Equine Glandular Gastritis and Ulceration: What Do We Really Know?
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Equine gastric ulcer syndrome (EGUS) has been recognized as a clinical entity in horses for almost 3 decades. EGUS is common in all types of horses and clinical signs are variable and include inappetence/slowed eating, colic, weight loss, poor hair coat, poor performance and behavior changes. Anatomy of the stomach, low forage diets, intense/increased exercise, high concentrate diets, regular/prolonged transport, interval feeding, management/housing change, water deprivation, weaning/movement to a new home, prolonged stabling and NSAID administration are risk factor for horses developing EGUS. In published reports, ulceration of the squamous mucosa is predominant and our understanding of the pathophysiology is relatively complete. However there is minimal published information on the pathophysiology and epidemiology of equine gastric glandular mucosal disease. It is this author’s experience gained in over 1800 gastroscopic examinations that glandular lesions are underrepresented in the current literature and that glandular lesions are present in 50-60% of horses diagnosed with ulcers (unpublished data). Based on the appearance of these lesions, response to acid suppression therapy may not be as expected.

Anatomy and Physiology
The horse has a simple, composite stomach that is relatively small and accounts for only 4% of the entire gastrointestinal tract capacity. The gastric mucosa is composed of about 1/2 stratified squamous epithelium and 1/2 glandular, compound, columnar epithelium. The margo plicatus, a distinct, roughly longitudinal demarcation divides the two surfaces. The glandular portion is divided into 3 distinct histological areas: the cardiac gland, fundic gland and pyloric gland regions. The cardiac region is a small strip of mucosa just ventral to the margo plicatus and contains a large number of somatostatin immunoreactive cells suggesting a role in gastric acid secretion regulation. The fundic mucosal region is the largest of the 3 regions and lines the bottom of the stomach along the greater curvature and up the sides to the cardiac region. It contains straight gastric or the ‘classic gastric glands’ that include parietal cells which secrete HCl and zymogen (chief) cells which secrete pepsinogen into the gastric lumen, as well as enterochromaffin-like (ECL) cells which may secrete histamine that, in turn, provokes the parietal cells to secrete acid by stimulation of histamine-2 receptors on their cell surface. Mucus neck cells are also found in the fundic glands and secrete thin mucus and bicarbonate which are important in maintaining mucosal defense. The antrum and pylorus are lined by pyloric mucosa containing branched gastric glands. This area is the major source of gastrin producing G-cells as well as mucus and bicarbonate secreting cells and ECL cells.

Acid secretion in the horse is continuous but variable and is stimulated by acetylcholine and histamine which is stimulated by gastrin. A ventrodorsal pH gradient exists relative to the ingesta mat density stratification. The high density mat in the pyloric antrum has a pH range from 2-4, the medium density mat of the glandular fundus pH ranges from 4-5 and the low density mat at the level of the cardiac region/margo plicatus ranges in pH from 5-7. Concentrated gastric juice has a pH of 1-2. Unlike the squamous mucosa, glandular mucosa is highly resistant to acid injury through a combination of anatomic, physiologic and physical characteristics; a robust blood flow supported by nitric oxide and PGE2, an abundance of salivary
epidermal growth factors leading to rapid cell repair and restitution, high cell turnover to minimize the effects of damaged cells, gastroduodenal motility which limits the buildup of gastric juice and a tightly adherent mucus curtain. The gastric mucus curtain is a hydrophobic, flexible gel covering the glandular epithelium in a continuous layer 100-400µm thick. The mucus gel is quite complex and is composed of water, electrolytes, glycoproteins, lipids and antibodies. Its formation is pH dependent and is a firm viscid gel at pH 2 while a loose solution at pH 7. The pH of the gel is 6-7 when the luminal pH is 1.5 providing a protective coating to the glandular mucosal surface.

Glandular Ulcers
Murray described the endoscopic appearance of glandular lesions in 162 clinical cases in 2001. The lesions were primarily identified in the pyloric antrum or adjacent to the pylorus in 58% of the cases with the remainder in the fundus (the cardia area was included in the fundus). The lesions consisted of rugal fold thickening and reddening, erosions, and ulcerations with at least one horse reported to have pyloric fibrosis. Murray also found that 50% of the horses with grade ≥2 antral lesions had no squamous mucosal defects (grade 0 or 1). In 591 cases where the antrum and pylorus were visualized, this author’s findings are very similar to those of Murray (unpublished data).

The results of 2 recent reports evaluating a total of 84 stomachs at post mortem suggest that the term “ulcer” is usually erroneous when describing glandular lesions as they generally do not involve defects to the level of the lamina propria. In one report of 21 horses, 14 had gross lesions while 18 were reported to have gastritis and 16 to have erosions and none to have true ulcers via histology. In the second study of 63 horses, 36 horses were reported to have gross lesions and only these were evaluated histopathologically and while 21 were reported to have erosions or ulcers only 1 true ulcer was identified.

In the most recent report on endoscopic appearances of glandular lesions, Hepburn describes 6 morphologic lesions types found in 53% of 500 cases: flat and hemorrhagic; flat and fibrinous; raised and hemorrhagic; raised and fibrinous; depressed; depressed and exudative. This author would add proliferative as well as mixed types within a lesion. Hepburn reported a variety of histopathologic changes but none of which appear specific to the different endoscopic lesion types. Described inflammatory patterns were consistent with acute, chronic, chronic active and suppurative gastritis. Epithelial sloughing and erosions were common but ulceration was rare. Gastric gland hyperplasia, hypertrophy atrophy and dysplasia; mucus gland metaplasia; and mucosal fibrosis were common. Bacterial colonies were found infrequently within the mucosa. In order to avoid confusion with squamous disease and to promote a consistent future approach to glandular disease, it has recently been proposed to use the terms Equine Squamous Gastric Disease (ESGD) and Equine Glandular Gastric Disease (EGGD) under the umbrella of EGUS.

Possible Mechanisms of EGGD
Stress is defined medically as the “sum of the biological reactions to any adverse stimulus, physical, mental, or emotional, internal or external, that tends to disturb the homeostasis of an organism”. When these reactions are inappropriate, they may lead to disease states. For example, a rise in bleeding gastric ulcers in elderly Japanese patients after a severe earthquake has been reported. The etiology of stress related gastric disease is incompletely understood, but
probably reflects splanchnic hypoperfusion, loss of host defenses and resultant gastric acid injury. In critically ill animals, the hypoperfusion may be severe. As splanchnic blood flow is reduced in fasted exercising ponies, could a similar, cumulative, lower grade effect potentially be contributing to glandular lesion development in performance horses? Exercise may contribute to mucosal stress; however, there is much variation in type, frequency and duration of exercise horses undergo. It could also be possible that much more prolonged, repeated exposure to the risk factors associated with squamous disease is causing neuro-humoral effects that result in glandular lesion development.

Reports of the presence and the activity of different bacteria in equine gastric contents and on the gastric mucosa are becoming more numerous, but Koch’s postulates have definitely not been fulfilled in the same way as they have for *H pylori* in humans. A diverse population of acid tolerant bacteria in equine gastric contents have been identified by culture, staining and molecular techniques. Two main genera have been identified: *Lactobacillus* and *Streptococcus*. The majority of this bacterial activity is in the squamous lined dorsal fundus. Horses ingest a range of bacteria from the environment. It is not known whether these merely pass through the stomach, or whether they are able to colonize ulcer beds or even induce primary injury. The ability of bacteria to delay ulcer healing in horses has been demonstrated by the observation that significant ulcer healing can occur with prolonged antibiotic therapy. There is controversy over the role of *Helicobacter* like organisms (HLOs) as one study showed no evidence while another showed evidence of HLOs in 11/20 horses. Hepburn suggest that equine gastric HLOs do exist but that their pathogenicity is minimal when compared to *H pylori* and other opportunistic bacteria are likely to be more important in the development and maintenance of glandular disease.

NSAID use in horses have been associated with glandular disease but the evidence is equivocal with some studies showing increased incidence at normal doses while others only demonstrating lesions at elevated doses. However, it is recognized that individual horses may show increased sensitivity to NSAID side effects and these horses often show “classic” circumferential pyloric lesions.

**Treatment**

Typically, omeprazole (GastroGard®) is used at 4 mg/kg PO q 24 hr for acid suppression combined with sucralfate at 12 mg/kg BID. Sucralfate’s mechanism of action is likely a combination of adherence to ulcerated mucosa, stimulation of mucous secretion, prostaglandin E synthesis and enhanced blood flow all of which are likely to be beneficial in EGGD. Glandular lesions may require prolonged therapy compared to squamous lesions and this author will add antimicrobials if there is minimal improvement or worsening of the endoscopic appearance at 28 day recheck or biopsy histology results at initial examination supports their use.