Gastroduodenal Ulceration in Small Animals: Part 1. Pathophysiology and Epidemiology

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ABSTRACT

Gastroduodenal ulceration in small animals is a complex and important comorbidity that occurs when the physiological homeostasis of the gastrointestinal tract is disrupted secondary to administration of medications or the presence of local or systemic diseases. The aim of this article is to provide a comprehensive review of the veterinary literature regarding the pathophysiology, epidemiology, and risk factors associated with gastroduodenal ulceration in small animals. Pertinent concepts from the human literature will be integrated into the discussion. This article serves as an introduction to the second part of this series, which will review current evidence regarding the use of H2-receptor antagonists and proton pump inhibitors in small animals. (J Am Anim Hosp Assoc 2017; 53:1–10. DOI 10.5326/JAAHA-MS-6635)

Gastric Mucosal Structure and Function

The stomach has the complex function of secreting acid and digestive enzymes to promote assimilation of food, while at the same time maintaining cytoprotective mechanisms to promote mucosal integrity. The stomach accomplishes both functions with the help of a highly specialized tight epithelial lining that is capable of secreting an assortment of specific chemical mediators.

Gastric anatomy is divided in five topographical regions: the cardia, fundus, body, antrum, and pylorus; and two functional regions: the proximal (oxyntic) and distal (pyloric) parts. The gastric mucosa is a continuous epithelial layer folded into gastric pits. The surface of the pits is lined with columnar epithelial cells and mucous-producing cells, while the base is lined by gastric or pyloric glands. The gastric (or oxyntic) glands are located mainly in the proximal part of the stomach (fundus and body) while pyloric glands are only present in the distal part of the stomach (pylorus).

There are five types of cells within the gastric glands: (1) mucous neck cells, which secrete mucus and gastric lipase in dogs; (2) chief or peptic cells responsible for the secretion of pepsinogen A and B; (3) parietal cells, which produce hydrochloric acid (HCl), haptocorrin, and intrinsic factor; (4) enterochromaffin-like cells (ECL) producing histamine; and (5) D cells, which secrete somatostatin. The pyloric glands are primarily void of parietal cells and peptic cells and instead have primarily mucous neck cells, D cells, and specialized cells called G cells, which are responsible for the secretion of gastrin.

A major role of the stomach is to produce gastric juice, which begins the chemical and enzymatic digestion of food. This juice is a complex fluid composed of organic and inorganic phases. Inorganic constituents consist of high concentrations of H⁺, K⁺, and Cl⁻ ions. The organic phase includes intrinsic factor, haptocorrin, and pepsinogen. Pepsinogen, a proenzyme, is transformed in the acidic environment of the gastric lumen to pepsin, which digests proteins. Intrinsic factor and haptocorrin (or R protein) play an essential role in the protection of cobalamin from degradation by the gastric juice and the absorption of vitamin B12, respectively. In dogs and cats, however, gastric secretion of intrinsic factor is much lower compared to pancreatic COX-1 (cyclo-oxygenase 1); COX-2 (cyclo-oxygenase 2); ECL (enterochromaffin-like cells); HCl (hydrochloric acid); IP3 (inositol trisphosphate); NSAID (nonsteroidal anti-inflammatory drug); PG (prostaglandin)
production. This is different than the situation in humans, in whom the majority of intrinsic factor is produced in the stomach. The parietal cells are responsible for the production of HCl via a highly specialized ultrastructure. Their cytoplasm contains large branching secreting canaliculi and a resting tubulovesicular system. When the parietal cell is activated, its tubulovesicular system, which contains numerous H\(^+\)/K\(^+\)-ATPase pumps, fuses with the secreting canaliculi, thereby increasing the numbers of functional proton pumps on the apical plasma membrane. These pumps, along with activation of apical chloride and potassium channels, result in the net secretion of HCl (Figure 1).

**Regulation of Acid Secretion**

Gastric acid secretion is tightly regulated by a combination of hormonal and paracrine factors as well as nervous stimuli. Secretion is separated into three phases: the cephalic, the gastric, and the intestinal. The cephalic phase of secretion is controlled primarily by parasympathetic stimulation via the vagus nerve in response to external stimuli such as food, taste, or smell. Efferent vagal nerve fibers release acetylcholine, which binds to muscarinic receptors on the parietal cells, ECL cells, and G cells. In parietal cells, this leads to the generation of inositol trisphosphate (IP3) and opening of the IP3 receptor on the endoplasmic reticulum which increases the intracellular calcium concentration. This increase in intracellular calcium is coupled to movement of the proton pump to the apical membrane of the parietal cell. The net result is the release of hydrogen ions into the lumen. Binding of acetylcholine to muscarinic receptors also stimulates the release of histamine from ECL cells and gastrin from G cells. In the gastric phase, secretion is stimulated by the parasympathetic nervous system, which activates mechanoreceptors on mucosal cells in response to luminal distension (the so-called vagovagal reflex). In addition to control of acid secretion, the parasympathetic system (vagal nerve) also stimulates the secretion of mucus, bicarbonate, and pepsinogen from mucous and peptic cells.

Histamine is an important mediator of gastric acid secretion. An important source of histamine is the ECL cells, which lie in close proximity to the parietal cells. Histamine release by the ECL cells is stimulated not only by release of acetylcholine as noted above, but also by the binding of gastrin to cholecystokinin 2 receptors on the ECL cells. Histamine released by the ECL cell then acts in a paracrine fashion by binding to H2 receptors present on the parietal cell plasma membrane. Binding to H2 receptors triggers increases in intracellular cAMP that stimulate the movement of the H\(^+\)/K\(^+\)-ATPase pump to the apical membrane of the parietal cell.

Gastrin is a hormone synthesized by G cells. Four main forms of gastrin have been reported in humans, dogs, and cats. They are commonly named according to the number of amino acids (G14, G17, G34, G71) or by component number (Gastrin component I, II, III, and IV). In cats, only component III (G17) and a very small proportion of component IV (G14) have been isolated in the gastric lumen. In dogs, components I (G71), II (G34) and III (G17) are secreted in the gastric lumen. Gastrin exerts a trophic

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**FIGURE 1** The intracellular pathway modulating acid secretion by the parietal cells is dependent on multiple processes. First, intracellular water dissociates into H\(^+\) and HCO\(_3^-\), catalyzed by the action of carbonic anhydrase (1). The H\(^+\) ion is then excreted in exchange for K\(^+\) in the canaliculi lumen via a H\(^+\)/K\(^+\)-ATPase pump (2). Potassium ions are available in the canaliculi lumen for exchange because of an active basolateral Na\(^+\)/K\(^+\)-ATPase pump and the leak of potassium through channels on the apical membrane (3). Activation of Cl\(^-\) channels and anion exchanger is necessary to maintain electroneutrality (4). Water follows the osmotic gradient created by the excretion of the hydrogen ions in the lumen to increase the final volume of gastric acid secretion.
effect on the gastric epithelium by stimulating the development of ECL cells and promoting gastric mucosal growth and blood flow.4 Gastrin mediates its effect through CCK-2 receptors present on the membrane of ECL cells, parietal cells, and D cells. CCK-2 receptor activation is coupled to activation of phospholipase C, which activates IP3 and diacylglycerol, promoting release of intracellular calcium.10 As discussed above, the main effect of gastrin on parietal cell acid secretion is mediated through the stimulation of histamine release by the ECL cells and not from direct stimulation of gastrin receptors on parietal cells.10,11,13

Stimulation of gastric acid secretion is regulated by negative feedback. These inhibitory pathways include nervous and hormonal pathways. The enterogastric reflex, which inhibits gastric acid secretion, is triggered when the myenteric nervous system detects either a decrease in the duodenal pH, distention of intestinal loops, or irritation of the gastrointestinal mucosa. Gastric inhibitory peptide and somatostatin are hormones that mediate negative feedback on acid secretion.5 Somatostatin, which is secreted by D cells in response to acidification of the intestinal content, is considered to be the main inhibitor of acid secretion and works in a paracrine fashion to inhibit parietal cell function.2,14 Gastric inhibitory peptide is secreted by K cells located throughout the intestines in cats, but is confined to the duodenum and proximal jejunum in dogs.

Gastric Homeostasis and Pathophysiology of Gastric Ulceration

Despite the harsh environment, the integrity of the stomach is preserved by an intricate system of homeostatic mechanisms. Gastric pH in dogs and cats, similar to humans, is acidic.15,16 In dogs, gastric pH is influenced by the presence of food, with fasting pH being significantly higher than in the fed state.16 In addition to acidic fluid, the stomach is exposed daily to numerous harmful substances, such as proteolytic enzymes, medications, microorganisms, and potential toxins in ingested foods.9,18,19 Protection against these substances, as well as gastric acid, is essential in preventing cell injury leading to gastric erosion or ulceration. Gastric injury occurs when noxious factors overwhelm the natural defenses, as seen when there is overproduction of gastric acid, and also when there is impairment of the gastric cytoprotective defense mechanisms.9,18

The cytoprotective mechanisms in the stomach can be divided in six categories: (1) pre-epithelial factors, including the mucous barrier and phospholipids; (2) the epithelial barrier, including the surface epithelial cells and tight junctions; (3) epithelial cell turnover; (4) trophic factors and prostaglandins; (5) high mucosal blood flow; and (6) sensory innervations.18,20,21

The first line of defense and one of the most important cytoprotective mechanisms is the presence of a hydrophobic unstirred layer of bicarbonate-buffered mucus that is immediately adherent to the surface epithelial cells.21 The mucus in this layer, which is secreted by the epithelial cells, traps bicarbonate, water, and trefoil factor peptides to form a gel-like structure that is closely associated with the surface epithelial cells and effectively protects them from injury.18,20,22,23

The surface epithelial cells themselves provide a second line of defense. They have hydrophobic membranes that are interconnected via tight junctions that provide a barrier resistant to the back diffusion of acid.18,24,25 The epithelial cell surface is also continuously renewed by proliferation of progenitor cells in the gastric glands, allowing the complete restitution of the gastric surface in a few days.18 This rapid turnover is supported by trophic factors, such as epidermal growth factor and insulin-like growth factor, and a high mucosal microcirculation that delivers oxygen and nutrients to the cells.18,19,21 When acid back-diffusion does occur, significant increases in mucosal blood flow in response to endogenous vasodilators, such as substance P, nitric oxide, and prostacyclin, protect the gastric mucosa and counteract vasoconstrictor substances, such as leukotriene C4 and thromboxane A2, released at the site of injury.18,21 The epithelial cells are also responsible for mucus and prostaglandin synthesis, both of which are important in cytoprotection.

Modulation of prostaglandin (PG) secretion plays a role in the protection of the stomach mucosa. The two main prostaglandins expressed in the gastrointestinal tract are prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2, or prostacyclin).19 These prostaglandins inhibit gastric acid secretion by binding to the prostaglandin E3 receptors on the parietal cells.18 Binding leads to partial inhibition of the H+/K+-ATPase pumps by inhibiting intracellular cAMP production. However, cytoprotection by prostaglandins is not due primarily to decreased acid production.19,26 More importantly, prostaglandins stimulate bicarbonate and mucus secretion from mucous neck cells (PGE2) and increase mucosal blood flow (PGE2 and PDI2).18,20,21,26,27 In addition, prostaglandins decrease epithelium permeability, the release of pro-inflammatory cytokines, and favor ulcer healing by stimulating re-epithelialization.19

Over the past decades, both of the prostaglandin-producing enzymes, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), have been extensively studied. Initially, their roles were thought to be very distinct, with COX-1 being a “house-keeping” constitutively expressed enzyme responsible for the basal
production of PGs, and COX-2 being an inducible enzyme upregulated with inflammation with little role in the maintenance of mucosal integrity.\textsuperscript{27} More recently, however, studies in humans and animals demonstrate that both COX-1 and COX-2 have a protective role in the gastrointestinal tract.\textsuperscript{27,28} COX-2 is expressed constitutively at low levels in the stomach and duodenum, and expression increases at sites of mucosal injury.\textsuperscript{19,29} Specific inhibition of COX-2 delays gastrointestinal healing and can promote progression of gastric epithelial injury.\textsuperscript{28} Additional evidence for an important role for COX-2 in maintaining mucosal integrity is seen in COX-1 knock-out animals or by specific COX-1 inhibition. Neither leads to significant mucosal injury, very likely due to compensation via up-regulation of COX-2 expression. Conversely, complete COX-2 inhibition does results in mucosal injury.\textsuperscript{18,27} COX-1 and COX-2 enzymes are now both considered important mediators of prostaglandin-associated gastrointestinal cytoprotection.\textsuperscript{27}

**Epidemiology of Gastroduodenal Ulceration in Small Animals**

Gastroduodenal ulceration and perforations are more common in dogs than cats.\textsuperscript{30–32} Several case series have focused on identifying the underlying risk factors for gastroduodenal ulceration and perforation in dogs.\textsuperscript{30–34} Although these studies are retrospective and have focused on gastroduodenal perforations and not just ulceration, these case series highlight crucial information regarding the epidemiology of gastroduodenal ulceration in dogs. Middle-aged large breed dogs appear to be over-represented. No breed predispositions have been reported, although rottweilers were more prevalent than expected in one study.\textsuperscript{32} One study found that significantly more males than females suffered from gastroduodenal perforation, but others have not found a male predisposition.\textsuperscript{31,32,34} Nonsteroidal anti-inflammatory drugs (NSAIDs) are the main risk factor for gastrointestinal ulceration in dogs. Other reported causes include extensive trauma (such as gunshot wounds and hit by car), severe systemic disease (such as severe pancreatitis or septicemia), strenuous exercise (sled dogs), liver disease (unspecified chronic hepatitis, vascular disease, acute liver failure), corticosteroids (usually in association with another risk factor), gastroduodenal inflammation, gastroduodenal neoplasia, hypoadrenocorticism, gastric or duodenal foreign bodies, or extra-gastrointestinal neoplasia (gastrinoma and mast cell tumors).\textsuperscript{31,32,34–37}

Gastroduodenal ulcerations and perforation in cats affects mainly middle-aged to older cats, without any breed predisposition.\textsuperscript{30,32,38} Gastroduodenal perforations are more commonly reported secondary to gastrointestinal neoplasia, particularly lymphoma.\textsuperscript{30,32,38} Other common underlying causes for perforations include distant neoplasia (e.g., mast cell tumor), inflammatory bowel disease, liver disease (unspecified type), and NSAID or corticosteroid administration. Anecdotally, toxicity from Dieffenbachia leaves and surgery have also been reported as causes of gastroduodenal perforation in cats.\textsuperscript{30}

**Clinical Presentation and Pathophysiology of Gastroduodenal Ulceration**

Most dogs with gastric ulceration have non-specific clinical signs such as lethargy (87–100%), vomiting (76–91%), decreased appetite (28–96%), and abdominal pain (28–42%).\textsuperscript{31,32,34} One study reported weight loss in 89% of the cases.\textsuperscript{32} Hematemesis or melena, which are considered specific indicators of upper gastrointestinal bleeding, were reported inconsistently in only 7–80% and 13–50% of the cases, respectively. Among the hematology results, neutrophilia (62–86%), left shift (40–71%), and anemia (64–80%), mainly normocytic and normochromic, were the most common findings. In one study, serum alkaline phosphatase and serum alanine transserase activity were increased in 65 and 38% of the cases, respectively, but this was not seen in other studies.\textsuperscript{31} Hypoalbuminemia was frequently reported (60–87%). Ulceration and perforation have been reported in all areas of the dog’s stomach and in the proximal duodenum, with the pyloric antrum being the most common site for NSAID-induced lesions. In one study, perforations secondary to ulcers were noticed more frequently at the parietal side of the stomach and the anti-mesenteric side of the duodenum.\textsuperscript{34} In dogs with liver diseases, ulcers are more frequently present at the level of the duodenum.\textsuperscript{31,35,39}

In both dogs and cats, abdominal ultrasound, abdominal radiographs, and endoscopy are the most commonly reported imaging modalities used to diagnose gastroduodenal ulceration or perforation.\textsuperscript{31–34,38} Endoscopy is considered the gold standard for the diagnosis of gastroduodenal ulceration. However, endoscopy detected gastroduodenal perforation in only 17–67% of the dogs depending on the study, was rarely performed in cats, and has been associated with gastrointestinal perforation in predisposed patients (Figure 2).\textsuperscript{30–32,38,40} An inability to visualize the gastric lesion has been attributed to excessive bleeding, presence of a mass, and/or excessive fluid or food retention.\textsuperscript{32} In one retrospective study, abdominal ultrasound and radiographs accurately diagnosed gastrointestinal perforation in 73 and 65% of cases, respectively.\textsuperscript{41} The most common ultrasonographic findings in both cats and dogs included hyperechoic mesenteric fat (40–100%), free peritoneal...
fluid (40–100%), fluid-filled stomach (20–63%), wall thickening (57–60%), ulceration (31–40%), presence of free gas (30–47%), and loss of wall layering (47%) (Figure 3). Radiographic findings included loss of serosal details (74–85%) and the presence of free abdominal gas (47–66%) (Figure 4). It is also important to note that not all gastroduodenal ulcers are perforated. In non-perforated ulcers, some of the previously described features will be absent, and changes will be more subtle (e.g., gas dissecting the gastric mucosa on ultrasound) (Figure 3). This likely decreases the sensitivity of ultrasound and radiographs and reduces the ability to detect non-perforated gastroduodenal ulcerations or erosions.

Similar to dogs, cats with gastric ulcerations also exhibit non-specific clinical signs such as decreased appetite (61–86%), vomiting (61–86%), or weight loss (38–100%). As in dogs, hematemes (0–22%) and melena (7–28%) are rarely reported in cats. The most common hematological changes are neutrophilia (62–86%), left shift (0–57%), and anemia (25–71%). On the biochemistry profile, hypoproteinemia, primarily due to hypoalbuminemia, was the most frequently reported abnormality (29–100%). The most common causes of gastroduodenal ulceration in dogs and cats are summarized in Table 1.

The use of NSAIDs has been linked to gastroduodenal ulceration in many species, including dogs, cats, and humans. Gastric mucosal damage from NSAIDs can be from direct toxicity or from inhibition of prostaglandin synthesis. Direct damage can result from “ion trapping” of the drug inside the gastric parietal cells. Because NSAIDs are weak acids, they remain unionized in the acidic pH of the stomach lumen and can readily diffuse across the apical membrane of the parietal cell. Once inside the cell, the NSAID becomes ionized due to the higher intracellular pH and is trapped within the cell. Within the cell, NSAIDs can induce mitochondrial damage and uncouple oxidative phosphorylation, leading to free radical damage. Another direct toxicity of NSAIDs is related to the fact that they can associate with...
Severe gastrointestinal side effects still occur. Studies looking at gastrointestinal side effects than non-specific NSAIDs, although development of NSAIDs with more specific COX-2 inhibition. In corticosteroids. However, a more recent meta-analysis found controversial. Older meta-analyses in human medicine found little for the gastrointestinal side effects of NSAIDs. This led to the inhibition of COX-1 was the main mechanism toxic effect of NSAIDs on the gastric epithelium. Since COX-1 is constitutively expressed and COX-2 is an inducible enzyme, it was originally felt that inhibition of COX-1 was the main mechanism for the gastrointestinal side effects of NSAIDs. This led to the development of NSAIDs with more specific COX-2 inhibition. In humans, COX-2 inhibitors are associated with slightly less gastrointestinal side effects than non-specific NSAIDs, although severe gastrointestinal side effects still occur. Studies looking at the safety of COX-2-selective NSAIDs in dogs have not shown a clear-cut advantage over nonselective COX inhibitors. Several studies describe gastric ulceration associated with COX-2-specific NSAIDs. Reasons behind this difference in dogs compared to humans may be multifactorial, and include a potential lack of statistical power in the veterinary studies, inaccurate assessment of the COX-2 specificity of the NSAIDs, and individual variability. Moreover, diverse studies show that COX-1 expression is not essential in preventing or healing gastroduodenal ulceration, but that induction of COX-2 is essential for ulcer healing and resolution.

The role of corticosteroids on gastroduodenal ulceration is controversial. Older meta-analyses in human medicine found little to no increased risk of gastric ulcer with administration of corticosteroids. However, a more recent meta-analysis found that corticosteroids increased the risk of gastrointestinal bleeding by 40% in hospitalized patients. In humans, the major risk of corticosteroid-induced gastric ulceration is the presence of other risk factors such as concurrent NSAID administration, gastrointestinal neoplasia or inflammation, older age, and smoking. In dogs, the combination of NSAIDs and corticosteroids also appears to promote gastric ulceration more than the administration of either NSAIDs or corticosteroids alone. The cause for this synergistic effect with supraphysiologic doses of corticosteroids is not completely understood. Paradoxically, physiologic levels of corticosteroids are necessary to maintain intestinal epithelial integrity, as they are important in maintaining normal gastric blood flow and mucus production. In rats, NSAID-induced lesions are significantly worse in adrenalec-tomized animals and dogs with hypoadrenocorticism are predisposed to developing gastrointestinal bleeding.

In dogs and humans, gastroduodenal ulcerations occur in association with brain or spinal cord injury, especially injury secondary to intervertebral disc disease. In the veterinary studies, macroscopic and/or microscopic gastroduodenal erosions or ulcerations occur in 76% of dogs with spinal cord injury. Many of the dogs with gastric lesions also received corticosteroids or NSAIDs, but gastroduodenal ulceration also occurred in the absence of administration of ulcerogenic medications. Thus, the increased risk of gastroduodenal ulceration in dogs with spinal injury appears to be independent of the administration of corticosteroids or NSAIDs. The pathophysiology of ulcer formation with spinal cord injury is still poorly understood, but the combination of autonomic dysfunction secondary to spinal compression, pain-mediated release of vasoactive hormones such as epinephrine, release of inflammatory cytokines, and systemic shock are suspected to play a role in the pathogenesis.

In humans, stress-associated gastric mucosal ulceration occurs in up to 75–100% of patients hospitalized in the intensive care unit. More importantly, 50% of these patients who go on to develop gastrointestinal bleeding from these ulcers eventually die from this complication. It is important to note that the “stress” described in these situations is pathologic stress secondary to severe systemic disease, which typically includes respiratory failure with mechanical ventilation, sepsis, coagulopathy, or thromboembolism. The two strongest predictors of stress-associated mucosal ulceration in humans are coagulopathy and respiratory failure. Length of hospitalization, male gender, sepsis, spinal cord injury, and acute renal failure are also risk factors. The pathophysiology of stress-related mucosal ulceration is incompletely understood, but a proposed mechanism is that disruption of the gastric microcirculation promotes gastric epithelial hypoperfusion, ischemia, and acidosis. Decreased epithelial cell turnover, gastrointestinal hypomotility, gastric edema, cytokine release, and the
presence of increased gastric acidity, which impairs platelet aggregation and promotes clot lysis, may also play a role.\textsuperscript{70,74} Lastly, reperfusion injury that occurs once the microcirculation is restored can further damage the gastric mucosa by production of oxygen radicals.

No studies of stress-related mucosal ulceration in critically ill dogs or cats have been done, so whether this gastric pathology occurs in small animals is unknown. Currently, there is no evidence in the literature to support that simple stress, such as hospitalization, is a risk factor for gastrointestinal ulceration. However, a recent study of people who survived the 2011 great earthquake and tsunami in Japan showed a significant increase in gastroduodenal ulceration.\textsuperscript{75,76} This finding suggests that intense societal and psychological stress may be risk factors for gastroduodenal ulceration in humans. No such studies have been done in dogs and cats.

Kidney disease is commonly considered as a risk factor for gastrointestinal ulceration in veterinary medicine.\textsuperscript{3,77,78} One hypothesis for this gastric pathology is hypergastrinemia due to decreased renal clearance of gastrin and resultant gastric hyperacidity. Other possible mechanisms for renal disease-induced gastroduodenal ulceration include accumulation of uremic toxins leading to uremic gastropathy, chronic metabolic acidosis, impaired platelet function, gastric wall edema, and vasculopathy. Despite the occurrence of gastrointestinal signs in dogs with renal disease, gastric hyperacidity and, indeed, an increase in gastroduodenal ulceration have not yet been demonstrated. In a retrospective study investigating the features of canine uremic gastropathy, no gastric ulceration was noticed in 28 dogs with severe renal azotemia (creatinine above 5 mg/dl).\textsuperscript{78} Gastric pathology, however, was present in 22/28 dogs. Histopathological changes in the stomach included edema (61%), glandular atrophy (50%), mineralization (46%), mucosal necrosis (14%), and vasculopathy (5%). Based on this study, it appears that gastric ulceration is rare in dogs with kidney disease. The association between gastroduodenal ulcerations and end-stage chronic kidney disease has also been investigated in humans, with contradictory results. Recent studies have demonstrated a significantly increased risk of gastroduodenal ulceration and bleeding, but comorbidities may have played an important role.\textsuperscript{79,80} Kidney disease has been only rarely associated with gastroduodenal ulceration in cats.\textsuperscript{30}

In some case series on gastroduodenal ulceration or perforation in dogs and cats, liver disease was a common risk factor.\textsuperscript{31,32} Unfortunately, these studies provided little detail on the type of liver disease. Therefore, the exact nature of the association between liver disease and gastroduodenal ulceration in small animals is unclear. Recently, a high incidence of gastrointestinal ulceration and bleeding (up to 21%) was described in dogs with congenital intra-hepatic shunts.\textsuperscript{36} In addition, duodenal perforation has been described as a co-morbidity in dogs with non-cirrhotic portal hypertension.\textsuperscript{8} Recent results also suggest that gastrointestinal bleeding is a common complication in dogs with acute liver failure.\textsuperscript{81} Association between gastrointestinal ulceration and chronic liver disease exists in humans, particularly those with portal hypertension.\textsuperscript{89} The pathophysiology of gastric erosion or ulceration in dogs with liver disease is unknown. A recent study showed that serum gastrin concentration in dogs with hepatocellular diseases and porto-systemic shunts was normal, so hyperacidity due to poor gastrin clearance is likely not an important factor.\textsuperscript{82} Other possibilities for gastric damage in hepatic disease include impaired gastric mucus and bicarbonate secretion, microvascular abnormalities, bile acid-induced epithelial cell apoptosis, impaired healing ability of the gastric mucosa, and portal hypertension.\textsuperscript{83} The role of portal hypertension in humans, however, has recently been questioned.\textsuperscript{39,84}

In human medicine, severe acute pancreatitis promotes gastroduodenal ulceration, with a prevalence of 52.6% in the studied population.\textsuperscript{85} In dogs with acute pancreatitis, up to 10% had evidence of gastrointestinal bleeding even if the exact location or cause of the bleeding was not assessed.\textsuperscript{86} Presence of gastrointestinal bleeding was also associated with a worse outcome.\textsuperscript{86}

One risk factor for gastroduodenal ulceration shared by both dogs and cats is gastrointestinal inflammation.\textsuperscript{30–32,38,87} In human patients, Helicobacter pylori is a significant risk factor for gastritis and gastric ulceration.\textsuperscript{88} It affects more than 50% of humans in the world, and 10% of them will develop peptic ulcers.\textsuperscript{88} Helicobacter spp. are commonly present in the gastrointestinal tract of dogs and cats, but no study has yet demonstrated any clear association between the presence of these organisms and gastric ulceration or inflammation.\textsuperscript{89–91} Gastric erosions and ulcerations have been demonstrated in Lundehunds with familial gastroenteropathy that is marked by atrophic gastritis and lymphoplasmacytic enteritis.\textsuperscript{92} Garcia-Sancho et al. investigated the potential role of gastrin in the pathogenesis of gastroduodenal ulceration associated with gastritis and enteritis.\textsuperscript{93} In this study, dogs with inflammatory bowel disease had a significantly higher gastrin level than control dogs, and this could explain the increased incidence of ulceration in this population. This finding is similar to what has been previously described in basenjis with severe familial enteropathy.\textsuperscript{94} This increase in gastrin secretion could be secondary to biliary reflux from the duodenum into the gastric antrum, which distends and alkalinizes gastric contents and subsequently stimulates the secretion of gastrin. Pathophysiology of gastroduodenal ulceration
in small animals with gastrointestinal inflammation is very likely multifactorial and potentially involves decreased cellular turnover, increased inflammatory cytokines, and impaired microcirculation.

Strenuous exercise such as long sled races predisposes dogs to gastroduodenal ulceration.95,96 This predisposition also occurs in horses and humans secondary to extreme exercise.97,98 In sled dogs, the severity of the gastric lesions is associated with the intensity but not the duration of exercise. Transient ischemia of the gastroduodenal mucosa is thought to represent the major mechanism of ulceration with strenuous exercise. Further causative factors could include sustained catecholamine secretion, increased tumor necrosis factor-alpha level, hypergastrinemia, and gastric hypomotility.95,98

Neoplasia can cause gastroduodenal ulceration in dogs and cats.30–32,38,99 In cats, infiltrative neoplasia of the gastrointestinal tract, such as mast cell tumors or lymphoma, is one of the most common causes of gastroduodenal ulceration.30,32,38 In dogs, infiltrative neoplasia has been less commonly reported to cause gastroduodenal ulceration.31,32

Paraneoplastic syndromes associated with mast cell tumors and gastrinomas cause erosions or ulcers due to the effects of excess production of histamine and gastrin, respectively, on the gastric mucosa. Serum histamine concentration is significantly increased in dogs with mast cell tumors.99 Gastrinomas are non-β-ιlet cell tumors of the pancreas or, more rarely, of extrapancreatic tissue such as the duodenum.100 Gastrinomas promote gastric ulceration by autonomous gastrin hypersecretion and severe gastric hyperacidity.101

Conclusion

Gastroduodenal ulceration is a complex and potentially life-threatening condition in small animals. The gastric epithelium must be constantly protected from a harsh luminal environment consisting of acid and digestive enzymes. When the intricate gastric cytoprotective mechanisms fail, epithelial damage occurs. The clinical presentation and laboratory tests in dogs and cats with gastric erosions or ulcers are often non-specific, and imaging may only be abnormal in very severe disease. Thus, it is important for the clinician to have a high index of suspicion that gastrointestinal ulceration may exist and be able to recognize the common comorbidities associated with gastric erosion/ulceration in dogs and cats, such as the administration of anti-inflammatory treatments, neoplasia, gastrointestinal inflammation, spinal injuries, liver disease, and hemodynamic disturbances in order to make a timely diagnosis. The second part of this series will discuss drug therapy to prevent and/or treat gastric ulcer disease.

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