GI-Lymphoma And IBD In Cats: Pitfalls And Progress In Diagnosis And Management

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Feline lymphoma in general

Lymphoma in the cat represents a diverse group of lesions that vary in cell type, rate of dissemination, and progression. The National Cancer Institute (NCI) Working Formulation (WF) has been used to histologically classify feline lymphomas into low, intermediate, and high-grade categories. The majority of lymphoma in cats has been classified as intermediate (35%) or high (54%) grade and behaves similarly as rapidly progressive diseases that are almost uniformly fatal despite aggressive chemotherapy. Approximately 10% of feline lymphomas are composed of small, relatively well-differentiated, neoplastic lymphoid cells and can be histomorphologically described as low-grade. A recent study describing clinical spectrum of lymphoma since the decline in Feline Leukemia Virus indicates that there has been a progressive rise in the diagnosis of alimentary lymphoma in cats.

The emergence of low grade T-cell alimentary lymphoma

Gastrointestinal lymphoma is typically characterized by the mucosal and sub-mucosal infiltration of neoplastic lymphocytes that may lead to ulceration, perforation and malabsorption. Focal forms of lymphoma may cause obstruction. While lymphoma has often been related to feline leukemia virus cats with GI lymphoma are usually FeLV negative. Concurrent involvement of the GI tract and the kidney, liver, pancreas or spleen may be observed. In cats GI lymphoma has been classified histologically as B, T and LGL in origin. The relative frequency of each type appears to vary according to geographical location and perhaps the time the study was performed (e.g. before or after the decline in FelV). Studies in Australia and UK report predominantly medium to High grade B cell lymphoma. In contrast recent studies in the US report the predominance of low grade T cell lymphoma, and have presented a simplified approach to categorizing GI lymphoma as lymphocytic (Low grade T cell) or lymphoblastic (generally B cell). This has meaningful clinical application as the low- grade lymphocytic form usually responds very well to chemotherapy.

Clinical findings: Middle aged and older cats, predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive inappettance are common features of GI lymphoma. Physical examination may reveal diffusely thickened or nodular intestines ± mesenteric lymphadenopathy. Hepatosplenomegaly, renomegaly, generalized lymphadenopathy and abdominal mass may also be detected. Acute abdominal pain and shock may be present if intestinal perforation has occurred.

Diagnosis: Routine biochemistry may reveal hypoalbuminemia. Anemia which is either normocytic normochromic non-regenerative or microcytic and hypochromic, and neutrophilia may also be present. Serum concentrations of cobalamin are often very low in cats with GI lymphoma and serum folate concentrations may also be reduced. High TLI or PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates or biopsies from enlarged intestinal or peripheral lymph nodes, but is more often made by intestinal biopsy. Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy and circumvent the endoscopy surgery debate.

Treatment and prognosis:

In a recent study of 41 cats with low-grade lymphoma, lymphoma was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems affected with or without gastrointestinal involvement. Extra-gastrointestinal sites involved included mesenteric lymph nodes (n = 6), liver (n = 10), spleen (n = 1), and pancreas (n = 1). Some cats had more than 1 site affected. Eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, while 8% (3 of 36) were of B-cell origin.

Fifty-five per cent of cats achieved a complete response to therapy and 37% achieved a partial response. The majority of cats (n = 31; 76%) received prednisone at a dose of 5 mg, PO, q 12-24 hrs and most (n = 35; 85%) received chlorambucil at a dose of 2 mg, PO, every other day. Eight percent of the cats experienced no response. There was no association between any risk factors and response to therapy. Overall median remission duration was 948 days. Partial response to therapy was associated with shorter remission duration (P = 0.002). Overall median survival time was 704 days. No factors were significantly associated with survival time. Interestingly, 78% of cats tested in this study had hypocobalaminemia, which was associated with short remission duration, but only in the univariable analysis. Thus

supplemental cobalamin (0.5ml SC q 2-3wks) and folate should be given as required. Lymphoblastic lymphoma, is much more aggressive than lymphocytic lymphoma, is generally treated with combination chemotherapy, and carries a poor prognosis.

Given the dramatic differences in outcome of lymphocytic vs. lymphoblastic lymphoma is there any way to distinguish these forms of the disease without a biopsy?
In the study of Fondacaro et al clinical signs, physical exam findings and endoscopic localization of disease overlapped in cats with lymphoblastic and lymphocytic lymphoma. Lethargy and the presence of an abdominal mass tended to be more frequent in cats with lymphoblastic lymphoma.

Can I diagnose intestinal lymphoma with an endoscopic biopsy?
Yes and No! Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can miss submucosal and serosal lesions or yield a diagnosis of "lymphoplasmacytic enteritis". Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy circumventing the endoscopy surgery debacle. Diagnosis also depends on the pathologist! Some pathologists are unwilling to diagnose lymphoma on endoscopic biopsies.

How can I distinguish gastrointestinal lymphoma from inflammatory bowel disease?
The signalment, clinical presentation, physical examination and results of clinical investigation are often very similar in cats with IBD and alimentary lymphoma. Hypoalbuminemia is a rare feature of IBD in cats and it's presence makes me think of high grade IBD or lymphoma. Intestinal perforation should place lymphoma high up the list. Concurrent renomegaly or splenomegaly should also prompt consideration of lymphoma and aspiration/biopsy. The presence of intestinal thickening and mesenteric lymphadenpoathy suggests lymphoma but is by no means pathognomonic. Moreover, fine needle aspiration of enlarged lymph nodes can yield reactive hyperplasia in cats with GI lymphoma. Endoscopy may reveal marked thickening of the gastric mucosa and increased friability of the intestinal mucosa in cats with lymphoma, but there is an overlap between cats with IBD and alimentary lymphoma. At the present time the accurate distinction of GI lymphoma from IBD relies on histopathological evaluation. This can be relatively straightforward where biopsies are considered adequate in size and number, and unequivocal lymphoblastic cells or a monomorphic population of small lymphocytes are present. However, some biopsies display features of lymphoma and IBD, and others such as endoscopic biopsies do not allow thorough evaluation of all tissue compartments, and make it difficult to distinguish IBD from lymphoma. Immunophenotyping for T and B cell lineage, and PCR to detect clonal expansion of B (feline immunoglobulin heavy chain variable region genes) and T cells (T cell receptor gamma variable region genes) have been developed to aid this process.

What causes low-grade small cell lymphoma?
Low-grade alimentary lymphoma in cats does not appear to be related to FelV or FIV. There is strong evidence in people that low grade mucosa associated lymphomas develop as a consequence of a genetic predisposition (typically chromosomal translocations that impact mucosal inflammation or apoptosis) and a chronic infectious stimulus such as *Helicobacter pylori* (gastric MALT). Intratumoral T cells responding to *Helicobacter* antigens are believed to drive the proliferation of B cells, and eradication of *Helicobacter* in early gastric MALT can be curative. Recent studies have shown that chromosomal translocations in pathways that regulate nuclear factor kB signaling e.g. t(11;18)(q21;q21) which leads to generation of an API2-MALT-1 fusion protein capable of activating nuclear factor kB, are significant risk factors for the development of MALT in *Helicobacter* infected people. Thus it is plausible that low-grade lymphoma in cats is the result of a chronic infectious or inflammatory stimulus in a genetically predisposed individual.

These observations with respect to MALT lymphoma are very much in step with current think in IBD. IBD in people is thought to arise as a consequence of an overaggressive immune response to a subset of the enteric flora in genetically susceptible individuals. The best-characterized genetic defects in people with IBD involve the innate immune system and its interactions with the enteric microflora. e.g. NOD2. A recent study in cats with IBD has shown that the number of mucosa-associated *Enterobacteriaceae* is higher in cats with signs of gastrointestinal disease than healthy cats. Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture and the density of cellular infiltrates, particularly macrophages. *Enterobacteriaceae* spp, *E. Coli*, and *Clostridium* spp. were associated with significant changes in mucosal architecture (principally atrophy and fusion), upregulation of cytokines (particularly IL-8), and the number of clinical signs exhibited by the affected cats. It is possible that this abnormal mucosal environment associated with IBD in cats may stimulate transformation of T cells and the progression to low grade lymphoma.

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MANAGING PERSISTENT VOMITING

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The clinical importance of vomiting stems from its association with a large and varied group of diseases and the potentially life threatening consequences of vomiting per se (e.g. aspiration pneumonia and fluid and electrolyte depletion). Patient management is directed at detecting and treating the cause and consequences of vomiting. Where the cause is undetermined it is necessary to adopt a rational approach to controlling emesis.

Initiation of vomiting

Vomiting is a reflex act initiated by stimulating the vomiting center in the medulla (1,2). The vomiting center can be stimulated directly, or indirectly via the chemoreceptor trigger zone (CRTZ) situated in the area postrema where the blood brain barrier is accessible to blood borne substances such as toxins or drugs. Neurological input from the vestibular nucleus can also stimulate the CRTZ (dog) or the vomiting center. Disease or irritation of the gastrointestinal tract, abdominal organs or peritoneum and cerebral diseases can directly stimulate the vomiting center via visceral receptors and vagal afferents. Once the vomiting center is adequately stimulated a set of visceral events is initiated - these include the sequential inhibition of proximal gastrointestinal motility, a retrograde power contraction in the small intestine and antral relaxation that enables transfer of intestinal contents to the stomach. These events are followed by moderate amplitude contractions in antrum and intestine and shortening of the intra abdominal esophagus. Dilatation of the cardia and lower esophageal sphincter enables transfer of gastric contents to the esophagus during retching and vomiting. Retching often precedes vomiting and is characterized by rhythmic inspiratory movements against a closed glottis. Negative intrathoracic pressure during retching prevents expulsion of esophageal contents. During vomiting the abdominal muscles contract and the intrathoracic and intrabdominal pressures are positive which results in the forceful expulsion of gastric contents from the mouth.

Causes of Vomiting

There are so many potential causes of vomiting that it is often easiest to think in broad terms initially i.e. gastric, intestinal, intra-abdominal non-GIT, metabolic-endocrine, drugs, toxins, dietary, neurologic, infectious diseases and consider more specific causes when vomiting is localized to one of these groups (Table 1).

Patient evaluation and diagnostic approach

The initial plan for vomiting animals is to separate those whose problems are acute and self-limiting from those in need of more thorough investigation and treatment. If vomiting is acute and the animal is systemically well, in-depth diagnostic testing is usually not warranted as vomiting frequently resolves on its own or after short-term symptomatic therapy.

If the animal is systemically unwell, has been vomiting for more than a week, or has vomiting associated with hematemesis, bloody diarrhea or abdominal pain a more aggressive work-up is necessary to define the nature of the problem.

Most non-gastrointestinal causes of vomiting, and gastrointestinal causes such as a foreign body or intussusception, are usually detected, or ruled out, by taking a detailed history, performing a thorough physical examination, routine laboratory tests (e.g. CBC, profile, UA, fecal, with evalauation of amylase/lipase/PLI, T_4, FelV, FIV, ACTH stim. where indicated) and abdominal radiographs. Abdominal ultrasound is useful for detecting pancreatic, hepatic and splenic lesions, GI thickening (focal or diffuse) and sampling masses and parenchymal abnormalities. If these tests are negative or show abnormalities compatible with primary gastric or diffuse intestinal disease, endoscopic examination of the stomach and upper duodenum or contrast radiography are the principal diagnostic options. Endoscopy enables detailed examination and sampling of the gastric and duodenal mucosa with minimal patient discomfort and is generally accepted as the best method of evaluating mucosal abnormalities. Radiographic contrast studies (± fluoroscopy) are generally restricted to examining functional (emptying) disorders of the stomach and the anatomy and patency of the intestinal tract distal to the duodenum. Patients with evidence of focal intestinal disease or concurrent involvement of multiple organs (e.g. liver, pancreas, intestine in cats with triaditis) are often best evaluated surgically.

Overview of therapy for vomiting

Patient management should be aimed at detecting, and treating the cause and consequences of vomiting. Parenteral fluid therapy (usually IV) should be tailored to correct volume depletion, and electrolyte and acid base abnormalities. Dietary alteration in patients with acute vomiting is traditionally NPO for 24-48hrs followed by a transition to a bland, carbohydrate rich diet (to facilitate gastric emptying) when vomiting decreases. However, this notion has been challenged by the results of early enteral nutrition in dogs with parvovirus enteropathy, where feeding was associated with decreased duration of hospitalization and reduced intestinal permeability (3). Modified diets may be useful in patients with delayed gastric emptying, or chronic gastroenteropathies associated with food intolerance. Gastric protectants (e.g. sucralfate) can be used to bind toxins and protect the GI mucosa where vomiting is associated with gastritis or gastric ulceration. Inhibitors of

gastric acid secretion (usually H_2 antagonists) are used to limit gastric erosion/ulceration in patients with gastritis / ulceration and those considered at risk of developing GI ulceration (e.g. shock) or esophagitis. Inhibition of gastric acid may also limit the hypochloremia and alkalosis associated with gastric outflow obstruction. Mucosal cytoprotection with PGE analogs may be beneficial where persistent vomiting is associated with NSAID administration. Analgesics may decrease vomiting associated with acute abdominal conditions e.g. buprenorphine for pancreatitis. Antiemetics are indicated in patients with vomiting that is compromising hydration status, affecting electrolyte and acid base balance, and those at high risk for esophagitis or aspiration pneumonia, and those distressed by repeated vomiting. Antibiotics are usually limited to suspected infections, acute abdominal conditions or gastritis associated with Helicobacter infection. Prokinetic agents are used to promote gastric and intestinal motility in patients with a patent GI tract. Surgery is indicated to remove large foreign bodies, treat some causes of pyloric outflow obstruction, and to obtain biopsies of the GI tract and concurrently diseased organs.

Pharmacological control of vomiting

The pharmacological control of vomiting involves antagonizing central and peripheral receptors that regulate emesis and stimulating receptors promoting ordered gastrointestinal motility (1,2,4). The receptor subtypes involved in vomiting and examples of drugs that are commonly used in the management of vomiting are summarised in Figure 1.

Some antiemetics have more than one mechanism of action e.g. Phenothiazines (e.g. chlorpromazine) are antagonists of a1 and a_2 adrenergic, H_1- and H_2-histaminergic and D_2-dopaminergic receptors; Metoclopramide antagonizes D_2-dopaminergic and $5HT_3$-serotonergic receptors and has cholinergic effects on smooth muscle.

Antiemetics are generally contraindicated in patients with gastrointestinal toxicity where they may limit expulsion of the toxic agent. Antiemtics can effectively mask signs of serious underlying disease hence a clinical response to antiemetics should not preclude a search for the underlying cause of vomiting. Non-selective cholinergic receptor antagonists (other than the M_1 specific antagonist- pirenzipine) e.g. atropine, scopolamine, aminopentamide, isopropamide, may cause ileus, delayed gastric emptying and dry mouth. It is recommended that phenothiazines and the NK_1 antagonist maropitant are not given to hypotensive patients. Phenothiazines may also cause unwanted sedation and decrease the seizure threshold in animals with epilepsy. Maropitant is metabolized by the liver and is heavily protein bound, hence careful monitoring is suggested in patients with liver disease and hypoproteinemia, and maropiatant should not be used for more than 5 consecutive days. Maropitant can prolong the Q-T interval and is contraindicated in dogs with bradycardia. Antiemetics with prokinetic activity, such as metoclopramide, are contraindicated where there is a suspicion of intestinal obstruction.

The animal species, and age may also impact selection of antiemetic. Certain antiemetics are not recommended / require caution / are ineffective when used in the cat e.g. the cat is resistant to apomorphine induced vomiting suggesting the D_2-dopaminergic metoclopramide may have less activity than a_2 adrenergic antagonists (1,4). Maropitant is currently not licensed for use in dogs <16 wks of age due to dose dependent bone marrow hypoplasia.

Despite the high frequency of antiemetic use in veterinary practice there is a paucity of controlled studies of their efficacy in dogs and cats.

The comparative efficacy of commonly used antiemetics against vomiting induced by apomorphine (central stimulus) and ipecac (peripheral stimulus) in laboratory dogs indicates that maropitant, chlorpromazine, and metoclopramide have similar activity against apomorphine induced emesis (all had greater activity than ondansetron), and that ondansetron and maropitant have equal activity against ipecac (both had greater activity than metoclopramide and chlorpromazine) (5). Two recent clinical trials, one in Europe, the other in the USA have focused on maropitant. In the US study of 275 dog, 50% of dogs treated with placebo (32/64) versus 22% (41/188) treated with maropitant vomited at some point after treatment (6). In the European study vomiting was controlled in 97% of dogs receiving maropitant vs. 71% of those receiving intermittent metoclopramide (0.5-1mg/kg /day over 3 doses) (7).

Strategies for managing persistent vomiting

Uremia

Vomiting in uremia is mediated via the effects of uremic toxins on the CRTZ and afferent inputs from the inflamed stomach. Control of vomiting is focused on ameliorating uremia with fluid therapy, antagonizing the effects of uremic toxins on the CRTZ and limiting potential afferent input from the GI tract e.g. uremic / hypergastrinemic gastritis. In dogs, CRTZ stimulation can be reduced by administering a D_2-dopaminergic antagonist such as metoclopramide (0.2-0.4mg/kg SC. IM, PO QID or 1mg/kg/24hrs continuous IV infusion) or maropitant (1mg/kg SC/24hrs for no more than 5d). The peripheral effects are usually addressed with an H_2 antagonist (e.g. famotidine 0.5-1.0mg/kg SID-BID) and mucosal protectant (sucralfate 0.25-1g PO TID), though a recent study has questioned the uremic ulcers (8) Metoclopramide should not be given to patients receiving dopamine to promote diuresis, and may not be an effective centrally acting antiemetic in the cat. Cats, or dogs with vomiting which is refractory to initial therapy for uremic gastritis, may benefit from

an a_2-adrenergic antagonist such as chlorpromazine (0.2-0.4mg/kg TID SC) or prochlorperazine (0.5mkg/kg TID SC IM) after ensuring adequate circulatory status.

Gastric ulceration

Vomiting in patients with suspected acute gastritis or gastric ulceration is managed by providing adequate fluid therapy and limiting afferent input from the inflamed gut by decreasing gastric acid secretion (e.g. H_2 antagonists) and providing mucosal protection (e.g. sucralfate). A PGE analog (misoprostol 3-5µg/kg PO TID) may be beneficial where persistent vomiting is associated with NSAID administration (9,10). Where ulceration is severe and vomiting is not adequately controlled antiemetics such as metoclopramide, maropitant (dogs), or chlorpromazine/ prochlorperazine (if circulating volume is Ok) can be used as an adjunct in the short term.

In patients with severe or persistent ulceration more complete inhibition of gastric acid secretion can be achieved with the H/K ATPase inhibitor - omeprazole (1 mg/kg BID PO). This drug may be particularly effective in patients with excessive secretion of gastric acid e.g. gastrinoma. The combination of omeprazole and the long acting somatostatin analog Octreotide (which decreases gastrin release and inhibits gastric acid secretion) effectively reduced vomiting in a dog with gastrinoma (11). Ompeprazole has also been shown to decrease gastric ulcers in sled dogs, though diarrhea was an unwanted side effect (12).

Mast cell tumors may cause vomiting in dogs via the central effects of histamine on the CRTZ and the peripheral effects of histamine on gastric acid secretion (with resultant hyperacidity and ulceration). Treatment of mastocytosis with H_1 and H_2 histamine antagonists (e.g. diphenhydramine and famotidine) may reduce the central and peripheral effects of histamine. Corticosteroids are used to decrease tumor size and release of histamine.

Gastritis

The treatment of dogs and cats with gastritis is guided by the presence or absence of gastric Helicobacter. In dogs or cats with chronic vomiting, lymphoid follicular / lymphocytic gastritis, and gastric Helicobacter spp. antibiotics directed against Helicobacter have produced positive clinical responses. In an uncontrolled trial of antibiotics in dogs and cats with gastritis and Helicobacter spp. infection clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine (13). 74% of 19 animals re-endoscoped had no evidence of Helicobacter spp. in gastric biopsies.(13) A recent controlled trial of amoxicillin (15mg/kg PO BID x 14d), metronidazole (10mg/kg PO BID 14d) and bismuth ± famotidine in 24 dogs found a similar decrease in vomiting (86.4%) and reduced gastritis scores in dogs that were Helicobacter negative at 6mo (14). The use of famotidine did not improve resolution of clinical signs or eradication of Helicobacter. Unfortunately, only 43% of dogs were free from Helicobacter at 6 months, which echoes the results of controlled studies in asymptomatic Helicobacter-infected dogs and cats. Another recent study gave metronidazole (11-15mg/kg PO BID), amoxicillin (22mg/kg PO BID) and bismuth subsalicylate (0.22ml/kg PO Q-TID) to 5 Helicobacter infected animals (3 dogs and 2 cats) for 21d, and documented resolution of vomiting and long term eradication of Helicobacter (9-38months) in all animals (15). The author has employed the combination of amoxicillin (20 mg/kg PO BID), clarithromycin (7.5 mg/kg PO BID) and metronidazole (10 mg/kg PO BID) for 14 days to succesfully eradicate Helicobacter pylori infection in cats. Taken as a whole, these studies suggest that a longer duration of treatment (21d) or the use of antibiotics that can eradicate intracellular Helicobacter (clarithromycin) improve eradication, but further studies are required before clear guidelines regarding the treatment of gastric Helicobacter spp. in dogs and cats can be made. The author recommends treating only symptomatic patients that have biopsy-confirmed Helicobacter spp. infection and gastritis.

Chronic Gastritis of Unknown Cause

Helicobacter negative lymphocytic plasmacytic gastritis is relatively common in dogs and cats (@ 25to 40% of cases, unpublished observations). The cellular infiltrate varies widely in severity and it may be accompanied by mucosal atrophy or fibrosis, and less commonly hyperplasia. Gastritis may also be accompanied by similar infiltrates in the intestines, particularly in cats (who should also be evaluated for the presence of pancreatic and biliary disease).

Patients with lymphoplasmacytic, Helicobacter-negative, gastritis are initially treated with diet. The diet is often restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrate and restricted in fat, which facilitates gastric emptying, and may contain other substances such as menhaden fish oil or antioxidants that may alter inflammation. The test diet is fed exclusively for a period of about 2 weeks while vomiting episodes are recorded. If vomiting is improved a challenge with the original diet is required to confirm a diagnosis of food intolerance. The introduction of a specific dietary component to the test diet, such as beef, is required to confirm sensitivity to that component. If vomiting is unresponsive the patient is usually placed on a different diet for 2 more weeks (usually the limit of client tolerance). If there is no response to dietary manipulation the next step is immuno-modulation with prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at

the lowest dose that maintains remission over 8 to 12 weeks). Antacids and mucosal protectants are added to the therapeutic regimen if ulcers or erosion are detected at endoscopy or if hematemesis or melena is noted.

If gastritis is unresponsive to antibiotics, diet, prednisolone, and antacids, additional immunosuppression may be indicated. However, it is important to carefully re-evaluate the patient record and histopathology (e.g. is lymphoma a possibility?) before ramping up immunosuppression. In dogs, immunosuppression is usually increased with azathioprine (PO 2 mg/kg SID for 5d then EOD, on alternating days with prednisolone). Chlorambucil may be a safer alternative to azathioprine in cats and has been successfully employed in the management of inflammatory bowel disease and small cell lymphoma (PO 5mg per cat every other day). Prokinetic agents such as metoclopramide, cisapride, and erythromycin can be used as an adjunct where delayed gastric emptying is present (see below).

Delayed gastric emptying

Delayed gastric emptying is caused by outflow obstruction or defective propulsion and is usually suspected by the vomiting of food 8-12hrs after ingestion (16,17). Other signs include abdominal discomfort, distention, bloating and intermittent anorexia. Outflow obstruction can be caused by polyps, foreign bodies, tumors, pyloric hypertrophy or stenosis, granulomata and extraluminal masses such as pancreatic tumors. Defective propulsion may result from primary gastric diseases such as gastritis, ulceration, neoplasia, and parasitism or non-gastric disorders such as stress, trauma, peritonitis, pancreatitis, infectious enteritis, electrolyte and metabolic derangements, drugs and surgery. Disordered motility may be involved in the initiation of gastric dilatation volvulus. The finding of hypochloremia, hypokalemia, and metabolic alkalosis, ± aciduria, should raise the suspicion of an upper GI obstruction or less commonly a hypersecretory state such as gastrinoma or mastocytosis.

Radiography is used to investigate vomiting and to confirm delayed gastric emptying (retention of food or fluid >16-17hrs after a meal, or delayed gastric emptying of liquid barium (30%w/v, 12-16ml/kg via stomach tube : the stomach should empty within 15-60 min in cats and 1-2hrs in dogs), barium meal (normal < 10-15hrs) or barium polyspheres (normal dogs, ten 5mm and thirty 1.5mm spheres: 50% empty by 7.5hrs, 75% by 13.1, 90% by 22.5hrs)). Endoscopy is useful for confirming gastric outflow obstruction and gastric and duodenal causes of decreased propulsion (e.g. ulcers, gastritis). Measurement of gastric pH and serum gastrin may help to determine the cause of gastric ulceration or mucosal abnormalities (11).

Treatment of gastric emptying disorders is directed at the underlying cause- e.g. surgery for pyloric stenosis or hypertrophic gastropathy, antacids, mucosal protectants and/or antibiotics for gastritis. In non-obstructive situations gastric emptying can be enhanced by dietary modification to facilitate gastric emptying (small amounts of semi-liquid, protein and fat restricted diets fed at frequent intervals e.g. intestinal diets blended with water and mixed with an equal volume of boiled rice may also be of benefit) and prokinetic agents such as metoclopramide (0.2-0.5mg/kg PO SC TID), cisapride (0.1-0.5mg/kg PO TID) or erythromycin (dog- 0.5-1.0mg/kg PO TID) (16-20). The H_2 antagonists ranitidine (1-2mg/ kg PO BID) and nizatidine (2.5-5mg/kg PO SID) have prokinetic activity in dogs that appears due to their acetyl cholinesterase-like activity (16,17).

Pancreatitis

Vomiting in dogs with pancreatitis is likely due to direct afferent input to the vomiting center from the inflamed pancreas and adjacent intestines and ileus secondary to inflammation. Analgesia (e.g. buprenorphine 0.01mg/kg SC BID) is used to decrease afferent stimulation of the vomiting center, and may also have direct central effects on emesis. The antiemetics traditionally employed in dogs with pancreatitis are metoclopramide (0.2-0.4mg/kg SC. IM, PO QID or 1mg/kg/24hrs continuous IV infusion, may have beneficial central and a peripheral effects), and phenothiazines (chlorpromazine or prochlorperazine, ensure adequate volume status). $5HT_3$ receptor antagonists such as ondansetron, and the NK_1 antagonist maropitant are increasingly used, and may offer the additional benefit of decreasing pancreatic or visceral stimulation of emesis.

Motion sickness

Stimuli from the vestibular system are thought to be the cause of motion sickness. Motion sickness in the dog can be decreased by the administration of receptor antagonists of NK_1 (maropitant 8mg/kg PO SID for 2d maximum), H_1 histaminergic (diphenhydramine 2-4mg/kg PO, IM TID) and M_1 cholinergic (scopolamine 0.03mg/kg QID SC IM) receptors (1,21). Motion sickness in the cat does not appear to be controlled by histamine antagonists and may be controlled with chlorpromazine (1).

Cancer chemotherapy

The emetic effects of the chemotherapeutic agent cisplatinum in dogs can be decreased by administering butorphanol (0.4 mg of butorphanol/kg), $5HT_3$- serotonergic antagonists (Dogs : ondansetron 0.5-1.0mg/kg PO -30 and 90 minutes after commencing cisplatinum; It is thought that blocking peripheral receptors accounts for the antiemetic effect) and the

NK_1 antagonist maropitant (22-27). Metoclopramide has some antiemetic effects against cisplatin but high, potentially toxic, doses may be required.

Persistent vomiting of undetermined etiology
Symptomatic fluid support, diet restriction or modification, analgesia and antiemetic therapy to control vomiting are considered where vomiting is frequent or severe enough to cause derangements of fluid, electrolyte and acid base balance. Antiemetic use and selection in patients with unknown causes of vomiting is based on a best guess, least harmful approach taking into consideration the potential contraindications to antiemetic use in general e.g. ingestion of toxic substances, and contraindications for specific agents e.g. age, hypotension, bradycardia, seizures.

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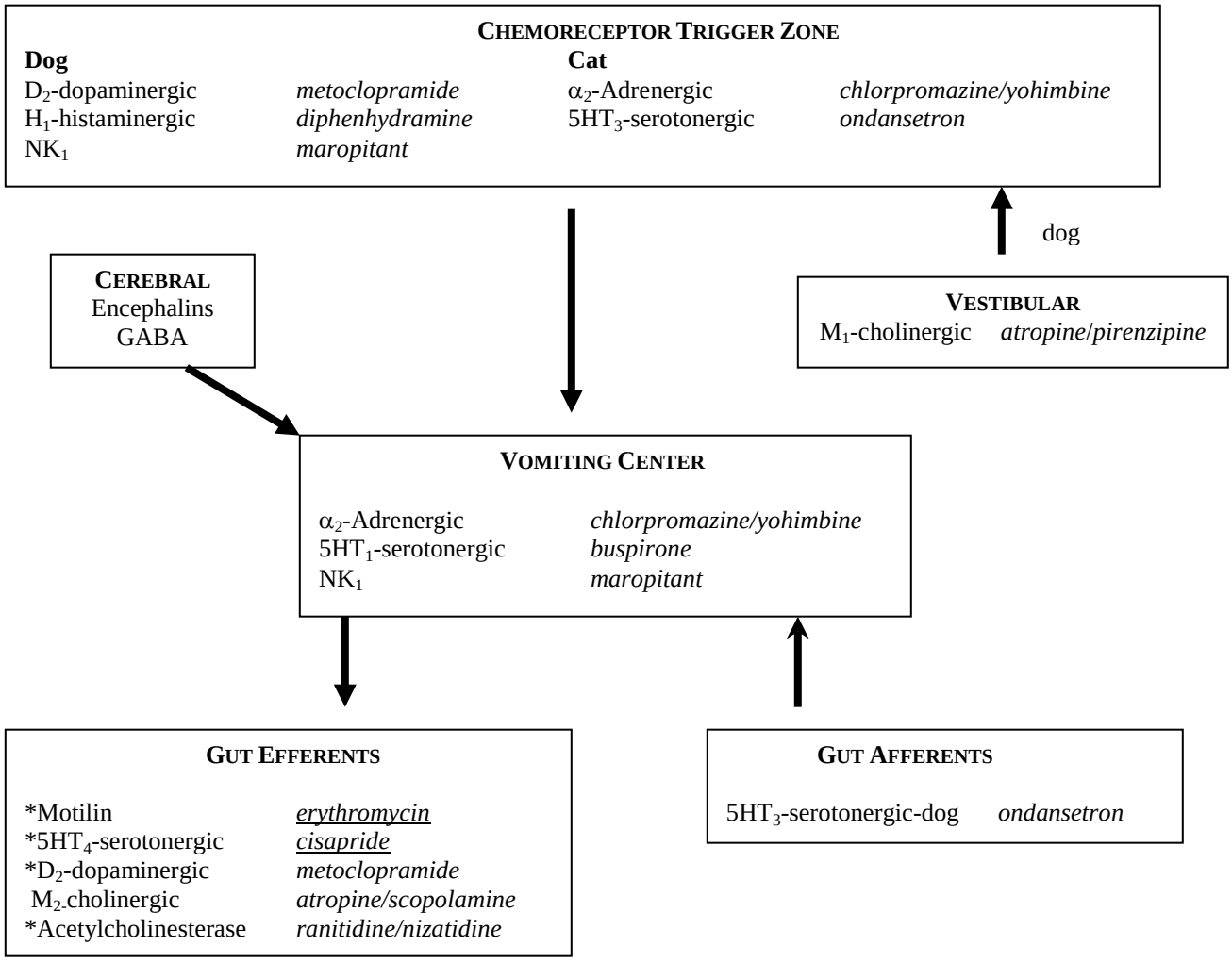
Table 1. Causes of vomiting

Gastric	Gastritis, Ulceration, Neoplasia, Outflow obstruction, Foreign bodies, Motility / functional disorders	
Intestinal	Inflammatory Bowel Disease, Neoplasia, Foreign bodies, Intussusception, Bacterial Overgrowth/antibiotic responsive enteropathy, Functional disorders	
Intra-abdominal	non-GIT	
	Pancreas	Pancreatitis, Pancreatic Neoplasia
	Liver	Hepatitis, Cholangitis, Mucocele, Biliary Obstruction
	Spleen	Torsion
	Genitourinary	Nephritis, Pyelonephritis, Nephrolithiasis, Urinary obstruction, Prostatitis, Pyomertra,
	Peritonitis	
Metabolic / Endocrine	Uremia, Hypoadrenocorticism, Diabetic Ketoacidosis, Hperthyroidism, Hepatic Encephalopathy, Hypercalcaemia, Septicaemia	
Drugs	Intravenous medications, Digoxin, Erythromycin, Chemotherapy, Apomorphine, Xylazine	
Toxins	Strychnine, Ethylene Glycol, Lead	
Dietary	Sudden change. Indiscretion, Intolerance, Allergy	
Neurologic	Vestibular disease, Encephalitis, Neoplasia, Raised intra-cranial pressure	
Infectious	Distemper, parvovirus, infectious canine hepattis, leptospirosis, feline panleucopenia, FIP, FelV, FIV, salmonellosis, feline heartworm	

1.

NEUROPHARMACOLOGY OF ANTI-EMETICS AND PROKINETICS



Underlined = receptor agonists, * = prokinetics