

CONSENSUS STATEMENT

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ACVIM consensus statement: Support for rational administration of gastrointestinal protectants to dogs and cats

Stanley L. Marks¹  | Peter H. Kook²  | Mark G. Papich³  | M. K. Tolbert⁴  |
Michael D. Willard⁴

¹Department of Medicine & Epidemiology, School of Veterinary Medicine, University of California, Davis, Davis, California

²Vetsuisse Faculty, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

³Department of Molecular Biomedical Sciences, North Carolina State University, College of Veterinary Medicine, Raleigh, North Carolina

⁴Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Texas A & M University, College Station, Texas

Correspondence

Stanley L. Marks, Department of Medicine & Epidemiology, School of Veterinary Medicine, University of California, Davis, One Shields Avenue, Davis, CA 95616.

Email: slmarks@ucdavis.edu

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The gastrointestinal (GI) mucosal barrier is continuously exposed to noxious toxins, reactive oxygen species, microbes, and drugs, leading to the development of inflammatory, erosive, and ultimately ulcerative lesions. This report offers a consensus opinion on the rational administration of GI protectants to dogs and cats, with an emphasis on proton pump inhibitors (PPIs), histamine type-2 receptor antagonists (H₂RAs), misoprostol, and sucralfate. These medications decrease gastric acidity or promote mucosal protective mechanisms, transforming the management of dyspepsia, peptic ulceration, and gastroesophageal reflux disease. In contrast to guidelines that have been established in people for the optimal treatment of gastroduodenal ulcers and gastroesophageal reflux disease, effective clinical dosages of antisecretory drugs have not been well established in the dog and cat to date. Similar to the situation in human medicine, practice of inappropriate prescription of acid suppressants is also commonplace in veterinary medicine. This report challenges the dogma and clinical practice of administering GI protectants for the routine management of gastritis, pancreatitis, hepatic disease, and renal disease in dogs and cats lacking additional risk factors for ulceration or concerns for GI bleeding. Judicious use of acid suppressants is warranted considering recent studies that have documented adverse effects of long-term supplementation of PPIs in people and animals.

KEY WORDS

acid, canine, feline, gastroesophageal reflux, histamine type-2 receptor antagonist, misoprostol, proton pump inhibitor, sucralfate, ulcer

Abbreviations: ANP, atrial natriuretic peptide; CKD, chronic kidney disease; DU, duodenal ulcer; EC, enterochromaffin cells; ECL, enterochromaffin-like cells; GCN, gastric cholinergic neurons; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GUE, gastroduodenal ulceration and erosion; GRP, gastrin-releasing peptide neurons; H₂RA, histamine type-2 receptor antagonist; ICU, intensive care unit; IRIS, international renal interest society; ITP, immune-mediated thrombocytopenia; MPT, mean percentage time; NAB, nocturnal acid breakthrough; NSAID, non-steroidal anti-inflammatory drug; PACAP, pituitary adenylate-cyclase activating peptide neurons; PPI, proton pump inhibitor; RAH, rebound acid hypersecretion; RCT, randomized controlled trial; SST, somatostatin; SRI, stress related injury; SRMD, stress-related mucosal damage; SUP, stress ulcer prevention; VIP, vasoactive intestinal peptide neurons

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1 | INTRODUCTION

Advances in the understanding of the regulation of gastric acid secretion have improved management of acid-related disorders in people. Knowledge of the acid secretion regulatory mechanisms led to the development of histamine type-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) that have reformed the treatment of acid-related disorders. The PPIs and H₂RAs are extensively overprescribed in human primary and secondary care hospitals. Existing guidelines often are not followed.^{1–4} A similar practice of inappropriate prescription of acid suppressants is commonplace in veterinary medicine. Judicious use of acid suppressants is warranted, considering recent studies documenting adverse effects of long-term PPI supplementation in people and animals.^{1,5,6}

The ability to accurately and noninvasively measure intragastric pH with catheter-less radiotelemetric pH monitoring devices (Bravo pH monitoring system, Medtronic Inc., Minneapolis, MN) in recent years has advanced our understanding of the effects of acid suppressants and dosing protocols on intragastric pH in animals^{7–12} and humans.^{13,14} Unfortunately, critical assessment of acid suppressants in experimental models and dogs and cats with spontaneous disease is sparse, and most of the studies evaluating the efficacy of acid suppressants were performed in healthy animals.

2 | PHYSIOLOGIC ROLE OF GASTRIC ACID

The stomach is an active reservoir that stores, triturates, and slowly dispenses partially digested food into the intestine for further digestion and absorption, and also controls appetite and satiety.¹⁵ Its main secretory function is secretion of gastric acid,¹⁶ which initiates peptic hydrolysis of dietary proteins, liberates vitamin B12 from dietary protein, facilitates duodenal absorption of inorganic iron¹⁷ and calcium,¹⁸ stimulates pancreatic HCO₃[–] secretion via secretin release,¹⁹ suppresses antral gastrin release, and modulates the intestinal microbiome by killing microorganisms and preventing bacterial overgrowth.²⁰ Comprehensive overviews of the regulation of gastric acid secretion (Supplement 1) and regulation of gastric mucosal barrier function (Supplement 2) are available in the Supporting Information.

3 | PHYSIOLOGIC CONSIDERATIONS OF DIFFERENCES BETWEEN HUMANS AND DOGS AND CATS

Dogs have lower basal acid secretory rates but considerably higher peak gastric acid responses compared to humans,^{21,22} but these early data are mostly derived from experiments using pharmacologic stimulation of gastric acid secretion in dogs and cats with surgically placed gastric fistulas.²³ Although higher fasting gastric pH was reported in some studies,²⁴ fasting gastric pH was comparable in dogs, cats, and humans in more recent studies.^{7,8,25–27} The intragastric pH of healthy control dogs measured with a catheter-less pH capsule remained <2.0 >85% of the time, with a mean percentage time (MPT) intragastric pH > 4.0 of only 4.7%.⁸ Similarly, in another study using the same

methodology, the median gastric pH was 1.1 and the median percentage of the investigation time that the gastric pH fluctuated between 0.5 and 2.5 was 90.32% (range, 78%–97.4%).⁷ In 2 recent studies recording intragastric pH in cats over 4 days using the same methodology, comparable results were reported.^{26,27} These results compare well to the MPT intragastric pH > 4 of 4.4% reported for healthy people.²⁸

Gastric pH in people increases with feeding because of the buffering effect of food, but dogs and cats differ because the buffering effect of food is not consistently observed and is much smaller in effect, if present at all.^{8,24,26} This observation may be caused by higher peak acid output in fed dogs. Another explanation may be differences in methodology, because the pH capsule methodology used in newer studies,^{7,8,26,27} unlike digital probes, allows direct adherence to the gastric mucosa and provides direct measurement of intragastric pH.

4 | MECHANISM OF ACTION, BIOLOGICAL TARGETS, EFFICACY, ADVERSE EFFECTS, AND DRUG INTERACTIONS OF GASTROPROTECTANTS IN HUMANS, DOGS, AND CATS

4.1 | Antacids

Antacids are the oldest of the gastrointestinal (GI) protectants and comprise a group of inorganic, relatively insoluble salts of aluminum hydroxide (Al(OH)₃), calcium carbonate (CaCO₃), and magnesium hydroxide (Mg(OH)₂) that lack systemic effects.²⁹

4.1.1 | Mechanism of action

Antacids also may be beneficial by decreasing pepsin activity, binding to bile acids in the stomach, and stimulating local prostaglandin (eg, PGE₂) synthesis. There is an outdated belief that antacids are effective because they increase gastric pH, but this action is unlikely, or only temporary, because these agents do not exhibit strong enough buffering capacity.^{30,31}

4.1.2 | Clinical efficacy

Antacids are used only in humans with gastroesophageal reflux disease (GERD) clinical signs that occur infrequently, or as breakthrough agents in patients taking H₂RAs or PPIs. One of the popular products used for reflux esophagitis in people is Gaviscon. The formulations in the United States contain aluminum hydroxide and magnesium trisilicate (tablet) or magnesium carbonate (oral suspension). The Gaviscon product available in the United Kingdom is more effective for reflux esophagitis than is the formulation sold in the United States. Whereas the US form of Gaviscon is primarily designed to neutralize acid, the formulation in the United Kingdom contains sodium alginate, with other antacid ingredients (Gaviscon Advance or Gaviscon Double Action Liquid). The addition of alginate is intended to form a physical barrier to prevent acid reflux into the esophagus³² or to neutralize the “acid pocket” that forms at the gastro-esophageal junction.³³ When alginate encounters gastric acid, it forms a foam that acts as a raft to

float on top of stomach contents. This feature may act as a physical barrier in the cardia region to prevent acid reflux or to neutralize the acid pocket that forms on top of stomach contents after a meal.

4.1.3 | Adverse effects and interactions

The most common adverse effect of aluminum-containing antacids is constipation, but adverse effects from antacids are rare because they are seldom administered long term. In renal failure, magnesium and aluminum accumulation may be a problem, and aluminum toxicity after administration of aluminum hydroxide has been documented in dogs with advanced renal failure.³⁴ Antacids interfere with the PO absorption of other drugs (eg, tetracyclines, fluoroquinolones, and digoxin), if administered concurrently. The magnesium (Mg^{2+}) and aluminum (Al^{3+}) components, like any tri- or di-valent cation can chelate fluoroquinolones or tetracyclines and inhibit PO absorption. If these drugs are used together, the antibiotic should be administered 2 hours before the antacid. Oral absorption of azole antifungal drugs can be decreased when gastric acidity is suppressed, and this effect is discussed in more detail later in this consensus statement.

4.1.4 | Dosing recommendations

Dosage recommendations for dogs and cats are based on anecdotal experience. The onset of action is rapid, and the effects last 30-60 minutes, necessitating frequent administration.³¹ Empirical dosing of 5-10 mL 6 times daily often is cited for dogs and cats, regardless of the animal's size or product used. The frequency of administration is an important disadvantage for administration to pets.

Consensus opinion on use of antacids in dogs and cats

Although antacids may produce partial short-term neutralization of gastric acid, insufficient evidence is available to recommend antacids for treatment of gastroduodenal ulceration and erosion (GUE) or GER disease in dogs and cats. These agents may be difficult to administer with the frequency needed to control gastric acid, and other longer acting and more effective acid-suppressing agents are available.

4.2 | Histamine type-2 receptor antagonists

4.2.1 | Mechanism of action

Histamine type-2 receptor antagonists (H_2 Rs; eg, cimetidine, ranitidine, and famotidine) inhibit acid secretion by competitively blocking H_2 receptors on the parietal cell, thus decreasing basal and meal-stimulated gastric acid secretion. The H_2 Rs are eliminated by a combination of renal excretion and hepatic metabolism. Continuous H_2 RA administration results in pharmacological tolerance.^{9,35,36} In dogs, such tachyphylaxis occurs within 13 days, and may be noticed within 3 days. The same phenomenon has been documented in cats. Daily famotidine administration resulted in a 60% decrease in MPT pH ≥ 3 in 16 healthy colony cats between days 1 and 13 of treatment.³⁷ The phenomenon of tolerance appears to occur even more rapidly (12-72 hours) in human subjects when the famotidine is administered IV.³⁸ Tolerance may be caused by gastrin-induced up-regulation of enterochromaffin-like cell (ECL) synthesis of histamine, which in turn competes with the antagonist at the parietal cell.^{39,40} Because of this tolerance, abrupt discontinuation of H_2 Rs causes rebound acid

hypersecretion in humans as a result of the trophic properties of gastrin on ECL cells.³⁵

4.2.2 | Clinical efficacy

Measures of efficacy of H_2 Rs in companion animals are scarce. Notably, the degree of gastric acid suppression necessary for GUE prophylaxis or treatment in dogs and cats is undetermined. The H_2 Rs are inferior to PPIs for increasing intragastric pH, as well as for prevention of exercise-induced gastritis in dogs.^{8,26,27,41-43} In a study of beagle dogs, famotidine (0.5 mg/kg q12h) increased intragastric pH more and for a longer time compared to ranitidine (2 mg/kg q12h) based on continuous 24-hour intragastric pH measurements via gastrostomy tube.⁴¹ Higher dosages of famotidine (1-1.3 mg/kg q12h) had only a weak effect on intragastric pH in a study in healthy mixed-breed dogs.⁸ Similarly, even though PO famotidine (1 mg/kg q24h) decreased the severity of gastric lesions in racing sled dogs compared with no treatment,⁴³ omeprazole (0.85 mg/kg PO q24h) significantly decreased the severity and prevalence of gastric lesions compared with famotidine (1.7 mg/kg PO q12h) in a similar study.⁴⁴ Similar findings were obtained in cats. Famotidine (0.88-1.26 mg/kg PO q12h) was significantly more efficacious than placebo but inferior to omeprazole in increasing intragastric pH in healthy colony cats.²⁶ In healthy cats, no difference was observed between ranitidine (1.5-2.3 mg/kg PO q12h) and placebo.²⁷

Consensus opinion on effectiveness of H_2 Rs for management of gastroduodenal ulceration or reflux esophagitis

There is a lack of benefit for administration of H_2 Rs on a once-daily basis in dogs and cats to treat GUE and reflux esophagitis. Monotherapy with an H_2 RA given twice daily is inferior to PPI treatment given twice daily in dogs and cats. There is no evidence of benefit of administration of an H_2 RA with a PPI for ulcer healing, and this combination may diminish the effectiveness of the PPI.

4.3 | Proton pump inhibitors

4.3.1 | Mechanism of action

The PPIs (eg, omeprazole, pantoprazole, esomeprazole, and lansoprazole) are substituted benzimidazole drugs that target the final common pathway of acid production. The PPIs are significantly more effective than H_2 Rs in increasing gastric pH and preventing and healing acid-related tissue injury in people.^{45,46} The PPIs are weak bases that are unprotonated at the physiologic pH of the blood. Once the PPI accumulates in the acidic environment of the active parietal cell, the drug becomes protonated and trapped where it forms disulfide bonds with cysteine residues on the alpha subunit of H^+-K^+ -ATPases, producing enzyme inactivation.^{47,48} Acid secretion resumes only after new proton pumps are synthesized, resulting in a prolonged effect after administration. Dormant parietal cells are activated after initial PPI administration. Thus, inhibition of acid secretion is approximately 30% of maximal on day 1 of administration because of incomplete binding to all H^+-K^+ -ATPases. Maximal inhibitory effect is achieved within approximately 2-4 days of PPI administration.⁴⁸⁻⁵¹ Because the inhibitory activity of PPIs is dependent on the ability to bind to active H^+-K^+ -ATPase enzymes, plasma concentrations of PPIs

do not necessarily predict their efficacy. The best surrogate predictors of the inhibitory effect of PPIs on gastric acid secretion are the area under the concentration-time curve and gastric pH profile.⁵²

Delay in maximal PPI activity also is related to their stability. When administered in an acid environment, the acid-labile drug may be degraded before it reaches the intestine where it is absorbed systemically. After repeated administration, acid secretion gradually diminishes to maximize intestinal drug absorption.⁵³ Initial treatment with IV formulations, administering an enteric-coated delayed-release formulation, or combining PO formulations with bicarbonate will decrease the lag-time for achieving maximal effect. Breaking or crushing an enteric-coated form, or using a compounded formulation may diminish this protective effect.^{54,55} Because of shorter intestinal transit in dogs and cats, compared to humans, it is unknown if delayed-release formulations are effective in small animals. Another hypothesis to explain increased concentrations with repeated doses is inhibition of cytochrome P450 enzymes by omeprazole, thus inhibiting its own metabolism.⁵⁶ Omeprazole is a well-known inhibitor of the predominant cytochrome P450 (CYP) enzyme in people, CYP 2C19. It is unknown which enzymes (if any) are inhibited in dogs or cats.

Acid secretion is activated by ingestion of a meal, and PPI effectiveness depends on the extent of activation of acid secretion at the time of drug administration. The PPIs are most effective when taken shortly before a meal (30–45 minutes) or with a meal. Effectiveness in people is compromised if taken without a meal.⁵⁷ In addition, effectiveness of omeprazole was markedly compromised in dogs if administered while acid secretion was inhibited by co-administration of H₂RAs.⁵⁸ The R-enantiomer of lansoprazole, dexlansoprazole, is a new slow-release PPI, and gastric pH may not be impacted by timing of meal intake and administration of newer PPIs.⁵⁹ It is unknown if these newer PPI formulations have an advantage for dogs and cats.

4.3.2 | Metabolism

The PPIs are metabolized by cytochrome P450 enzymes. Omeprazole can inhibit its own metabolism or inhibit the metabolism of other drugs metabolized by the same enzyme.^{60–62} Drugs affected in people include warfarin, clopidogrel, and diazepam. The population of CYP enzymes is not the same in people and dogs.^{63,64} Therefore, it is undetermined if omeprazole inhibits metabolism of these, or other drugs, in dogs.

The differences among the PPI drugs include, but are not limited to, the cysteine residue with which they form disulfide bonds, their pharmacokinetic properties (eg, half-life, maximum concentration of the drug achieved in the plasma after dose administration [C_{max}], time at which C_{max} is attained [t_{max}]), drug interactions, and susceptibility to CYP metabolism. These differences can translate into slight variation in acid suppression, but the magnitude of efficacy in people remains similar.⁶⁵ Standard doses of esomeprazole, the S-enantiomer of omeprazole, resulted in greater gastric acid control compared to standard doses of traditional PPIs.^{66,67} The pharmacokinetics and acid suppressant efficacy of esomeprazole after IV, PO, and SQ administration in healthy beagles has been studied,⁶⁸ but it was not compared to other PPIs.⁶⁸ Intravenously administered esomeprazole was documented to significantly increase gastric and esophageal pH in dogs

undergoing elective orthopedic procedures.⁶⁹ However, with the exception of esomeprazole in the treatment of GERD, most clinical studies in people suggest that older generation PPIs (eg, omeprazole and pantoprazole) have similar efficacy for treatment of acid-induced tissue injury.

Consensus opinion on the superiority of one PPI over another

There is no conclusive evidence in dogs and cats to show that one PPI is clinically more effective than another for the treatment of GUE in dogs or cats.

4.3.3 | Clinical efficacy

Clinical studies investigating the efficacy of PPIs in dogs and cats are limited. Most PPI studies in cats and dogs were designed as preclinical development trials for humans. Many of these studies involved pharmacologic stimulation of gastric acid secretion using healthy animals with surgically placed gastric fistulas. It is unknown if such results accurately reflect the clinical response of gastric pH to PPIs. In healthy dogs and cats, PPIs are consistently superior to H₂RAs for increasing intragastric pH and prevention of exercise-induced gastritis in dogs.^{8,26,27,41,44} With regard to frequency, omeprazole should be administered twice daily to approach pH goals in dogs and cats that were established for the treatment of acid-related disorders in people.^{8,27,41,70,71} This conclusion is supported by a single report showing no benefit of once-daily PO-administered omeprazole compared to cimetidine or placebo in ulcer healing scores in dogs with aspirin-induced ulcers.⁷² No benefit was detected in MPT intragastric pH \geq 3 and 4 in healthy dogs when famotidine was administered concurrently with IV pantoprazole.⁷³ Proton pump inhibitors should be gradually tapered after administration for \geq 4 weeks to avoid rebound gastric acid hypersecretion (RAH).⁵ The dose can be decreased by 50% on a weekly basis, with cessation of evening dosing during the first week.

Consensus opinion on effectiveness of PPIs in dogs and cats

Based on evidence from studies in humans and research animals, PPIs administered twice daily are superior to other gastroprotectants for treating acid-related GUE. Our consensus opinion is that PPIs should be tapered in dogs and cats after prolonged use of >3–4 weeks.

4.3.4 | Drug interactions with proton pump inhibitors

Several documented and potential drug-drug interactions have been associated with PPI administration. Administration of PPIs increases gastric lumen pH from a normal of 1-2 units to \geq 4 for a greater part of the day. Absorption of some drugs and nutrients requires acid because they exhibit pH-dependent drug solubility or dissolution (ie, weak bases), others require an acidic pH for drug release from its protective coating. Therefore, simultaneous PPI administration with some drugs may affect PO absorption, decreasing systemic exposure and clinical effect.

Antifungal drugs

Antifungal drugs of the azole class (eg, ketoconazole, itraconazole, voriconazole, and posaconazole) are inherently poorly soluble. They must undergo dissolution at a low pH for PO absorption and are

ideally administered PO with food to stimulate acid secretion. Dietary lipids also help drug solubilization. Itraconazole solution for PO use is an exception because it is formulated in a cyclodextrin complex to maintain solubility in solution. Fluconazole also is an exception because it is more water soluble. Significant impairment of dissolution and PO absorption of ketoconazole has been shown experimentally when increasing the gastric pH profile in dogs.⁷⁴ Similar results are expected from PO administration of itraconazole and posaconazole with acid-suppressing agents.

Iron

Hydrochloric acid in the stomach promotes iron absorption because it reduces the ferric acid form to the more soluble ferrous form. Human patients on chronic PPI treatment may have decreased PO absorption of iron. The effect of chronic administration of PPIs on PO iron absorption has not been explored in small animals.

Mycophenolate

Mycophenolate is administered as mycophenolate mofetil, an ester prodrug that must be converted to mycophenolic acid to produce inhibition of purine synthesis and an immunosuppressive effect. Because intestinal disturbances are common among mycophenolate-treated patients, PPIs often are prescribed to decrease GI problems.⁷⁵ Mycophenolate mofetil requires acidic pH for dissolution of the medication and for hydrolysis to mycophenolic acid. If PPIs are administered concurrently, the increased pH decreases absorption of the active drug.⁷⁵ This interaction has been identified in people, but has not been explored in dogs or cats.

Clopidogrel

The prodrug clopidogrel must be converted to the active form before inhibiting platelet function. In humans, the CYP enzymes are responsible for conversion to the active metabolite, but whether or not dogs and cats metabolize clopidogrel with the same enzymes is unknown. Because omeprazole inhibits the CYP2C19 enzyme in people, it potentially can interfere with the biotransformation responsible for the formation of the active metabolite of clopidogrel and compromise antiplatelet treatment.⁷⁶ The US Food and Drug Administration (FDA) recommends that "concomitant use of drugs that inhibit CYP2C19 should be discouraged." However, the importance of this interaction is controversial.⁷⁶ Other factors contribute to variable effects of clopidogrel in people, including CYP2C19 enzyme polymorphism and variations in the enzyme paraoxanase-1, which affects the biological activity of clopidogrel.^{77,78} In a recent study, coadministration of omeprazole and clopidogrel to experimental dogs did not decrease the antiplatelet effects of clopidogrel, but the active metabolite was not measured.⁷⁹

Consensus opinion on drug interactions with PPIs

Although there is no direct evidence in dogs or cats, there is compelling evidence based on pharmacologic principles and reports from human medicine that PPIs should not be administered concurrently with other agents that require an acid milieu for oral absorption.⁷⁹

4.3.5 | Adverse effects of PPIs

Retrospective reports have linked PPIs to acute interstitial nephritis, acute kidney injury, and chronic kidney disease (CKD) in people,⁸⁰⁻⁸² but these studies did not identify cause and effect and were limited by inability to control for bias and confounding variables. Other adverse effects associated with chronic PPI administration in people include dementia,⁸³ cobalamin deficiency,⁸⁴ osteoporosis and pathologic fractures,⁸⁵ community-acquired pneumonia,⁸⁶ hypomagnesemia,⁸⁷ cardiovascular events, *Clostridium difficile*-associated diarrhea,^{88,89} drug interactions, and spontaneous bacterial peritonitis in patients with hepatic cirrhosis.⁹⁰ Virtually, all of these associations were published in observational cohort and retrospective studies, with similar limitations as highlighted above. Despite the long list of potential adverse effects associated with PPI treatment, the quality of evidence underlying these associations is consistently low. When treating dogs and cats, judicious use of PPIs and a critical evaluation of the risks versus benefits of PPI use are advised on a case-by-case basis. The implementation of standardized guidelines describing appropriate indications for PPI use may help limit the overuse of these agents.

Because these drugs are not FDA-approved for dogs or cats, there is no mandatory reporting requirement and the incidence of adverse effects from PPIs is unknown in dogs and cats. Two potential adverse effects from chronic administration of PPI have received attention. Because of loss of negative feedback mechanisms, blood gastrin concentrations are increased as a result of PPI administration.⁹¹ Consequently, gastrin exerts a trophic effect on the gastric mucosa and has been linked to development of gastric tumors arising from ECL cells in rats. After years of experience with PPI use, this issue is no longer a concern in people. No similar studies have been done in dogs and cats.

Small intestinal bacterial overgrowth is another adverse consequence of chronic PPI administration in people.^{92,93} Proton pump inhibitors increased survival of swallowed bacteria in the upper GI tract by decreased intestinal peristalsis, decreased gastric emptying, changes in epithelial mucus composition, increased pH, and increased bacterial translocation. Increased growth of bacteria in the upper GI tract may increase the risk of bacterial aspiration pneumonia.

Bacterial overgrowth can have deleterious consequences when PPIs are administered with other drugs that can injure the small intestinal (SI) mucosa.⁹⁴ It is common to prescribe PPIs in patients at risk for upper GI injury from nonsteroidal anti-inflammatory drugs (NSAIDs), but PPIs can alter the SI microbiome, increasing the risk of injury to the intestinal epithelium caused by NSAIDs. This effect is acid-independent and unrelated to gastric mucosa injury caused by NSAIDs. Inhibition of intestinal cyclooxygenase 1 and 2 (COX-1, COX-2) enzymes injures the SI mucosa. Enterohepatic recycling of NSAIDs likely plays a role whereby high concentrations of NSAIDs in bile are secreted into the duodenum in close proximity to the major duodenal papilla. Some of the most serious intestinal lesions in dogs caused by NSAIDs occur in this region.^{10,95,96} Small intestinal injury may be caused by increased numbers of gram-negative facultative anaerobic bacteria that flourish in the SI of patients treated with PPIs. Lesions are characterized by loss of villi, erosions, and multifocal ulcers distributed throughout the small bowel. Anemia also may occur.

Whereas some bacteria play a protective role against intestinal mucosal injury by NSAIDs, the intestinal dysbiosis arising from PPI administration increases the risk of NSAID-induced intestinal injury.⁹⁴ Administration of antibiotics or probiotics may mitigate injuries caused by this drug combination,⁹⁴ but such studies have not been conducted in dogs or cats.

Diarrhea is the most common adverse effect reported in association with PPI administration in dogs.^{41,97} This adverse effect has not been reported in cats.^{26,27} A pilot study performed in 6 healthy cats suggested that RAH may occur after abrupt PPI discontinuation after prolonged PPI administration and cause a mild transient change in the fecal microbiota.⁹⁸

Consensus opinion on adverse effects of PPIs in dogs and cats

Evidence is lacking to show that administration of PPIs causes serious adverse effects in dogs or cats. However, intestinal dysbiosis is possible, which could lead to other complications, such as bacterial pneumonia or complications from NSAIDs.

4.4 | Misoprostol

4.4.1 | Mechanism of action

Misoprostol is a synthetic prostaglandin E₁ analogue that has relative specificity for parietal cell receptors and decreases histamine, pentagastrin, and meal-stimulated gastric acid secretion.⁹⁹ Misoprostol binds to prostaglandin receptors and inhibits histamine-stimulated cAMP formation, but its cytoprotective effects occur at dosages below those necessary to inhibit gastric acid secretion. Cytoprotective effects are caused by increased bicarbonate secretion, decreased pepsin content of gastric secretion, preservation of tight junctions among epithelial cells, increased mucus layer, increased mucosal blood flow, and improvement of mucosal regenerative capacity.¹⁰⁰ In dogs, absorption of PO misoprostol is nearly complete. Rate of absorption is slowed by food in the stomach, which may decrease adverse effects such as diarrhea.¹⁰¹

4.4.2 | Efficacy

Results from 41 control dogs and 39 dogs treated with misoprostol and aspirin at dosages ranging from 25 to 35 mg/kg q8h have been published in refereed journals, (but only 1 was a randomized controlled trial [RCT]¹⁰²⁻¹⁰⁶; Table 1). Misoprostol dosages ranged from 3 µg/kg PO q12h to 15 µg/kg PO q8h. Dosing misoprostol once daily appears inadequate compared to administration q8h to q12h.¹⁰⁴ Misoprostol significantly decreased GUE or hemorrhage associated with aspirin, but it did not completely eliminate gastric lesions. Misoprostol can be considered as prophylaxis for NSAID treatment if there is clearly a need for prophylaxis and PPIs fail or cannot be used. Except for aspirin, effectiveness of misoprostol for GI injury from other NSAIDs has not been tested in dogs and cats. Misoprostol is less effective for treating or preventing duodenal ulcer (DU) compared to GUE in both dogs and cats.^{107,108}

No evidence supports the use of misoprostol for preventing corticosteroid-induced GUE in dogs.^{109,110} Misoprostol administration to laboratory dogs at 4-6 µg/kg q8h did not prevent endoscopically visible gastric hemorrhage associated with methylprednisolone

administration (30 mg/kg initially and then 15 mg/kg for an additional 6 doses over 48 hours).¹¹⁰ The RCTs assessing the efficacy of misoprostol in dogs with intervertebral disc disease treated with surgery and high-dose corticosteroids did not show a benefit from misoprostol or other gastroprotectant drugs.^{109,111}

Two published studies have evaluated the efficacy of misoprostol in cats. A constant rate infusion of misoprostol to laboratory cats in which septic shock was induced was found to be superior to administration of superoxide dismutase in decreasing GUE.¹¹² Misoprostol administered at 3 µg/kg q12h also was shown to decrease aspirin-associated GUE (but not duodenal ulceration) in a study comparing the efficacy of misoprostol and cimetidine.¹⁰⁸

4.4.3 | Adverse effects

Adverse effects, in particular abdominal pain and diarrhea, are the main reasons why misoprostol is used infrequently in people to prevent GUE.¹¹³ Abortion (because of increased tonus of the uterus and cervical softening) is an important adverse effect of the drug and has become the primary reason for misoprostol administration as an abortifacient in people.¹¹⁴

Consensus opinion on the effectiveness of misoprostol in dogs and cats

Misoprostol is effective for decreasing gastric lesions in dogs treated with high-dose aspirin, but it is unknown if misoprostol is effective for preventing GUE associated with administration of other NSAIDs in dogs and cats. There is no evidence that misoprostol decreases GUE from glucocorticoids in dogs and cats.

4.5 | Sucralfate

4.5.1 | Mechanism of action

Sucralfate (Carafate) is a complex salt of sucrose octasulfate and aluminum hydroxide.¹¹⁵ Its mechanism of action in acid-peptic disease is multifactorial. Sucralfate forms stable complexes with protein in damaged mucosa where there is a high concentration of protein, either from fibrinogen, albumin, or globulins from the exudate of an ulcer or from damaged cells.¹¹⁵

4.5.2 | Metabolism

In an acidic environment, sucralfate becomes viscous and partially dissociates into sucrose sulfate and aluminum hydroxide. The sucrose sulfate moiety is an anion and binds electrostatically with the positively charged proteins in the damaged mucosa.¹¹⁵ Sucralfate interferes with the action of pepsin either by preventing pepsin digestion of protein substrates, by binding to pepsin, or by providing a barrier to prevent diffusion of pepsin.¹¹⁵ In addition, the protection afforded by sucralfate against esophageal acid injury is mediated by intraluminal pH buffering via aluminum hydroxide and protection against H⁺ entry and injury via sucrose octasulfate.¹¹⁶

4.5.3 | Clinical efficacy

In an ex vivo model of acid-induced mucosal bleeding in dogs, sucralfate was effective in promoting repair of the gastric mucosal tissue when applied at the time of or shortly after acid-induced injury.¹¹⁷

TABLE 1 Published studies on the effect of misoprostol on dogs and cats treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or *Escherichia coli*

Author	Species	Type of study (n = number of animals in group)	Dose of MIS	Aggressor agent and dose	Effects
Arvidsson ¹	Cat	Experimental	5 µg/kg/h IV	Live <i>E. coli</i> IV	
Arvidsson ²		The relationship between this abstract and the experimental study listed above is uncertain. Hence, the data are not listed.			
Holtroyde ³	Dog	Experimental	1, 5, and 10 µg/kg PO given before each dose of ACA	ACA (65 mg/kg 4X in 24 hours)	MIS reduced gastric mucosal injury as determined endoscopically
Johnson ⁴	Dog	Experimental ACA alone (6), MIS alone (6), ACA + MIS (6)	3 µg/kg PO q8h	ACA (35 mg/kg q8h)	MIS reduced gastric mucosal injury as determined endoscopically
Bowersox ⁵	Dog	Experimental No treatment (5), ACA alone (5), MIS alone (5), ACA + MIS (5)	15 µg/kg PO q8h for 5 days, then 7.5 µg/kg q8h	ACA (35 mg/kg q8h)	MIS eliminated all gastric mucosal injury as determined endoscopically except 1 dog that had 1 petechia
Ward ⁶	Dog	Experimental ACA alone (6), ACA + MIS at q8 (6) or q12 (6) or q24h (6)	3 µg/kg PO at either q8h, q12h or q24h	ACA (25 mg/kg q8h)	MIS administered q8h and q12h reduced gastric mucosal injury as determined endoscopically
Guanoukous ⁷	Dog	Experimental VAG alone (10), DIC alone (10), VAG + DIC (10), DIC + MIS (10), VAG + DIC + MIS (10)	8-20 µg/kg PO q6h	DIC (1 mg/kg IM q24h for 12 days) mucosal injury	MIS alone did not prevent mucosal injury as determined by necropsy; MIS plus VAG reduced gastric
Rohrer ⁸	Dog	Placebo controlled trial Surgery + steroid (9), Surgery + steroid + MIS (9)	4-6 µg/kg PO q8h	Methylprednisolone 30 mg/kg IV, then 15 mg/kg q6h	MIS did not reduce gastric hemorrhage as determined endoscopically
Doğra ⁹	Dog	Experimental All dogs received steroid until ulcer formation, then lansoprazole (4), sucralfate (4), famotidine (4), MIS (4), herbal (4)	10 µg/kg PO (frequency uncertain)	Dexamethasone 1 mg/kg q12h until have ulcer	MIS administration associated with slowest rate of healing of previously formed steroid-associated ulcers
Murtaugh ¹⁰	Dog	Randomized, double-blind trial ACA only (8), ACA + MIS (10)	100 µg/dog PO q8h = 3.1 µg/kg (mean), range 2.3-5 µg/kg	ACA (25 mg/kg q8h)	MIS reduced gastric mucosal injury as determined endoscopically
Hansen ¹¹	Dog	Randomized clinical trial All dogs had spinal surgery + steroids: control (10), cimetidine (10), sucralfate (10), MIS (10)	4 µg/kg PO q8h ± 2nd dose 15-30 mg/kg IV	Methylprednisolone 30 mg/kg IV, ± 2nd dose 15-30 mg/kg IV	MIS did not reduce GI blood loss as determined by gross examination or stool guiac slide test
Neiger ¹²	Dog	Randomized clinical trial All dogs had spinal surgery + dexamethasone: control (8), MIS (8), omeprazole (9)	2 µg/kg PO q8h	Dexamethasone 2 mg/kg IV followed by 1 mg/kg and then 0.5 mg/kg	MIS did not reduce gastric mucosal injury as determined endoscopically
Satoh ¹³	Cat	Experimental ACA only (4-6), ACA + MIS (4-6), ACA + cimetidine (4-6)	3 µg/kg PO q12h	ACA (20 mg/cat)	MIS reduced gastric mucosal injury as determined by necropsy examination

Abbreviations: ACA, aspirin; DIC, diclofenac; IV, intravenous; MIS, misoprostol; PO, per os; VAG, highly selective vagotomy.

Sucralfate also may provide a barrier for bile salts. Sucralfate is known to stimulate prostaglandin production in the gastric epithelium. This may be a potential secondary effect of sucralfate in the esophagus, although the importance and effectiveness of sucralfate as an agent for the treatment of erosive esophagitis is not as established as it has been for H₂RAs or PPIs.

In rabbits, esophagitis induced by acid and pepsin was prevented by administration of sucralfate.¹¹⁸ In another study, cats pretreated with liquid sucralfate before acid infusion were protected against esophagitis.¹¹⁹ Studies in humans have compared sucralfate to other forms of treatment including alginic acid/antacid, cimetidine, and ranitidine. Sucralfate was as effective as Gaviscon containing sodium alginate with regard to healing of esophagitis and symptomatic improvement.^{120,121} The H₂RAs, ranitidine and cimetidine, and sucralfate had equal efficacy for treating reflux esophagitis,^{121–125} although higher grade esophagitis did not heal as well compared to lower grade esophagitis. In foals, sucralfate had a protective effect on oral, esophageal, and gastric ulcers associated with IV administration of high-dose phenylbutazone.¹²⁶ When sucralfate is compared to placebo, conflicting data regarding therapeutic benefit have been obtained in human patients with reflux esophagitis.¹²⁷ Limited esophageal retention time may decrease effectiveness. In a study of technetium-labeled sucralfate, the drug was retained within the esophagus for 3 hours in <50% of the patients with reflux esophagitis.¹²⁸ In addition, sucralfate deposited in a nonacidified esophagus was rapidly cleared and poorly timed to provide protection against reflux injury.¹²⁹ Sucralfate decreased the frequency of stricture formation in human patients with advanced corrosive esophagitis,¹³⁰ and topical sucralfate was effective for post-tonsillectomy analgesia in people.¹³¹ No controlled studies have been completed to assess the analgesic effects of sucralfate in people or animals with severe esophagitis, but anecdotal evidence indicates the drug's analgesic properties in people with esophagitis. In addition, in controlled studies, no significant benefit of treatment was observed involving a combination of sucralfate and H₂RA, compared to either drug alone in treating acute duodenal ulcer, in ulcer maintenance treatment, in stress bleeding, or in reflux esophagitis.

4.5.4 | Adverse effects

Sucralfate is a relatively safe compound and has minimal adverse effects. Aluminum absorption during sucralfate treatment is comparable to that during treatment with aluminum hydroxide, and caution should be exercised with long-term treatment in patients with renal insufficiency to avoid aluminum intoxication.^{132,133} Constipation, caused by aluminum hydroxide, is one of the most common adverse effects, and typically occurs in 1%-3% of human patients taking the drug.¹³⁴ Other adverse effects in humans include xerostomia, nausea, vomiting, headache, urticaria, and rashes in 0-5% of patients.^{134,135}

4.5.5 | Drug interactions with sucralfate

Coadministration of the following drugs with sucralfate results in a substantially decreased bioavailability of single doses of the drug: ciprofloxacin,^{136–138} theophylline,¹³⁹ tetracycline, doxycycline,

minocycline,^{140,141} phenytoin,¹⁴² and digoxin.¹⁴³ The bioavailability of digoxin, tetracycline, doxycycline, and phenytoin was not decreased when they were given 2 hours before sucralfate. Sucralfate impairs absorption of ciprofloxacin in humans and dogs when administered concurrently,^{136,144} but the bioavailability of ciprofloxacin is markedly increased when administration of sucralfate is delayed by 2 hours. Interestingly, no significant difference in bioavailability was documented for enrofloxacin coadministered with sucralfate in dogs.^{136,144}

In contrast to sucralfate suspension, administration of sucralfate tablets had no effect on the absorption of doxycycline in dogs.¹⁴⁰ This lack of interaction with sucralfate tablets suggests sucralfate tablets do not adequately disintegrate in dogs and should be administered as a suspension rather than an intact tablet.

Consensus opinion on the effectiveness of sucralfate for managing esophagitis or gastroduodenal ulceration

There is weak evidence in experimental animals and humans to support the use of sucralfate for preventing or treating esophageal injury. There is moderate evidence that sucralfate may have analgesic effects in people post-tonsillectomy, but no studies have evaluated the analgesic properties of sucralfate in people or animals with esophagitis. No evidence supports either a benefit or interaction when sucralfate is administered concurrently with H₂RAs or PPIs. When administered to dogs (and perhaps cats), intact tablets may not fully disintegrate and may not be as effective as a liquid suspension. No evidence indicates that combining sucralfate with either a PPI or an H₂RA for treatment of GUE is beneficial or indicated. Proton pump inhibitors are superior to sucralfate for management of GUE.

5 | INDICATIONS AND GUIDELINES FOR GASTROPROTECTANTS IN HUMANS

In a meta-analysis involving >14 000 patients, healing of gastric and duodenal ulcers and erosive esophagitis were directly related to the extent and duration of gastric acid suppression over a 24-hour period.^{70,71} Healing of esophagitis was significantly correlated with maintaining gastric pH ≥ 4.0 for at least 16 hours per day, whereas treatment of duodenal ulcers was optimized by maintaining gastric pH ≥ 3 for 18-20 hours per day.⁷¹ Control of nocturnal acidity (as opposed to 24-hour acidity) was directly proportional to healing of duodenal ulcers.¹⁴⁵ In a meta-analysis involving 56 published clinical trials in people, healing of benign gastric ulcers was most strongly correlated with the duration of treatment, unlike with duodenal ulcers.¹⁴⁶

The FDA has listed indications for the use of PPIs in adult human patients (Table 2), and treatment of *Helicobacter pylori* peptic ulcers¹⁴⁷ and GERD¹⁴⁸ are universally considered indications for PPIs. Treatment of erosive esophagitis,¹⁴⁹ benign gastric ulcers,¹⁵⁰ dyspepsia,¹⁵¹ hypersecretory states (eg, Zollinger-Ellison syndrome),¹⁵² and prophylaxis for NSAID-associated ulcers¹⁵³ also are listed as indications for PPI treatment.

TABLE 2 The Food and Drug Administration (FDA) indications for the use of proton pump inhibitors in people compared to lists of questionable indications found in other publications

Diseases	US FDA ^a	Kelly et al. ²²⁴	Rotman et al. ²²⁵	Reid et al. ²²⁶
Duodenal ulcer (ie, peptic ulcer)	X	X	X	X
Treatment of <i>Helicobacter pylori</i>	X	X	X	X
Esophagitis	X		X	X
GERD	X	X	X	X
Gastric ulcers	X		X	X
Drug prophylaxis for NSAID	X	X	X	
Hypersecretory (Zollinger-Ellison)	X			X
"Heartburn"	X		X	
Functional dyspepsia		X	X	X
Gastritis			X	X
Barrett's esophagus			X	
Esophageal varices			X	X
Malignant neoplasm of stomach/esophagus			X	
Hepatic disease			X	
Abdominal pain			X	
Chest pain			X	
Cough			X	
Drug prophylaxis for steroids or antiplatelet drugs			X	
Esophageal perforation			X	
Duodenitis			X	
Gastroparesis			X	
Unspecified hemorrhage of GIT		X	X	

^a See <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ppi-adult-dosingchart.pdf>.

6 | EVIDENCE TO SUPPORT CLINICAL USE OF GASTROPROTECTANTS IN DOGS AND CATS

6.1 | Gastroduodenal ulceration and erosion

Gastrointestinal and pancreatic neoplasia, NSAIDs, hepatic disease, and inflammatory bowel disease were reported in 2 retrospective studies to be associated with GUE in dogs.^{95,154} Non-neoplastic causes of GUE including NSAID-induced injury are associated with ulceration of the gastric fundus, body, pylorus, antrum, and duodenum.¹⁵⁴ In cats, overt GI bleeding secondary to ulcerative disease is not as common as in dogs,¹⁵⁵ but GI and pancreatic neoplasia are common causes of GUE in cats.¹⁵⁶ Gastrointestinal ulceration in cats induced by NSAIDs is uncommon. Duodenal ulceration tends to be more common in cats with extraintestinal neoplasia such as gastrinoma. It is challenging to identify the causes of non-neoplastic GUE in cats.¹⁵⁶ The efficacy of gastroprotectants in cats for the treatment of GUE secondary to these conditions is underexplored and limited to a few reports.^{95,154–156} Regardless of the cause of GUE in dogs and cats, suppression of acid secretion should improve healing. If PPIs are

used, twice-daily administration is superior to once-daily administration to achieve goals of acid suppression for treatment of GUE.

Consensus opinion on gastroprotectants for the management of gastroduodenal ulceration and erosion

Proton pump inhibitors are superior to H₂RAs, sucralfate, and misoprostol for most causes of GUE in people, and should be considered as standard of care for the medical treatment of GUE in dogs and cats.

6.2 | Gastritis (acute versus chronic)

In small animal medicine, gastric acid suppressants often are administered in suspected and histologically confirmed cases of gastritis. The benefit of this regimen is largely extrapolated from human medicine where gastric acid suppression is used to treat *H. pylori* gastritis, a distinct infection not recognized in dogs and cats. The benefit of gastric acid suppression in cases of idiopathic gastritis is not explored. Vomiting may be the primary sign of gastritis in dogs and cats, but acid-suppressant drugs should not be used as antiemetics. Acid suppression with famotidine (0.5 mg/kg q24h) did not affect treatment efficacy or frequency of clinical signs in 23 dogs with histologic evidence of gastritis and spiral bacteria in gastric mucosal biopsy samples.¹⁵⁷ *Helicobacter*-negative gastritis can occur in people and may be comparable to idiopathic gastritis in cats and dogs, but no therapeutic regimens have been reported effective for this condition.¹⁵⁸

Consensus opinion on prophylactic use of gastroprotectants for management of dogs and cats with non-erosive gastritis

There is no evidence to support the prophylactic use of gastroprotectant therapy in dogs and cats with nonerosive gastritis.

6.3 | Hepatic disease

Although hepatic disease has been associated with GUE in dogs, evidence that it is a direct cause of GUE is scarce,^{154,159} and the prevalence of upper GI bleeding has not been assessed in dogs and cats with hepatic disease. The pathogenesis of GUE associated with hepatic disorders is uncertain. Altered mucosal blood flow because of portal hypertension (ie, hypertensive gastropathy) is the most common cause for GI bleeding in humans.¹⁶⁰ Decreased hepatic degradation of gastrin and subsequent stimulation of acid hypersecretion may occur in dogs.¹⁶¹ In a study of dogs with experimentally induced hepatic disease however, low serum gastrin concentrations refuted hypergastrinemia as a cause of GUE in dogs with hepatic disease (Bothe DM. Serum gastrin levels in dogs with progressive liver disease. J Vet Intern Med. 1990;4:122). No difference was found in serum gastrin concentrations between dogs with hepatic disease and healthy controls,¹⁶² but continuous intragastric pH monitoring and GI endoscopy were not performed. Experimental bile duct ligation also can produce gastric ulceration.¹⁶¹ In humans, gastric acid suppression generally is not considered effective at decreasing bleeding associated with portal hypertensive gastropathy, because these patients already have hypochlorhydria.¹⁶⁰ However, PPIs indirectly may stop gastric bleeding by increasing intraluminal gastric pH and thereby stabilizing blood clots.¹⁶³ An auxiliary finding in a recent study on endovascular

treatment of intrahepatic shunts in dogs was a substantial decrease in deaths attributed to GI hemorrhage or ulceration after implementation of peri- and postsurgical lifelong administration of PPIs.¹⁶⁴ However, the mechanism for GI bleeding in these dogs is uncertain and may not be related to hepatic dysfunction or portal hypertension.

Consensus opinion on prophylactic use of acid suppressants in dogs and cats with hepatic disease

There is weak evidence to support the prophylactic use of acid suppressant therapy in dogs and cats with hepatic disease that is not associated with GI bleeding.

6.4 | Stress-related mucosal damage (SRMD)

The benefits of stress ulcer prevention in intensive care unit (ICU) patients currently are unresolved. Administration of H₂Rs to people receiving enteral nutrition was associated with an increased risk of hospital acquired pneumonia and mortality.¹⁶⁵ In a meta-analysis of 14 randomized, controlled parallel group trials involving 1720 people in an ICU, PPIs were more effective than H₂Rs in preventing clinically important upper GI bleeding, but their use did not decrease mortality in the hospital or the duration of ICU stay.¹⁶⁶

Stress-related mucosal damage occurs in some critically ill dogs and cats, but its prevalence, severity, and the efficacy of prophylactic gastroprotection is unknown.¹⁶⁷ In a retrospective study evaluating SRMD in critically ill dogs from 3 ICUs in the United Kingdom, hemorrhagic gastric disease was significantly associated with mortality. However, gastroprotectant drugs did not improve survival in this population of dogs.¹⁶⁸

Although no evidence supports the routine use of H₂Rs or PPIs for prevention of SRMD in critically ill dogs and cats, they may prevent GUE in performance animals. Most of the research on SRMD in dogs has been performed on racing Alaskan sled dogs. Strenuous exercise in increments of 100 miles/d for 5 days was associated with development of SRMD.¹⁶⁹ Gastric erosions, ulcers, and hemorrhage were observed in 48% of 70 dogs after completing the Iditarod sled dog race.⁹⁷ The study was limited by not examining the dogs before and after the race, precluding confirmation of when the lesions might have been present. Omeprazole (0.85 mg/kg PO q24h) was significantly superior to high-dose famotidine (1.7 mg/kg q12h) in decreasing SRMD in a randomized positive control study of 52 dogs before and after a 300-mile race.⁴⁴ Stress-related mucosal disease also has been documented in Labrador retrievers undergoing explosive detection training in North Carolina during the summer months.¹⁷⁰ In an experimental study on 20 horses, gastric ulceration was associated with decreases in physiologic indices of performance.¹⁷¹ Therefore, in highly competitive events (eg, sled dog racing) or working dogs in adverse environments (eg, military working dogs), there may be benefits to PPI administration.

Consensus opinion on the use of gastroprotectants in critically ill dogs and cats

There is no compelling evidence that gastroprotectant therapy is beneficial or indicated in critically ill human and animal patients unless definite risk factors such as GI hemorrhage or concurrent NSAID administration are present. Prophylactic PPI administration to animals competing in

strenuous, competitive events might decrease SRMD and improve overall performance.

6.5 | Renal disease

Gastric acid secretion is variably affected by renal dysfunction in humans and may partially depend on *H. pylori* infection status.¹⁷² However, gastritis and GUE can be complications of end-stage renal disease in human patients.^{173,174} Acid suppression in people is often recommended for renal disease patients with ulcer bleeding.¹⁷⁵ There is no recommendation for the use of prophylactic acid suppressant treatment in human patients with renal disease, but acid suppressants generally are recommended if other risk factors (eg, NSAID or corticosteroid treatment) for ulcer development are present. Dose adjustments of H₂Rs based on projected glomerular filtration rate are recommended because of the renal elimination of these drugs.¹⁷⁶

Gastroduodenal ulceration and erosion is not a typical finding in dogs and cats with advanced renal disease.¹⁷⁷⁻¹⁸⁰ Moreover, in a recent study of 10 cats with chronic renal disease and 9 healthy age-matched control cats, no significant differences were observed in serum gastrin concentrations and gastric pH between groups, suggesting that cats with CKD may not have gastric hyperacidity compared to healthy cats, and therefore, may not need acid suppression.¹⁸¹ However, despite this evidence, acid suppressants are commonly prescribed to dogs and cats with CKD.¹⁸² Chronic administration of acid suppressants to dogs and cats with CKD may not be benign. Prolonged administration of acid suppressants has been associated with derangements in serum calcium and PTH concentrations, osteoporosis, and pathologic fractures in at-risk human populations.¹⁸³

Approximately 36%-80% of cats with moderate to severe CKD have renal secondary hyperparathyroidism,^{184,185} with possible consequences of decreased bone mineral density and increased bone resorption cavities.¹⁸⁶ Thus, the deleterious effects of chronic acid suppressant administration on calcium metabolism and bone remodeling in dogs and cats with CKD could lead to serious sequelae. Positive fecal occult blood tests have been documented in dogs with CKD,¹⁸⁷ but the mechanism of GI bleeding and benefit of acid suppressant treatment have not been investigated. Until such studies are published, acid suppression should be restricted to dogs and cats with renal disease that have additional risk factors for ulceration or when concern for severe GI bleeding (eg, melena, severe iron deficiency anemia) or vomiting-induced esophagitis exists.

Consensus opinion on prophylactic use of gastroprotectant treatment in dogs and cats with renal disease

There is no evidence to support the prophylactic use of gastroprotectants in dogs and cats with International Renal Interest Society (IRIS) stages 1-3 renal disease. Additional studies are warranted to determine the benefits of acid suppression in animals with IRIS stage 4 renal disease.

6.6 | Pancreatitis

Gastric acid suppressants frequently are used in the management of acute pancreatitis in dogs and cats. The rationale for acid suppression is the perceived increased risk of upper GI bleeding with pancreatitis

secondary to hypovolemia and local peritonitis, but the incidence of upper GI bleeding in dogs and cats with pancreatitis currently is unknown. Similarly, severe illness, hypoxemia, and use of NSAIDs for pain relief, together with GI hypoperfusion, have been proposed as potential causes of GI mucosal barrier failure, and contribute to acute mucosal lesions or ulcers in people with severe acute pancreatitis.¹⁸⁸ In some reports, PPIs are anti-inflammatory and decrease pancreatic secretions, whereas in others there is no effect or a pro-inflammatory effect.^{189–191} Pantoprazole possesses reactivity toward hydroxyl radicals and ameliorates inflammation in rodent models of pancreatitis,¹⁹¹ but a recent placebo-controlled study failed to demonstrate a benefit of pantoprazole administration in human patients with acute pancreatitis.¹⁹²

Consensus opinion on use of acid suppressants in dogs and cats with pancreatitis

There is no evidence that acid suppression treatment is beneficial or indicated in the management of dogs or cats with pancreatitis, unless the animal has concurrent evidence of GUE.

6.7 | Reflux esophagitis

Gastroesophageal reflux during anesthesia is associated with 46%–65% of cases of benign esophageal stricture in dogs and represents the most common cause of high-grade esophagitis and stricture formation in dogs.^{193,194} Relaxation of the lower esophageal sphincter (LES) is mediated by nonadrenergic noncholinergic pathways¹⁹⁵ and has been shown to occur with the administration of injectable preanesthetic and inhalant anesthetic agents.^{196–198} The LES may be rendered incompetent by a sliding hiatal hernia, which often is accompanied by GER and can be exacerbated by increased inspiratory effort typical of brachycephalic breeds.¹⁹⁹

Esophagitis results from abnormal exposure to activated pepsin-containing acid gastric contents because of distortion of the physiological function of the LES. The prolonged exposure of the esophageal mucosa to acid is an important cause of esophagitis and potential stricture formation, particularly when pH is <4.0 because the proteolytic pH range for the conversion of pepsinogen to pepsin is between 1.5 and 3.5.^{200,201} Preanesthetic administration of IV esomeprazole at 12–18 hours and 1–1.5 hours before anesthetic induction to 22 dogs undergoing elective orthopedic procedures was associated with a significant increase in gastric and esophageal pH throughout the surgery procedure compared to a placebo group, but did not have an impact on the number of reflux events.⁶⁹ Similarly, preanesthetic administration of 2 PO doses of omeprazole in cats at 18–24 hours and 4 hours before anesthetic induction, respectively, was associated with significant increases in gastric and esophageal pH within 24 hours.²⁰² Other preventive measures for decreasing reflux esophagitis in dogs undergoing surgery are administration of cisapride or metoclopramide, with cisapride being more effective.^{203–205}

The superiority of PPIs in healing erosive esophagitis and decreasing rate of relapse compared to that of H₂RA has been well established in people.^{46,206,207} In addition, treatment with PPIs provided quicker and more complete relief from heartburn clinical signs (11.5% per week) compared with H₂RA (6.4% per week). Proton pump inhibitors were found to provide greater clinical sign relief in patients with erosive reflux

disease (70%–80%) as compared to those with nonerosive reflux disease (50%–60%).²⁰⁸ Additional studies are warranted to determine the benefits of preanesthetic administration of H₂RA in dogs and cats in which prolonged maintenance of esophageal pH > 4.0 is not necessary.

Consensus opinion on the use of acid suppressants for prevention of reflux esophagitis

There is a lack of empirical evidence in dogs and cats, but compelling evidence from studies in people, that acid-suppressing agents may be beneficial for prevention of esophagitis secondary to GER, particularly in animals when it is associated with an anesthetic procedure. Administration of PPIs does not decrease gastric reflux, but may prevent injury by increasing the pH of the refluxate.

6.8 | Helicobacter

Treatment of *H. pylori* in people currently consists of multiple drugs, either simultaneously or sequentially, and PPIs are almost always an integral component of treatment.^{209,210} Infected dogs and cats almost always have non-*H. pylori* Helicobacter (NPH) that appears to have different pathophysiologic effects and different responses to treatment compared to *H. pylori*. The importance of triple or quadruple treatment for effective management of *H. pylori* in people might not translate to the same recommendation for dogs and cats with NPH. Ten studies report treatment of spontaneous NPH in dogs and cats (Table 3). The variety of therapies employed, the relatively small number of animals studied, and the different means and times by which elimination of *Helicobacter* were determined make it impossible to draw meaningful conclusions about the value of acid suppression treatment when treating dogs or cats with NPH. A single RCT compared antibiotics with and without acid suppression and showed no benefit from adding famotidine, but the study was relatively underpowered.¹⁵⁷ Because PPIs are superior to H₂RA in decreasing gastric acidity, a similar study with PPIs might have different results. However, based upon currently available information, acid suppression treatment with H₂RA is not indicated for first-line treatment when treating NPH in dogs or cats.

Consensus opinion on the use of acid suppression treatment for the management of NPH

There is no evidence that acid suppression treatment is beneficial or indicated in dogs or cats undergoing treatment for NPH.

6.9 | Thrombocytopenia-induced bleeding

In experimental studies, platelet aggregation at an ulcer is essentially normal at a gastric pH 7.4, but progressively diminishes until absent at pH ≤ 6.2.²¹¹ Increasing gastric pH may limit degradation of previously formed platelet plugs and decrease proteolytic activity of pepsin on existing thrombi. Proton pump inhibitors in combination with other therapies have been successful for treatment of gastric bleeding in human patients with myelodysplasia and thrombocytopenia or idiopathic thrombocytopenia purpura.^{212,213} Despite this phenomenon, acid suppressants are not routinely administered in humans with immune-mediated thrombocytopenia (ITP). Gastrointestinal hemorrhage is rarely observed in human patients with ITP.²¹⁴ In contrast,

TABLE 3 Results of treatment of *Helicobacter* spp. in dogs and cats

Author	Species	Type of study/ design (n) = # animals/group	Antibacterials used (days)	Acid suppression used	Results	Means of evaluating efficacy (time of testing post treatment)
Kubota ¹	Dogs	Uncontrolled experiment	AMO, MET (14)	OME	6/6 cleared	HIST, RUT, PCR (uncertain)
		All dogs treated (6)				
Simpson ²	Dogs	Controlled experiment	AMO, MET (14)	FAM	6/8 cleared at 4 days	HIST, RUT, IMP (4 days)
		Treated (8), untreated (6)			0/8 cleared at 29 days	HIST, RUT, IMP (29 days)
Mirzaeian ³	Dogs	Uncontrolled experiment	AMO, CLA (7)	LAN	20/20 cleared	HIST, RUT (uncertain)
		All dogs treated (20)				
Costa ⁴	Dogs	Controlled experiment	AMO, MET (15)	OME	7/7 cleared	HIST (uncertain)
		No tx (7), antibiotics (7) garlic oil (7)				
Happonen ⁵	Dogs	Uncontrolled clinical trial (9)	AMO, MET (10-14) + BIS	None	7/9 cleared	HIST (within 84 days)
		Repeated tx for initial failures	TET (10)	OME	1/1 cleared	HIST (within 84 days)
Jergens ⁶	Dogs	Uncontrolled clinical trial (3)	AMO, MET, BIS (21)	None	3/3 cleared	HIST, FISH, PCR (4-14 weeks)
	Cats	Uncontrolled clinical trial (2)	AMO, MET, BIS (21)	None	2/2 cleared	HIST, FISH, PCR (4-14 weeks)
Leib ⁷	Dogs	Randomized clinical trial	AMO, MET, BIS (14)			
		Tx with antibiotics (10)		None	7/10 cleared	HIST (4 weeks)
		Tx with antibiotics + famotidine (14)		FAM	11/14 cleared	HIST (4 weeks)
Khoshnegah ⁸	Cats	Uncontrolled experiment	AMO, MET, CLA (14)	OME	13/13 cleared	HIST (uncertain)
		All cats treated (13)				
Perkins ⁹	Cats	Controlled experiment	AMO, MET (21)	OME	6/6 cleared	CUL of mucosa/ fluid (2 weeks)
		Treated (6), untreated (2)			1/6 cleared	PCR (2 weeks)
Neiger ¹⁰	Cats	Controlled clinical trial				
		Untreated (4), Antibiotics-1 (6)	AZI, BIS, TIN (4)		4/6 cleared	Urea breath test (10 days)
		Antibiotics-2 (11)	CLA, MET, BIS (4)	RAN	11/11 cleared	
		Antibiotics-3 (8)	CLA, MET, BIS (7)	RAN	8/8 cleared	

Abbreviations: AMO, amoxicillin; AZI, azithromycin; BIS, bismuth subsalicylate or subsalicylate; CLA, clarithromycin; CUL, culture; FAM, famotidine; FISH, fluorescent in situ hybridization; HIST, histology of gastric mucosa; IMP, impression smears of gastric mucosa; LAN, lansoprazole; MET, metronidazole; OME, omeprazole; PCR, polymerase chain reaction testing; RAN, ranitidine; RUT, rapid urea testing of gastric mucosa; TET, tetracycline; TIN, tinidazole.

GI bleeding is relatively common in dogs with ITP.²¹⁵ Platelet aggregation and clot formation in vitro are optimal at pH > 6.8.^{216,217} For this reason, acid suppressants are commonly used as adjunctive treatment of dogs with ITP-related GI bleeding. However, in a recent study, acid suppressants did not influence the probability of survival to discharge.²¹⁶ In studies of healthy dogs and cats, twice-daily administration of acid suppressants did not achieve the target of pH > 6 for a prolonged period.^{178-180,182} More studies are warranted to determine the efficacy and optimal dosage of acid suppressants for the treatment of thrombocytopenic-induced GI bleeding in dogs and cats.

Consensus opinion on use of acid suppression for the prevention or management of thrombocytopenia-induced bleeding

There is insufficient evidence to support the use of standard dosages of acid suppressant treatment for prevention or management of thrombocytopenia-induced bleeding.

6.10 | Spinal cord injury and intervertebral disc surgery

Spinal cord injury and intervertebral disc surgery in dogs have been associated with GI complications in dogs. Information for cats is not available to make any conclusions.

A consistent finding in the published reports of GI complications in dogs with spinal cord disease and spinal surgery is that high doses of corticosteroids were administered (eg, 30 mg/kg methylprednisolone, which is equivalent to 3.75 mg/kg dexamethasone). In these reports, there were high rates of GI complications, including diarrhea, melena, bleeding, and perforation.^{111,218-221} The same findings have been reported in research dogs that had spinal surgery in combination with high-dose corticosteroids.²²²

These reports concluded that the high doses of corticosteroids contributed to GI complications rather than disc disease or surgery alone. High doses of corticosteroids administered to otherwise healthy dogs can produce gastric hemorrhage.²²³ Injury from glucocorticoids is not caused by hypersecretion of acid, but is more likely

the result of decreased defense mechanisms and altered gastric mucosal blood flow. Sympathetic-parasympathetic imbalance in spinal surgery patients may contribute to the GI problems.¹⁰⁹

No evidence from clinical reports of dogs or from research studies shows that gastroprotectant drugs are beneficial for preventing or decreasing GI complications from high doses of corticosteroids. The gastroprotectants used in these reports were sucralfate, misoprostol, and H₂RAs. We acknowledge that some of these reports were from the 1980s, before the use of PPIs, although a more recent study showed no benefit in healing or preventing development of gastric mucosal lesions in dogs using either misoprostol or omeprazole.¹⁰⁹

Consensus opinion on gastroprotectants for prevention or management of glucocorticoid-associated gastroduodenal ulceration/erosion

Gastrointestinal complications associated with spinal cord disease and spinal surgery are more likely caused by the administration of high doses of glucocorticoids than other factors. In these cases, there is no convincing evidence that gastroprotectant drugs are beneficial.

7 | FUTURE CONSIDERATIONS

This consensus statement has highlighted the problems our panel faced when attempting to provide recommendations for or against the use of gastric protectants in dogs and cats. There is a need for the use of selected GI protectants in some patients, but there is ample evidence documenting overuse of these drugs for many disorders in dogs and cats. Veterinarians need to better define the appropriate clinical applications for the use of gastroprotectants in small animals. Technological advances have become available with the use of GI telemetric monitoring devices and capsule endoscopy that should facilitate future research to more precisely identify the efficacy of these drugs in dogs and cats. Well-defined endpoints and goals of treatment should be established. The benefits of gastroprotectants that we have defined in this article are largely based on extrapolation from human medicine or from studies in healthy dogs and cats. More information is needed to define optimal dosage, timing of doses, and selection of products (eg, one PPI versus another), particularly in clinical patients. Newer generation PPIs, such as delayed-release and longer-acting PPIs, are commercially available and may improve dosing and effectiveness in dogs and cats. We are cognizant that not a single agent listed in this article is FDA-approved for use in dogs or cats. Clearly, the pharmaceutical industry should become involved in evaluating these drugs. Controlled studies evaluating the efficacy of gastroprotectant drugs in clinical patients, as well as the judicious application of these drugs, should further optimize the management of reflux esophagitis and GUE in dogs and cats.

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CONFLICT OF INTEREST DECLARATION

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OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

ORCID

Stanley L. Marks  <https://orcid.org/0000-0001-7991-702X>

Peter H. Kook  <https://orcid.org/0000-0002-9492-3484>

Mark G. Papich  <https://orcid.org/0000-0002-7591-7898>

M. K. Tolbert  <https://orcid.org/0000-0001-8725-9530>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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