# Gastroesophageal Reflux and Helicobacter-Associated Disease

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Gastroesophageal reflux is the act of retrograde movement of gastric contents across the gastroesophageal junction and into the esophagus. The clinical constellation of signs associated with reflux is characterized by the term GERD (gastroesophageal reflux disease).

GERD represents one of the most common ailments in people today (estimated 10-20% of the population) with health implications estimating up to 10 billion dollars a year annually. Persistent reflux can result in esophageal injury and resultant acute and long term complications. Esophageal stricture formation represents a potential acute sequelae, while Barrett's esophagus and esophageal neoplasia representing long term sequelae. The clinical signs in people are caused by gastric acid and its local effect on the esophageal and/or laryngeal mucosa. This burning sensation is known in people as heartburn. External manifestations of disease are generally minimal in people with the majority of patients being clinically silent. Additionally, it has been shown that monitoring effective therapy is unreliable when depending solely on clinical response and that histopathologic confirmation of resolved esophageal inflammation (esophagitis) is the gold standard. The pathophysiology in people is believed to be related to is lower esophageal sphincter (LES) dysfunction in the majority of patients.

The disease in animals is less well defined with likely a gross underestimation of prevalence. The reasons for this are unquestionably related to the lack of our patients to verbalize the sensation of heartburn, the reliance on external clinical signs (ie. overt regurgitation) and the poor characterization of the veterinary community. Furthermore, gastroesophageal reflux has been dubbed normal on esophagrams in normal dogs. Therefore, a diagnosis of the condition, may not currently equal a diagnosis.

#### Diagnosis

It is important to remember that reflux can be intermittent and diagnostics are limited due to timing of the procedure. Traditional radiography is a poor test to evaluate for reflux, as this is a dynamic process and will not be noted on static imaging. However, radiographs are important in helping to identify other features that may be suggestive of reflux mediated disease or directly associated with reflux. The majority of radiographs will be normal, however, fluid in the esophagus (generally caudal) and the presence of concurrent hiatal hernia, esophageal dilation or pectus excavatum may provide some clues. Esophagoscopy will allow documentation of reflux by direct visualization of reflux within the esophageal lumen or indirect evidence through identification of residual esophageal food/fluid. Furthermore, esophagitis may be noted grossly and could suggest reflux mediated disease. However, it is well documented in people that esophagitis can be endoscopically normal and histology is the only reliable assessment and has been demonstrated in several patients on post mortem examinations. Finally, documentation of contributory conditions including hiatal hernias and "reduced GES tone" can be made. It should be noted that, while this test is complimentary to documenting this condition, reflux can be missed during the examination (intermittent nature) and may be exacerbated from anesthetic effects on GES tonicity. In my experience, continued reflux under anesthesia is uncommon and is more commonly seen in patients with suspected reflux mediated disease. However, these factors limit observation and interpretation of pathology and prevent this test as being the gold standard. Fluoroscopic evaluation is considered the ideal diagnostic test, as the patient can be observed in an awake setting. Additionally, it offers the ability of assessing esophageal motility and for concurrent/complicating conditions (ie. hiatal hernias). However, it should be noted that intermittent reflux may be missed and could be interpreted as normal.

Lower esophageal sphincter tone can also be assessed with manometry. This evaluation has been used in people to document alterations in lower esophageal tone relaxation and/or tonic pressure. This is rarely performed in veterinary medicine due to patient tolerance and the need for general anesthesia (which affects sphincter tonicity).

#### **Clinical syndromes**

#### Laryngeal reflux

This is characterized by reflux of gastric acid/ingesta into the airway. The resultant clinical sign are characterized by associated edema, swelling and inflammation of the laryngeal and peri-laryngeal tissues. These signs may be acute and severe in nature manifesting as stridor, inspiratory dyspnea and/or heat stroke. However, chronic low grade clinical signs are possible and may be manifested in a myriad of ways including changes in phonation, intermittent "throat clearing" type cough and/or inspiratory stridor. Because laryngeal inflammation can improve when reflux abates, the clinical signs may occur sporadically or be more consistent.

#### Episodic signs

Esophageal/laryngeal reflux has been associated with several different clinical presentations of episodic behavior patterns. These manifestations are thought (in my opinion) to represent inflammation and esophageal pain. Multiple common clinical presentations have been observed over time and include

- 1. episodic panting
- 2. episodic vocalization
- 3. neck extension and rapid breathing

It should be noted that other clinical presentations are possible and any behavior that could be interpreted liberally as esophageal in origin, should be considered (assuming other reasonable differentials are dismissed).

## **Bilious vomiting syndrome**

Classically associated with vomiting on an empty stomach, this bilious vomiting that occurs is often observed over night or in the morning but can occasionally occur during other times. The pathogenesis of this condition is uncertain and is believed that this may represent alterations in gastric empyting and/or changes in gastric pH.

I suggest that this condition could be a manifestation of esophageal disease given its response to medications that suppress acid and/or modify motility

## Esophagitis signs

These signs are associated with subtle signs that can occur together or independently. The following is a list of common behaviors noted with esophageal inflammation.

- Repetitive swallowing
- Hard swallowing
- Licking lips
- Licking inantimate objects
- Drooling/hypersalivating
- Halitosis
- Reluctance to eat (often times variable)
- Gagging
- Reverse sneezing
- Coughing

These findings can be seen as isolated findings or can occur together. Additionally, these findings can be seen as sporadic observations or daily observations.

## **Recurrent aspiration pneumonia**

Occasionally, recurrent pneumonia is observed and no identifiable underlying etiology is identified. In these cases, common causes of recurrent pneumonia should be eliminated including laryngeal dysfunction and local predispositions (ie. bronchiectasis, etc.). Following elimination of these more common considerations, one should consider GERD and/or hiatal hernias.

## **Concurrent diseases**

GERD is commonly associated with hiatal hernias as these are associated with loss of the normal GES tonicity and protective mechanisms for reflux prevention. Additionally, any cause of inspiratory dyspnea or inspiratory effort can be associated with reflux. This is most commonly observed with brachycephalic airway syndrome but has been identified in dogs and cats with laryngeal neoplasia, laryngeal paralysis, laryngeal scarring and nasopharyngeal polyps. Any cause of inspiratory effort should be considered at risk of GERD.

## Subtle clues that GERD may be contributing

- Nocturnal exacerbation of signs
- Brachycephalic signs
- Generally not associated with weight loss, progressive disease

## General principles of diagnosis

- Maintain an open mind to potential GERD
- Do not forget more common diagnoses
- Remember that signs can vary greatly in frequency (acute, chronic with acute exacerbates, chronic intermittent signs, etc.)
- Remember that signs may be occult

## Therapeutic intervention

## Acid suppression

The most effective medications that suppress acid production are proton pump inhibitors. These medications act on H+K+ ATPase pumps that represent the end result of various stimuli for acid suppression (gastrin, histamine, acetylcholine). These medications have been shown to be significantly more effective in dogs and cats when compared to H2 blockers.

At this time, it appears that esomeprazole and omeprazole seem to be the most effective at raising the gastric pH > 3 or 4. Twice daily therapy appears to be more effective at maintaining consistently elevated gastric pH levels with omeprazole, this has not been studied with esomeprazole but is suspected. Pantoprazole has been studied and showed superiority to H2 blockers but did not

demonstrate superiority to omeprazole. It should be noted that every patient is slightly unique in there response to these medications with one being more effective than another at times.

When considering using H2 blockers, famotidine is the only medication that has been shown in a controlled manner to reliably suppress acid production. Therefore, it can be the only H2 blocker that we can recommend at this time. It should noted that this does not affect motility (ie. nizatidine, ranitidine). Famotidine is generally used for breakthrough signs, despite PPI therapy. Additionally, it has been considered for step down therapy when signs are controlled.

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Omeprazole	1-2 mg/kg q 12-24
Esomprazole	0.8 mg/kg q 24 (12?)
Lansoprazole	1-2 mg/kg q 12-24 (??)
Pantoprazole	1 mg/kg IV q 24
	1 mg/kg/day CRI
Famotidine	0.5-1 mg/kg q 12

## Motility modification/GES tonicity manipulation

Manipulation of lower esophageal tone can play a major role in reducing reflux and can sometimes be the difference between effective therapy and ineffective therapy.

In addition to altering GES tonicity, several of these medications also help with gastric emptying which can reduce reflux. It is clear that serotonin antagonists (5HT4 receptors) are the single most effective class of medications, however, D2 antagonists and motlin-like drugs also have some activity.

Cisapride	0.25-1 mg/kg q 12
Metoclopramide	0.2-0.4 mg/kg q 6 PO, SQ, IM, IV
Erythromycin	0.5-1 mg/kg q 8

#### Helicobacter associated disease

In veterinary medicine, the controversy of helicobacter and its influence on pathology and clinical signs has long been debated. The presence of helicobacter has not been definitively associated with histologic alterations or clinical findings.

Many different types of helicobacter have been documented in dogs and cats with H. pylori being uncommonly represented. Dogs more commonly have H. felis, H. bizzozeronii, H. salomonis, H. bilis, Flexispira rappini and H. heilmannii-like infections. Cats more commonly have H. felis, "H. heilmannii" H. bizzozeronii, and H. pametensis. These organisms seem to be associated with degeneration of gastric glands

Diagnosis of helicobacter organisms in animals can be obtained via gastric biopsy evaluation (ie. traditional H&E, silver staining), gastric cytology and urease slant testing. Distribution appears to be more dense in the cardia or fundus than the pylorus.

#### Potential findings on biopsy

- Gastric glandular degeneration
- Lymphoid hyperplasia
- Mononuclear inflammation (\* can be very subtle)
- No reported ulcerations
- Regardless of the method of diagnosis, the bigger question is if the findings are significant or not.

I believe that patients with helicobacter can be clinical for the infection and that with appropriate selection of cases therapeutic interventions can result in improved clinical signs.

#### General principles of interpretation

- Consider more common diagnoses
- Consider when the signs are compatible
- Do not consider when the signs are not compatible
- Elimination of other disease should be considered first

#### Common findings with helicobacter associated disease

- Mild or intermittent signs
- Hypersalivation, ptyalism
- Trismus
- Lip licking
- Hard swallowing, repetitive swallowing
- Reduced appetite, dietary preferences
- Intermittent bilious vomiting
- Rarely hematemesis

## Red flags that helicbacter is NOT likely significant

- Weight loss
- Moderate to severe signs
- Diarrhea
- Hypocobalaminemia
- Hypoalbuminemia
- Anorexia
- Generalized unthriftiness

## **Treatment options**

Option 1	Clarithromycin 7.5 mg/kg q 12
	Amoxicillin 20mg/kg q 12
	Metronidazole 10-15mg/kg q 12
Option 2	Metronidazole 10-15 mg/kg q 12
	Amoxicillin 20mg/kg q 12
	Bisthmuth subsalicylate 262 mg tablets q 12
	• < 5 kg: 0.25 tablet
	• 5-9.9 kg: 0.5 tablet
	• 10- 24.9 kg: 1.0 tablet
	• 25 kg: 2.0 tablets
	+/- Omeprazole 1 mg/kg q 12