enlargement, and over circulation (both arteries and veins enlarged). In severe cases pulmonary cardiogenic edema is present. Left ventricular enlargement results in elevation of the carina due to increased height of the cardiac silhouette on the lateral view. Increased convexity of the left border and rounding of the cardiac apex with elongation of the heart is seen on the VD/DV view. Left atrial enlargement results in elevation of the trachea and left mainstem bronchus due to increased height of the cardiac silhouette and loss of the caudal cardiac waist on the lateral view. Bowing of the mainstem bronchi and an enlarged left auricle (at the 3 o'clock position) is seen on the DV/VD view. Increased opacity in the perihilar region can be present on all views.

In rare cases increased pulmonary vascular resistance will result in elevated right ventricular pressure (Eisenmenger's syndrome) in which case the PDA will shunt from right to left. In these cases there will be right ventricular enlargement and dilation of the main pulmonary artery.

Radiographic abnormalities associated with pulmonic stenosis (PS)

Typically pulmonic stenosis is caused by an abnormality at the level of the pulmonic valve, which leads to restriction of flow from the right ventricle into the main pulmonary artery. Occasionally the abnormality may be subvalvular, but radiographic findings are similar in both cases. The three main radiographic findings are a prominent main pulmonary artery, right ventricular enlargement, and normal to under circulation (decreased size of arteries and veins).

Right ventricular enlargement is identified by increased sternal contact, increased intercostal space width (increased craniocaudal dimension), and elevation of the apex of the heart from the sternum all seen on the lateral view. On the ventrodorsal view there is

rounding and prominence of the right ventricle resulting in a reverse D shape of the cardiac silhouette. With severe RV enlargement the height of the heart may also become elevated, although this is more commonly seen with left-sided heart enlargement.

Main pulmonary artery enlargement is identified by at bulge or prominence at the 1-2 o'clock position on the VD/DV view. On the lateral view there may be loss of the cranial cardiac waist.

Radiographic abnormalities associated with aortic stenosis

Aortic stenosis is most commonly subvalvular, caused by a fibrous ring below the valve. The hallmark radiographic features are enlargement of the aortic arch with or without left ventricular enlargement. An enlargement of the aortic arch will result in an elongate heart on the ventrodorsal view and loss of the cranial cardiac waist/bulge at the craniodorsal heart margin on the lateral view. There is potential for left atrial enlargement if mitral insufficiency occurs.

Radiographic abnormalities associated with ventricular septal defects

Ventricular septal defects are generally located in the dorsal part of the septum. Because the pressure in the left ventricle is greater than the right ventricle during systole blood shunts from left to right. Depending on the age and severity of the shunting the cardiac silhouette may be normal or range to severe generalized (both right and left side) cardiac enlargement. Variability from normal size to over circulation of pulmonary vessels can be seen.

Radiographic abnormalities associated with atrioventricular dysplasia

Both mitral and tricuspid dysplasia will result in atrial overload. If the mitral valve is affected left atrial enlargement and pulmonary venous congestion can be seen. With tricuspid valve dysplasia the right atrium will enlarge with concurrent enlargement of the caudal vena cava and ascites as common radiographic findings. Right atrial enlargement is seen as focal elevation of the trachea cranial to the carina and loss of the cranial cardiac waist on the lateral view. There is rounding and enlargement of the right atrium (9-11 o'clock) on the VD/DV view.

Radiographic abnormalities associated with Tetralogy of Fallot

The four cardiac abnormalities seen with tetralogy are PS, VSD, overriding aorta, and RV hypertrophy (secondary to the PS). These will result in a mildly enlarged right ventricle as described above in the PS section, or a boot-shaped heart on the VD view. As with PS pulmonary vessels are generally decreased in size.

Radiographic abnormalities associated with peritoneopericardial diaphragmatic hernia

Communication between the abdomen and pericardial space will result in a globoid or abnormal shape to the cardiac silhouette. Because the liver, falciform fat, spleen, and gastrointestinal tract can all be present within the pericardial sac there is often a mixed opacity to cardiac silhouette. Lack of visualization of an intact diaphragm (cardiac silhouette and cupula of diaphragm blend together) is a key finding. A dorsal peritoneal pericardial remnant extending from the diaphragm to the caudodorsal pericardium is sometimes recognized.

Is that Intestinal Tract Normal?
Ultrasound of the GI Tract

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Normal gastrointestinal ultrasound

Ideally the patient should be fasted prior to ultrasonography to decrease the amount of gas and ingesta, particularly in the stomach. A complete exam of the abdomen is recommended to assess for concurrent disease such as mesenteric lymphadenopathy, pancreatic disease, carcinomatosis, etc. A high frequency transducer is important (> 10 MHz is ideal) to maximize resolution and completely evaluate wall layering.

Abdominal radiographs are complimentary to abdominal ultrasound and my preference particularly for patients with gastrointestinal disease is to obtain the radiographs first. Radiographs will help determine if there is abnormal distention of bowel and help evaluate the gastrointestinal content, which can be obscured by gas on ultrasound. Other additional important findings, such as pulmonary metastases or osseous lesions, may be detected with radiographs.

Complete ultrasonographic examination of the gastrointestinal tract includes evaluation of wall thickness (from inner mucosal margin to outer serosal margin) and layering, evaluation of luminal contents and determination of peristaltic function. The gastrointestinal tract should be scanned in multiple planes. For the stomach and duodenum this can be accomplished by scanning the cranial and right abdomen. For the small intestines it is best to examine the entire central abdomen in a zigzag pattern. The colon can be scanned based on anatomic location. The appearance of the gastrointestinal tract will vary greatly depending on the degree of distention and the luminal contents.

The stomach is rarely empty in the dog and often contains gas, even when fasted. When the stomach is empty it will look like a "flower" especially in the cat. In the normal dog the gastric wall is less than 5 mm in thickness and in the cat less than 3.5 mm. These thickness measurements are taken in between rugal folds. Gastric rugae can be recognized in the fundus and body of the stomach with the visibility and thickness dependent on the degree of gastric distension.

The normal thickness of the jejunum in dogs is less than 5 mm and in cats less than 2.5 mm. The duodenum tends to be the thickest area in dogs measuring up to 6 mm. In cats the ileum can measure up to 3.2 mm and has a prominent bright submucosa. The cat ileum has a distinctive "spoke-wheel" appearance. The large intestine is the thinnest part of the gastrointestinal tract and is usually less than 1.5 mm, but can be up to 3 mm in the dog and 2.5 mm in the cat if non-distended.

Ultrasonography allows for differentiation of the layers of the gastrointestinal tract, which alternate in echogenicity. Under optimal conditions, five separate layers can be identified. These include the luminal-mucosal interface (hyperechoic), mucosa (hypoechoic), submucosa (hyperechoic), muscularis (hypoechoic), and subserosa-serosa (hyperechoic). The submucosa and subserosa-serosa are hyperechoic because of the presence of relatively more fibrous connective tissue. The mean number of peristaltic contractions in the gastrointestinal tract is 4-5 per minute.

Abnormal luminal findings

Foreign bodies

Ultrasonography can be useful for the identification of a number of different types of gastrointestinal foreign bodies. The ability to detect objects depends on the location, gastrointestinal contents and distention, and the object composition.

One of the most common abnormalities of the gastrointestinal tract is distention. The two broad categories that should be distinguished are mechanical (obstructive) versus functional (paralytic) disease. Determining the degree and extent of dilation of the bowel will usually help with this distinction. Typically mechanical disease has a focal or segmental distribution, where functional disease is more diffuse. Mechanical obstructions usually cause bowel distention that is moderate to severe (this will be duration dependent) where functional disease usually causes mild to moderate distention. There are exceptions to these general rules. Dysautonomia often has a pattern more consistent with mechanical rather than functional disease. Very proximal duodenal obstructions may have very little distention if vomiting occurs. The identification of segmental bowel distension with fluid or gas may signify obstruction and should prompt a careful search for foreign material or mural disease that may be causing the obstruction. Because gas can surround foreign material these can be missed with ultrasound.

Objects that transmit sound are more accurately represented than are objects that attenuate sound. All but the near margin of strongly attenuating objects are obscured by the acoustic shadow that they produce. Although this shadow prevents full visualization of the object, its presence can be an indicator that foreign material is present. Objects that attenuate sound produce a highly echogenic linear interface at their near surface, followed by an acoustic shadow that may have either a "clean" or "dirty" appearance. The shape of the echogenic line may help to identify the type of foreign material present. Food/ingesta can shadow to various degrees and should not be mistaken for foreign material. Similarly feces within the colon can have a similar appearance to foreign material within

the small intestine. It is very important to recognize and distinguish large intestine from small intestine. The large intestine can often be traced cranially starting at the distal descending colon dorsal to the urinary bladder.

With ultrasound linear foreign objects are often associated with bowel wall thickening and plication. The foreign material is often hyperechoic with variable degrees of shadowing. Gastrointestinal parasites can sometimes mimic linear foreign material.

Intussusception

The sonographic diagnosis of an intussusception is generally straightforward. An intussusception in the transverse plane is that of concentric layers of bowel wall within the intussuscepted segment (target or bulls eye). On the longitudinal scan an intussusception has the appearance of a thickened segment of bowel with an excessive number of layers that alternate in echogenicity. Hyperechoic mesenteric fat is generally seen associated within the intussusceptum.

Abnormal mucosal findings

Neoplasia

Lymphosarcoma is the most common type of feline gastrointestinal neoplasm and occurs in the dog as well. The most common ultrasonographic features of lymphosarcoma are thickening of the stomach or bowel wall, loss of its normal layered appearance with reduced echogenicity of the wall, decreased motility, and lymphadenopathy. Diffuse disease can also occur with lymphoma.

Carcinomas are the most common gastric neoplasia in the dog. These usually originate in the pylorus, but may occur in any location in the stomach and also within the intestine. If the mass lesion is in the outflow region (pylorus) the stomach may appear severely distended with fluid, fluid and gas or empty post vomiting. Focal changes are often seen with carcinoma. Wall thickening is more often asymmetric, but it can be symmetric. The loss of the normal layered appearance of the gastrointestinal wall reflects infiltration of neoplastic and inflammatory cells, necrosis, edema, and hemorrhage. Carcinomas can have associated ulceration that is sometimes visible with ultrasound.

Fungal disease

Fungal diseases can cause both focal and diffuse lesions of the intestinal tract. Similar to neoplasia fungal disease can cause bowel wall thickening and loss of layering with a variable echogenicity.

Inflammatory disease

Inflammatory bowel disease has a broad spectrum of changes, which are relatively non-specific (animals with disease may have normal ultrasound examinations). Changes that have been reported are focal to diffuse thickening, altered echogenicity of the wall, poor intestinal wall layer definition and enlargement of adjacent lymph nodes. The most common small intestinal finding would be mild, diffuse wall thickening with intact wall layering. In comparison neoplasia is more often focal, with greater thickness of the wall and loss of the normal layering. These categories can overlap; therefore, cytology or histopathology is required for definitive diagnosis.

Lymphocytic-plasmacytic enteritis is highly variable in appearance. In cats increased thickness of the muscularis layer can be seen with chronic disease.

Gastritis can be diffuse or focal wall thickening and is often associated with decreased motility. Gastric wall edema is generally diffuse with thickening of the wall and altered appearance of the layering. Mineralization of the mucosa (hyperechoic, shadowing area) is seen occasionally with chronic uremia.

Lymphangiectasia

The ultrasound appearance of lymphangiectasia includes thin linear bands, oriented perpendicular to the lumen or an overall increase in echogenicity within the normally hypoechoic mucosa. These changes are thought to occur secondary to dilation of lacteals. Concurrent anechoic peritoneal effusion may be present.

Miscellaneous

Corrugation of the intestinal tract has been described with many disease processes. These include inflammation (enteritis, pancreatitis, focal peritonitis), neoplasia, and ischemia. Regional extension from pancreatitis often affects the stomach, duodenum, or colon.

Methods of diagnosis

When considering methods of diagnosis the two main considerations are the location and size of the lesion. With a mural lesion of the stomach or proximal duodenum, endoscopy is the preferred method of sampling. If the lesion is located in the small intestine or involves the entire stomach wall and is greater than 1cm in thickness then ultrasound guided fine needle aspirates can be obtained. For fine needle aspirates a 1 to 1 ½ inch 22-gauge needle should be used. If the lesion is thicker than the throw of the biopsy gun (usually 1 ½ to 2 ½ cm) a biopsy can be safely performed. It is important to avoid the lumen during aspiration and biopsy. Commonly, adjacent enlarged lymph nodes may be easier to sample than the affected bowel wall and if possible it is recommended that both areas be aspirated to increase the likelihood of an accurate diagnosis. Diffuse, mild wall thickening (especially if the thickened layer is the muscularis) is best diagnosed with full-thickness surgical biopsies.

When is Thoracic CT Indicated? Correlations with Thoracic Radiographs

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How does CT work?

Computed tomography (CT) provides cross-sectional imaging, which allows for visualization of structures without the superimposition that is present with radiographs. This is especially useful for the thorax. Consider the structures you see at the 3rd intercostal space on a lateral radiograph: both sides of the thoracic wall, pleural space, mediastinal structures and right and left cranial lung lobes. Another advantage of CT over radiographs is the superior contrast resolution CT provides.

CT units produce a very thin fan of x-rays which are directed through the patient and strike a row of radiation detectors. The amount of radiation going through a specific part of the patient, and therefore reaching the detector is related to the density of the body part. This data is then manipulated by the computer to form a grey scale image for viewing.

As with radiographs, when looking at a CT bone=white, air=black, fat=dark grey, and soft tissues/fluid=various shades of gray. Metal is also white, but creates streak artifacts that sometimes severely degrade image quality. Once the image has been acquired, post-processing parameters can be adjusted to best visualize bone, soft tissue, or lung. For example when viewing a thoracic CT three windows would be used: lung window, soft tissue window, and bone window.

CT studies of the thorax are normally performed with slices in the transverse (axial) plane. This information can then be used to reformat the area of interest into a different plane (sagittal, coronal, oblique), therefore maximizing interpretation. The patient is scanned in ventral recumbency to allow maximum aeration of the dorsal lung fields. This sometimes results in atelectasis of the ventral lung. Patients are normally under general anesthesia for the CT. For proper evaluation of the lung it is important to provide positive pressure ventilation to maximize lung aeration (thus maximizing contrast).

General indications for thoracic CT

Thoracic CT has many indications including: detection of pulmonary metastatic disease, characterizing pulmonary parenchymal disease, determining the cause of pneumothorax, defining the margins of mediastinal and thoracic wall masses, evaluating the severity of thoracic trauma, and evaluation of the pulmonary vasculature. Specifically, CT of the thorax is useful for determining the extent of involvement of disease when conventional radiographic studies are inconclusive, staging neoplasia (anatomic relationships, surgical planning, prognostic indicators), and monitoring response to therapy.

CT of the thorax

Multiple cases examples will be presented showing the significance of thoracic CT for the following diseases.

Pulmonary metastasis

Detection of pulmonary metastasis is greater with CT than radiographs. If detection of pulmonary metastasis will alter therapy or prognosis then CT may be indicated. In general a soft tissue nodule has to be at least 0.5 cm (often larger in a big dog or dependent on the location of the metastases) for detection on radiographs. CT can detect metastasis in any location in the lung as small as 2 mm.

Pulmonary masses

CT is useful for pulmonary masses for 3 reasons. First, detection of pulmonary metastases may preclude surgery. Secondly, for determination if surgical resection of the mass is possible. Often solitary pulmonary masses are closely associated with the hilus, which may make surgical removal difficult or impossible. Lastly, for detection of enlarged tracheobronchial lymph nodes that also need to be surgically excised.

Pulmonary parenchymal disease

CT is useful for defining the distribution of the disease and the portion of the lung most affected (interstitial/peribronchial, bronchial, alveolar). This information is useful for determining the best test for diagnosis and also defining the appropriate treatment.

Pneumothorax and thoracic trauma

Pneumothorax can be traumatic or spontaneous in origin. CT is useful for determining the cause of pneumothorax in animals who have persistent or recurrent disease. CT is especially useful for defining the location of small blebs or bulla in these cases. CT can readily define thoracic trauma and is particularly useful for suspected thoracic spine trauma.

Mediastinal disease

Most commonly US would be used for mediastinal masses, however, CT can also determine if mediastinal widening is due to fat or fluid accumulation. The location of a mediastinal mass and proximity to the major vessels within the mediastinum is important when determining whether surgical resection is feasible.

Thoracic wall and pleural disease

CT is indicated for determination of the extent of thoracic wall masses if surgery is being considered. Iodinated contrast material can be used to help define the extent of the mass. CT is also used for radiation therapy planning in certain cases of skin or subcutaneous malignant masses.

Pulmonary vasculature

Although not as commonly used in animals as people, CT can be used for detection of pulmonary thromboembolic disease.

CT guided aspirates and biopsies

When abnormalities are detected CT can be used as a guide for fine needle aspiration or biopsy. Peripheral lung masses, mediastinal masses, and spinal lesions are the most common locations for aspirates. The most common complications are pneumothorax and hemorrhage.

To Cut or Not to Cut:
Answers from Your Abdominal Radiographs

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Preparation for abdominal radiographs

Fast for 12-24 hours prior to radiography if possible. Often this is not feasible, especially when the animals present acutely. Medications should be discontinued or avoided prior to radiography when feasible (acepromazine and butorphanol are ok in the dog or cat or ketamine with acepromazine in cats if sedation is required to perform radiographs). For gastrointestinal disease I prefer the right and left lateral views as well as the ventrodorsal view. Taking both lateral views allows redistribution of gas not only within the stomach, but also the small intestine and colon. If you place the patient in left lateral prior to taking the VD view you will often have a better chance of visualizing gas in the duodenum. The gas provides negative contrast, which is often helpful in distinguishing luminal or mural disease. Recall in general you are not able to define stomach or intestinal wall thickness on survey radiographs.

Mechanical vs. functional disease of the stomach

With both mechanical and functional stomach abnormalities there is variability in the degree of stomach distention. This will depend on the duration of the obstruction/disease and the frequency of vomiting. With either obstructive or functional disease it is common to see moderate to severe distension of the stomach with a fluid gas mixture. In chronic obstructive diseases mineral opacities are sometimes seen within the pylorus (gravel sign).

Animals that have a distended stomach that is only gas filled most likely have aerophagia. The position of the stomach is important to consider from a surgical standpoint. Gastric distention and volvulus is best identified on the right lateral radiograph with the hallmark features of dorsal displacement of the pylorus with a soft tissue band (compartmentalization) between the pylorus and fundus. Unless you can identify the cause of stomach distention on radiographs, it can be difficult to distinguish between mechanical and functional disease.

Radiolucent foreign bodies can be difficult to define on radiographs. The simplest technique to visualize these structures is variation in patient position during radiography, using the principle of shifting the gas to the non-dependent portion of the stomach in an attempt to outline the foreign material. This works best for pyloric foreign bodies that can be outlined by gas when the patient is in left lateral recumbency. This is particularly useful for trying to determine if a foreign body can be removed with endoscopy or if there is extension into the duodenum and surgery is more appropriate.

Negative or positive contrast may be helpful to distinguish the cause of gastric distention. If you are planning to ultrasound the patient do not use either of these techniques or it will make US much more difficult. Air for negative contrast (pneumogastrography) may help if there is not much air within the stomach. This can be done with an orogastric tube and 5ml/lb of air.

Positive contrast may be useful for identifying abnormalities. A full dose of barium may obscure material within the stomach leading to a false-negative result. If the foreign material is absorbent, such as cloth, it may not be seen initially with a positive gastrogram; however, retention of contrast within the material after the stomach empties will provide a diagnosis.

Pyloric obstructions can be caused by infiltrative mural disease such as neoplasia or granulomatous disease. Survey radiographs often show distention of the stomach with a fluid-gas pattern. The left lateral view can be useful in these cases as well.

Positive contrast upper gastrointestinal series

The stomach should be free of ingesta prior to the administration of contrast. The standard dose of 30% w/v barium is 6-12 ml/kg given as a bolus via an orogastric tube. Iohexol (a non-ionic iodinated contrast medium) can also be used in a 1:1 dilution with water at the same dose. Non-contrast radiographs and radiographs taken immediately after administration of contrast should be included. In cats radiographs are taken at 5 minutes then every 15-20 minutes until contrast reaches the colon and emptied from the stomach. In dogs radiographs are usually made at 15 and 30 minutes then every hour until contrast reaches the colon and has emptied from the stomach.

Normal radiographic anatomy of the intestines

The small intestine should be evaluated for serosal margin definition. The margin should be smooth. Serosal margins are normally visible due to fat in the peritoneum. Loss of serosal detail occurs when the animal is young (< 6 months), emaciated, or if abdominal fluid or cellular infiltrates are present. The normal diameter of the small intestine in the dog is < 2-3 rib widths or less than 1.6 times the dorsoventral dimension of the 5th lumbar vertebral body at the narrowest area. The normal diameter in the cat is up to 12 mm. The small bowel should be evenly distributed throughout the abdomen. In the obese cat it is common for the intestines to be localized in the ventral abdomen to the right of midline. The small bowel should have a smooth, continuous, curved appearance. The radiopacity of the bowel loop is dependent upon the contents (fluid filled, gas filled, or filled with a combination of fluid and gas). A

small amount of gas above fluid will give the false appearance of bowel wall thickening; therefore, bowel wall thickness should never be evaluated on survey films. Thickness is best evaluated with the use of contrast or abdominal ultrasound. In the fasted cat there should be minimal intestinal gas. In the normal dog 30-60% of the intestine can be gas-filled.

Positive contrast radiography

In the duodenum of young dogs it is common to see "pseudoulcers" along the antimesenteric border during an upper gastrointestinal series. These are a result of indentations in the mucosa at the site of lymphoid follicles. In cats the "string of pearls" is a common finding in the duodenum and is due to normal peristalsis.

Radiographic distention of the intestine

The two broad categories of intestinal distention are recognized on radiographs. These are mechanical (obstructive) versus functional (paralytic) disease. Determining the degree and extent of dilation of the bowel will usually help with this distinction. Typically mechanical disease has a focal or segmental distribution, where functional disease is more diffuse. Mechanical obstructions usually cause bowel distention that is moderate to severe (this will be duration and location dependent) where functional disease usually causes only mild to moderate distention. There are exceptions to these general rules. Dysautonomia often has a pattern more consistent with mechanical rather than functional disease. Very proximal duodenal obstructions may have very little distention if vomiting occurs.

As with the stomach taking the opposite lateral radiograph may be beneficial in diagnosing intestinal abnormalities, as the redistribution of gas may highlight an area that otherwise may be overlooked. The opposite lateral radiograph may help further define the location of the abnormality (i.e. often gas enters the duodenum on a left lateral radiograph).

Positive contrast radiography can be used to distinguish functional from mechanical ileus, as intraluminal and mural causes of obstruction can be defined. Intraluminal foreign bodies will present as filling defects within the contrast column. If the foreign body is causing a complete obstruction, minimal contrast will be seen aboral to the obstruction and the intestine will be distended orally. Contrast material may continue if a partial obstruction is present. Contrast radiography may be needed to diagnose high or proximal obstructions (ex. duodenal) as typical radiographic findings of mechanical obstruction are often not present.

Linear foreign bodies have a characteristic radiographic pattern that includes plication of the bowel and an abnormal gas pattern consisting of crescent or comma-shaped bubbles. The plication of the small bowel is more readily identified with positive contrast radiography.

Intussusceptions can sometimes be seen with radiographs if there is enough gas to outline the intussusceptum; however, more commonly signs are consistent with a mechanical obstruction. The ultrasound diagnosis of an intussusception is pathognomonic.

Enteritis is a non-specific term, but is often used to describe acute inflammation commonly seen with gastroenteritis or parvovirus. Radiographs may be normal or be consistent with functional ileus. With positive contrast the intestines may have abnormal motility and irregularity of the mucosal surface. Corrugation of the intestine may be seen as well.

Peri-intestinal inflammation usually appears as a focal loss of serosal detail on radiographs. This is seen most commonly associated with the duodenum secondary to pancreatitis. The duodenum may contain gas and appear corrugated.

Intestinal neoplasia may result in radiographic findings of a mass effect and/or mechanical ileus.

Compression radiography is an excellent technique for evaluation of suspected masses in the central abdomen. Compression radiography utilizes a radiolucent spoon (wood or Lucite) to decrease superimposition of structures. The abdomen is compressed in the region of interest and a radiograph repeated (the exposure should be decreased by 10% because the thickness is decreased). This will often define the origin of a mass.

Positive contrast radiography is helpful in determining if mural disease is present. Mural lesions range in radiographic appearance from intraluminal protrusions to infiltrative thickening of the bowel wall. Wall lesions may be asymmetric or circumferential. It is common for the lumen to be narrow at the region of infiltration, resulting in mechanical obstruction.

Pneumocolon and partial barium enema

Differentiation of the small and large intestinal tract can sometimes be difficult. Pneumocolon- administration of air via a lubricated red rubber tube in the colon; up to 5 mL air/pound or a partial barium enema- administration of barium contrast via a red rubber tube; up to 5 mL/pound, can be performed to help distinguish the small intestine from colon.

The Tricky Cat Thorax: How Helpful are Radiographs?

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General principles of thoracic radiography in cats

As with thoracic radiographs of the dog it is important to obtain radiographs in maximum inspiration. In the cat the diaphragm will generally be at the level of T13 to L1 on an inspiratory view. A minimum of two orthogonal views should be obtained (three views often recommended). Accurate positioning is important as obliquity can mimic disease, particularly when evaluating the cardiac silhouette.

Variations that are specific to the cat include a change in the position of the cardiac silhouette on the lateral radiograph as the cat ages. In most cats the cardiac silhouette is vertically positioned on the lateral radiograph. In some older cats the heart will "lie down" and become more horizontal in position, which results in an increase in sternal contact. Additionally, the aorta may be redundant or tortuous in appearance on the lateral view. This will result in a fairly discreet round bulge at the 1 to 2 o'clock position on the VD view often referred to as the aortic knob.

Obese cats present a challenge for evaluation of the thoracic cavity, particularly the cardiac silhouette. Typically these obese cats will have a large amount of pericardial fat, which will result in indistinct margins of the cardiac silhouette, particularly on the VD or DV views. On the lateral view it is sometimes possible to distinguish between the fat opacity and the true cardiac margin.

The cat heart should be very petite on both views. There is usually 1 intercostal space between the apex of the heart and diaphragm (unless the cat is obese). The normal VHS (vertebral heart score) is < 8 in the cat.

Feline pulmonary pathology

Allergic airway disease in cats has a bronchial pattern. Due to the small airway size in cats bronchial disease will sometimes mimic a nodular pattern as seen with fungal disease. Particularly close evaluation of the caudodorsal lung fields for the classic linear parallel lines (tram tracks) and donuts (bronchi in cross section) is important. Cats with allergic airway disease may have concurrent right middle lung lobe syndrome (alveolar increased soft tissue opacity throughout the lung lobe) and air trapping (caudal displacement and flattening of the diaphragm with a barrel-shaped appearance).

Pulmonary metastatic disease and primary pulmonary neoplasia in cats is similar to that seen in dogs. Recall in cats you may see lung-digit syndrome with the cat presenting for clinical signs related to digit disease. Always take radiographs of these cats to rule out concurrent pulmonary pathology (generally bronchogenic adenocarcinoma). A solitary mass is most common, but a multitude of appearances have been described. Primary pulmonary neoplasia often will metastasize to the pleural cavity; therefore, concurrent pleural effusion is not uncommon. Pulmonary lymphoma is not very common in the cat, but has a highly variable radiographic appearance.

Granulomatous disease generally has a diffuse structured nodular pattern that is miliary (very small nodules giving a snowstorm appearance). Concurrent lymphadenopathy in the tracheobronchial region may be present.

Cats with parasitic infections, such as heartworm disease and *Toxocara cati*, will have an interstitial to bronchial/peribronchial pattern with some cats also having concurrent pulmonary artery enlargement.

Feline mediastinal pathology

Mediastinal lymph node enlargement is the most common mediastinal pathology in cats. Lymph node enlargement, depending on severity, may be seen as an increased soft tissue mass cranial to the cardiac silhouette and ventral to the trachea. A mass effect is seen with severe enlargement with dorsal displacement of the trachea and caudal displacement of the carina, which is typically located at the 5-6th intercostal space. The cranial mediastinum will be wide on the ventrodorsal view and there can be concurrent caudal displacement and reduction in size of the cranial lung lobes. Thymic enlargement can mimic lymphadenopathy; however, thymic disease will generally be more left sided on the ventrodorsal view rather than midline as the lymph nodes are. Concurrent pleural effusion can be seen.

Mediastinal cysts are immediately cranial to the cardiac silhouette and ventral in location. Confirmation of a anechoic thin-walled structure with thoracic ultrasound is useful as these cysts are typically incidental findings.

Feline cardiac pathology

Enlargement of the cardiac silhouette in cats can be due to numerous causes including fat as described above, cardiac chamber enlargement, pericardial disease (such as effusion and peritoneopericardial hernia), and masses (uncommon).

Cats with hypertrophic cardiomyopathy (HCM), restrictive, and unclassified cardiomyopathies can have normal radiographs; therefore, if cardiac disease is suspected and the cardiac silhouette appears normal echocardiography is recommended. In general cats

with HCM will have varying degrees of left atrial enlargement. Cats with restrictive and unclassified disease tend to have biatrial enlargement. A valentine shaped heart on the ventrodorsal view is primarily due to left atrial enlargement in cats. Right atrial enlargement generally only changes the heart shape on the VD view if there is concurrent, severe left atrial enlargement.

In cats with dyspnea if the VHS can be performed (cardiac silhouette well visualized) and is < 8 cardiac disease is unlikely as the cause of dyspnea. A VHS between 8-9.3 is equivocal and echocardiography is recommended. If the VHS is > 9.3 cardiac disease is likely the cause of dyspnea. Echocardiography would still be recommended to determine the underlying cause of disease.

Feline pleural pathology

There are numerous causes of pleural effusion in cats including chylothorax, transudates (often secondary to heart disease), exudates (including infectious and neoplastic causes), and hemorrhage. All effusions have a similar opacity on radiographs; however, differentials may be prioritized based on concurrent disease. Ultimately thoracocentesis with cytologic evaluation is recommended for confirmation. In cases of chronic pleural effusion the lung lobe margins may be rounded. This is a poor prognostic indicator as it suggests some degree of fibrosing pleuritis.

Musculoskeletal Disease Imaging: Is that Neoplasia, Infection, or Degenerative Disease?

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Determining that a bone or joint is abnormal can be difficult. If an abnormality is suspected an interpretation should be made as to the aggressiveness of the lesion. If an aggressive lesion is suspected then often invasive procedures are indicated for cytologic or histopathologic diagnosis. Additionally, thoracic radiographs are indicated for aggressive disease. Neoplasia and infectious disease both result in aggressive bone and joint lesions. Generally these can be prioritized based on the singalment, history, physical exam, and radiographic findings. Characterization of the location within the bone (epiphyseal, physeal, metaphyseal, or diaphyseal) and defining if the disease is monostotic vs. polyostotic (or monoarticular vs. polyarticular) are also important factors.

Aggressive versus non-aggressive bone lesions

Most cases of aggressive bone lesions are easily determined if the basic principles of radiologic assessment are followed. Evaluate the following: soft-tissues, periosteal reaction, bone lysis/bone disruption particularly of the cortex, and the zone of transition (between normal and abnormal bone). Non-aggressive lesions have minimal soft-tissue swelling, minimal lysis, a short zone of transition and smooth, distinct periosteal reaction. Aggressive lesions have moderate to severe soft-tissue swelling with bone lysis and aggressive types of periosteal reaction (spiculated to amorphous) with a long zone of transition.

Patterns of lysis ranging from the least to the most aggressive include geographic, moth eaten, and permeative. Geographic lysis is actually the easiest to visualize, as it is a focal area that has a well-defined margin. Geographic lysis is most commonly seen with bone cysts or abscess. Moth eaten lysis is smaller, multifocal regions of lysis. Permeative lysis is generally the hardest to define, as it is pinpoint areas of lysis. Both moth eaten and permeative lysis are seen with infectious and neoplastic disease.

Patterns of periosteal reaction ranging from the least to most aggressive include smooth/solid, multilayered (lamellar), spiculated/columnar, sunburst, and amorphous new bone. The smooth/solid and lamellar reactions will have well defined margins, while the others tend to be less distinct with very irregular margins. Amorphous new bone refers to mineralization that is not in contact with the bone, rather it is within the surrounding soft tissues.

Often there is more than one pattern of lysis and periosteal reaction present. The lesion should be defined by the most aggressive pattern present. If the margin of the lesion is discreet and easy to define this is referred to as a short zone of transition, which is less aggressive. If it is difficult to define the exact margins of the lesion then a long zone of transition is present, which is more aggressive.

Aggressive versus non-aggressive joint disease

Animals that have severe degenerative joint disease can sometimes be mistaken for more aggressive lesions (infectious or neoplastic diseases; rheumatoid arthritis). The three main components to evaluate are the soft-tissue changes (intracapsular, extracapsular, or both), bone production, and bone lysis. Degenerative changes will have a mild to moderate degree of intracapsular soft tissue changes, while more aggressive disease will have moderate to severe swelling (this can be located both intra- or extracapsular).

In general, degenerative disease is predominately a productive process while aggressive disease is more lytic. In severe, chronic cases of degenerative disease there may be subchondral bone cystic changes that are inappropriately characterized as aggressive lysis.

In small animals bacterial septic arthritis is more commonly a result of a direct wound rather than hematogenous spread. The most common neoplastic disease of the joints is synovial sarcoma. Infectious arthritis, joint neoplasia, and chronic/severe erosive arthritis can all have a similar radiographic appearance; however, erosive arthritis is polyarthritic.

Stress radiographs for joint instability

Joint instability may be seen with trauma or severe infectious and neoplastic diseases. The integrity of the multiple ligaments and tendons present at many joints can be assessed using stress radiography. Stress radiography applies forces against the suspected area that is of concern. An example we see very commonly is the cranial drawer in dogs with cranial cruciate rupture (we are often unknowingly applying that stress when the radiographs are made). Although stress radiography can be performed almost anywhere it is most useful at the carpus and tarsus due to the complexity of the joint.

Biopsy or wait and see?

If you are confident or have a high suspicion that a lesion is aggressive then fine needle aspiration or biopsy is indicated. A three-view thoracic metastases check should be performed as this may also help define aggressiveness. If you are less confident or suspect the disease is non-aggressive or degenerative then it is appropriate to take the wait and see approach and recommend repeat radiographs at a later time. Aggressive lesions will change quickly with in 2-3 weeks, while degenerative or benign changes have a much slower progression.

Strategies for Minimizing Hospital-Acquired Infections

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The goal is to review the concepts of endemic vs epidemic hospital acquired infections, to examine relevant research available in the veterinary literature, and to discuss strategies for minimizing these infections in our veterinary hospitals.

Types of hospital-acquired infections

Also known as nosocomial infections or healthcare-associated infections, hospital-acquired infections (HAIs) are by definition infections that develop in a hospital or clinic but were neither present nor incubating at the time of admission. Most HAIs in human healthcare (>80%) are from IV-catheters, pneumonia, surgical site infections, and urinary tract infections (UTIs), and these are the most common HAIs in veterinary patients as well. Endemic infections result from a patient's endogenous flora contaminating a normally sterile site to cause infection. These are likely a result of underlying immunosuppression or breaches in normal anatomic barriers (IV or urinary catheters, endotracheal intubation, surgical incisions, implants). Endemic infections occur in a single patient at a time; however, this type of infection is likely to occur more frequently than epidemic infections. On the other hand, epidemic infections result from a point source of contamination, originating from the environment or a contaminated individual other than the patient. In a typical veterinary hospital or clinic, numerous veterinary patients are housed in the same room (in ICU or a hospital ward), allowing veterinary patients to be at risk of patient-to-patient transmission of infectious agents, either through direct or indirect contact. An example of indirect contact is transmission of a virus or bacterium on a fomite, such as a thermometer, between patients. Since epidemic infections can occur from a point source, these infections may occur as an outbreak, with multiple patients affected. Although we do not know the prevalence of epidemic infections in veterinary private practices, one study found that eighty-two percent of teaching hospitals reported an outbreak of HAI over a 5 year span; 45% reported ≥1 outbreak, and 32% reported having to close part of the hospital to control disease spread.

Risk factors in veterinary medicine

Being able to recognize veterinary patients that are at increased risk for HAI is the first step in protecting individual patients. Veterinary patients can have specific intrinsic risk factors including primary (rare) or secondary immunodeficiencies that can increase their risk of developing endemic HAI. Underlying diseases that cause secondary immunodeficiencies are often overlooked as contributing to a patient acquiring a HAI. These include infections (distemper, parvovirus, panleukopenia, ehrlichiosis, demodicosis, FeLV, FIV, and sepsis), age-related concerns (failure to ingest colostrum), metabolic disturbances (diabetes mellitus, renal failure, hyperadrenocorticism), nutritional deficiencies, drug therapies (glucocorticoids, cytotoxic drugs, cyclosporine), and miscellaneous causes of neutropenia (increased use, drug therapy, infectious agents, bone marrow disease, immune-mediated destruction). Extrinsic risk factors for HAI include exposure to invasive medical and surgical devices, being in close contact with other patients who may be harboring and shedding resistant bacteria, suboptimal hygiene practices, and antimicrobial use allowing selection for resistant opportunistic bacteria.

Intravenous catheter related infections

Prevalence of catheter-tip contamination has been reported to be about 25% in a veterinary ICU setting and 19% in a non-ICU clinical veterinary setting. The most likely time for contamination of intravenous catheters to occur is during catheter placement, originating from the patient's skin or the technician's hands. It is therefore important to maintain careful attention to hygiene during intravenous catheter placement. Other possible sources of bacteria include introduction of a contaminated medication or contaminated skin-prep solution. Numerous species of bacteria including *Staph* spp., *Enterobacter, Streptococcus, Klebsiella, Serratia, E. coli, Acinetobacter*, and *Citrobacter*, as well as *Candida* spp., have been isolated from intravenous catheters from dogs and cats. Risk factors for catheter associated infections have included: duration of catheter, infusion of non-sterile fluid and dextrose, and underlying immunosuppression; but studies have found mixed results when investigating risks in this area. One veterinary study found that IV catheters can be left in place up to 10 days if aseptic technique is used during placement and good catheter care is performed; while it is recommended to remove catheters as soon as possible, routinely changing them is not recommended. Clinical signs suggestive of IV-catheter infections include warmth, swelling, and redness at the catheter site, pain on injection, and fever. These signs could indicate local phlebitis but a catheter-related infection could also progress to sepsis, especially in an immunosuppressed patient. Definitive diagnosis of a catheter associated HAI is made by removing and culturing the catheter; blood cultures can also be performed. Infections should be treated based on culture and susceptibility results. Recommendations to minimize IV catheter infections include: washing hands before placement and wearing gloves while placing IV catheters, shaving hair circumferentially around the limb, sterile preparation of catheter site, securing the bandage well to minimize catheter movement, keeping the bandage clean and dry, minimizing manipulation of the port, and only inserting sterile fluids/medications into the catheter. Maintaining multi-

use tubs of preparation supplies (such as alcohol and chlorhexidine) is not recommended, as these can be contaminated with bacteria and consequently infect multiple patients.

Hospital acquired pneumonia

Unlike in human medicine, where most hospital-acquired pneumonias are a consequence of ventilator use, the majority of veterinary cases of hospital-acquired pneumonia occur from aspiration of gastrointestinal contents in a patient who is vomiting, regurgitating, undergoing anesthesia or sedation, or has neurologic or laryngeal deficits. These infections typically involve bacteria from the oropharynx and GI tract. Guidelines for minimizing risk of hospital-acquired pneumonia in our patients could include: appropriate fasting prior to anesthesia, properly inflating endotracheal cuffs during all intubation procedures, suctioning excess fluid from the airways, elevating the head of sedated or anesthetized patients to prevent reflux and aspiration, using sterile endotracheal tubes for ventilator patients, keeping circuit tubing clean, using sterile nebulization units, and avoiding unnecessary antacid therapy in the perioperative period.

Surgical site infections

Surgical site infections are those infections diagnosed within 30 days of surgery, or within 1 year of surgery if an implant was surgically placed. Traumatized tissue, seromas, hematomas, and dead space all decrease the body's ability to defend itself against bacterial colonization. The incidence of surgical site infections in small animals is about 5% in clean or clean-contaminated wounds, and about 10% in contaminated or dirty wounds. Risk factors for veterinary patients include: duration of anesthesia, degree of wound contamination, surgical technique, number of people in the operating room, infections at sites other than the surgical site, immune competency, and prolonged use of antimicrobial agents after surgery. There is also increased risk in dogs who have a concurrent endocrinopathy (especially diabetes), due to immunosuppression. Prophylactic antimicrobial agents are indicated for certain surgeries: clean surgeries involving implants, clean surgeries lasting longer than 90 minutes, clean-contaminated surgeries, and dirty surgeries. Antimicrobial agents should be administered so that they peak in the patient's blood at the first incision (current recommendations are to give 30 minutes prior to first incision, and every 90 minutes during surgery). Cefazolin is a good choice, because it reaches high tissue levels and has good activity against common veterinary wound isolates. Strategies to minimize surgical site infections include: clipping after induction, not before induction; following aseptic technique for patient preparation and during surgery; minimizing anesthesia and surgery times; remembering the adage "antibiotics cannot replace the performance of a skilled surgeon," thus striving to minimize tissue trauma during surgery; for contaminated surgeries using copious lavage and monofilament nonabsorbable suture; and keeping the incision as clean as possible postoperatively.

Hospital acquired UTIs

UTIs are the most common HAIs in both animals and human beings, accounting for about 40% of nosocomial infections in people, and consequences can include pyelonephritis, sepsis, and death. Changes in the patient's immune system due to illness or local changes such as an indwelling urinary catheter immunity can allow easier access for GI flora to enter, colonize, and adhere within the urinary tract, leading to infection. This emphasizes the importance of keeping our patients clean, especially when they have diarrhea (wrapping their tails, frequent baths). The presence of a urinary catheter is a well-known risk factor for developing a nosocomial UTI. Bacteria can travel either on the interior or exterior surface of the urinary catheter. Biofilm formation can occur on the surface of catheters with *E. coli*, *Enterococcus*, *Proteus*, *Klebsiella*, and *Pseudomonas*, making antimicrobial penetration more challenging. In one study, 10% of dogs with indwelling catheters developed a UTI. For catheterized dogs, the odds of UTI increased 27% for each day of catheterization, and 454% with catheterization and concurrent antimicrobial administration. Strategies to minimize catheter-associated UTIs include: only using indwelling catheters when absolutely necessary (acute renal failure, post-obstruction, recumbent patients) rather than for convenience, placing catheters sterilely and with minimal trauma, washing hands and wear gloves for catheter placement, using closed systems and preventing retrograde flow of urine, washing hands or wear gloves to empty urine, avoiding concurrent antimicrobial therapy if possible, removing the urinary catheter as soon as possible, and culturing urine at the time of catheter removal if a UTI is suspected. Antimicrobial therapy can be reserved for documented UTIs based on culture and susceptibility of urine at the time of catheter removal.

Additional strategies for minimizing hospital acquired infections

Handwashing may be the single most effective control measure to prevent HAI. Soap and water are still the best way to thoroughly wash your hands, mainly because hand sanitizers are not effective against some important bacteria and viruses (*Clostridium difficile* spores, calicivirus). Proper handwashing should involve 20 seconds of mechanical scrubbing with soap and water (water doesn't have to be hot) covering all aspects of the hands, followed by a thorough rinse, and completely drying with a paper towel. Hand air dryers, whether they are warm wide jets of air (traditional dryers) or very high velocity unheated air intended to be faster and save electricity (jet air dryers) have been shown to disseminate bacteria and are not recommended. Alcohol-based hand sanitizers should also be available, because these products may be preferred by staff and increase overall hand hygiene compliance. The CDC recommends

soap and water when hands are visibly dirty and accepts alcohol-based sanitizer for other routine decontamination. CDC recommendations include performing hand hygiene before and after direct contact with each patient, before donning gloves, after removing gloves (sterile or unsterile), after contact with any bodily fluid, after using the restroom, and before eating or drinking.

Keeping the hospital clean is also an important way to minimize HAIs. Developing and following a standard operating procedure for cleaning is a good place to start. A basic quaternary ammonium compound is effective for most infectious agents and can be used routinely, but bleach and/or potassium peroxymonosulfate should also be stocked, as these are required to kill others such as parvovirus or calicivirus. Manually removing organic debris, followed by a ten-minute contact time with disinfectants on surfaces is recommended for optimal cleaning.

As always, patients with highly infectious diseases (parvovirus, *Bordetella*) should be kept in a fully pre-stocked isolation ward, with minimal foot traffic, to protect the rest of the hospitalized patients from acquiring those infections. For highly immunosuppressed patients, such as puppies with parvoviral enteritis, staff should be reminded to wash their hands well prior to contact, to minimize spread of infections to these pets. It's also important to isolate certain patients within ICU, to the best of our ability. Patients who are immunosuppressed or those with urinary catheters, jugular catheters, on ventilators, receiving total parenteral nutrition, or any potential MRSA patients should be placed in end cages away from the rest of the population, if possible, to minimize potential acquisition or spread of infection.

Proactive and frequent continuing education of hospital personnel regarding the importance of infection control is an important way to keep these issues a priority in each hospital and maximize the safety for all patients, staff, and clients. Using passive surveillance to maintain records of suspected and confirmed HAIs is also valuable so that trends can be recognized and addressed in a timely fashion.

References

Benedict KM, Morley PS, Van Metre DC. Characteristics of biosecurity and infection control programs at veterinary teaching hospitals. JAVMA 2008;233:767-773

Mathews KA, Brooks MJ, Valliant AE. A prospective study of intravenous catheter contamination. JVECC. 1996;6:33-43.

Seguela J, Pages JP. Bacterial and fungal colonization of peripheral intravenous catheters in dogs and cats. JSAP 2011;52:531-535.

Marsh-Ng ML, Burney DP, Garcia J. Surveillance of infections associated with intravenous catheters in dogs and cats in an intensive care unit. JAAHA 2007;43:13-20.

Brown DC, Conzemius MG, Shofer F, et al. Epidemiologic evaluation of postoperative wound infections in dogs and cats. JAVMA. 1997;210(9):1302-6.

Eugster S, Schawalder P, Gaschen F, et al. A prospective study of postoperative surgical site infections in dogs and cats. Vet Surg. 2004;33:542-50.

Nicholson M, Beal M, Shofer F, et al. Epidemiologic evaluation of postoperative wound infection in clean-contaminated wounds: A retrospective study of 239 dogs and cats. Vet Surg 2002;31:577-81.

Whittem TL, Johnson AL, Smith CW, Schaeffer DJ, Coolman BR, Averill SM, Cooper TK, Merkin GR. Effect of perioperative prophylactic antimicrobial treatment in dogs undergoing elective orthopedic surgery. JAVMA 1999;15:212-216.

Smarick SD, Haskins SC, Aldrich J, et al. Incidence of catheter-associated UTI among dogs in a small animal ICU. JAVMA 2004;224:1936-40.

Bubenik LJ, Hosgood GL, Waldron DR, et al. Frequency of UTI in catheterized dogs and comparison of bacterial culture and susceptibility testing results for catheterized and noncatheterized dogs with UTIs. JAVMA 2007;231:893-99.

Best EL, Redway K. Comparison of different hand-drying methods: the potential for airborne microbe dispersal and contamination. J Hosp Infection 2015;89:215-217.

Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPA/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR Recomm Rep, 2002;51:1-44.

Feline Upper Respiratory Infections: Sneezes, Snuffles, and Snorts…Oh My!

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Upper respiratory signs are a common presenting complaint for cats visiting small animal veterinary practices. Typical signs include sneezing, nasal and ocular discharge, congestion, and altered appetite, with some cats having additional coughing, conjunctivitis, keratitis, and oral ulceration. There is a lot of overlap in clinical signs and presentation among the various differential diagnoses, and determining the true underlying cause can be challenging. With certain diagnoses, successful management can be frustrating for both owners and veterinarians and requires client education and establishment of realistic expectations.

Diagnostic evaluation

A thorough physical examination is critical for each cat presenting with upper respiratory signs. This exam should include assessment of airflow, symmetry, and pain during palpation of nasal cavities, retropulsion of eyes, otoscopic exam, dental exam, and lymph node evaluation. Together with signalment and history, exam findings allow the clinician to rank differential diagnoses and create a logical diagnostic and treatment plan. For example, young cats with decreased airflow will have an inflammatory polyp higher on their differential list, whereas an old cat may have cancer highest. Similarly, a cat with mild serosanguinous nasal discharge and sneezing 1 week after July 4th is likely to be having a herpes flare-up, whereas a cat with an ulcerated nasal lesion is more likely to be ill from Cryptococcus. If the cat's clinical presentation fits with a simple viral infection, further diagnostic testing may not be warranted, and the clinician may be best to educate the owner about feline viruses, supportive care options, and reinforce vaccination importance. In other cases where bacterial or fungal infection are suspected, diagnostic testing is warranted to determine exact etiology and optimal therapy. Although there are many infectious causes of upper respiratory disease in cats, part of the thorough workup is to investigate the possibility of non-infectious causes as well, such as foreign body, lymphoplasmacytic rhinitis, dental disease, polyps, and neoplasia. These diagnostic tests may include CBC, FeLV/FIV testing, cytology, Cryptococcus antigen testing, sedated dental exam and polyp check, skull radiographs or CT scan, rhinoscopy, bacterial culture, PCR, and virus identification.

Feline herpevirus-1

The most common viral cause of upper respiratory disease in cats is feline Herpesvirus-1. Clinical signs can be severe, including nasal and ocular discharge (typically serous), sneezing, stertorous breathing, depression, anorexia, gingivostomatitis, fever, conjunctivitis, and keratitis, and these signs are the most severe in young, unvaccinated, or immunosuppressed cats. Both virus isolation and PCR can be used to confirm presence of herpes in cats, but their diagnostic utility is limited because viral detection does not prove illness from the virus; thus rarely do we confirm the presence of herpes in clinical cases. Feline herpesvirus-1 is a self-limiting infection, and clinical signs resolve in most cats in about a week. Supportive care to keep their nares clean and nutritional support can be very helpful. All cats remain latent carriers with intermittent shedding; flare-ups can occur a week after a stressful event and last for 1-2 weeks. Flare-ups are self-limiting but frustrating and may be confused with secondary bacterial infections. Antimicrobial therapy will not help the primary herpes infection and should be prescribed judiciously to minimize development of resistance. L-lysine can be used in attempt to suppress viral replication during outbreaks or as maintenance therapy long-term and may help some cats. Good hygiene and isolation protocols decrease exposure to kittens, and routine vaccination will help minimize severity of clinical signs. Client education is beneficial regarding the recurrent nature of the disease, importance of minimizing stressful events, and providing supportive care during recurring episodes.

Feline calicivirus

Calicivirus is seen much less commonly in cats than herpesvirus, but can show similar clinical signs, including nasal and ocular discharge (typically serous), sneezing, fever, depression, oral ulceration, gingivostomatitis, conjunctivitis, and lameness. Calicivirus is a single-stranded non-enveloped RNA virus with a high mutation rate. Calicivirus is shed in upper respiratory secretions and transmitted by fomites, surviving several weeks in the environment. Diagnosis can be made with virus isolation and PCR. Like herpes, calicivirus is self-limiting and thus treatment is supportive only. Infected cats should be isolated, and the environment should be cleaned with bleach (diluted ½ cup 5% bleach in a gallon of water) or potassium peroxymonosulfate to minimize spread of this virus.

Bordetella bronchiseptica

Bordetella bronchiseptica, one causative agent of canine kennel cough, is a Gram-negative aerobic bacterium that can be either a primary or secondary pathogen in feline upper respiratory tract infections. Cats at increased risk are those from rescue organizations or multi-cat households, cats with exposure to dogs with kennel cough, and cats with concurrent respiratory infections. *Bordetella*

colonizes respiratory mucosa, adheres to cilia and causes ciliostasis and destruction of cilia, ultimately leading to mucociliary clearance failure. Clinical signs include sneezing, nasal and ocular discharge (often mucopurulent), dyspnea, and sometimes cough that can progress to bronchopneumonia. Diagnosis is made by bacterial culture and susceptibility (notify the lab if you suspect *Bordetella* so that proper media can be used) or PCR. Most cases are susceptible to doxycycline 5mg/kg PO BID for 3+ weeks (use liquid formulation or follow with water bolus to minimize risk of esophageal damage). *Bordetella bronchiseptica* is potentially zoonotic, especially to immunosuppressed children.

Mycoplasma spp.

Mycoplasma spp. are bacterial organisms lacking a cell wall that are part of the normal flora in the cat's upper respiratory tract. Although their role is still not fully understood, it is believed they can also be either a primary or secondary pathogen causing or contributing to respiratory disease including conjunctivitis, chronic rhinitis, and pneumonia. Transmission occurs via direct contact, although aerosol droplets and fomites likely play a minor role. Diagnosis is by culture or more commonly PCR. Without a cell wall, they are not susceptible to Beta-Lactams, but instead most often respond to doxycycline, azithromycin, or fluoroquinolones.

Secondary bacterial infections

Upper respiratory infections in cats can be frustrating because of the influence of underlying viral disease as well as secondary bacterial infections, and it can be challenging to differentiate between these etiologies and other concerning conditions. Factors that contribute to secondary bacterial infections include immunosuppression from viral infection and stress, permanent turbinate damage from viral infection, and alteration of normal protective flora from antimicrobial therapy. Although empirical antimicrobial therapy such as doxycycline or amoxicillin-clavulanic acid can be helpful in some circumstances, empirical antimicrobial agents should be used sparingly to minimize resistance and adverse effects. Culture and susceptibility are recommended to identify inciting bacteria and most appropriate therapy, but optimal method of sample collection is still debated, including submitting biopsies for culture, nasal flushes, or nasal swabs.

Cryptococcus neoformans

Cryptococcus neoformans is the most common fungal organism causing upper respiratory disease in cats. It is a dimorphic fungus whose mycelia are found in the soil, thus outdoor cats are at increased risk of infection, but we also see infections in indoor-only cats. Infection occurs via inhalation of spores that can remain in their nose (approximately 80%) or infect their lungs and spread hematogenously. Nasal cryptococcosis is typically very invasive, destroying turbinates and causing skin erosions, ulcerations, and facial asymmetry. Infection can involve the CNS by direct extension through the cribriform plate causing various neurologic signs. Ocular involvement can include chorioretinitis, retinal hemorrhages or detachment, and blindness. Diagnosis is with either cytologic identification of organisms from a nasal lesion or latex agglutination test for capsular antigen (on serum or CSF). This antigen test is a highly sensitive and specific test. CT can be used to evaluate the extent of disease if needed. Fluconazole is considered the first choice for antifungal therapy because of good penetration into the CSF and ocular tissue.

Selected references

Johnson LR, Kass PH. Effect of sample collection methodology on nasal culture results in cats. J Fel Med Surg 2009;11:645-649.
Litster AL, Wu CC, Constable PD. Comparison of the efficacy of amoxicillin-clavulanic acid, cefovecin, and doxycycline in the treatment of upper respiratory tract disease in cats housed in an animal shelter. J Am Vet Med Assoc 2012;241:218-226.
Ner Z, Ross LA, Horn MV, et al. *Bordetella bronchiseptica* infection in pediatric lung transplant recipients. *Pediatr Transplant* 2003;7:413-417.
Sykes JE. Pediatric feline upper respiratory disease. Vet Clin Small Anim 2014;44:331-342.
Vier JK, et al. Prevalence of selected infectious organisms and comparison of two anatomic sampling sites in shelter cats with upper respiratory tract disease. *J Fel Med Surg* 2008;10:551-7.

Zoonotic Concerns for Small Animal Veterinary Clinics

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Zoonoses are infectious agents able to be transmitted directly from animals to humans. Due to occupational exposure, small animal practitioners and staff are likely exposed to zoonotic agents with some regularity although incidence of illness stemming from this risk is unknown, as there is a paucity of literature in this area. Although there are too numerous to count zoonoses that small animal practitioners may face, a recent survey of small animal practitioners in the U.S. found that the zoonoses most veterinarians were concerned about included ringworm (71%), GI bacteria (39%), GI parasites (37%), leptospires (34%), rabies (22%), *Toxoplasma gondii* (21%), and unknown or emerging pathogens (21%). Despite recognized concern of zoonotic exposure, there appears to be a disconnect with veterinary personnel failing to take proper measures to protect themselves from acquiring these diseases.

Specific zoonotic diseases of concern

Dermatophytosis, caused by *Microsporum canis, Trichophyton mentagrophytes,* and *Microsporum gypseum,* is one of the most common zoonotic agents that veterinarians encounter. In a recent study surveying practicing veterinarians about their personal history with zoonotic disease, ringworm infection was reported most commonly, with 54% of veterinarians reporting acquiring this infection, mostly from exposure to cats. The highly infectious spores can be spread through direct contact, fomites, or fleas. With its high level of contagiousness, ringworm is also a nosocomial concern; in one study 15/50 veterinary clinics had *M. canis* isolated from the floor of the waiting room, exam room, or wards. Prevention of ringworm transmission relies on wearing gloves when examining pets with skin lesions (especially those with any known contact), treating all pets in a home, quarantining or preventing contact in the home until three negative cultures have been obtained, and proper cleaning of the hospital and home environment.

With the emergence of antibiotic resistant *Staphylococcus* spp and the high prevalence of *Staph* pyodermas seen in dogs and cats, zoonotic and anthroponotic transmission of *Staph* spp. has become a concern. While dogs and cats can carry antibiotic sensitive *S. aureus* and methicillin resistant *S. aureus* (MRSA), it continues to be more common for dogs and cats to carry *S. pseudintermedius* (previously known as *S. intermedius*). *S. pseudintermedius* remains the most common cause of pyodermas in veterinary patients, and is usually sensitive to many antibiotics, including cephalosporins. For veterinary patients with pyodermas that do not respond to first-line antibiotics, a culture to identify the infecting organism (including the species of *Staphylococcus*) and antibiotic susceptibility is recommended; this is important to guide therapy for the veterinary patient as well as to allow optimal recommendations for the household. Both *S. pseudintermedius* and *S. aureus* can spread between species (canine and human) in both directions. Immunosuppressed people may be at increased risk for acquiring resistant *S. pseudintermedius* from a pet, and these patients should be isolated from immunosuppressed people during treatment if possible. We also worry that MRSA can spread anthroponotically (from humans to pets); dogs and cats may be transient carriers or subclinical reservoirs (colonized) with MRSA or could develop clinical illness (post-operative wound infections, catheter-associated infections, urinary tract infections). Many pets colonized with MRSA will clear the MRSA on their own if isolated from the infected owner while the owner is treated, while pets with clinical illness require topical or systemic antibiotic therapy. One study found 18% of veterinary staff, 9% of canine patients, and 10% of environmental samples within a teaching hospital in the UK to be contaminated with MRSA, often the same strain. Sources of contamination in the environment can include stethoscopes, cell phones, door handles, cage doors, and water bowls. Prevention of *Staphylococcus* transmission between species relies on preventing direct contact (wearing gloves), keeping the environment clean, and prompt treatment of ill individuals (pets or owners).

Bartonella spp are Gram-negative bacteria that are highly adapted to one or more mammalian hosts. They have evolved to survive intracellularly, allowing some protection from the immune system, persistent infections, and challenging diagnoses. *Bartonella henselae* is transmitted among young cats via flea vectors, and transmission to humans can occur through the bite or scratch of an infected cat or by infected flea feces contaminating an open wound. Disease in humans is often (>75%) self-limiting, mild, and flu-like with lymphadenomegaly; however up to 25% of infected people can have complications including endocarditis, encephalitis, ocular abnormalities, and renal disease among others. Most infected cats are subclinical, although the full extent of *Bartonella's* pathogenesis in cats is still being investigated. Prevention centers on flea control in cats. Risk of bartonellosis is increased in veterinary personnel (due to increased exposure), and a recent survey found this to be the second most commonly reported zoonoses among practicing veterinarians. Immunosuppressed people are also at increased risk. Precautions for minimizing exposure for all people includes using caution during feline restraint and discouraging rough play with young cats (to prevent scratches and bites), strict flea control, maintaining good hygiene (wash hands frequently), and specifically it is recommended that households with immunosuppressed people own adult cats rather than kittens.

Kennel cough, frequently caused by *Bordetella bronchiseptica*, is a commonly diagnosed condition in pet dogs and occasionally in pet cats. There are reports of *Bordetella bronchiseptica* being diagnosed in pediatric lung transplant patients and HIV patients who had

contact with ill dogs, suggesting potential zoonotic transmission. Further research is needed to confirm this route of transmission and zoonotic risk. Until further research is available, immunosuppressed people should avoid contact with dogs suspected or confirmed to be infected with *Bordetella* as well exposure to live *Bordetella* vaccines which can rarely revert to virulence.

Leptospirosis, caused the Gram-negative spirochete *Leptospira interrogans*, is a zoonotic agent of worldwide importance. Transmission occurs from direct contact with infected urine or from water, food, or soil that is contaminated with infected urine. In small animal practice, dogs with clinical signs consistent with leptospirosis (acute renal failure, liver disease) should be tested promptly to confirm infection and precautions taken until results are available. Within veterinary hospitals, dogs suspected or confirmed to have leptospirosis should either have an indwelling urinary catheter or urinate in an isolated area that is easily bleached. Personnel should wear protective clothing (gloves, mask, booties, and gown) when handling these patients and when cleaning their cages to avoid exposure through direct contact or aerosolization of bacteria. All waste should be disposed of as biohazardous material. Caution should also be taken with pet rats, as exposure to their urine is another reported route of zoonotic transfer of leptospirosis to veterinary personnel. Although data are not available regarding the prevalence of leptospirosis in pet rodents, a high proportion of inner city rats carry and shed leptospires. Therefore wearing gloves is advised when handling pet rats, and thorough hand hygiene is recommended if any contact with urine is experienced.

Although exposure to *Salmonella* spp. is a known risk whenever handling reptiles and amphibians, small animal practitioners and staff may also be at risk of exposure when examining dogs and cats who eat raw diets. Research shows that pets eating raw diets shed increased *Salmonella* in their feces (compared to those eating cooked foods) but may not show symptoms of diarrhea. With grooming and licking behaviors typical in most pets, *Salmonella* from these pets' feces could spread throughout the pets' hair and then to the hands of their owners and veterinary personnel, as well as other surfaces in the clinic. Ingestion of raw diets pose risk of additional infections for the pet, resulting in additional exposures for clients and veterinary personnel, including: *Campylobacter, E. coli, Toxoplasma, Cryptosporidium*, and others. For this reason, educating veterinary personnel about the risks of handling reptiles and pets who eat raw foods (in addition to educating clients who may not understand these risks themselves) is important. Immunosuppressed individuals should avoid exposure all together, and others should take care to wear gloves during contact and wash hands thoroughly after exposure.

Veterinary personnel and cat owners have long been considered at increased risk for exposure and seropositivity to *Toxoplasma gondii*; however, newer studies have challenged this risk. A study by Jones et al found that seropositivity in Americans over the age of 12 years was 22.5%, while a study by Shuhaiber et al performed at the Ontario Veterinary Medical Association Conference found that healthy veterinarians and technicians who expected positive results based on exposure had a 14.2% seropositivity rate. Cat ownership, contact with cats, including those who hunt or eat raw meat, and cleaning litter boxes were not found to be risk factors for seropositivity in recent studies. While these studies help to clarify risk of toxoplasmosis, education about its zoonotic potential remains paramount to prevent human illness. Continued focus on hygiene around cats and their feces is important, as well as education about transmission through undercooked meats and exposure to contaminated soil (including gardening and handling fresh produce).

Legal implications

A practice owner could be held liable for a staff member (employee or volunteer) becoming ill from a zoonotic disease acquired during employment at that small animal practice. Owners of veterinary clinics should be proactive about ensuring a safe working environment for all veterinary staff. This includes creating an infection control plan (if not already in place) and education of new staff and frequent updates for existing staff about zoonotic concerns and personal protection. It is also important to be sure staff know how to implement proper infection control measures to minimize this risk and maintain a safe working environment. Involvement of staff in development and revisions of the infection control plan as well as in continuing education (i.e. rotating who presents brief topic rounds regarding an infection control topic during a staff meeting) is a great way to keep infection control at the forefront and to establish an environment of awareness and safety in your hospital. Veterinarians should also make it clear to staff and volunteers that they should seek medical attention from their physicians if they have any concerns of acquiring a zoonotic disease. For legal reasons, it is recommended to keep records of all training of staff, just as you should record discussions of zoonotic risk with a client in their patient's medical record.

Selected references

Wright JG, Jung S, Holman RC, Marano NN, McQuiston JH. Infection control practices and zoonotic disease risks among veterinarians in the United States. JAVMA 2008;232:1863-1872.

Marsh AE, Babcock S. Legal implications of zoonotic disease transmission for veterinary practices. Vet Clin Small Animal 2015;45:393-408.

Jackson J, Villarroel A. A survey of the risk of zoonoses for veterinarians. Zoonoses and Public Health 2011;59:193-201.

Mancianti F, Papini R. Isolation of keratinophilic fungi from the floors of private veterinary clinics in Italy. Vet Res Commun 1996;20:161-166.

Weese JS. Methicillin-resistant *Staphylococcus aureus:* an emerging pathogen in small animals. 2005;41:150-157.

Loeffler A, Boag AK, Sung J, et al. Prevalence of MRSA among staff and pets in a small animal referral hospital in the UK. J Antimicrob Chemo 2005;56:692-697.
Brunt J, Guptill L, Kordick DL, et al. American Association of Feline Practitioners 2006 Panel report on diagnosis, treatment, and prevention of *Bartonella* spp. Infections. J Fel Med Surg 2006;8:213-226.
Ner Z, Ross LA, Horn MV, et al. *Bordetella bronchiseptica* infection in pediatric lung transplant recipients. Pediatr Transplantation 2003;7:413-417.
Dworkin MS, Sullivan PS, Buskin SE, et al. *Bordetella bronchiseptica* infection in human immunodeficiency virus-infected patients. Clin Inf Dis 1999;28:1095-9.
Barmettler R, Schweighauser A, Bigler S, et al. Assessment of exposure to *Leptospira* serovars in veterinary staff and dog owners in contact with infected dogs. JAVMA 2011;238:183-188.
Baer R, Turnberg W, Yu D, et al. Leptospirosis in a small animal veterinarian: reminder to follow standardized infection control procedures. Zoonoses and Public Health 2010;57:281-284.
Joffe DJ, Schlesinger DP. Preliminary assessment of the risk of *Salmonella* infection in dogs fed raw chicken diets. Can Vet J 2002;43:441-442.
KuKanich KS. Update on *Salmonella* contamination of pet food, treats, and nutritional products and safe feeding recommendations. J Amer Vet Med Assoc 2011; 238:1430-4.
LeJeune JT, Hancock DD. Public health concerns associated with feeding raw meat diets to dogs. JAVMA 2001;219:1222-1225.
Jones JL, Kruszon-Moran D, Wilson M, et al. *Toxoplasma gondii* infection in the U.S.: seroprevalence and risk factors. Amer J of Epi 2001;154:357-365.
Shuhaiber S, Koren G, Boskovic R, et al. Seroprevalence of *Toxoplasma gondii* infection among veterinary staff in Ontario, Canada (2002): Implications for teratogenic risk. BMC Inf Dis 2003:3:8.
Cook AJC, Gilbert RE, Buffolano W, et al. Sources of toxoplasma infection in pregnant women: European multicenter case-control study. BMJ 2000;321:142-147.

Parvo Puppy Management: Is there Anything New?

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Diagnosis of parvovirus

Quick recognition of clinical signs and confirmation of parvovirus infection is the first step towards successful management of this disease. Classic parvovirus enteritis is characterized by severe vomiting, followed by hemorrhagic diarrhea, anorexia, dehydration, and lethargy. In-house fecal enzyme-linked immunosorbent assay (ELISA) antigen tests are the most commonly used diagnostic tests for parvovirus. All young dogs with consistent clinical signs should be tested for parvovirus. Although sensitivity of fecal ELISAs has varied, specificity is consistently high. If testing is delayed 5 days after onset of clinical signs, false negative test results may occur due to decreased viral shedding. A false negative may rarely occur if a viral mutation prevents identification by the ELISA test. If a false negative is suspected, PCR or virus isolation from a fecal sample can be submitted for further analysis. PCR and DNA sequencing are available to distinguish between variants of CPV (2b and 2c); however this information may not be clinically relevant for clinicians. Additional diagnostic testing should also be performed including minimally a PCV/TS, blood glucose, blood smear (to evaluate number of neutrophils), and fecal flotation. Ideally, a CBC and chemistry would also be performed to assess the patient's status and assist in developing an optimal treatment plan.

Isolation of puppies with parvovirus

Once a diagnosis of parvovirus has been confirmed, it is important to quarantine parvovirus puppies in an isolation ward to minimize potential transmission to other dogs within the hospital population. An isolation ward should be cleaned thoroughly between patients and fully stocked with basic equipment (stethoscope, thermometer, fluid pump, IV catheter kit, etc.) to prevent cross-contamination between isolation and traditional wards. Limited personnel should be permitted to enter isolation, to decrease exposure and risk of transmission via fomites to other patients. To minimize spread of disease to neutropenic parvovirus puppies, all personnel entering isolation should wash their hands and use a footbath prior to entry, and should wear a cap, gown, booties, and gloves throughout the visit. Intravenous catheters should be placed as sterilely as possible and well maintained, as bacterial colonization of IV catheters is a reported and potential complication for this population of dogs. Personnel should use the footbath again on exit, and wash hands thoroughly with soap and water (ideally) or gel sanitizer. Staff should be reminded that dogs with parvovirus are extremely immunosuppressed, and there should be equal concern for what microbes we bring into isolation as what we bring out of isolation.

Treatment strategies for parvovirus puppies

Therapy for dogs with parvovirus is supportive, with the goals of rehydration, correcting and maintaining electrolyte and glucose abnormalities, and providing antimicrobial and antiemetic support. Fluid rates should be calculated based on percent dehydration (8% dehydrated equates to 0.08xbody weight in kilograms to determine the number of liters of fluid to replace) plus maintenance needs (60ml/kg/day). A replacement isotonic fluid such as LRS or 0.9% saline is typically appropriate, although many good options exist. Most puppies require dextrose supplementation (2.5-5%) as well as potassium chloride, and inclusion of these supplements should be based on initial lab work findings. Fresh frozen plasma can be beneficial as oncotic support for dogs who are losing excessive proteins through their gastrointestinal tracts and for dogs who develop DIC.

Antimicrobial therapy is typically provided because these dogs are considered to be highly immunosuppressed with severe neutropenia and at risk of gastrointestinal translocation and secondary bacterial infections, such as sepsis, UTI, and pneumonia. Either ampicillin-sulbactam (30mg/kg IV TID) or ampicillin (22mg/kg IV TID) is a good choice for broad-spectrum coverage. Traditionally many clinicians have used additional antimicrobial therapy for enhanced Gram-negative spectrum, such as an aminoglycoside or fluoroquinolone, but these agents are often not warranted and should be used with caution due to the potential for adverse effects.

Antiemetic therapy is usually needed and can include metoclopramide (1-2mg/kg/day continuous rate infusion), maropitant (1mg/kg SQ q 24hrs), or ondansetron (0.2mg/kg IV BID); the ideal anti-emetic should be chosen based on the individual patient recognizing that only maropitant is labeled for use in dogs and each has potential adverse effects. Dogs should be encouraged to eat as soon as possible, as early enteral nutrition may result in further clinical improvement and improved outcome.

Many treatments have been tried in the past but have NOT been shown to be helpful and are therefore not currently recommended in the management of parvovirus, including steroids, antiendotoxin, and flunixin meglumide. Other treatments have had minimal research performed to date, and while not enough data yet exist to recommend adding these medications to our treatment protocols, the results are interesting and some may prove useful in the future pending further studies.

The antiviral medication oseltamivir (Tamiflu) was tested in a randomized prospective trial on 35 dogs with parvovirus but no clear benefit was found of this therapy.

Immune-plasma taken from dogs surviving parvovirus enteritis was used in a prospective randomized double-blinded placebo-controlled clinical trial with 7 treated dogs and 7 control dogs (receiving 0.9% saline). No significant differences were identified between groups among neutrophil counts, magnitude of viremia, body weight change, length of hospitalization, or cost of treatment.

Interferon-omega has been studied in beagles with clinical parvovirus and control beagles in a double-blinded placebo-controlled study, and in this study 4/5 treated dogs survived and 5/5 placebo dogs had progressive disease and passed away in 10 days. Unfortunately the placebo control group was treated with only subcutaneous fluids without antimicrobial or antiemetic therapy, likely explaining the low survival rate, which is considerably lower than expected and reported for dogs treated in most ICUs. Thus the results of this study and benefits of this medication warrant further investigation.

Recombinant *human* granulocyte-colony stimulating factor (G-CSF) has been evaluated in attempt to address the severe neutropenia that many puppies develop. In a randomized controlled clinical trial 23 puppies with parvovirus and <1000 neutrophils were enrolled and 11 of these puppies received the G-CSF daily until their neutrophils were >1500 while 12 control puppies did not receive the therapy; all puppies received standard supportive care. No significant differences were seen with regards to time of hospitalization or neutrophil counts between the treatment and control groups. A second G-CSF study enrolled 62 dogs with parvovirus and neutropenia (28 received recombinant *canine* G-CSF, 34 controls, and all 62 received supportive care). In this study the treated dogs had improved neutrophil counts and shorter hospitalization stays, but also shorter survival times with 4 treated dogs being euthanized or dying in the first week compared with no deaths in the control group within the first week. With these limited data, it cannot yet be recommended to administer G-CSF to clinical patients with parvovirus, but further research regarding efficacy, safety, and optimal dosing may be fruitful.

Monitoring and complications during hospitalization for parvovirus

Thorough physical exam including body weight should be performed at least twice daily (ideally more often) to assess hydration, so that changes in fluid administration can be made as needed. An estimate of fluid losses should be made including production of vomitus and diarrhea, to aid in calculation of fluid replacement requirements. Additional things to look for in the physical exam include crackles on thoracic auscultation suggestive of aspiration pneumonia, acute abdominal pain or a palpable mass suspicious for an intussusception, and evidence of intravenous catheter-site irritation/infection. Secondary infections including urinary tract infections and pneumonia are common because of the leukopenia and possibility of GI translocation of bacteria causing sepsis. Urinary tract infections may remain subclinical or silent, and are seen in up to 25% of parvovirus puppies; all attempts to keep these puppies clean should be made to minimize fecal contamination of their distal urethras. If concern exists for these infections, a urinalysis, urine culture, and/or chest radiographs should be performed as indicated. Blood glucose and blood smear to assess neutrophil count should be monitored at least daily throughout hospitalization as well, and if puppies are not improving as expected, a full CBC and chemistry (+/- coagulation profile) are recommended to reevaluate their status (white cell differential, proteins, electrolytes, glucose, organ function, etc.). Rarely, infected dogs may develop neurologic signs from the virus itself, or more likely from electrolyte imbalances, hypoglycemia, sepsis, or from disseminated intravascular coagulopathy causing hemorrhage into the central nervous system, underscoring the need for close monitoring with physical exams and laboratory work.

Prevention of parvovirus

No discussion regarding management of parvovirus would be complete without mention of the importance of vaccinating our canine patients. Vaccination is critical for the prevention of parvovirus. Developing a hospital protocol for vaccination and educating clients about the benefit of vaccination versus the severity of parvoviral enteritis is advised. Clients should be taught about the window of susceptibility for their puppy to develop parvovirus, and the importance of keeping them isolated from potential exposure during this vulnerable time. Although puppies are at highest risk, clients should be educated that unvaccinated adult dogs too can become infected and ill from parvovirus, and that vaccination is important in these dogs as well. Currently available vaccines have been demonstrated in prospective studies to offer cross-protection against both CPV-2b and CPV-2c variants. In order to provide full protection and to avoid perceived vaccine breaks, vaccines should be administered by veterinarians, so that proper schedules, storage, and administration can be strictly followed.

Selected references

Lobetti RG, Joubert KE, Picard J, et al. Bacterial colonization of intravenous catheters in young dogs suspected to have parvoviral enteritis. J Amer Vet Med Assoc 2002;220:1321-4.

Kalli I, Leontides LS, Mylonakis ME, et al. Factors affecting the occurrence, duration of hospitalization and final outcome in canine parvovirus infection. Res Vet Sci 2010;89:174-178.

Mohr AJ, Leisewitz AL, Jacobson LS, et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003;17:791-798.

Bragg RF, Duffy AL, DeCecco FA, et al. Clinical evaluation of a single dose of immune plasma for treatment of canine parvovirus infection. J Amer Vet Med Assoc 2012;240:700-704.

Mantione NL, Otto CM. Characterization of the use of antiemetic agents in dogs with parvoviral enteritis treated at a veterinary teaching hospital: 77 cases (1997-2000). J Amer Vet Med Assoc 2005;227:1787-1793.
Savigny MR, Macintire DK. Use of oseltamivir in the treatment of canine parvoviral enteritis. J Vet Emerg Crit Care 2010;20:132-142.
Martin V, Najbar W, Gueguen S, et al. Treatment of canine parvoviral enteritis with interferon-omega in a placebo-controlled challenge trial. Vet Microbiol 2002;89:115-127.
Rewerts JM, McCaw DL, Cohn LA, et al. Recombinant human G-CSF for treatment of puppies with neutropenia secondary to canine parvovirus infection. J Amer Vet Med Assoc 1998;213:991-992.
Duffy A, Dow S, Ogilvie G, et al. Hematologic improvement in dogs with parvovirus infection treated with recombinant canine G-CSF. J Vet Pharmacol Therap 2010;33:352-356.
Otto CM, Jackson CB, Rogell EJ, et al. Recombinant bactericidal/permeability-increasing protein (rBPI21) for treatment of parvovirus enteritis: a randomized double blinded placebo-controlled trial. J Vet Intern Med 2001;15:355-360.
Goddard A, Leisewitz AL, Christopher MM, et al. Prognostic usefulness of blood leukocyte changes in canine parvoviral enteritis. J Vet Intern Med 2008;22:309-316.

Tips for Antibiotic Treatment Success

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Which organism are we treating?

We often have high index of suspicion for a bacterial infection based on clinical signs and examination, and even if we submit a bacterial culture, clinicians often prescribe empirical antimicrobial therapy while the culture results are pending. In some situations, empirical therapy is considered acceptable, such as for an uncomplicated UTI in a young female dog or a superficial pyoderma. During this time, choice of empirical therapy is important, as it could either be successful to treat the clinical signs and infection or fail to do so. Rather than taking an approach of using a "broad spectrum" antimicrobial agent, a better strategy may be to consider where the suspected infection is (which organ) and which bacterial species are most likely to cause infections at that site (i.e., *E. coli* is the most common bacteria to cause UTIs but we also see *Staph*, *Enterococcus*, etc.). If possible, use any preliminary information available, such as an urinalysis or skin cytology to gain further information about the bacterial culprit, such as Gram stain status (negative or positive) and shape of bacteria (rod or cocci), as this can narrow down your list of likely bacterial species. On occasion this cytology will surprise us and suggest that the infection is not bacterial at all but instead fungal or may not even be infectious but instead be cancerous or of other etiology entirely. Once you have a narrow list of possible bacterial species, prevalence data about susceptibility can help you decide which antimicrobial agent may be the best choice for empirical therapy. This type of prevalence data can come from the veterinary literature or may be available through your local bacteriology laboratory. If initial empirical therapy fails or if a culture identifies a different bacterial species, further therapy can then be based on specific information gained from culture and susceptibility. A sample for culture and susceptibility should be submitted for any infection which has already been a challenge to treat as well as for any new infection in which it is difficult to predict which empirical antimicrobial agent is likely to be successful.

Interpreting the culture and susceptibility

Bacterial cultures are best performed in a laboratory that adheres to the standards set by the CLSI (Clinical Laboratory for Standards Institute) which provides recommendations for best methods of isolating bacteria and determining susceptibility. The CLSI provides breakpoints for correlating susceptibility results to likelihood of therapeutic success or failure based on veterinary research whenever available, and based on human research when veterinary information is not yet available. A breakpoint is the MIC cutoff that the CLSI concludes is most appropriate for determining if an isolate is susceptible to the antimicrobial (greater likelihood of clinical cure than resistant) or resistant (isolate not inhibited by the antimicrobial at the achievable blood concentration based on typical dosing, or therapeutic success unlikely based on previous treatment studies). Ideally breakpoints should be specific to a single drug (cephalexin), single host (dog), a single bacterial species (*Staph. pseudintermedius)*, and single site (skin), as well as dose/route/frequency/duration of antimicrobial therapy, but realistically this detailed information is rarely available and many breakpoints available to us from CLSI are based on drug classes (beta lactams), human studies, bacterial classes (Enterobacteriaceae), and concentration of drug reached in the bloodstream. These generalities may make interpretation and application of susceptibility results to an individual case less than straight-forward. For this reason, seeing an "R" on a susceptibility report does not necessarily mean that therapeutic success is not achievable with that particular drug, and similarly it is certainly possible to have therapeutic failure with a drug that appears "S" *in vitro*.

Managing resistant infections

It can be frustrating to receive a culture and susceptibility report documenting an infection that appears to be resistant to nearly every antimicrobial agent available. In these situations, before prescribing an injectable antimicrobial that needs to be given every 6 hours, one with known worrisome adverse effects, or one that is of vital importance for treating human infections, it is worth revisiting why the infection is there to begin with. What about this patient is allowing these bacteria to gain access, survive, and multiply in the site of infection? Is there a nidus of infection that can be removed, such as a urolith or bone plate? Is there systemic or local immunosuppression that can be medically or surgically managed? Can changes in husbandry be made that will improve the patient's ability to fight the infection? Thorough investigation into these areas should be made and all attempts to correct any identified abnormalities made prior to prescription of further antimicrobial therapy. For patients with comorbidities or niduses of infection that cannot be controlled or eliminated, successful treatment of resistant infections can be nearly impossible, and prescription of additional antimicrobial therapy in accordance with results of a susceptibility report is likely to quickly result in resistance to that antimicrobial agent as well. In these situations, recurrent and resistant infections are likely, and difficult decisions need to be made regarding when treatment is indicated. Factors to consider when making these decisions include site of infection, which organism is identified, how many bacteria are present (i.e., what is the CFU count/ml, was the bacteria grown on enrichment only?), is the patient showing clinical signs consistent with infection in the site (i.e., trying to determine if true infection is present vs. asymptomatic bacteriuria), and what is

the likelihood that not treating this infection would result in worsening disease (i.e., pyelonephritis, sepsis). In these cases it can be beneficial to consult with an internal medicine specialist to be certain no additional comorbidities can be identified and corrected that may make the infection easier to control. Similarly, it may be warranted to consult with a veterinary clinical pharmacologist to discuss the culture report and creative options for antimicrobial therapy.

Considerations for treatment of specific infections

Resistant urinary tract infections

If a seemingly simple UTI does not resolve with empirical antimicrobial therapy or the veterinary patient has a recognized reason for having a complicated UTI, a culture and susceptibility is essential for appropriate management. While in-house culturing is an option, several studies have documented that bacterial identification and antimicrobial susceptibility results may not be accurate, leading to inappropriate treatment and therapeutic failure. In-house testing may be utilized to "rule-out" infection, but any growth should prompt submission of a new urine sample to an outside diagnostic laboratory that follows CLSI guidelines. Submitting a fresh urine sample is better than submitting an isolate from an in-house plate because it allows for determination of CFU/ml urine, which is an important factor in determining whether treatment with antimicrobial therapy is warranted at all. In general, a UTI is consider worthy of treatment if the patient has clinical signs consistent with UTI, a urine sediment showing inflammation, and a urine culture (collected by cystocentesis) with >1000 CFU/ml bacteria, although there are always exceptions to this rule. Most simple UTIs are easy to treat once the inciting bacteria is identified and susceptibility report is available. While these infections may have several susceptible therapeutic options that could lead to treatment success, clinicians should consider the potential for adverse effects, evidence for efficacy, cost, compliance issues, and stewardship when choosing any antimicrobial protocol. For example, trimethoprim sulfa may be very effective at treating many UTIs, but its potential for causing devastating adverse effects keeps it off the first tier of antimicrobial options. Ciprofloxacin can also be effective for treating UTIs in some dogs, but its wide variability in absorption make it less reliable for achieving UTI therapeutic success than fluoroquinolones that are labeled for use in dogs. For complicated infections with resistant isolates much fewer options may exist on a susceptibility report. In these cases, it is always prudent to ensure that any underlying comorbidity is controlled as well as possible prior to proceeding with a change in antimicrobial therapy. If an oral antimicrobial option does not appear to be available on the susceptibility report, a phone call to the diagnostic laboratory or a clinical veterinary pharmacologist may help to determine further options for an extended spectrum of susceptibility testing or alternative treatment strategy. In some cases, despite seeing an R on the report, therapeutic success can be achieved with an antimicrobial due to its high concentration in the urine, and a veterinary pharmacologist can help evaluate the individual case to determine if that may be an option. This type of consult should be performed early in the resistant UTI case, to optimize the chance of finding a successful therapeutic option before resorting to antimicrobials that may require hospitalization for frequent injectable administration, those which come with undesired adverse effects, or those which are of critical importance in human medicine. Urinary nutraceuticals, such as cranberry extract, D-mannose, and forskolin, have also been used in conjunction with appropriate antimicrobial therapy to assist in control of patients with recurrent UTIs (mainly for prevention, not treatment); at this time evidence is lacking to suggest that these are effective in clinical veterinary patients, and information about safety is not available.

Resistant pyodermas

Bacterial pyodermas continue to be one of the more common reasons why dogs are presented to general practicing veterinarians. An important fact about pyodermas is that they are almost always secondary, and identifying and treating the underlying cause can be as important as addressing the pyoderma itself. Underlying causes can include anatomical (skin fold), allergic (atopy), parasitic infections, and endocrine disorders (hyperadrenocorticism). Cytology should be performed to evaluate the affected area and look for presence of inflammation and bacteria, as well as to rule in/out other potential causes for skin disease, such as other fungal or parasitic infections, immune disease, or neoplasia. Good empirical choices for bacterial pyodermas continue to be cephalosporins, clindamycin, or erythromycin; on the other hand, fluoroquinolones should not be on the first tier of drugs for empirical treatment of a pyoderma. Bacterial culture of pustules or of a punch biopsy should be performed in cases that do not respond to empirical antimicrobial therapy, if cytology shows a mixed infection, or if the infection recurs. This has become more important recently as the prevalence of methicillin and multidrug resistant *Staph* spp has been increasing and previous antibiotic usage has been associated with development of methicillin resistance among *Staph* isolates. Treatment for any pyoderma should include addressing the underlying cause as well as possible, which in some cases can be a challenge but is of vital importance. Basic pyoderma management tools remain unchanged, such as clipping and cleaning hotspots, using an E-collar to prevent further trauma, and using topical shampoos and medications in conjunction with systemic medication. Chlorhexidine baths (usually twice weekly) can be an excellent complement to antimicrobial therapy and help to minimize pyoderma recurrence. Topical mupirocin ointment can effectively treat some focal pyodermas (even MRSPs) without concurrent systemic antibiotic therapy. Various wipes with chlorhexidine and/or antifungal medication can also be quite useful for skin fold pyodermas and other focal infections. For resistant infections, it is best to use topical medications instead of systemic antimicrobials whenever possible, and if systemic antimicrobial therapy is required that

therapy should be based on culture and susceptibility. Close follow-up is necessary to ensure progression towards therapeutic success, and consultation with a dermatologist is recommended if improvement is not seen.

References

Bemis D, et al. Evaluation of susceptibility test breakpoints used to predict mecA-mediated resistance in *Staphylococcus pseudintermedius* isolated from dogs. J Vet Diag Invest. 2009;21:53-58.

Bryan J, Frank L, Rohrbach BW, et al. Treatment outcome of dogs with MRSP and MSSP pyoderma. Vet Derm 2012;23:361-368.

Clinical Laboratory Standards Institute (CLSI). Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals. Approved standard – 4th edition. Wayne (PA): Clinical and Laboratory Standards Institute; 2013. CLSI documents VET01-A4 and Second Informational Supplement VET01-S2.

Papich MG. Antibiotic treatment of resistant infections in small animals. Vet Clin Small Animals 2013;43:1091-1107.

Papich MG. Antimicrobials, susceptibility testing, and minimum inhibitory concentrations (MIC) in veterinary infection treatment. Vet Clin Small Animals 2013;43:1079-1089.

Papich MG. Ciprofloxacin pharmacokinetics and oral absorption of generic ciprofloxacin tablets in dogs. AJVR. 2012;73:1085-91.

Trepanier, L. A. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. J Vet Pharmacol Ther 2004;27:129–138.

Weese S, Morley P, Giguere S, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. JVIM 2015;29:487-498.

Histoplasmosis:
Recognition, Diagnosis, and Treatment

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Epidemiology and pathogenesis

Histoplasma capsulatum is a saprophytic dimorphic fungus commonly found in the Missouri, Mississippi, and Ohio River valleys. In soil, it exists in a mycelial form; however when exposed to mammalian body temperatures, usually by inhalation, the fungus converts into a yeast. Yeasts survive intracellularly within monocytes and travel from the lungs to other organs of the body leads to dissemination of the organism and systemic histoplasmosis.

Clinical presentation

Histoplasmosis affects mostly young to middle-aged dogs who have outdoor exposure. Histoplasmosis can affect any age cat. Cats who spend their time strictly indoors can also become infected; in one study approximately one-third of affected cats were considered by their owners to live strictly indoors. Presenting complaints most commonly include inappetence, weight loss, vomiting, fever, respiratory problems, large bowel diarrhea, and ocular disease, although other signs can also occur. On physical examination, pale or icteric mucous membranes, lymphadenomegaly, ocular changes (uveitis, retinal granulomas, etc.), increased respiratory rate and effort, hepatomegaly, splenomegaly, thickened intestines, and fever may all be appreciated.

Diagnosis

The most definitive method for diagnosing histoplasmosis in dogs and cats is by identification of the fungal organism by cytology or histopathology. The organism appears as a small (2-4μm diameter) yeast with a thin clear rim. Organisms are usually found intracellularly in multiples but occasionally exist as singlets and extracellularly. In some cases with bone marrow involvement, *Histoplasma* organisms can be seen in circulating monocytes on a CBC. Otherwise, a CBC may show a nonregenerative anemia, variable white count, and variable platelet count (may be low). Patients with histoplasmosis may have hypoalbuminemia, hyperglobulinemia, hypercalcemia, elevated liver enzyme activities, and hyperbilirubinemia. Chest radiographs frequently document a military or unstructured nodule interstitial pattern. As mentioned above, the most accurate diagnostic test is an aspirate or biopsy to document presence of the organisms. Affected organs with lower risk for sample collection, such as lymph nodes, skin lesions, and rectal scrape, should be sampled first. If a definitive diagnosis is not obtained with these tests, samples can be collected by aspiration from other affected organs such as liver, spleen, lung, and marrow, followed by more invasive tests as needed, such as intestinal biopsy.

For patients where cytology/histopathology are not able to provide a diagnosis or collection of these samples is considered unsafe, other diagnostic options exist. Serologic testing is available by various methods, but little research is available regarding the utility of this test for clinical veterinary patients with histoplasmosis and there has been concern regarding false negative results. Antigen testing has received much research attention recently and has become a helpful addition to our diagnostic options for patients with suspected histoplasmosis. A preliminary study using a third generation enzyme-linked immunosorbent assay (ELISA) for detection of *Histoplasma* antigen (MiraVista; Indianapolis, IN) identified *Histoplasma* antigen in 17/18 cats with histoplasmosis confirmed by either cytology or histopathology, resulting in a sensitivity of 94.4%. The same test was found to have 100% specificity based on 20 cats who had diagnostic workups including cytology, histopathology, or necropsy to confirm non-histoplasmosis illness. Research is ongoing to investigate the utility of this test with dogs, as well as the utility for using this test to guide decisions about length of treatment and relapses of fungal disease. Fungal culture is also an available diagnostic tool, but prolonged turnaround times to obtain results have made its use less practical for clinical veterinary cases.

Treatment

Little research exists regarding the optimal treatment drug choice and dosing protocols for histoplasmosis in dogs and cats. Traditionally, itraconazole has been considered the oral treatment of choice for histoplasmosis in dogs and cats, with dosing recommendations ranging from 5mg/kg PO BID for cats (Hodges) to 10mg/kg PO q 12-24h for dogs or cats (Bromel). Generic itraconazole is considered to be an acceptable option to brand name (Sporonox©), but compounded itraconazole should be avoided. Fluconazole is also commonly used and is especially helpful in cases with ocular or CNS involvement. Further research is warranted to determine the optimal dose for efficacy and safety of fluconazole in dogs and cats; current dose recommendations range from 2.5-5mg/kg PO q 12-24h (Bromel) to 10mg/kg PO BID (Reinhart), the latter being currently used at the author's institution. Treatment should extend at least 2 months past resolution of all clinical signs, laboratory abnormalities, and radiographic changes, with most patients requiring therapy for at least 6 months. Relapses are somewhat common and owners should be educated to watch for recurrent signs. During therapy, patients are monitored closely (usually monthly) for adverse effects to the azole therapy (hepatotoxicity, altered

appetite) as well as improvement or worsening of disease. Amphotericin B can be used in patients with fulminant disease or those who cannot absorb oral medications due to severe intestinal histoplasmosis. Additional medications including terbinafine, voriconazole, and others can also be considered for those patients not responding or having adverse effects to the above medications.

Select references

Atiee G, Kvitko-White H, Spaulding K, Johnson M. Ultrasonographic apprearance of histoplasmosis identified in the spleen in 15 cats. Vet Radiol Ultrasound 2014;55:310-314.

Greene CE. Chapter 60: Histoplasmosis. Infectious diseases of the dog and cat 2006.

English K, Cowell RL, Tyler RD, Meinkoth LH. Chapter 16: Transtracheal and Bronchoalveolar Washes. Diagnostic cytology and hematology of the dog and cat 2008.

Bromel C, Sykes JE. Histoplasmosis in dogs and cats. Clin Tech Small Anim Pract 2005; 20: 227-32.

Cook AK, Cunningham LY, Cowell AK, Wheat LJ. Clinical evaluation of urine Histoplasma capsulatum antigen measurement in cats with suspected disseminated histoplasmosis. J Fel Med Surg 2012;14:512-515.

Hodges RD, Legendre AM, Adams LA, Willard MD, Pitts RP, Monce K, Needels CC, Ward H. Itraconazole for the treatment of histoplasmosis in cats. J Vet Intern Med 1994;8:409-413.

Mawby DI, Whittemore JC, Genger S, Papich MG. Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs. J Vet Intern Med. 2014;28:72-77.

Reinhart JM, KuKanich KS, Jackson T, Harkin KR. Feline histoplasmosis: fluconazole therapy and identification of potential sources of Histoplasma species exposure. J Fel Med Surg 2012;14:841-848.

McMillan CJ, Taylor SM. Transtracheal aspiration in the diagnosis of pulmonary blastomycosis (17 cases: 2000-2005). Can Vet J 2008;49:53-55.

Enterococcal Infections: To Treat or Not to Treat?

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Although the role of enterococci in veterinary medicine is not yet fully clear, we do know that enterococci are not simply benign flora within the gastrointestinal tract. Enterococci may possess genes for virulence and antimicrobial resistance that can be transferred among enterococcal strains to other GI flora, allowing them to cause illness and making treatment complicated. Enterococcal infections have become a leading cause of nosocomial disease in human healthcare, and clinical cases have been emerging in veterinary medicine in the past decade. Ongoing research and improved knowledge regarding the epidemiology, pathogenesis, and antimicrobial resistance of these infections will allow better control and management of enterococcal cases in veterinary medicine.

***Enterococcus* species characteristics, virulence, and resistance**

Enterococci are Gram-positive facultative anaerobic bacteria that are commensal organisms in the GI tract of companion animals and human beings but can be opportunistic pathogens in these individuals as well. There are 37 species in this genus, with *E. faecalis*, and *E. faecium* most commonly associated with clinical disease. Enterococci are hearty bacteria that can tolerate a wide range of extreme environmental conditions, including temperature (5-65°C), pH (4.5-10), and high NaCl and bile concentrations, and this helps them to survive stressors in the body and in the environment and contribute to hospital-acquired infections. Certain virulence genes (such as *esp, asa1, GelE, cylA*) are believed to help enterococci to survive in the environment, colonize patients, and contribute to specific infections. Research is ongoing to investigate the relationship between specific virulence genes and clinical disease in veterinary medicine. It is also hypothesized that transfer of virulence genes between bacteria via conjugation could be linked to transfer of antimicrobial resistance genes.

Antimicrobial resistance among enterococci is a well-known and well researched problem with both inherent and acquired resistance occurring. Enterococci are inherently resistant to clindamycin, sulfas, aminoglycosides, and have some inherent resistance to penicillins. However, many enterococcal isolates are susceptible to and DO clinically respond well to treatment with amoxicillin, ampicillin or amoxicillin-clavulanic acid. Another clinically relevant resistance is that enterococci may appear to be susceptible to cephalosporins *in vitro* (on a culture report), but cephalosporins are a NOT clinically effective treatment for enterococcal infections and should not be used. Furthermore, use of extended-spectrum cephalosporins in people has been labeled a risk factor for development of MDR and vancomycin-resistant enterococcal infections. Due to these known resistance issues, the CLSI Guidelines recommend that diagnostic laboratories do not report susceptibility results for enterococcal isolates to cephalosporins, clindamycin, sulfas, and aminoglycosides (at a typical low level). For resistant isolates some laboratories will do additional testing to determine if that isolate is susceptible to higher level of aminoglycosides, as this can be a therapeutic option especially in combination with ampicillin for synergistic effect. Fluoroquinolone resistance is acquired and somewhat common among veterinary isolates, but when susceptible fluoroquinolones can be quite useful to achieve clinical success for resistant urinary tract infections. Acquired resistance among enterococcal isolates has also been documented for aminoglycosides, tetracyclines, erythromycin, and vancomycin.

Gastrointestinal flora, disease, and probiotics

Enterococci can be isolated from the feces of about 53% of healthy dogs and 44% of cats, as a component of their normal gastrointestinal flora, with *E. faecalis* being found with highest prevalence in both dogs (60%) and cats (45%), followed by *E. hirae* and *E. faecium*. As part of the normal flora, enterococci rarely contribute to gastrointestinal disease. However, sporadic case reports suggest that enterococci can cause diarrhea in young animals, including puppies and kittens. In recent years, marketing of probiotics has increased dramatically and been directed towards promoting overall digestive health, providing healthy flora to compete with pathogens for nutrients and binding in the intestine, and improving immune function. Although rarely found in human probiotics due to concerns of safety, enterococci are commonly found in veterinary probiotic formulations. Research has been done to select strains that are able to survive and adhere within the gastrointestinal tract and are considered safe, meaning that they do not carry and cannot receive genes for antimicrobial resistance and certain virulence traits. While *E. faecium* SF68 is generally considered to be safe, it may be wise to use caution with probiotics containing other strains of enterococci, as it may be possible for some strains to receive and carry the vanA gene cluster (carrying resistance for vancomycin) as well as other genes for antimicrobial resistance and/or virulence.

Managing enterococcal infections

As recognized in human healthcare, in veterinary medicine enterococci have now been documented to cause infections in many organs outside of the intestinal tract, including pyodermas and wound infections, otitis, respiratory infections, biliary infections, and urinary tract infections. The most important question to ask when a culture taken from a dog or cat reports enterococci, whether it be in the urinary tract or elsewhere, is why is this organism able to thrive in this organ system? What is the underlying problem allowing these

opportunistic bacteria to survive and multiply? In most situations the clinician can identify a primary problem altering the patient's systemic or local immunity that contributes to the success of the enterococci. Finding that underlying problem and addressing it to reverse the local or systemic immunosuppression can be the most effective way to address the enterococcal infection. In some instances, antimicrobial therapy directed towards the enterococci may not be required. If an underlying problem cannot be addressed, enterococci may continue to thrive despite seemingly appropriate antimicrobial therapy (based on susceptibility testing), which commonly results in development of resistance to each antimicrobial agent used. This emphasizes the need for a thorough diagnostic evaluation to determine any underlying predisposing comorbidity and the importance of doing everything possible surgically, medically, and with husbandry efforts to address these underlying problems. Consultation with an internal medicine specialist to help identify comorbidities is recommended for persistent or frustrating enterococcal infections.

Enterococcal urinary tract infections

While significant enterococcal infections outside of the urinary tract of dogs and cats are still relatively uncommon, enterococcal UTIs have become a clinical frustration for veterinary practitioners. A retrospective study performed of all canine urine samples submitted for culture from the Western College of Veterinary Medicine Veterinary Teaching Hospital in Saskatchewan found 10.2% of all positive cultures to have *Enterococcus* spp. Enterococci were commonly (26.7%) found in mixed-bacterial urine cultures, and they were responsible for 5.5% of recurrent UTIs. A study performed at Michigan State University found that canine enterococcal UTIs were most commonly caused by *E. faecium* (37%), followed by *E. gallinarum* (31%), and *E. faecalis* (20%), but this species distribution has varied by location. In that study, the majority of enterococcal isolates were resistant to 3+ antibiotics, and one *E. faecium* isolate was resistant to vancomycin. The bottom line is that enterococcal UTIs are seen routinely now, and frequently they come with MDR susceptibility panels.

Are these truly UTIs or are some of these cases of asymptomatic bacteriuria? We likely see both true enterococcal UTIs and cases of asymptomatic bacteriuria with enterococci. Unfortunately, there is not yet enough evidence based research to accurately distinguish between these, but labeling them as UTI/bacteriuria may be less important than remembering the opportunistic nature of these bacteria. As mentioned above, identifying and fixing the underlying comorbidity may be all that is needed to allow the body to clear the enterococci on its own. If the CFU/ml is low and there is a fixable underlying comorbidity, treatment with antimicrobial therapy may not be necessarily warranted. Specific comorbidities to consider for these cases are the same that we would think about for any complicated UTI, including: systemic immunosuppression (corticosteroid therapy, chemotherapy, hyperadrenocorticism, etc.) and local conditions creating a nidus of infection or otherwise altering the patient's defense against a UTI (urinary catheter, uroliths, anatomic defect, prostatitis, etc.).

When antimicrobial treatment is deemed necessary, antimicrobial therapy for enterococcal UTI should be based on culture and susceptibility, and both intrinsic and acquired resistance in these species should be considered. Antimicrobial agents that are often effective for human and companion animal enterococcal UTIs include amoxicillin, amoxicillin-clavulanic acid, fluoroquinolones, and nitrofurantoin. Anecdotally, for mixed-bacterial UTIs, therapeutic success has been found by tailoring therapy towards the non-enterococcal species (i.e. choosing an antibiotic to which the *E. coli* is susceptible, even if the enterococci appear resistant) and monitoring cultures closely. For more challenging and resistant infections, exploiting the synergism between beta-lactams and aminoglycosides can also be used with caution; in these cases clinicians should ask their diagnostic lab for susceptibility testing to high level aminoglycoside if not already available. While the majority of enterococcal infections are susceptible to vancomycin, linezolid, and quinopristin-dalfopristin (*E. faecium* only), these antibiotics are best reserved for use in human infections; if a canine or feline UTI becomes resistant to all other antimicrobials, consultation with an internal medicine specialist and clinical veterinary pharmacologist is recommended to be certain all agree that we are not missing alternate comorbidities and therapeutic possibilities, respectfully.

Selected references

Went, C., B. Wiesenthal, E. Dietz, and H. Ruden. (1998). Survival of vancomycin resistant and vancomycin susceptible enterococci on dry surfaces. *Journal of Clinical Microbiology*. **36**:3734-3736.

Kuhn, I., A. Viersen, L. G. Burman, B. Olsson-Liljequist, A. Franklin, M. Finn, F. Aarestrup, A. M. Seyfarth, A. R. Blanch, H. Taylor, J. Caplin, M. A. Morena, L. Dominguez, and R. Mollby. (2000). Epidemiology and ecology of enterococci, with special reference to antibiotic resistant strains, in animals, humans and the environment. Example of an ongoing project within the European research programme. *Int. J. Antimicrob. Agents* **14**:337-342.

Upadhyaya GPM, Lingadevaru UB, Lingegowda RK. Comparative study among clinical and commensal isolates of *Enterococcus faecalis* for presence of esp gene and biofilm production. J Infect Dev Ctries 2011;5:365-369.

Rice LB. Emergence of vancomycin-resistant enterococci. Emerg Inf Dis 2001;7:183-7.

Rice EW, et al. Detection of intrinsic VRE in animal and human feces. Diag Micro Inf Dis 2003;46:155-158.

Marothi, Y. A., H. Agnihotri, and D. Dubey. (2005). Enterococcal resistance-An overview. *Indian. J. Med. Microbiol.* **23**:214-219.

Murray BE, Singh KV, Markowitz SM, Lopardo HA, Patterson JE, et al. Evidence for clonal spread of a single strain of beta-lactamase producing Enterococcus faecalis to 6 hospitals in 5 states. J Infect Dis 1991;163:780-785.

Damborg P, Top J, Hendrickx AP, et al. Dogs are a reservoir of ampicillin-resistant E. faecium lineages associated with human infections. Appl Environ Microbiol 2009;75:2360-5.
Jackson, C. R., P. J. Fedorka-Cray, J. A. Davis, J. B. Barrett, and J. G. Frye. (2009). Prevalence, species distribution and antimicrobial resistance of enterococci isolated from dogs and cats in United States. *Journal of Applied Microbiology.* **107**: 1269-1278.
Collins JE, et al. *Enterococcus (Streptococcus) durans* in the small intestines of a diarrheic pup. Vet Path 1988;25:396.
Nicklas JL, et al. In situ molecular diagnosis and histopathologic characterization of enteroadherent *Enterococcus hirae* infection in preweaning-age kittens. J Clin Microbiol 2010;48:2814-20.
Lund B, Edlund C. Probiotic *Enterococcus faecium* strain is a possible recipient of the vanA gene cluster. CID 2001;32:1384-5.
Rinkinen M, Jalava K, Westermarck E, Salminen S, Ouwehand AC. Interaction between probiotic lactic acid bacteria and canine enteric pathogens: a risk factor for intestinal *E. faecium* colonization? Vet Microbiol 2003;92:111-119.
Ball KR, Rubin JE, et al. Antimicrobial resistance and prevalence of uropathogens at the Western College of Veterinary Medicine Teaching Hospital, 2002-2007. Can Vet J 2008;49:985-990.
Simjee S, White DG, et al. Characterization of TN1546 VRE isolated from canine UTIs. J Clin Microbiol 2002;40:4659-65.

Canine RMSF and its Zoonotic Potential

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Rocky Mountain spotted fever (RMSF) is caused by a Gram-negative obligate intracellular bacteria, *Rickettsia rickettsii*, and it is transmitted to dogs and human beings by ticks. Dogs in the U.S. can also be infected with *R. Montana*, *R. rhipicephali*, *R. belli*, and *R. akari*; however, *R. rickettsii* is the only *Rickettsia* known to be pathogenic in dogs. While ticks are the vectors, small mammals (mostly rodents) act as the reservoir host for *R. rickettsii*. RMSF is seen throughout the continental U.S., reflecting the host range of susceptible tick populations: the American dog tick (*Dermacentor variabilis*) in the eastern United States, and either the Rocky Mountain wood tick (*Dermacentor andersonii*) in the western United States and Canada, or the brown dog tick (*Rhipicephalus sanguineus*) in the southwestern United States. Despite its name, the highest prevalence of RMSF is in the Southeastern and south central United States. Most cases are diagnosed from April until October, coinciding with peak tick activity. Ticks must be attached and feeding for 6-20 hours before *Rickettsia* are transmitted. Transmission may also occur by ingestion of *Dermacentor* ticks or from contamination of a wound with tick feces or secretions.

Transmission does not occur directly between dogs and humans; however infected dogs are considered a sentinel for potential concurrent tick exposure and disease transmission to humans. In people, the overall incidence of rickettsial infections is increasing, with male Caucasian children less than 15 years old having the highest incidence of infection. People who live near wooded areas or areas with tall grass are also at increased risk. The main risk factor for dogs is spending time outdoors; however, young purebred dogs are overrepresented in some reports.

Pathophysiology

After infection, the incubation period for RMSF is approximately 1 week (range 2-14 days), as rickettsiae disseminate via the circulation and multiply within vascular endothelium and smooth muscle. Three main mechanisms of pathogenesis exist: 1) endothelial response to injury leading to promotion of a pro-inflammatory state and pro-thrombotic state, 2) microvascular thrombosis and endothelial injury causing oxidative stress leading to cell death, and 3) immune-mediated platelet destruction. A diffuse vasculopathy, perivascular inflammation, and microvascular thrombosis occur, especially within the brain, skin, gastrointestinal organs, heart, lungs, kidneys, and skeletal muscle. Vasculitis leads to increased vascular permeability and edema.

Clinical manifestations of RMSF

The earliest and most common signs of RMSF seen in dogs are nonspecific and include lethargy, anorexia, and fever. Lymphadenomegaly, rapid weight loss, and edema may also be noted on physical exam. Evidence of bleeding can also be seen as petechiae, melena, epistaxis, or hematuria. Recent history of tick exposure is suggestive, but not necessary, and was only reported in 17% of dogs in one study.

Ocular signs occur in up to 80% of RMSF cases in dogs, secondary to vasculitis, and can include: discharge, scleral injection, conjunctival injection, scleral/conjunctival/iridal/retinal hemorrhage, conjunctivitis, scleral petechiae, anterior uveitis, hyphema, and retinitis. Ocular signs are mostly bilateral, generally mild, and with proper treatment most ocular signs resolve in 2-5 days.

Dyspnea and other respiratory signs such as epistaxis are reported in up to 20% of canine RMSF cases. Dyspnea can be attributed to vasculitis causing pulmonary edema, hemorrhage, or could be secondary to anemia or neurologic dysfunction in some cases. A small study reviewing thoracic radiographs of dogs with RMSF found that a mild unstructured interstitial pattern was the most common abnormality.

Arthralgia and myalgia are less commonly seen in canine RMSF than in other tick-borne diseases but may be seen in up to 20% of cases.

Cutaneous lesions can occur on the face, ears, oral cavity, extremities, ventrum, vulva, scrotum, or prepuce, and include: edema, hyperemia, necrosis, petechiae, and ecchymosis. Discrete vesicles and erythematous macules can also occur on the buccal mucosa. Cutaneous necrosis is uncommon but can be severe and can occur weeks after proper therapy has been initiated and improvement in other signs has been seen. Necrosis occurs in the extremities and previously edematous regions. Necrosis may occur more in dogs that have a delay in treatment, and may be more severe in German shepherds and Springer spaniels. Histopathology has shown focal coagulative dermal necrosis, suggestive of ischemia from vascular occlusion, but direct immunofluorescence for *R. rickettsii* in the same biopsy tissue has been negative.

Neurologic dysfunction may occur in up to 43% of dogs with RMSF, and can be focal or generalized, including hyperesthesia, tremors, ataxia, paresis, vestibular disease, altered mental status, stupor, seizures, or coma. The most common neurologic manifestation is vestibular disease, usually central, and often with strabismus. Dogs with RMSF can also have meningitis progressing to encephalomyelitis. CSF analysis may show increased cell and protein counts, mostly neutrophils or pleomorphic, and CSF can be

submitted for RMSF titer. Higher mortality rate has been reported for dogs with RMSF and neurologic dysfunction, but prognosis depends on type of neurologic disease manifested (many vestibular dogs recover fully).

Hepatopathies are reported in human cases of RMSF, but information regarding liver involvement is scarce in the veterinary literature. In human cases of RMSF, hepatic lesions are described as having inflammation and vasculitis of the portal triad with large mononuclear cells, neutrophils, and rickettsial organisms. There is no hepatocellular necrosis. Hyperbilirubinemia is likely from a combination of mild cholestasis from inflammation, edema, and hemolysis.

Intact dogs can develop orchitis, scrotal edema, hyperemia, and epididymal pain related to RMSF. Orchitis induced by RMSF can mimic testicular neoplasia and torsion and can be differentiated using ultrasound.

Diagnostic testing

The most typical laboratory abnormalities in dogs with RMSF include thrombocytopenia, moderate leukocytosis, hypoalbuminemia, and elevated ALP activity. This is similar in human beings with RMSF who commonly have thrombocytopenia and mild liver enzyme activity elevations. Dogs with pulmonary signs can have radiographic evidence of a mild unstructured interstitial pattern. Diagnosis is based on tick exposure, consistent clinical presentation, and serology results, and treatment should be started while serology is pending. The indirect immunofluorescence assay (IFA) is used in dogs and human beings to detect IgM and IgG antibodies. IgM antibodies can be detected 1 week after clinical signs appear and decline after 2 months. An IgM single titer of 1:64 or greater with consistent exposure and clinical signs is diagnostic for RMSF. However, the serologic gold standard for diagnosis involves a 4-fold increase in IgG titer from the acute initial phase to the convalescent phase 3 weeks later. IgG antibodies can be detected 2-3 weeks after infection but titers can remain elevated long-term; thus a single IgG titer is only indicative of exposure. Cerebrospinal fluid analysis can identify antibodies in patients with CNS signs. PCR may be useful during acute infections before dogs have seroconverted and to confirm active infection in seropositive dogs.

Treatment

There are 3 documented effective antibiotics for canine RMSF: doxycycline, enrofloxacin, and chloramphenicol. Doxycycline (5mg/kg PO BID for 7-14 days for dogs) is the treatment of choice, due to its efficacy and coverage against other tick-borne infections with which the dog may be co-infected. Co-infection cases may require 3-4wks of treatment. With the challenges of acquiring doxycycline in the current market, minocycline can also be used (7.5mg/kg PO BID), although research to confirm efficacy for RMSF in dogs is lacking. Enrofloxacin (5mg/kg PO BID for 7-14 days for dogs) works well if dogs cannot tolerate doxycycline, or if parenteral antibiotics are needed and you do not have access to injectable doxycycline. Enrofloxacin should be avoided in growing animals and clinicians should use caution or ideally avoid enrofloxacin in CNS cases (especially seizuring dogs). Enrofloxacin is not effective against *E. canis* and other tick-borne diseases. Steroid therapy is not typically required (or recommended) for successfully treatment RMSF in dogs, but it may be needed in rare cases with a severe immune-mediated component (ITP) or strong inflammatory component (meningitis or ocular cases). Prednisone has been shown to have no detrimental effects when given in combination with doxycycline to dogs with RMSF. Most patients show rapid response to appropriate antimicrobial therapy within 48 hours if treated early in the course of disease; however this disease can be fatal in both human beings and in dogs if not recognized and treated promptly.

Public health considerations

RMSF has been considered the most prevalent and severe human rickettsial disease in the United States. Manifestations of human RMSF include: fever, rash, headache, fatigue, joint and muscle pain, nausea, and decreased appetite. Rash is the most common clinical finding, occurring in 85-90% of infected human beings, and beginning on the extremities, especially the palms and soles. Signs can rapidly progress if undiagnosed, and multi-systemic vasculitis can lead to gangrene, shock, acute respiratory distress, thrombotic stroke, and death. Human mortality is reported to be 2-10%. Dogs bring ticks in closer proximity to their owners, and dogs can be sentinels for disease, often becoming infected and sick before their owners. Therefore, client education about how RMSF is acquired and prevented is important to protect the family members as well. Prevention of RMSF includes limiting exposure to and removal of ticks after each exposure, as well as using tick repellants, sprays, and veterinary approved products. Veterinarians can also inform clients of clinical signs that are seen with RMSF infection in people, and vets should always suggest that clients contact their physician with any concerns about human illness or infection. Reporting cases of RMSF to local or state health authorities is recommended but not required.

Selected references

Warner RD, Marsh WW. Zoonosis Update: Rocky Mountain spotted fever. *J Am Vet Med Assoc* 2002;221:1413-1417.
Low RM, and Holm JL. Canine Rocky Mountain spotted fever. *Compend Contin Educ Pract Vet* 2005;July:530-538.
McQuiston H, et al. Evidence of exposure to spotted fever group rickettsiae among Arizona dogs outside a previously documented outbreak area. Zoonosis and Public Health 2009 epub doi: 10.1111/j.1863-2378.2009.01300.x

Gasser AM, Birkenheuer AJ, and Breitschwerdt EB. Canine Rocky Mountain Spotted Fever: A retrospective study of 30 cases. *J Am Anim Hosp Assoc* 2001;37:41-48.
Davidson MG. Ocular manifestations of RMSF in dogs. JAVMA 1989;194:777-781.
Drost WT, et al. Thoracic radiographic findings in dogs infected with *R. rickettsii*. Vet Rad and US 1997;38:260-266.
Weiser IB and Green CE. Dermal necrosis associated with RMSF in four dogs. JAVMA 1989;195:1756-8.
Mikszewski JS, et al. CNS dysfunction associated with RMSF infection in 5 dogs. JAAHA 2005;41:259-266.
Jackson MD, et al. RMSF: Hepatic lesions in childhood cases. Pediatric Pathology 1986;5:379-388.
Adams JS and Walker DH. The liver in RMSF. Am J Clin Pathol 1981;75:156-61.
Ober CP, et al. Orchitis in 2 dogs with RMSF. Vet Rad and US 2004;45:458-65.
Grindem CB, et al. Platelet-associated immunoglobulin in canine RMSF and erhlichiosis. JAAHA 1999;35:56-61.
Breitschwerdt EB, et al. Efficacy of chloramphenicol, enrofloxacin, and tetracycline for treatment of experimental RMSF in dogs. Antimicrobial Agents and Chemo 1991;35:2375-2381.
Breitschwerdt EB, et al. Prednisone at anti-inflammatory or immunosuppressive doses in conjunction with doxycycline does not potentiate the severity of *R. rickettsii* infection in dogs. Anti Agents and Chemo 1997;41:141-7.
Elchos BN and Goddard J. Implications of presumptive fatal Rocky Mountain spotted fever in two dogs and their owner. *J Am Vet Med Assoc* 2003;223:14501452.
Paddock CD, et al. Short report: concurrent RMSF in a dog and its owner. Am J Trop Med 2002;66:197-199.