GASTROENTEROLOGY

by

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The Eight Principles of Therapy of Canine Inflammatory Bowel Disease

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IBD has been defined clinically as a spectrum of gastrointestinal disorders associated with chronic inflammation of the stomach, intestine and/or colon of unknown etiology. A clinical diagnosis of IBD is considered only if affected animals have: (1) persistent (>3 weeks in duration) gastrointestinal signs (anorexia, vomiting, weight loss, diarrhea, hematochezia, mucousy feces), (2) failure to respond to symptomatic therapies (parasiticides, antibiotics, gastrointestinal protectants) alone, (3) failure to document other causes of gastroenterocolitis by thorough diagnostic evaluation, and (4) histologic diagnosis of benign intestinal inflammation. Small bowel and large bowel forms of IBD have been reported in both dogs and cats, although large bowel IBD appears to be more prevalent in the dog.

Treatment – Management of IBD consists of 1) dietary therapy, 2) exercise, 3) antibiotics, 4) probiotics, 5) anti-diarrheal agents, 6) restoration of normal motility, 7) anti-inflammatory or immunosuppressive therapy, and 8) behavioral modification.

1. Dietary Therapy

The precise immunologic mechanisms of canine and feline IBD have not yet been determined, but a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens. Accordingly, dietary modification may prove useful in the management of canine and feline IBD. Several nutritional strategies have been proposed including novel proteins, hydrolyzed diets, anti-oxidant diets, medium chain triglyceride supplementation, low fat diets, modifications in the omega-6/omega-3 (ω-6/ω-3) fatty acid ratio, and fiber supplementation. Of these strategies, some evidence-based medicine has emerged for the use of novel protein, hydrolyzed, and fiber-supplemented diets.

Food sensitivity reactions were suspected or documented in 49% of cats presented because of gastrointestinal problems (with or without concurrent dermatologic problems) in a prospective study of adverse food reactions in cats. Beef, wheat, and corn gluten were the primary ingredients responsible for food sensitivity reactions in that study, and most of the cats responded to the feeding of a chicken- or venison-based selected-protein diet for a minimum of 4 weeks. The authors concluded that adverse reactions to dietary staples are common in cats with chronic gastrointestinal problems and that they can be successfully managed by feded selected-protein diets. Further support for this concept comes from studies in which gastroenterologic or dermatologic clinical signs were significantly improved by the feeding of novel proteins.

Evidence is accruing that hydrolyzed diets may be useful in the nutritional management of canine IBD. The conceptual basis of the hydrolyzed diet is that oligopeptides are of insufficient size and structure to induce antigen recognition or presentation. In one preliminary study, dogs with inflammatory bowel disease showed significant improvement following the feeding of a hydrolyzed diet although they had failed to respond to the feeding of a novel protein. Clinical improvement could not be solely attributed to the hydrolyzed nature of the protein source because the test diet had other modified features, i.e., high digestibility, cornstarch rather than intact grains, medium chain triglycerides, and an altered ratio of ω-6 to ω-3 polyunsaturated fatty acids. Additional studies will be required to ascertain the efficacy of this nutritional strategy in the management of IBD.
Fiber-supplemented diets may be useful in the management of irritable bowel syndrome (IBS) in the dog. IBS is a poorly defined syndrome in the dog that may or may not bear resemblance to IBS in humans. Canine IBS has been defined as a chronic large-bowel type diarrhea without known cause and without evidence of colonic inflammation on colonoscopy or biopsy. Dogs fulfilling these criteria were successfully managed with soluble fiber (psyllium hydrophilic mucilloid) supplementation of a highly digestible diet.

2. Exercise

Experimental IBD in the dog is accompanied by significant abnormalities in the normal colonic motility patterns. Physical exercise has been shown to disrupt the colonic MMCs and to increase the total duration of contractions that are organized as non-migrating motor complexes during the fed state. Exercise also induces GMCs, defecation, and mass movement in both the fasted and fed states. The increased motor activity of the colon and extra GMCs that result from physical exercise may aid in normal colonic motor function.

3. Antibiotics

Some IBD cases are initiated by true enteric pathogens, while others are complicated by small intestinal bacterial overgrowth. Some IBD cases may show short term responsiveness to one or more antibiotics, e.g., tylosin, metronidazole, or oxytetracycline.

4. Probiotics

Probiotics are living organisms with low or no pathogenicity that exert beneficial effects (e.g., stimulation of innate and acquired immunity) on the health of the host. The Gram-positive commensal lactic acid bacteria (e.g., Lactobacilli) have many beneficial health effects, including enhanced lymphocyte proliferation, innate and acquired immunity, and anti-inflammatory cytokine production. Lactobacillus rhamnosus GG, a bacterium used in the production of yogurt, is effective in preventing and treating diarrhea, recurrent Clostridia difficile infection, primary rotavirus infection, and atopic dermatitis in humans. Lactobacillus rhamnosus GG has been safely colonized in the canine gastrointestinal tract, although probiotic effects in the canine intestine have not been firmly established. The probiotic organism, Enterococcus faecium (SF68), has been safely colonized in the canine gastrointestinal tract, and it has been shown to increase fecal IgA content and circulating mature B (CD21+/MHC class II+) cells in young puppies. It has been suggested that this probiotic may be useful in the prevention or treatment of canine gastrointestinal disease. This organism may, however, enhance Campylobacter jejuni adhesion and colonization of the dog intestine, perhaps conferring carrier status on colonized dogs.

Two recent studies have shown that many commercial veterinary probiotic preparations are not accurately represented by label claims. Quality control appears to be deficient for many of these formulations. Until these products are more tightly regulated, veterinarians should probably view product claims with some skepticism.

5. Anti-Diarrheal Agents

Prostaglandin Synthetase Inhibitors
- Sulfasalazine - 10-25 mg/kg TID-QID, PO
- 5-aminosalicylate - 5-10 mg/kg PO, TID-QID (dog)

μ,δ-Opioid Agonists – These drugs stimulate circular smooth muscle contraction and, therefore, intestinal segmentation. It has been shown more recently that these drugs also stimulate absorption, and inhibit secretion of, fluid and electrolytes.
- Loperamide 0.08 mg/kg TID, PO-preferred drug
- Diphenoxylate 0.05-0.10 mg/kg TID-QID, PO-available in Lomotil
5-HT₃ Serotonin Antagonists - Antagonists of the neuronal 5-HT₃ receptor inhibit Cl⁻ and H₂O secretion from intestinal epithelial cells.
- Ondansetron (Zofran, Glaxo) - 0.5-1.0 mg/kg BID, PO
- Granisetron (Kytril, SmithKline Beecham) - 0.5-1.0 mg/kg BID, PO

α₂-Adrenergic Antagonists - These drugs must be used carefully as they can activate α₂-adrenergic receptors in the chemoreceptor trigger zone and cause vomiting.
- Clonidine 5-10 μg/kg BID-TID, SQ/PO

6. Restoration of Normal Motility

The mixed µ,δ-opioid agonist, loperamide, stimulates colonic fluid and electrolyte absorption while inhibiting colonic propulsive motility. Loperamide (0.08 mg/kg PO TID-QID) may be beneficial in the treatment of difficult or refractory cases of large bowel-type IBD.

7. Anti-Inflammatory/Immunosuppressive Therapy

Sulfasalazine – Sulfasalazine is a highly effective prostaglandin synthetase inhibitor that has proven efficacy in the therapy of large bowel IBD in the dog. Sulfasalazine is a compound molecule of 5-aminosalicylate (meselamine) and sulfapyridine linked in an azo chemical bond. Following oral dosing, most of the sulfasalazine is transported to the distal gastrointestinal tract where cecal and colonic bacteria metabolize the drug to its component parts. Sulfapyridine is largely absorbed by the colonic mucosa but much of the 5-aminosalicylate remains in the colonic lumen where it inhibits mucosal lipoxygenase and the inflammatory cascade. Sulfasalazine has been recommended for the treatment of canine large bowel IBD at doses of 10-25 mg/kg PO TID for 4-6 weeks. With resolution of clinical signs, sulfasalazine dosages are gradually decreased by 25 per cent at 2-week intervals and eventually discontinued while maintaining dietary management. Salicylates are readily absorbed and induce toxicity in cats, therefore this drug classification should be used with great caution in cats. If used in cats, some authors have recommended using half of the recommended dog dose (i.e., 5-12.5 mg/kg PO TID). Sulfasalazine usage has been associated with the development of keratoconjunctivitis sicca in the dog, so tear production should be assessed subjectively (by the pet owner) and objectively (by the veterinarian) during usage.

Other 5-Aminosalicylates – This drug classification was developed to reduce the toxicity of the sulfapyridine portion of the parent molecule (sulfasalazine) and to enhance the efficacy of the 5-aminosalicylate portion. Meselamine (Dipentum, Asachol) and dimeselamine (Olsalazine) are available for use in the treatment of canine large bowel IBD. Olsalazine has been used at a dosage of 5-10 mg/kg PO TID in the dog. Despite the formulation of sulf-a-free 5-aminosalicylate preparations, instances of keratoconjunctivitis sicca have still been reported in the dog.

Metronidazole – Metronidazole (10-20 mg/kg PO BID-TID) has been used in the treatment of mild to moderate cases of large bowel IBD in both dogs and cats. Metronidazole has been used either as a single agent or in conjunction with 5-aminosalicylates or glucocorticoids. Metronidazole is believed to have several beneficial properties, including anti-bacterial, anti/protozoal, and immunomodulatory effects. Side effects include anorexia, hypersalivation, and vomiting at recommended doses and neurotoxicity (ataxia, nystagmus, head title, and seizures) at higher doses. Side effects usually resolve with discontinuation of therapy but diazepam may accelerate recovery of individual patients.

Glucocorticoids – Anti-inflammatory doses of prednisone or prednisolone (1-2 mg/kg PO SID) may be used to treat IBD in dogs that have failed to respond to dietary management, sulfasalazine, or metronidazole, and as adjunctive therapy to dietary modification in feline IBD. Prednisone or prednisolone is used most frequently, as both have short durations of action, are cost-effective, and are widely available. Equipotent doses of dexamethasone are equally effective but may have more deleterious effects on brush border enzyme activity. Prednisone should be used for 2-4 weeks depending upon the severity of the clinical signs. Higher doses of
Prednisone (e.g., 2-4 mg/kg PO SID) may be needed to control severe forms of eosinophilic colitis or hypereosinophilic syndrome in cats. Combination therapy with sulfasalazine, metronidazole, or azathioprine may reduce the overall dosage of prednisone needed to achieve remission of clinical signs. As with sulfasalazine, the dose of glucocorticoid may be reduced by 25% at 1-2 week intervals while hopefully maintaining remission with dietary modification.

Because of steroid side effects and suppression of the hypothalamic-pituitary-adrenal axis, several alternative glucocorticoids have been developed that have excellent topical (i.e., mucosal) anti-inflammatory activity but are significantly metabolized during first pass hepatic metabolism. Budesonide has been used for many years as an inhaled medication for asthma, and an enteric-coated form of the drug is now available for treatment of IBD in humans (and animals). There is little evidence-based medicine in support of the use of this medication in canine or feline IBD, but doses of 1 mg/cat or 1 mg/dog per day have been used with some success in anecdotal cases.

Azathioprine – Azathioprine is a purine analog that, following DNA incorporation, inhibits lymphocyte activation and proliferation. It is rarely effective as a single agent, and it should instead be used as adjunctive therapy with glucocorticoids. Azathioprine may have a significant steroid-sparing effect in IBD. Doses of 2 mg/kg PO q 24 hours in dogs and 0.3 mg/kg PO q 48 hours in cats have been used with some success in IBD. It may take several weeks or months of therapy for azathioprine to become maximally effective. Cats particularly should be monitored for side effects, including myelosuppression, hepatic disease, and acute pancreatic necrosis.

Cyclosporine – Cyclosporine has been used in the renal transplantation patient for its inhibitory effect on T cell function. In more recent times, cyclosporine has been used in a number of immune-mediated disorders, including keratoconjunctivitis sicca, perianal fistula (anal furunculosis), and IMHA. Anecdotal reports suggest that cyclosporine (3-7 mg/kg PO BID) may be useful in the treatment of some cases of refractory IBD. Evidence-based medicine studies will be needed to establish efficacy, but anecdotal experience would suggest that cyclosporine may be useful in some of the more difficult or refractory cases of IBD.

Chlorambucil – Chlorambucil (2 mg/m² PO every other day) has been used in place of azathioprine in some difficult or refractory cases of feline IBD.

8. Behavioral Modification
Inflammatory bowel disease and irritable bowel syndrome very likely have underlying behavioral components. Abnormal personality traits and potential environmental stress factors were identified in 38% of dogs in one study. Multiple factors were present in affected households, including travel, re-location, house construction, separation anxiety, submissive urination, noise sensitivity, and aggression. The role of behavior in the pathogenesis and therapy of canine and feline gastrointestinal disorders remains largely unexplored.

Prognosis
Most reports indicate that the short-term prognosis for control of IBD is good to excellent. Following completion of drug therapy, many animals are able to maintain remission of signs with dietary management alone. Treatment failures are uncommon and are usually due to 1) incorrect diagnosis (it is especially important to rule out alimentary lymphosarcoma), 2) presence of severe disease such as histiocytic ulcerative colitis and protein-losing enteropathy or irreversible mucosa lesions such as fibrosis, 3) poor client compliance with appropriate drug/dietary recommendations, 4) use of inappropriate drugs or nutritional therapy, and 5) presence of concurrent disease such as small intestinal bacterial overgrowth or hepatobiliary disease. The prognosis for cure of IBD is poor, and relapses should be anticipated.
Canine Idiopathic Megaesophagus

Etiology - *Idiopathic megaesophagus is the most common cause of regurgitation in the dog. The disorder is characterized by esophageal hypomotility and dilation, progressive regurgitation, and loss of body condition. Several forms of the syndrome have been described, including congenital idiopathic, acquired secondary, and acquired idiopathic megaesophagus.*

Congenital idiopathic megaesophagus is a generalized hypomotility and dilation of the esophagus causing regurgitation and failure to thrive in puppies shortly after weaning. An increased breed incidence has been reported in the Irish setter, Great Dane, German shepherd, Labrador retriever, Chinese Shar-Pei, and Newfoundland breeds, and autosomal dominant inheritance has been demonstrated in the Miniature Schnauzer and Fox terrier breeds. The pathogenesis of the congenital form is incompletely understood, although several studies have pointed to a defect in the vagal afferent innervation of the esophagus. Congenital idiopathic megaesophagus has been reported in several cats, and in one group of cats secondary to pyloric dysfunction. Acquired secondary megaesophagus may develop in association with a number of other conditions. Myasthenia gravis accounts for 25-30% of the secondary cases. In some cases of myasthenia gravis, regurgitation and weight loss may be the only presenting signs of the disease, whereas in most other cases of acquired secondary megaesophagus regurgitation is but one of many clinical signs including peripheral muscle weakness. Acquired secondary megaesophagus has also been associated with hypoadrenocorticism, lead poisoning, lupus myositis, and severe forms of esophagitis. Hypothyroidism has been suggested as a secondary cause of idiopathic megaesophagus but retrospective risk factor analysis has not identified it as an important cause.

Most cases of adult-onset megaesophagus have no known etiology and are referred to as acquired idiopathic megaesophagus. The syndrome occurs spontaneously in adult dogs between 7 to 15 years of age without sex or breed predilection. The disorder has been compared erroneously to esophageal achalasia in humans. Achalasia is a failure of relaxation of the lower esophageal sphincter and ineffective peristalsis of the esophageal body. A similar disorder has never been rigorously documented in the dog. Several important differences between idiopathic megaesophagus in the dog and achalasia in humans have been documented. Although the etiology(ies) has not been identified, some studies have suggested a defect in the afferent neural response to esophageal distension similar to what has been reported in congenital megaesophagus.

Clinical Examination

Routine hematology, serum biochemistry, and urinalysis should be performed in all cases to investigate possible secondary causes of megaesophagus (e.g. hypoadrenocorticism). Survey radiographs will be diagnostic for most cases of megaesophagus. Contrast radiographs may be necessary in some cases to confirm the diagnosis, evaluate motility, and exclude foreign bodies or
obstruction as the cause of the megaesophagus. Endoscopy will confirm the diagnosis and may further reveal esophagitis, a frequent finding in canine idiopathic megaesophagus.

If acquired secondary megaesophagus is suspected, additional diagnostic tests should be considered, for example: serology for nicotinic acetylcholine receptor antibody, ACTH stimulation, serology for antinuclear antibody, serum creatine phosphokinase activity, electromyography and nerve conduction velocity, and muscle and nerve biopsy. Additional medical investigation will be dependent upon the individual case presentation. Hypothyroidism has been cited as an important cause of idiopathic megaesophagus in the dog, although risk factor analysis has not revealed a clear association. Thyroid function testing (e.g., TSH assay, TSH stimulation, free and total thyroid hormones) should be performed in individual suspicious cases.

Treatment

Animals with secondary acquired megaesophagus should be appropriately differentiated from other esophageal disorders and treated. Dogs affected with myasthenia gravis should be treated with pyridostigmine (1.0-3.0 mg/kg PO BID) and/or corticosteroids (prednisone 1.0-2.0 mg/kg PO or SQ BID), dogs affected with hypothyroidism should be treated with levothyroxine (22 µg/kg PO BID), and dogs affected with polymyositis should be treated with prednisone (1.0-2.0 mg/kg PO BID). If secondary disease can be excluded, therapy for the congenital or acquired idiopathic megaesophagus patient should be directed at nutritional management and treatment of aspiration pneumonia. Affected animals should be fed a high-calorie diet, in small frequent feedings, from an elevated or upright position to take advantage of gravity drainage through a non-peristaltic esophagus. Dietary consistency should be formulated to produce the fewest clinical signs. Some animals handle liquid diets quite well, while others do better with solid meals. Animals that cannot maintain adequate nutritional balance with oral intake should be fed by temporary or permanent tube gastrostomy. Gastrostomy tubes can be placed surgically or percutaneously with endoscopic guidance.

Smooth muscle prokinetic (e.g., metoclopramide or cisapride) therapy has been advocated for stimulating esophageal peristalsis in affected animals, however metoclopramide and cisapride will not likely have much of an effect on the striated muscle of the canine esophageal body. Bethanechol has been shown to stimulate esophageal propagating contractions in some affected dogs and is therefore a more appropriate prokinetic agent for the therapy of this disorder. Because of the high incidence of esophagitis in canine idiopathic megaesophagus, affected animals should also be medicated with oral sucralfate suspensions (1 g q8h for large dogs 0.5 g q8h for smaller dogs 0.25 to 0.5 g q8h to q12h for cats).

Prognosis

Animals with congenital idiopathic megaesophagus have a fair prognosis. With adequate attention to caloric needs and episodes of aspiration pneumonia, many animals will develop improved esophageal motility over several months. Pet owners must be committed to months of physical therapy and nutritional support. The morbidity and mortality of acquired idiopathic megaesophagus remain unacceptably high.

Gastric Emptying Disorders

Gastric emptying disorders are fairly common in dogs and cats. They result from disease processes that alter normal gastric functions, i.e. storage of ingesta, mixing and dispersion of food particles, and timely emptying of gastric contents into the small intestine. Disorders of gastric emptying arise from mechanical obstruction, or from defective propulsion. Anatomic lesions (e.g. malignancy, hyperplasia, foreign bodies) cause delayed gastric emptying because of
mechanical obstruction. Diagnosis and management of mechanical obstruction is usually straight-forward. Disorders of defective propulsion, on the other hand, cause delayed gastric emptying because of abnormalities in myenteric neuronal or gastric smooth muscle function, or because of abnormalities in antropyloroduodenal coordination. A number of primary conditions have been associated with these functional disorders, including infectious or inflammatory disease, ulcer, and post-surgical gastroparesis. Delayed gastric emptying has also been associated with a number of secondary conditions, including electrolyte disturbances, metabolic disorders, concurrent drug usage (cholinergic antagonists, adrenergic agonists, opioid agonists), acute stress, and acute abdominal inflammation. Recovery from gastric dilation/volvulus is almost always associated with significant myoelectrical and motor abnormalities in the dog. Diagnosis and management of the delayed gastric emptying disorders may not be so straight-forward. Nutritional and medical management, including smooth muscle prokinetic agents (e.g., cisapride, erythromycin, and ranitidine), are important components of therapy.

Small Intestinal Transit Disorders

A number of small intestinal transit disorders have been described in dogs and cats, including enteritis, post-surgical pseudo-obstruction, nematode infection, intestinal sclerosis, and radiation enteritis. Vomiting and diarrhea are the most important clinical signs associated with these disorders. Overgrowth of small intestinal bacteria, a common sequela to disordered motility, contributes to these clinical signs. Transit disorders associated with mechanical obstruction should always be differentiated and treated appropriately. Delayed transit associated with functional disorders should be managed with dietary modification (low fat diets) and prokinetic agents (cisapride, tegaserod, or metoclopramide). Tegaserod, a new 5-HT₄ partial agonist, has recently been reported to normalize intestinal transit in opioid-induced bowel dysfunction in dogs.

Colonic Motility Disorders

History

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed, however, most cases are observed in middle aged (mean = 5.8 years), male cats (70% male, 30% female) of Domestic Shorthair (46%), Domestic Longhair (15%), or Siamese (12%) breeding. Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate in the litter box, while other cats may sit in the litter box for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litter box. Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea due to the mucosal irritant effect of dehydrated feces.

Physical Examination

Colonic impaction is a consistent physical examination finding in affected cats. Other findings will depend upon the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe in such cases as to render it difficult to differentiate impaction from colonic, mesenteric, or other abdominal neoplasia. Cats with constipation due to dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation due to megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia. Digital rectal
examination should be carefully performed with sedation or anesthesia especially in those cats with recurring bouts of constipation. Pelvic fracture malunion may be detected on rectal examination in cats with pelvic trauma. Rectal examination might also identify other unusual causes of constipation, such as foreign bodies, rectal diverticula, stricture, inflammation, or neoplasia. Chronic tenesmus may be associated with perineal herniation in some cases. A complete neurologic examination with special emphasis on caudal spinal cord function should be performed to identify neurologic causes of constipation, e.g. spinal cord injury, pelvic nerve trauma, and Manx sacral spinal cord deformity.

**Differential Diagnoses**

Several authors have emphasized the importance of considering an extensive list of differential diagnoses (e.g. neuromuscular, mechanical, inflammatory, metabolic/endocrine, pharmacologic, environmental, and behavioral causes) for the obstipated cat. A review of published cases, however, suggests that 96% of cases of obstipation are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%). A smaller number of cases are accounted for by complications of colopexy (1%) and colonic neoplasia (1%); colonic hypo- or aganglionosis was suspected, but not proved, in another 2% of cases. Inflammatory, pharmacologic, and environmental/behavioral causes were not cited as predisposing factors in any of the original case reports. Endocrine factors (obesity, n=5; hypothyroidism, n=1) were cited in several cases, but were not necessarily impugned as part of the pathogenesis of megacolon.

**Pathogenesis**

The pathogenesis of idiopathic megacolon has been historically attributed to a primary neurogenic or degenerative neuromuscular disorder. While it seems clear that a small number of cases (11%) result from neurologic disease, the vast majority (>90%) of cases have no evidence of neurologic disease. Some of the idiopathic cases may instead involve disturbances of colonic smooth muscle as suggested by several studies. In vitro isometric stress measurements were performed on colonic smooth muscle segments obtained from cats suffering from idiopathic dilated megacolon. These studies suggested that the disorder of feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle, and that treatments aimed at stimulating colonic smooth muscle contraction might improve colonic motility.

**Therapeutic Plan**

The specific therapeutic plan will depend upon the severity of constipation and the underlying cause. Medical therapy may not be necessary with first episodes of constipation. First episodes are often transient and resolve without therapy. Affected animals should always be re-hydrated if dehydration has contributed to the onset of clinical signs. Mild to moderate or recurrent episodes of constipation usually require some medical intervention. These cases may be managed, often on an outpatient basis, with dietary modification, water enemas, oral or suppository laxatives, and/or colonic prokinetic agents. Severe cases of constipation usually require brief periods of hospitalization to correct metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Followup therapy in such cases is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon. These cats, by definition, are unresponsive to medical therapy. Pelvic osteotomy without colectomy may be sufficient for some cats suffering from pelvic canal stenosis and hypertrophic megacolon.
NEW DEVELOPMENTS IN PROKINETIC THERAPY

Cisapride (Janssen Pharmaceutical)

Cisapride was widely used in the management of canine and feline gastric emptying, intestinal transit, and colonic motility disorders throughout most of the 1990’s. Cisapride was withdrawn from the American, Canadian and certain Western European in July of 2000 following reports of untoward cardiac side effects in human patients. Cisapride causes QT interval prolongation and slowing of cardiac repolarization via blockade of the rapid component of the delayed rectifier potassium channel (I_{Kr}). This effect may result in a fatal ventricular arrhythmia referred to as torsades de pointes. Similar effects have been characterized in canine cardiac Purkinje fibers, but in vivo effects have not yet been reported in dogs or cats. The withdrawal of cisapride has created a clear need for new G.I. prokinetic agents although cisapride continues to be available from compounding pharmacies throughout the United States. Two new prokinetic agents, prucalopride and tegaserod, are in differing stages of drug development and may prove useful in the therapy of G.I. motility disorders of several animal (dog, cat, horse) species.

Tegaserod (SDZ HTF 919 – Novartis Corporation)

Tegaserod is a potent partial non-benzamide agonist at 5-HT\textsubscript{4} receptors and a weak agonist at 5-HT\textsubscript{1D} receptors. Tegaserod has definite prokinetic effects in the canine colon. Intravenous doses of tegaserod (0.03-0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration. The highest doses of tegaserod (0.1 and 0.3 mg/kg) have no greater efficacy than lower doses (0.03 mg/kg), suggesting the possibility that tegaserod may stimulate canine colonic motility through a receptor-independent mechanism, or that tegaserod may act at sites other than 5-HT\textsubscript{4} receptors at higher doses.

The motor mechanisms responsible for tegaserod-induced canine colonic propulsion are unclear. High amplitude propagated phasic contractions are thought to be responsible for mass movements, but they were not observed during tegaserod infusion. Contraction, amplitude, and motility indices were not different postprandially among treatment groups, so the mechanism of the tegaserod effect will require more detailed investigation in the dog. In vitro studies suggest that tegaserod does not prolong the QT interval or delay cardiac repolarization as has been occasionally reported with cisapride. Clinical efficacy has been demonstrated in human motility disorders, and new drug approval was rewarded by the U.S. Food and Drug Administration in September 2002. Tegaserod has been marketed under the trade name of Zelnorm in the United States, and under the trade name of Zelmec in the United Kingdom.

Gastric effects of tegaserod have not been reported in the dog, so this drug may not prove as useful as cisapride in the treatment of delayed gastric emptying disorders. Tegaserod at doses of 3-6 mg/kg PO has been shown to normalize intestinal transit in opioid-induced bowel dysfunction in dogs, and it may be useful in other disorders of intestinal ileus or pseudo-obstruction.
Prucalopride (R093877 – Janssen Pharmaceutical)

Prucalopride is a potent partial benzamide agonist at 5-HT$_4$ receptors, but is without effect on other 5-HT receptors or cholinesterase enzyme activity. Prucalopride dose-dependently (0.02-1.25 mg/kg) stimulates giant migrating contractions (GMC’s) and defecation in the dog. The prucalopride effect is observed most prominently in the first hour after administration, suggesting that the prucalopride effect is a direct effect on the colon rather than on total gut transit time. Oral and intravenous doses appear to be equipotent again implying a high oral bioavailability. Prucalopride also enhances defecation frequency in healthy cats. Cats treated with prucalopride at a dose of 0.64 mg/kg experience increased defecation within the first hour of administration. Fecal consistency is not altered by prucalopride at this dosage. Prucalopride also appears to stimulate gastric emptying in the dog. In lidamide-induced delayed gastric emptying in dogs, prucalopride (0.01-0.16 mg/kg) dose-dependently accelerates gastric emptying of dextrose solutions. The prucalopride effect is equipotent following oral and intravenous administration suggesting that prucalopride may have a high oral bioavailability. Prucalopride has not yet been marketed in the United States or elsewhere.
Difficult Vomiting Disorders: Pathogenesis, Diagnosis, and Therapy

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I. History Taking

A complete and detailed history is the first step in establishing a correct diagnosis of a vomiting disorder. The patient's signalment will usually establish some level of probability for many of the differential diagnoses. For example, adrenocortical insufficiency would be an important differential diagnosis for a two year old dog presented with an acute history of vomiting and muscular weakness, with or without diarrhea. Similarly, the acute onset of vomiting in an unvaccinated puppy should alert the veterinarian to the possibility of an infectious disease, for example, parvoviral or distemper viral gastroenteritis. Chronic vomiting in an eleven year old dog, on the other hand, would elicit a different set of differential diagnoses.

Following consideration of the patient's signalment, the history taking should ascertain vaccination status, travel history, and any recent dietary changes. Previous medical problems, medication history, and the possible ingestion of toxic substances or foreign bodies should also be ascertained. These pieces of information can be quite useful in formulating a list of differential diagnoses. Next, the veterinarian should be convinced that the pet owner is describing vomiting, and not some other sign. For example, the coughing associated with inflammatory disorders of the upper airway will often be described as vomiting by many pet owners. Gagging is also occasionally confused with vomiting. A careful history taking will usually discriminate coughing and gagging from vomiting. Pet owners will also often confuse regurgitation and dysphagia with vomiting. Regurgitation is the passive evacuation of ingested food from the pharynx and/or esophagus; the premonitory signs of retching and abdominal contractions seen with vomiting are not observed with regurgitation. The description of regurgitation by a pet owner would suggest a more proximal disorder of the pharynx or esophagus. Dysphagia or difficulty in swallowing would also suggest a more proximal disorder of the pharynx.

The history taking should then elicit the duration, frequency, and time of vomiting episodes, as well as the relationship of vomiting to food and water consumption. Disorders of vomiting that are of short duration are usually self-limiting and not worthy of extensive investigation; chronic vomiting histories, on the other hand, are more serious and certainly require a more detailed investigation. Frequent vomiting usually occurs as result of systemic, metabolic, or endocrine disorders or severe inflammatory disorders of the primary gastrointestinal tract. Vomiting that occurs in the immediate post-prandial period is usually suggestive of overeating, excitement, or disorders of the esophageal body or esophageal hiatus (e.g. hiatal hernia). Conversely, vomiting of undigested or partially digested food 8 or more hours post-prandially would suggest a distal gastric (corpus, antrum, and pylorus) motility disorder or obstruction. Vomiting of water would be more suggestive of a proximal gastric (cardia, fundus) motility disorder. Vomiting during the early morning hours often may result from gastroesophageal reflux.
Finally, the physical characteristics of the vomitus, including the color, amount, odor, consistency, and the presence or absence of blood or bile should be ascertained. Undigested food in the vomitus implies a gastric etiology, while digested food (chyme) implies an intestinal etiology for the vomiting. The presence of blood in the vomitus implies disruption of the gastrointestinal mucosa; blood may appear as frank red clots or as a dark brown "coffee-grounds" material resulting from acid proteolysis. Bile in the vomitus usually suggests only that the pylorus has permitted bile reflux. However, bile salts are known to increase the permeability of the gastric mucosal barrier resulting in a syndrome of bile reflux gastritis. Bilious vomiting, therefore, might provide a clue to the pathogenesis of the disorder. A fecal odor has been described with lower intestinal (jejuno-ileal) obstruction.

II. Physical Examination

Examination of the mouth and pharyngeal structures often provide important clues to the pathogenesis of vomiting, e.g. uremic breath or ulcers, icteric mucous membranes, severe pharyngitis or pharyngeal string foreign bodies. The physical examination finding of generalized lymphadenopathy would suggest neoplasia or a systemic inflammatory disease as the pathogenesis of the vomiting. Hence, all lymph nodes should be carefully palpated to determine if they are enlarged and/or painful. The presence of fever on physical examination would likewise suggest an inflammatory pathogenesis for the vomiting disorder. Extreme bradycardia or other rhythm disturbance detected upon cardiac auscultation might be an important sign of a metabolic disturbance such as adrenocortical insufficiency or septic shock. The abdomen should then be carefully palpated for effusion (e.g. peritonitis), masses (e.g. carcinomatosis or other malignancy), pain (e.g. peritonitis, pancreatitis, or nephritis), gaseous or fluid distension of the intestine (e.g. obstruction), kidney size and shape (e.g. end-stage fibrotic kidneys or nephritis), liver size (e.g. hepatitis), uterine distension (e.g. pyometra), and urinary bladder size (e.g. bladder obstruction). Rectal examination might also provide some evidence of pain or hematochezia (e.g. colitis), worms (e.g. hook or whipworms), or painful prostatomegaly (e.g. prostatitis or prostatic neoplasia). Finally, examination of the central nervous system should be considered, especially in the animal in which the cause of vomiting is not so obvious. Some animals with intervertebral disc disease will vomit because of pain.

III. Differential Diagnosis

After identifying problems from the history and physical examination, a reasonable list of differential diagnoses may then be considered based upon pathogenetic mechanism: abdominal alimentary, abdominal extra-alimentary, systemic-metabolic-endocrine, drug-induced, toxicity, diet-related, and neurologic disorders.

IV. Diagnostic Workup

If a definitive diagnosis is not established from the history and physical examination, then the following "initial tests" are warranted: complete blood count, serum chemistry, urinalysis, fecal parasitologic examination, and abdominal radiographs.
Peripheral eosinophilia in a complete blood count would suggest the possibilities of systemic mast cell disease, intestinal parasitism, or adrenocortical insufficiency. Leukopenia and neutropenia might be observed in the acute phase of a viral gastroenteritis. Leukocytosis, on the other hand, might suggest an inflammatory disorder like acute pancreatitis. The serum chemistry will often help identify systemic, metabolic, and endocrine causes of vomiting. For example: 1) azotemia and hyperphosphatemia suggest that the vomiting has resulted from chronic renal failure; 2) hyperglycemia, acidosis, glucosuria, and ketonuria suggest diabetic ketoacidosis as the cause of vomiting; 3) hyponatremia and hyperkalemia suggest adrenocortical insufficiency; 4) amylasemia and lipasemia suggest acute pancreatitis; 5) increases in serum liver enzyme activities (ALT, AST, ALP) suggest primary liver disease; and, 6) hypercalcemia suggests parathyroid or other malignancy. Urinalysis will be useful in differentiating pre-renal and primary renal azotemia, while fecal examination may provide evidence of intestinal helminth infestation.

Survey radiographs of the abdomen are certainly indicated in the initial workup of a vomiting disorder. The abdominal radiographs will provide useful information about the abdominal alimentary and extra-alimentary structures. The decision to perform additional tests is based on response to empirical therapies and initial test results. Further tests might include: thoracic radiography, abdominal ultrasonography, contrast radiography, ACTH stimulation, liver function tests, gastrointestinal endoscopy, and laparotomy.

V. Anti-Emetic Therapy

Physiology of Emesis: The essential components of the emetic reflex are visceral receptors, vagal and sympathetic afferent neurons, a chemoreceptor trigger zone (CRTZ) located within the area postrema that is sensitive to blood-borne substances, and an emetic center within the reticular formation of the medulla oblongata receiving input from vagal and sympathetic neurons, CRTZ, vestibular apparatus, and cerebral cortex. An important concept dating from the early 1950's is that vomiting occurs either through activation of the CRTZ by blood-borne substances (humoral pathway), or through activation of the emetic center by vago-sympathetic, CRTZ, vestibular, or cerebrocortical neurons (neural pathway). Thus, activation of the CRTZ by a variety of humoral emetogenic substances (e.g. uremic toxins, cardiac glycosides, and apomorphine) is abolished by surgical ablation of the area postrema, but not by vagotomy or sympathectomy. In contrast, neural activation of the emetic center by gastric disease (e.g. gastritis) is abolished by vagotomy or sympathectomy, but not by ablation of the area postrema. Many experimental data have been readily explained by this two-component model. Despite contemporary reexamination, there is still good agreement on the two general patterns of emesis, one humoral and one neural. Current therapy is largely based on these assumptions.

Many of the spontaneous vomiting disorders of cats and dogs, particularly those of the primary gastrointestinal tract, are believed to result from activation of the neural pathway. Vomiting associated with primary gastrointestinal tract disease (e.g., inflammation, infection, malignancy, toxicity) results from activation of visceral receptors, afferent neurons, and the emetic center. Efferent information transmitted back to the gastrointestinal tract stimulates the motor correlates of vomiting (retrograde duodenal and gastric contractions, relaxation of the caudal esophageal sphincter, gastroesophageal reflux, opening of the proximal esophageal sphincter, and evacuation of gastrointestinal contents). A neural pathway can also be involved in vomiting associated with motion sickness. Motion within the semicircular canals is transduced to vestibulo-cochlear neurons that ultimately synapse in the CRTZ or emetic center. Cats and dogs experience motion
sickness, although the neuroanatomy and pharmacology appear to be somewhat different between the two species. Histaminergic neurons and the CRTZ are involved in motion sickness in the dog, whereas neither are involved in motion sickness in the cat. A neural pathway involving cerebrocortical neurons may be involved in vomiting disorders associated with anxiety or anticipation, but these are probably more important in human beings.

The essential component of the humoral pathway is the chemoreceptor trigger zone (CRTZ) located within the area postrema that is sensitive to blood-borne substances. Receptors within the CRTZ may be activated by many endogenous (e.g., uremic-, hepatoencephalopathic-, or endo-toxins) and exogenous (e.g., digitalis glycosides, apomorphine) blood-borne substances. Most pharmacological approaches to anti-emetic therapy have been based on neurotransmitter-receptor interactions at the CRTZ, emphasizing the humoral pathway of emesis. The neural pathway has received much less emphasis even though it is a much more important pathway.

**Pharmacology of Emesis:** Vomiting is initiated through activation of one or more neurons in the CRTZ or emetic center.

**Anti-Emetic Classifications**

A number of anti-emetic drugs have been formulated based on the aforementioned neurotransmitter-receptor systems. These drugs may be classified as: \( \alpha_2 \) adrenergic antagonists, \( D_2 \) dopaminergic antagonists, \( H_1 \) and \( H_2 \) histaminergic antagonists, \( M_1 \) muscarinic cholinergic antagonists, ENK enkephalinergic mixed agonists/antagonists, and \( 5-HT_3 \) serotonergic antagonists. The \( 5-HT_4 \) serotonergic agonists are not direct anti-emetic drugs *per se*, but may have an indirect anti-emetic effect by promoting gastrointestinal motility.
Rational Use of Anti-Emetic Agents in the Diagnosed Patient:

1. Motion Sickness - Motion sickness is believed to arise from stimulation of labyrinthine structures in the inner ear. The chemoreceptor trigger zone and H₁ histaminergic receptors are involved in this pathway in the dog, but apparently they are less importantly involved in the cat. Motion sickness in the cat is probably best treated with an α-adrenergic antagonist, e.g., chlorpromazine, instead of a pure H₁ histaminergic antagonist.

2. Uremia – Vomiting associated with uremia has both central and peripheral components. The central component of uremic vomiting is associated with activation of CRTZ D₂ dopaminergic receptors by circulating uremic toxins. The central component is best treated with a D₂ dopaminergic antagonist, e.g. metoclopramide. The peripheral component of uremic vomiting is associated with uremic gastritis and is best treated with acid secretory inhibitors (e.g. ranitidine 1-2 mg/kg q 12 h IV; omeprazole 0.7 mg/kg q 12 h PO) to diminish gastric parietal cell H⁺ ion secretion, and with chemical barrier diffusion barriers (e.g., sucralfate 0.25-0.5 grams q 8-12 h PO) to provide a barrier to H⁺ ion back diffusion.

3. Cancer Chemotherapy – Certain cancer chemotherapies (e.g. cisplatinum, cyclophosphamide) are associated with a high incidence of vomiting. Chemotherapy-induced emesis is mediated by 5-HT₃ serotonergic receptors, either in the CRTZ or in vagal afferent neurons. Antagonists of the 5-HT₃ serotonergic receptor (e.g. ondansetron, granisetron, tropisetron) abolish the vomiting associated with cisplatinum administration in the cat. Although metoclopramide has some 5-HT₃ antagonistic properties, it has not proved very useful in chemotherapy-induced emesis.

4. Delayed Gastric Emptying Orders – Disorders of delayed gastric emptying (e.g. gastritis, metabolic derangements, post-operative gastric dilatation and volvulus) may cause an animal to experience nausea and vomiting. Treatment of these disorders with cholinomimetic agents has been associated with untoward side effects. Contemporary therapy consists of 5-HT₃ serotonergic agonists (e.g., cisapride, metoclopramide), cholinesterase inhibitors (e.g., ranitidine or nizatidine), and motilin agonists (e.g., low dose erythromycin – dog only). Cisapride is superior to metoclopramide in the treatment of gastric emptying disorders in cats and dogs. Ranitidine and nizatidine inhibit acetylcholinesterase activity in addition to their effects on histamine H₂ receptors in the gastric mucosa. Both drugs (ranitidine and nizatidine) stimulate gastric emptying in the cat and dog. Erythromycin stimulates phase III migrating myoelectric complex (MMC) activity in the dog, but the migrating spike complex (MSC) activity of the cat is under different physiologic regulation.

Newer Anti-Emetic Therapy - Neurokinin-1 Receptor Antagonists

<table>
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<th>Examples</th>
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<tr>
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<td>Cerenia</td>
<td>Pfizer</td>
<td>1.0 mg kg SQ SID x 5</td>
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<tr>
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<td>Dapitant</td>
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- FDA Application – January 29, 2007 – NADA 141-262 & 141-263 - Maropitant 1.0 mg/kg SQ effective against emesis due to syrup of ipecac, apomorphine, and cisplatin.

**Anti-Emetic Strategies for the UnDiagnosed Patient**

1. NK1 Neurokinin Antagonists
2. 5-HT3 Serotonergic Antagonists
3. α2-Adrenergic Antagonists
4. D2 Dopaminergic Antagonists

**Irrational Usage of Anti-Emetic Agents**

- Systemic hypotension → Phenothiazines
- Pre-existing epilepsy → Phenothiazines
- G.I. obstruction → Prokinetic agents
- G.I. infection → All Classes
- G.I. toxicity → All Classes
- Prolonged usage → All Classes
FELINE EXOCRINE PANCREATIC DISEASE:
A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Etiology

The etiologies of acute necrotizing pancreatitis are probably not yet completely recognized. Biliary tract disease, gastrointestinal tract disease, ischemia, pancreatic ductal obstruction, infection, trauma, organophosphate poisoning, and lipodystrophy all have known associations with the development of acute necrotizing pancreatitis in the cat. Hypercalcemia, idiosyncratic drug reactions, and nutritional causes are suggested but poorly documented causes of the disease.

Concurrent Biliary Tract Disease – Concurrent biliary tract pathology has a known association with acute necrotizing pancreatitis in the cat. Cholangitis is the most important type of biliary tract disease for which an association has been made, but other forms of biliary tract pathology (e.g., stricture, neoplasia, and calculus) have known associations. Epidemiologic studies have shown that cats affected with suppurative cholangitis have significantly increased risk for pancreatitis. The pathogenesis underlying this association is not entirely clear but relates partly to the anatomic and functional relationship between the major pancreatic duct and common bile duct in this species. Unlike the dog, the feline pancreaticobiliary sphincter is a common physiological and anatomic channel at the duodenal papilla. Mechanical or functional obstruction to this common duct readily permits bile reflux into the pancreatic ductal system.

Concurrent Gastrointestinal Tract Disease – Like concurrent biliary tract disease, inflammatory bowel disease (IBD) is an important risk factor for the development of acute necrotizing pancreatitis in the cat. Several factors appear to contribute to this association: (1) High incidence of inflammatory bowel disease – IBD is a common disorder in the domestic cat. In some veterinary hospitals and specialty referral centers, IBD is the most common gastrointestinal disorder in cats. (2) Clinical symptomatology of IBD – Vomiting is the most important clinical sign in cats affected with IBD. Chronic vomiting raises intraduodenal pressure and increases the likelihood of pancreaticobiliary reflux. (3) Pancreaticobiliary anatomy – The pancreaticobiliary sphincter is a common physiological and anatomic channel at the duodenal papilla, thus reflux of duodenal contents would perfuse pancreatic and biliary ductal systems. (4) Intestinal Microflora – Compared to dogs, cats have a much higher concentration of aerobic, anaerobic and total (10^9 vs. 10^4 organisms/ml) bacteria in the proximal small intestine. Bacteria readily proliferate in the feline small intestine because of differences in gastrointestinal motility and immunology. If chronic vomiting with IBD permits pancreaticobiliary reflux, a duodenal fluid containing a mixed population of bacteria, bile salts, and activated pancreatic enzyme would perfuse the pancreatic and biliary ductal systems.

Ischemia – Ischemia (e.g., hypotension, cardiac disease) is a cause or consequence of obstructive pancreatitis in the cat. Inflammation and edema reduce the elasticity and distensibility of the pancreas during secretory stimulation. Sustained inflammation increases pancreatic interstitial and ductal pressure which serves to further reduce pancreatic blood flow, organ pH, and tissue viability. Acidic metabolites accumulate within the pancreas because of impaired blood flow. Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.
Pancreatic Ductal Obstruction – Obstruction of the pancreatic duct (e.g., neoplasia, pancreatic flukes, calculi, and duodenal foreign bodies) is associated with the development of acute necrotizing pancreatitis in some cases. Pancreatic ductal obstruction has marked effects on pancreatic acinar cell function. During ductal obstruction, ductal pressure exceeds exocytosis pressure and causes pancreatic lysosomal hydrolases to co-localize with digestive enzyme zymogens within the acinar cell.

Infection – Infectious agents have been implicated in the pathogenesis of feline acute necrotizing pancreatitis although none have been reported as important causes of ANP in any of the recent clinical case series. The pancreas is readily colonized by *Toxoplasma gondii* organisms during the acute phase of infection. In one survey of *T. gondii*-infected cats, organisms were found in 84% of the cases, although organ pathology was more severe in other organ systems. *Feline herpesvirus I* and feline infectious peritonitis viruses have been implicated as causative agents in several case reports, and feline paroviral infection has been associated with viral inclusion bodies and pancreatic acinar cell necrosis in young kittens. Pancreatic (*Eurytrema procyonis*) and liver fluke (*Amphimerus pseudofelineus, Opisthorchis felineus*) infections are known causes of feline acute necrotizing pancreatitis in the southeastern United States and Caribbean Basin. Recent reports of virulent calici viral infections have been reported in multiple cat households or research facilities. Affected cats manifest high fever, anorexia, labored respirations, oral ulceration, facial and limb edema, icterus, and severe pancreatitis. Caliciviral infection has not been reported in any of the recent clinical case series of feline acute necrotizing pancreatitis, but some cases of active infection could have been overlooked. The importance of calicivirus infection in the pathogenesis of feline acute pancreatic necrosis remains to be determined.

Trauma – Automobile and fall (“high rise syndrome”) injuries have been associated with the development of acute necrotizing pancreatitis in a small number of cases. These tend to be isolated cases that do not show up as important causes in clinical case surveys.

Organophosphate Poisoning – Organophosphate poisoning is a known cause of acute necrotizing pancreatitis in humans and dogs, and several cases have been reported in the cat. In one survey, several cats developed ANP following treatment for ectoparasites, and two cats developed ANP following treatment with fenthion. Diminishing organophosphate usage will probably lead to a reduced incidence of this lesion.

Lipodystrophy - Lipodystrophy has been cited as an occasional cause of acute necrotizing pancreatitis in the cat, but it has not been reported in any of the large clinical case series.

Hypercalcemia – Acute necrotizing pancreatitis develops in association with the hypercalcemia of primary hyperparathyroidism and humoral hypercalcemia of malignancy in humans, and a weak association with hypercalcemia has been reported in dogs. Moderate hypercalcemia was found as a pre-existing laboratory finding in 10% of the cases of fatal canine acute pancreatitis. Acute experimental hypercalcemia does indeed cause acute pancreatic necrosis and pancreatitis in cats, but it is probably not very clinically relevant. Acute hypercalcemia is an uncommon clinical finding in feline practice. Chronic hypercalcemia, a more clinically relevant condition, is not associated with changes in pancreatic morphology or function.

Nutrition – High fat feedings and obesity have been associated with the development of pancreatitis in the dog, but similar associations have not been made in the cat. Most recent surveys have associated underweight body condition with the development of feline ANP.
Clinical Signs

History - Siamese cats were initially reported to be at increased risk for the disease in one of the first retrospective studies of feline pancreatitis. Clinical case surveys of the past 10 years suggest that most cases of feline pancreatitis are seen in the Domestic Short Hair breed. Anorexia (87%) and lethargy (81%) are the most frequently reported clinical signs in cats with acute pancreatitis, but these clinical signs are not pathognomonic for pancreatitis. Anorexia and lethargy are the most important clinical signs in many feline diseases. Gastroenterologic signs are sporadic and less frequently reported in the cat. Vomiting and diarrhea are reported in only 46% and 12% of cases, respectively. In dogs, vomiting (90%) and diarrhea (33%) appear to be more important clinical signs.

Physical Examination Findings

Physical examination findings in cats with acute necrotizing pancreatitis include dehydration (54%), hypothermia (46%), icterus (37%), fever (25%), abdominal pain (19%), and abdominal mass (11%). These findings suggest that a “classic textbook” description of acute pancreatitis (e.g. vomiting, diarrhea, abdominal pain, and fever) is not consistently seen in the domestic cat. Many of these physical examination findings are more commonly reported in canine acute pancreatitis. Abdominal pain (58% in dogs; 19% in cats) and fever (32% in dogs; 25% in cats), for example, are more commonly reported in dogs with acute pancreatitis.
Diagnosis

Laboratory Findings

In cats affected with acute necrotizing pancreatitis, laboratory abnormalities have included: normocytic, normochromic, regenerative or non-regenerative anemia (38%), leukocytosis (46%), leukopenia (15%), hyperbilirubinemia (58%), hypercholesterolemia (72%), hyperglycemia (45%), hypocalcemia (65%), hypoalbuminemia (36%), and elevations in serum alanine aminotransferase (57%) and alkaline phosphatase (49%) activities. Changes in red blood cell counts, serum activities of liver enzymes, and serum concentrations of bilirubin, glucose, and cholesterol are fairly consistent findings in feline acute necrotizing pancreatitis, just as they are in dogs. Important differences between cats and dogs appear to be reflected in white blood cell counts and serum calcium concentrations. Leukocytosis is a more important clinical finding in the dog (62% in dogs; 46% in cats). Leukopenia is sometimes seen instead of leukocytosis in cats, and a worse prognosis has been attributed to leukopenia in the cat. Hypocalcemia also appears to be a more frequent finding in cats (3-5 % in dogs; 45-65% in cats). Hypocalcemia (total and serum ionized) may result from several mechanisms, including acid-base disturbances, peripancreatic fat saponification, and parathormone resistance. Regardless of the mechanism, hypocalcemia appears to confer a worse clinical prognosis in cats. This finding suggests that cats should be monitored fairly closely for the development of hypocalcemia and treatment should be initiated, accordingly.

Special Tests of Pancreatic Function

Lipase and Amylase Activity Assays – Serum lipase activities are elevated in experimental feline pancreatitis, but serum lipase and amylase activities do not appear to be elevated or of clinical value in the diagnosis of clinical pancreatitis. Serum lipase activity may still have some clinical utility in the diagnosis of acute necrotizing pancreatitis in the dog. Assays of serum lipase activity are complicated by the fact that there may be as many as five different isoenzymes circulating in the blood, consequently general serum lipase activity assays have been superseded by the development of pancreatic lipase immunoreactivity assays (e.g., cPLI, fPLI).

Trypsin-like Immunoreactivity (TLI) – Serum TLI mainly measures trypsinogen but also detects trypsin and some trypsin molecules bound to proteinase inhibitors. TLI assays are species-specific, and different assays for feline (fTLI) and canine (cTLI) have been developed and validated. Serum TLI concentration is the diagnostic test of choice for feline exocrine pancreatic insufficiency because it is highly sensitive and specific for this disease in the cat. The use of this test in the diagnosis of feline acute necrotizing pancreatitis is less clear. Serum trypsinogen-like immunoreactivity (TLI) concentrations are transiently elevated in experimental feline acute pancreatitis, but elevations in clinical cases are less consistently seen. The poor sensitivity (i.e., 33%) of this test precludes its use as a definitive assay for feline acute necrotizing pancreatitis.

Pancreatic Lipase Immunoreactivity (PLI) – A radioimmunoassay for the measurement of pancreatic lipase immunoreactivity (fPLI) has been developed and validated in the cat. fPLI elevations have been cited in preliminary reports of experimental and clinical feline acute necrotizing pancreatitis. Multi-institutional prospective clinical studies will be required to determine the true sensitivity and specificity of fPLI in the diagnosis of feline ANP.
**Imaging Findings**

Radiography – The radiographic findings of feline acute necrotizing pancreatitis have not been very well characterized. The radiographic hallmarks of canine acute pancreatitis (e.g. increased density in the right cranial abdominal quadrant, left gastric displacement, right duodenal displacement, and gas-filled duodenum/colon) have not been substantiated in the cat. Indeed, in several recent reports, many of these radiographic findings were not reported in cats with documented acute pancreatic necrosis. In spontaneous clinical cases, hepatomegaly and abdominal effusion appear to be the only radiographic findings associated with feline APN.

Ultrasonography – Enlarged, irregular, and/or hypoechoic pancreas, hyperechogenicity of the peripancreatic mesentery, and peritoneal effusion have been observed with abdominal ultrasonography in many cats with spontaneous acute pancreatitis. The specificity of this imaging modality appears to be high (>85%), but the sensitivity has been reported as low as 35% in some studies. The low sensitivity suggests that imaging the pancreas in cats with pancreatitis is technically more difficult than imaging the pancreas in dogs or that the ultrasonographic appearance of pancreatitis in cats differs from that reported for dogs. New diagnostic criteria may be needed if abdominal ultrasonography is to be a more effective tool in the diagnosis of pancreatitis in cats.

Computed Tomography – CT scanning appears to be useful in identifying the normal structures of the healthy feline pancreas, but preliminary clinical reports have been somewhat disappointing. The sensitivity of CT scanning in detecting lesions consistent with feline acute necrotizing pancreatitis may be as low as 20%. Additional study will be needed to determine the specificity and sensitivity of this imaging modality in the diagnosis of feline acute necrotizing pancreatitis.

**Biopsy**

If clinically indicated, pancreatic biopsy may be obtained by laparoscopy or exploratory laparotomy.

**Therapy**

Supportive care continues to be the mainstay of therapy for feline acute pancreatitis. Efforts should be made to identify and eliminate any inciting agents, sustain blood and plasma volume, correct acid/base, electrolyte, and fluid deficits, place the pancreas in physiologic rest (NPO) for short periods of time, and treat any complications that might develop. Important life-threatening complications of acute pancreatitis in cats include hypocalcemia, disseminated intravascular coagulation, thromboembolism, cardiac arrhythmia, sepsis, acute tubular necrosis, pulmonary edema and pleural effusion.

Historically, a short period of fasting of food and water has been recommended for cats with acute necrotizing pancreatitis. This recommendation should be applied only in those cats in which there is severe vomiting and risk for aspiration pneumonia. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during prolonged starvation. Moreover, recent studies suggest that it may be appropriate and necessary to stimulate pancreatic secretion (via feeding) in affected animals. Esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals.

Other therapies that may be of some benefit in the treatment of this disorder include:
- Relief of pain – Analgesic agents should be used when abdominal pain is suspected. Most cats do not manifest clinical signs of abdominal pain, but clinicians should be suspicious for it. Meperidine at a dose of 1-2 mg/kg administered intramuscularly or subcutaneously every 2-4 hours or butorphanol at a dose of 0.2-0.4 mg/kg administered subcutaneously every 6 hours have been recommended.

• Anti-emetic agents – Nausea and vomiting may be severe in affected animals. The α₂ adrenergic antagonists and 5-HT₃ antagonists appear to be the most effective anti-emetic agents in the cat. Cats may be treated with chlorpromazine (α₂ adrenergic antagonist) at a dose of 0.2-0.4 mg/kg administered subcutaneously or intramuscularly every 8 hours, or with any of the 5-HT₃ antagonists (ondansetron 0.1-1.0 mg/kg, granisetron 0.1-0.5 mg/kg, or dolasetron 0.5-1.0 mg/kg, orally or intravenously every 12-24 hours). Dopaminergic antagonists, e.g., metoclopramide, are less effective anti-emetic agents in the cat. NK₁ antagonists have not yet been studied in feline acute pancreatitis.

• Calcium gluconate supplementation – Hypocalcemia is a frequent complication of feline acute necrotizing pancreatitis and is associated with a worse prognosis. Calcium gluconate should be given at doses of 50-150 mg/kg intravenously over 12-24 hours and serum total or ionized calcium concentrations should be monitored during therapy.

• H₁ and H₂ histamine antagonists – Histamine and bradykinin-induced increases in microvascular permeability are associated with the development of hemorrhagic necrosis in experimental feline pancreatitis. Treatment with H₁ (mepyramine, 10 mg/kg) and H₂ (cimetidine, 5.0 mg/kg) histamine receptor antagonists protects against the development of hemorrhagic pancreatitis in these models. Efficacy has not been established in clinical pancreatitis, but the use of these drugs in suspected or proven clinical cases would seem to make sense since they are associated with few side effects.

• Low dose dopamine infusion – Low dose dopamine infusion (5 μg/kg/min) improves pancreatic blood flow and reduces microvascular permeability in feline experimental pancreatitis. Low dose dopamine infusion is effective treatment in experimental pancreatitis even when it is given up to 12 hours after induction of the disease. Part of the appeal of dopamine as a potential treatment for feline pancreatitis lies in the diversity of its actions. Dopamine’s effect on the kidney in promoting renal blood flow and urinary output, and its cardiac inotropic effect make it an ideal agent, although it has not yet been studied in controlled clinical trials.

• Broad spectrum antibiotics – Acute necrotizing pancreatitis may begin as a sterile process, but necrosis and inflammation predispose to colonic bacterial translocation and colonization of the pancreas. E. coli and other coliforms are the principal pathogens. High colonization rates suggest that bacteria may spread to the inflamed pancreas more frequently than is currently thought, and that broad spectrum antibiotics may be appropriate in suspected cases of feline acute pancreatitis. Cefotaxime at a dose of 50 mg/kg administered intramuscularly every eight hours prevents bacterial colonization of the pancreas.

• Ductal decompression – Surgical decompression of the pancreaticobiliary duct should be considered in cases of acute ductal obstruction, e.g., calculus, neoplasia, and fluke infection. Ductal decompression may also be useful in acute cases that have progressed to the more chronic form of the disease. Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.

Toxic Hepatopathy

Pathogenesis and Etiology – Toxic hepatopathy is a direct injury to hepatocytes or other cells in the liver attributable to therapeutic agents or environmental toxins. Cats are particularly sensitive to phenolic toxicity because of limited hepatic glucuronide transferase activity. The discriminatory eating habits of cats may account for the relatively uncommon occurrence of hepatotoxicity from ingested environmental toxins such as pesticides, household products, and other chemicals. Medical therapies (acetaminophen, acetylsalicylic acid, megestrol, ketoconazole, phenazopyridine, tetracycline, diazepam, griseofulvin) and environmental toxins (pine oil + isopropanol, inorganic arsenicals, thallium, zinc phosphide, white phosphorus, Amanita phalloides, aflatoxin, phenols) may contribute to liver pathology. A severe idiosyncratic hepatotoxicity has been reported with diazepam administration in several groups of cats. Clinical signs in affected cats include anorexia, vomiting, weight loss, ascites, encephalopathy, and death. The histology is characterized by severe central lobular necrosis and mild vacuolation.

Mechanisms of Hepatotoxicity - The liver is an important site of drug toxicity and oxidative stress because of its proximity and relationship to the gastrointestinal tract. Seventy-five to 80% of hepatic blood flow comes directly from the gastrointestinal tract and spleen via the main portal vein. Portal blood flow transports nutrients, bacteria and bacterial antigens, drugs, and xenobiotic agents absorbed from the gut to the liver in more concentrated form. Drug-metabolizing enzymes detoxify many xenobiotics but activate the toxicity of others. Hepatic parenchymal and non-parenchymal cells may all contribute to the pathogenesis of hepatic toxicity. The major mechanisms of hepatotoxicity include: Bile Acid-Induced Hepatocyte Apoptosis, Cytochrome P4502E1-Dependent Toxicity, Peroxynitrite-induced Hepatocyte Toxicity, Adhesion Molecules and Oxidant Stress in Inflammatory Liver Injury, Microvesicular and Nonalcoholic Steatosis.

Diagnosis of Hepatotoxicity – Clinical evidence includes supportive history, normal liver size to mild generalized hepatomegaly, elevated serum liver enzyme activities (predominantly ALT and AST), hypoalbuminemia and hypocholesterolemia, and recovery or death depending upon severity and magnitude of exposure. There are no pathognomonic histologic changes in the liver, although necrosis with minimal inflammation and lipid accumulation are considered classic findings.
**Treatment of Hepatotoxicity** – Few hepatotoxins have specific antidotes, and recovery relies almost exclusively on symptomatic and supportive therapy. If recognized, acetaminophen toxicity may be treated with acetylcysteine (sulphydryl group donor), ranitidine or cimetidine (cytochrome P450 enzyme inhibition), ascorbic acid (anti-oxidant), and androstanol (constitutive androstane receptor [CAR] inhibition).

**Hepatic Lipidosis**

Pathogenesis and Etiology – Feline hepatic lipidosis is now a well-recognized syndrome characterized by intracellular accumulation of lipid with clinicopathologic findings consistent with intrahepatic cholestasis. The precise incidence of the syndrome is unknown but pathology surveys have revealed 5% of animals affected with this lesion. While some cases result from diabetes mellitus, the majority of cases are felt to result from the nutritional and biochemical peculiarities of the cat. It has been suggested, for example, that the cat is not very capable of regulating intermediary metabolism during starvation. Although the biochemistry of this lesion has not been completely worked out, there are several biochemical and nutritional peculiarities that predispose the cat to this syndrome. Some of the known biochemical peculiarities of the cat are: essentiality of dietary arginine; low levels of hepatic ornithine; high dietary protein requirements; lack of hepatic enzymatic adaptation to low dietary levels of protein; relative insufficiency of intestinal pyrroline-5-carboxylate synthase activity; relative insufficiency of intestinal and hepatic glutamate reductase; relative insufficiency of intestinal ornithine transcarbamylase; peculiarities in lipoprotein metabolism; and, differences in orotic acid metabolism.
**Clinical Features** – Most studies suggest that there are no breed, sex, or age predilections. A recent retrospective study by Center and her colleagues suggests that female and middle-age cats are at greater risk for the illness. Obesity may be a predisposing factor, although the syndrome readily develops in fit animals. It has been suggested that obesity followed by a period of anorexia and weight loss are particularly at risk. Cats affected with this syndrome are often presented with a complaint of anorexia, often of several weeks duration. These cats are also commonly presented with jaundice. Other reported clinical signs include vomiting, weakness, weight loss, and diarrhea. Physical examination often reveals dehydration, cachexia, jaundice, and hepatomegaly. All of these findings are also reported in cats with acute pancreatitis and other hepatobiliary disease.

**Diagnosis** – Hyperechoic changes in the hepatic parenchyma at ultraonography have been cited as a pathognomonic finding, but these changes may be seen in other feline hepatic disorders. Diagnosis should be substantiated by aspiration cytology, or better still, tissue biopsy (percutaneous, trans-abdominal ultrasound guidance, laparoscopy, or open laparotomy). Aspiration cytology has weak sensitivity and specificity, and may miss other diagnoses.

**Therapy** – Nutritional support is the cornerstone of therapy of this disorder. Most studies suggest that enteral feeding (by “forced” or encouraged feeding, pharyngostomy, gastrostomy, or enterostomy feeding tube) of commercially available cat foods will effect recovery in 90-95% of affected animals. Biourge and his colleagues have characterized some of the metabolic changes that take place during fasting in obese cats. They have been particularly interested in the effects of protein, lipid, or carbohydrate supplementation on hepatic lipid accumulation during rapid weight loss in obese cats. They found that small amounts of protein administered to obese cats during fasting significantly reduced accumulation of lipids in the liver, prevented increases in alkaline phosphatase activity, eliminated negative nitrogen balance, and appeared to minimize muscle catabolism. Carbohydrate supplementation reduced hepatic lipid accumulation, but metabolic abnormalities still developed. Lipid supplementation alone did not ameliorate hepatic lipidosis and even resulted in more severe lipid accumulation than under conditions of fasting alone. The use of benzodiazepine agonists (e.g., diazepam, oxazepam, elfazepam) and 5-HT\_2 agonists (e.g., cyproheptadine) as appetite stimulants has been encouraged in anorexic cats. These compounds particularly the benzodiazepine agonists, should be used with caution as they may exacerbate pre-existing hepatic encephalopathy. Benzodiazepine agonists have been shown to worsen hepatoencephalopathy in other animal species through activation of the neuronal benzodiazepine/GABA receptor-chloride channel complex.

**Feline Cholangitis**

**Pathogenesis and Etiology** – This syndrome has been classified in three different ways:

University of Minnesota Classification (Doug Weisse; 1996) – Lymphocytic portal hepatitis and suppurative cholangitis. This classification system implies that there are two different inflammatory conditions involving the feline liver: inflammatory liver disease (lymphocytic portal hepatitis) and inflammatory biliary tract disease (suppurative cholangitis). Limitations of this classification system – It fails to recognize that acute (i.e., suppurative) cholangitis can
progress to more chronic forms (i.e., lymphocytic) of the disease. This system also implies that there is suppuration, which, in fact, is rarely seen. Neutrophilic infiltrates do occur, but rarely does it progress to suppuration. Finally, it’s not entirely clear whether lymphocytic portal hepatitis is a distinct clinical entity or just a histologic lesion.

WSAVA International Liver Standardization Group Classification (Multi-Institutional Group; 2002) – Neutrophilic cholangitis, lymphocytic cholangitis, lymphocytic portal hepatitis. This classification system implies that there are acute (neutrophilic) and chronic (lymphocytic) forms of cholangitis, and that there may be a separate form of portal hepatitis in cats. Limitations of this classification system – We still don’t know if lymphocytic portal hepatitis is a disease or a histologic lesion.

Neutrophilic cholangitis – This disorder has been seen primarily in young to middle-aged male cats with clinical signs of acute vomiting, diarrhea, anorexia, and lethargy. Physical examination findings often reveal fever, icterus, abdominal pain, and hepatomegaly (<50% of cases). Laboratory findings frequently reveal mild to moderate leukocytosis with mild to moderate elevations in ALT, AST, GGT, and ALP. Based on recent studies, cats affected with this form of cholangitis often have related disease, e.g., pancreatitis and inflammatory bowel disease. The diagnosis of suppurative cholangiohepatitis is achieved by serum liver enzymology; ultrasonographic characterization of the liver parenchyma; culture - bile, gallbladder, cholelith, liver; Gram staining; and, biopsy of the liver and/or extrahepatic biliary system. Common bacterial isolates in affected cases include E. coli, Clostridia, Bacteroides, Actinomyces, α-Strep. The treatment of this syndrome has included appropriate antibiotic based on culture and sensitivity, cholelith removal where appropriate, bile duct decompression if necessary, fluid and electrolyte maintenance, and ursodeoxycholate therapy (10-15 mg/kg P.O. SID).

Lymphocytic cholangitis – Chronic lymphocytic cholangitis is characterized by a mixed inflammatory response (equal numbers of lymphocytes or plasma cells and neutrophils) within portal areas and bile ducts. Other features of chronicity include marked bile duct proliferation, bridging fibrosis, and pseudolobule formation. Chronic cholangiohepatitis may progress to progressive biliary cirrhosis and the death of the patient. Lymphocytic cholangitis may represent a persistent bacterial infection or an immune-mediated response may result in a chronic self-perpetuating disorder. Clinical signs are usually of a chronic, intermittent or persistent nature. With chronic cholangiohepatitis, a long-standing history over a period of weeks or months is more likely. Vomiting, icterus, hepatomegaly and ascites are common findings. Hepatic encephalopathy and excessive bleeding are uncommon unless severe end-stage liver disease is present. The best treatments for this syndrome are not clearly understood. It has been suggested that many cats require multi-component therapy, e.g., glucocorticoids - 1-2 mg/kg PO SID; metronidazole - 7.5 mg/kg PO BID; ursodeoxycholate 10-15 mg/kg PO SID; vitamin K₁ - 1.5-5 mg Q 2-3 weeks; dietary manipulation for presumed I.B.D.; and, immune modulation with azathioprine or chlorambucil.

Lymphocytic portal hepatitis – A retrospective review of liver biopsies of cats with inflammatory liver disease identified a subset of cats with lymphocytic portal infiltrates which had histopathologic features distinct from cats with acute or chronic cholangitis. The term lymphocytic portal hepatitis has been proposed for this disorder. As opposed to findings in cholangitis, there is a lack of
neutrophilic inflammation, bile duct involvement, infiltration of inflammatory cells into hepatic parenchyma, or periportal necrosis. Lymphocytic portal hepatitis is not associated with inflammatory bowel disease or pancreatitis. Previous reports of progressive lymphocytic cholangitis or lymphocytic cholangitis referred to varying degrees of neutrophilic inflammation and the condition may actually have been a chronic form of cholangitis. Lymphocytic portal hepatitis is a common finding in liver biopsies of older cats, suggesting that it is a common aging change or that a sub-clinical form of disease is prevalent. Lymphocytic portal hepatitis appears to progress slowly with varying degrees of portal fibrosis and bile duct proliferation but no pseudolobule formation. Concurrent hepatic lipidosis is less likely than with cholangitis.

**Hepatic Neoplasia**

**Pathogenesis and Etiology** – Primary neoplasms of the feline liver are uncommon. Cholangiocellular carcinoma and hepatocellular carcinoma are the most important of the primary feline liver neoplasms, but they are of very low incidence and therefore minor importance. Metastatic liver neoplasia are much more important in cats. The most common metastatic tumors to the liver are lymphoma, systemic mast cell disease, hemangiosarcoma, and myeloproliferative disorders.

**Clinical Features** – Clinical signs are fairly non-specific, but may be similar to clinical signs reported in cats with other liver disorders, for example: lethargy, anorexia, weight loss, and intermittent vomiting. Abdominal effusion, jaundice, and encephalopathy may be seen terminally.

**Diagnosis** – Laboratory data are also usually non-specific. Elevations in serum liver enzyme activities and abnormalities in bile salt metabolism should be obvious, but they are not remarkably different from cats with other liver disorders. Imaging studies (radiography, ultrasonography) may provide evidence of diffuse hepatomegaly or of discrete tumors involving one or more liver lobes. Definitive diagnosis always requires aspiration cytology, or better yet, tissue biopsy. Aspirates and/or tissue biopsies may be obtained by percutaneous trans-abdominal ultrasound guidance, laparoscopy, or laparotomy techniques.

**Therapy** – The cell of origin of a metastatic tumor should always be identified, if possible. Chemo- or other therapies may then be selected based on a working knowledge of the biologic basis of the tumor. Focal tumors of the liver may be best managed by hepatic lobe resection.

**Extra-Hepatic Bile Duct Obstruction**

**Pathogenesis and Etiology** – Extra-hepatic cholangitis, malignancy, pancreatitis, cholelithiasis, and liver flukes (*Eurytrema procyonis, Platynosomum concinnum*) are the major causes of extra-hepatic biliary obstruction in cats. Progressive cholangitis accounts for over 50% of the cases of hepatic duct obstruction, common bile duct obstruction, and progressive hepatobiliary failure.
Clinical Features – Affected cats have marked persistent hyperbilirubinemia, and marked elevations in serum ALT, AST, ALP, GGT, and serum bile acids. Ultrasonographic evidence of obstruction is obvious, and many cats undergo exploratory laparotomy and biliary decompression.

Diagnosis – As with other feline hepatobiliary disorders, diagnosis of extra-hepatic bile duct obstruction requires careful integration of history, physical examination, laboratory data, and imaging findings.

Prognosis and Therapy – The prognosis for cats with extra-hepatic biliary obstruction, regardless of underlying pathogenesis is guarded to poor, and perioperative morbidity and mortality is high. The majority of cats have a prolonged disease course, and long-term complications include recurring bouts of cholangitis, weight loss, and biliary tract obstruction.

Congenital Portosystemic Shunts

Pathogenesis and Etiology – Diversion of portal blood flow to the central circulation depletes the liver of nutrients, hormones, and growth factors. Portosystemic shunts in cats are generally extra-hepatic and most arise from the left gastric vein. Portosystemic shunting results in poor hepatocyte growth and function, and the liver undergoes progressive atrophy.

Clinical Features and Diagnosis – Affected cats appear stunted, fail to grow, and have excessive salivation perhaps as an early manifestation of hepatoencephalopathy. Cats may manifest other behavioral and neurologic abnormalities such as seizures, dementia, visual disturbances, and ataxia. Onset of clinical signs with feeding and delayed recovery from anesthetic events are reported more frequently with canine portosystemic shunts. Affected cats may have only subtle laboratory abnormalities (mild increases in ALT & AST; mild hypoalbuminemia and hypocholesterolemia; low blood urea nitrogen; and microcytosis). Diagnosis is best achieved by coupling a liver function test (bile salts and/or NH$_3$ quantitations) to a liver imaging technique, e.g., ultrasonography, scintigraphy, or contrast portal venography. Liver biopsy typically reveals portal venous hypoplasia, arterial smooth muscle hypertrophy, hepatocellular atrophy with lipogranulomas, and sometimes periportal sinusoidal dilatation.

Prognosis and Therapy – The prognosis is generally good if recognized early in the course of the disease. Cats are best managed with surgical attenuation or ligation of the shunting vessel. Some cats, especially those with incomplete attenuation of the shunt, may still require medical therapy following surgical repair.

References – Available upon request.
The initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell. Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become co-localized along with lysosomal hydrolases in large vacuoles. Cell biology studies have revealed that lysosomal and zymogen granule fractions become co-localized through a process known as crinophagy, a process used by many cells to degrade accumulated secretory products when the need for secretion is no longer present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and N-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm. Trypsin acts auto-catalytically to activate other trypsigen molecules and other zymogens, each inducing a unique chemical pathology in pancreatic and extra-pancreatic cells. A variety of inflammatory mediators and cytokines (tumor necrosis factor-α, interferon-α, interferon-γ, platelet-activating factor), interleukins (IL-1, IL-2, IL-6, IL-8, IL-10), nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation.

New Findings in Canine Acute Pancreatitis

Canine acute pancreatitis (AP) is a common disorder which may result in death if not diagnosed in a timely fashion. This frequently encountered disease remains difficult to diagnose because the clinical signs, physical examination findings, and clinicopathologic changes are often non-specific. Therefore, knowledge of risk factors of canine AP and recognition of the clinical manifestations of this disorder are important.

The risk factors discussed in this manuscript were identified in a group of dogs in which all dogs had histopathologic confirmation of AP. The control group included dogs in which histopathologic examination excluded the possibility of AP. Clinicopathologic, radiographic, and ultrasonographic findings also pertain to dogs in which a diagnosis of AP was confirmed by histopathologic examination of the pancreas.
Risk factors for canine acute pancreatitis:

Breed

Yorkshire terriers are at increased risk of developing AP, whereas miniature poodles and Labrador retrievers are at decreased risk for AP. Breed predisposition may suggest that there is a hereditary component to AP. Hereditary pancreatitis in humans can occur in association with a genetic defect of lipoprotein lipase, in individuals with hypertriglyceridemia and diabetes mellitus, or as an autosomal dominant trait, of unknown etiology, with a chronic recurrent presentation, and an early onset (usually in childhood). Further investigation is needed to determine if familial lipid metabolism disorders, or other genetic defects, predispose Yorkshire terriers to AP.

Age

The mean age of dogs with AP is 8 years. Dogs with AP may be middle to older age dogs because several of the risk factors for AP (diabetes mellitus, hyperadrenocorticism, and hypothyroidism) develop in middle to older aged dogs. Obesity, which is another risk factor for AP may also be a problem of middle-aged dogs. Additionally, the increased age of dogs with AP could be a reflection of a degenerative pancreatic or extrapancreatic process, or a result of accumulating metabolic disorders that increase the risk of AP.

Sex

Males and neutered females are at increased risk compared to intact female dogs. This finding may indicate that sex hormones or other gender specific factors are involved in the pathophysiology of AP.

Overweight body condition

Overweight and obese dogs are at an increased risk of developing AP. Increased body mass index (kg/m$^2$) has been reported to be a risk factor and a poor prognostic indicator in humans. Increased retroperitoneal and peripancreatic fat deposition is thought to increase the risk of peripancreatic fat necrosis in humans.

Diabetes mellitus, hyperadrenocorticism, and hypothyroidism

Diabetes mellitus, hyperadrenocorticism, and hypothyroidism are all associated with increased risk for AP. It is possible that lipid metabolism disorders are responsible for the increased risk. Hypertriglyceridemia is a risk factor in humans and is seen in dogs with diabetes mellitus, hyperadrenocorticism, and hypothyroidism. Hypertriglyceridemia has been reported in association with naturally occurring canine AP. Experimentally induced hypertriglyceridemia initiates pancreatic injury but does not seem to be a consequence of experimentally induced pancreatitis in the dog. These findings would support a hypothesis of hypertriglyceridemia being a risk factor, rather than a consequence of canine AP. However, many other metabolic abnormalities associated with endocrinopathies could be involved.
Prior gastrointestinal disease

Prior gastrointestinal disease (colitis, gastrointestinal parasites, hiatal hernia, or inflammatory bowel disease) is a risk factor for canine AP. Chronic inflammation of the gastrointestinal tract, e.g. proximal duodenum and transverse colon, may increase local inflammation and predispose to AP.

Epilepsy

Epilepsy is a risk factor for canine AP. The reason for this association is not known, however, it may be due to anticonvulsant therapy or pancreatic ischemia during seizure activity.

Possible risk factors for canine acute pancreatitis

Thromboembolic disease

Thromboembolism was observed more commonly in dogs with AP compared to control dogs. However, thromboembolism may develop as a result of AP and is not necessarily a risk factor for AP. It is possible that proteolytic enzymes released from the pancreas cause endothelial damage which results in infarct and thrombus formation. On the other hand, it is conceivable that an underlying coagulopathy, such as that associated with hyperadrenocorticism, causes infarct and thrombus formation, impairs pancreatic blood flow, and results in AP.

Atherosclerosis

Atherosclerosis was more common in dogs with AP compared to control dogs. Hypothyroid dogs are predisposed to atherosclerosis; however, atherosclerosis was also observed in a dog that had no evidence of hypothyroidism on post mortem examination. In humans, hypertriglyceridemia is a risk factor for pancreatitis, but its role in atherosclerosis remains controversial. Hypertriglyceridemia may be a risk factor for both AP and atherosclerosis in the dog.

Administration of trimethoprim/sulfa antibiotics

Dogs with AP receive significantly more trimethoprim/sulfa than other dogs. This finding may reflect the severity of the disease and not necessarily a risk factor. Sulfonamides have been reported as a risk factor in humans, and in some of the human patients the association was confirmed with re-challenge. Hypersensitivity reaction or toxic effects are suspected. Although trimethoprim/sulfa administration has not been reported as a risk factor for AP in dogs, other adverse reactions have been documented, and some were suspected of being immune-mediated.
Factors that may not be risk factors for canine acute pancreatitis:

Steroids

Dogs with and without AP receive a variety of glucocorticoids administered at different doses and frequencies, prior to referral. However, dogs with AP do not receive significantly more glucocorticoids than other dogs. Therefore, in the wide range of inconsistent clinical use of steroids, steroid administration prior to referral does not appear to increase the risk of AP in dogs. These clinical findings agree with experimental evidence that shows that glucocorticoid administration does not cause AP in the dog.\(^7,^8\)

Some clinicopathologic abnormalities associated with canine acute pancreatitis:

Hypercalcemia or hypocalcemia

Hypercalcemia occurs in about 15% of dogs with AP. Hypercalcemia is a risk factor for human AP, and acute but not chronic hypercalcemia has been shown to experimentally induce AP in cats.\(^9,^{10},^{11}\) Calcium is thought to facilitate the activation of trypsinogen, and increase the stability and activity of trypsin, thereby increasing the activation of other pancreatic digestive enzymes. Additionally, calcium is thought to cause pancreatic hypersecretion by increasing cholecystokinin release. Hypocalcemia has also been reported in dogs with AP.

Hypoglycemia or hyperglycemia

Serum glucose concentrations may vary considerably in dogs with AP. Hypoglycemia may be due to, sepsis, concurrent liver disease, differences in breed-related metabolism, or insulin treatment of diabetic dogs that have anorexia or vomiting. Hyperglycemia has been reported in dogs with spontaneous AP with and without diabetes mellitus, and in dogs with experimentally induced AP with and without permanent diabetes mellitus. In experimental dog models of concurrent diabetes mellitus and AP, dogs with both diseases had decreased glucose tolerance and prolonged hyperglycemia when compared to dogs with diabetes mellitus alone.\(^12\)

Amylase and lipase activity

Serum amylase activity was increased in 69% of dogs however, serum lipase activity was increased in less than 40% of dogs with AP. Therefore, serum amylase and lipase elevations are not a consistent finding in canine AP. Since elevations in serum amylase and lipase activities are also not specific for AP it is concluded that the diagnostic value of these tests is limited.

Coagulopathies

Evidence of bleeding such as petechiation, ecchymosis, epistaxis, bruising, or a hematoma, is observed in 11% of dogs with AP. Thrombocytopenia has been documented in up to 59% of dogs with AP. Additionally, prolonged partial thromboplastin time (PTT) and prothrombin time (PT) were noted in 61% and 43% of the dogs in which they were measured, respectively. These clinical abnormalities are in agreement with evidence of thrombocytopenia and coagulopathies.
associated with experimental canine AP. In experimental canine AP, a decrease in platelets, complement, and antithrombin III was observed along with an increase in fibrinogen and plasminogen, and prolongations in PTT and PT. It is possible that complement catabolism by pancreatic proteolytic enzymes causes a consumptive coagulopathy. In human patients with spontaneous AP, increased degradation of von Willebrand’s factor, as well as activation of the kallikrein-kinin system have been documented. It is possible that bleeding abnormalities contribute to the fatal outcome of some dogs with AP. Coagulation testing is therefore recommended in all dogs suspected of having AP. Prompt diagnosis and appropriate treatment of bleeding disorders may improve the prognosis of dogs with AP.

Lipemia

Gross lipemia was observed in 26% of dogs with AP, and cholesterol concentration was elevated in 48% of dogs. Lipemia and hypercholesterolemia may be the result of concurrent endocrinopathies. Obesity or overweight body condition is also associated with abnormal lipid metabolism. Lipoprotein profiles found in obese dogs are similar to those found in dogs with experimentally induced AP. Hypertriglyceridemia is a risk factor for AP in humans, and is associated with AP in dogs, however, the causality of this association is not yet defined.

Abdominal radiographic and ultrasonographic abnormalities in canine acute pancreatitis:

Abdominal ultrasonographic abnormalities are consistent with a diagnosis of AP more frequently than abdominal radiographic abnormalities. However, in some cases, abdominal ultrasonographic abnormalities are not apparent, while abdominal radiographs are suggestive of AP. Therefore, it is recommended that both imaging studies should be performed when faced with a suspected case of AP. Additionally, abdominal radiographs are a valuable diagnostic tool in any case of suspected AP because other causes of gastrointestinal disease must be ruled out. Abdominal radiographs are not suggestive of AP in 76% of dogs with histopathologic confirmation of AP. Therefore, in dogs suspected of having AP, abdominal ultrasonography should be performed even if abdominal radiographs are not suggestive of AP.

References


