

Equine Gastric Ulcer Syndrome (EGUS) – Keeping Up with Evolution

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The mechanical breakdown and mixing of food occurs in the stomach and reduces meals into smaller particle size that can pass into the small intestine. The lining of the equine stomach is divided into an upper **squamous mucosa** (non-glandular) and the lower **glandular mucosa**. The squamous mucosa does not absorb or secrete anything, but has the primary role of aiding the mechanical breakdown of ingested foods. The glandular mucosa, on the other hand, produces hydrochloric acid (HCl), pepsin, lipase, gastrin, histamine, somatostatin, and several other physiologic mediators. The glandular mucosa of the stomach has a complex mechanism for protecting itself from its own corrosive agents. The essence of this barrier is a combination of mucus and bicarbonate that is produced by cells of the gastric glands, and through which secreted acid and pepsinogen can easily move out into gastric lumen, but not vice versa (1). Thus, under normal conditions, the pH of the area just adjacent to the glandular mucosal surface is biologically neutral.

The two digestive enzymes of note secreted by the equine stomach are pepsin and lipase, which is in concordance with most other mammalian species. Pepsin is proteolytic when in an acidic environment. We really know nothing about the extent to which pepsin contributes to the digestion of ingested dietary protein in the horse. Equine gastric lipase is produced by the zymogen cells primarily in the glandular mucosa (2). Horses produce a large amount of gastric lipase but, as with pepsin, nothing is known about its role in the processing of food. Of related interest is that, on a relative basis, the equine pancreas produces much more lipase than any of the other digestive enzymes it produces. Also interesting, recent studies have shown that horses can effectively assimilate quite large amounts of dietary fat (3, 4), which is broken down by these pancreatic enzymes.

Like most other species, horses secrete some gastric acid even when the stomach is empty. When equine gastric contents are continually collected over time, the acid concentration (and thus pH) is quite spontaneously variable (5). Ingestion of food naturally has a significant impact on intra-gastric pH. The pH of intra-gastric contents in the free-feeding adult horses is anything but uniform. Duodenal contents can readily reflux into the stomach of the horse, especially when the stomach is empty. Because of the high sodium and substantial bicarbonate concentration of those contents, they provide an additional buffer of the gastric acid, and thus provide more protection for the gastric mucosa (6). It appears in the adult horse at least, that duodenal reflux is more responsible for this variability than is saliva. This idea is supported by the endoscopic observation that the pyloric sphincter region of the horse is open most of the time. It is reasonable to assume that this backflow is less when the stomach is full, and the general gradient of contents movement is more aborad, but this remains to be determined. The equine stomach takes approximately 12-14 hours to completely empty of solid material (hay) but grain exits rapidly; a recent study demonstrated that one pound of grain consumed on an empty stomach took just 4.5 hours to exit into the intestine. In other words, fiber and roughage lingers in the equine stomach, while a meal of only grain empties rapidly. These observations have important clinical implications with respect to the potential for ulcerogenesis in horses that have empty stomachs, either because of illness-related anorexia or human-imposed management conditions.

Ulcers that occur in the glandular portion of the stomach are found most often in the region of the antrum and the pylorus (7), and are often caused by a breakdown in the protective buffers. The squamous mucosa, however, is highly sensitive to HCl; in fact damage (represented by ulceration or discoloration) can occur within 30 minutes of exposure (8). Ulcerogenic stresses that impact the glandular portion are different from those that impact the squamous portion.

Ulcerogenic stresses that have been identified in controlled studies include transportation, serious illness, diet, management changes, high doses of non-steroidal anti-inflammatory drugs (NSAIDs), withholding feed from horses, stall confinement (9) and exercise (10, 11, 12). Both prevalence and severity of ulcers increase as the intensity and duration of training increase, which has been demonstrated in racehorse and even in research with horses trained on a treadmill. Risk factors, acting singly or interacting together, contribute to the pressures experienced by a horse, and the expression of these pressures as a gastric ulcer depends on a horse's individual characteristics as well as the risk factors themselves.

Equine gastric ulcer syndrome (EGUS) is a term coined to describe a unique set of conditions that are manifested as erosions and ulcerations in the distal esophagus, stomach (squamous/non-glandular and glandular regions) and/or proximal duodenum of horses (13). Clinical signs of gastric ulceration, while nonspecific, include poor appetite or failure to completely consume a meal, dullness, attitude change, decreased performance or reluctance to train, poor body condition (rough hair coat, weight loss) and/ or low-grade colic.

Despite modern emphasis and attention, gastric ulcerations in the horse are not necessarily a new disease; they had been observed at necropsy for decades. During postmortem examinations, pathologists would frequently observe gastric ulcerations, predominantly in the squamous mucosa (non-glandular portion) near the margo plicatus. These lesions were not considered significant, were apparently not accompanied by clinical signs of gastrointestinal distress, and were previously judged as an incidental, inconsequential finding. Hammond brought gastric ulcers to our attention in 1986 with a study of Thoroughbreds from the Royal Hong Kong Jockey Club. Due to land constraints in China, horses had been submitted for necropsy mainly because they were unsuitable for riding or chronically lame (14). Some of these horses trained until euthanasia at the end of racing season, while others were euthanized after retirement from training. Fifty percent (50%) of the horses studied (whether in training or retired) had minor (what is now called Grade 1) ulcerations in their stomach while 10% of the horses in training had severe ulcerations (what is now called Grade 3 or 4). Coincidentally, it was 1985 when the first equine three-meter gastroscope (15) became available. Due to the availability of the longer endoscope, a large number of publications appeared in the subsequent 10 years. Early gastroscopic studies in Thoroughbreds trained in the United States indicated that up to 90% of horses in training had erosive and ulcerative lesions of the

squamous mucosa of the stomach with varying degrees of severity. From the collaboration of these early studies, the presence of gastric ulcerations has been further defined, refined to location and graded by degree of ulceration. A modern breakdown of equine gastric ulcer syndrome recognizes three categories of ulcers: 1) primary lesions within the cardiac glandular mucosa of highly stressed neonates, 2) primary glandular or upper duodenal mucosal ulcerations that disrupt gastric outflow, and 3) primary squamous (non-glandular) ulcerations not associated with any problems with gastric emptying. Likewise, lesions within the stomach are graded on a scale of 0-4, with Grade 0 defined as intact mucosa with or without areas of reddening and Grade 4 defined as extensive lesions with areas of apparent deep ulceration. Obviously, interpretation of early publications without the benefit of this evolved understanding is now challenging, as many early studies did not separate ulcer location or severity in the reporting of their findings.

Historically the first form of EGUS to be reported in the literature, the syndrome of consequential gastric mucosal ulcerations in ill foals was first reported by Rooney in 1964 in a retrospective post mortem study (16). Within 20 years of the first published study, the syndrome had been recognized as a well-established clinical problem, now categorized as **primary lesions within the cardiac glandular mucosa of highly stressed neonates**. The occult nature of the disease provides few clues to its existence until the advanced stages. In a study conducted in Virginia, 94 of 183 (51%) foals examined had endoscopic evidence of gastric ulcerations. The distribution of lesions included both squamous and glandular portions of the stomach, duodenum, esophagus and, less frequently, the pylorus. Many of the mechanical principles regarding exposure of the squamous portion of the stomach in equine athletes (discussed later) apply to foals that have significant erosions and ulcerations in this region (17). They have liquid diets that exit their stomachs rapidly, and they frolic and lie down a lot more than adults do, resulting in more exposure of their squamous mucosa to acidic contents.

This problem of secondary squamous ulcerations with the primary lesion located in the duodenum or glandular mucosa is virtually never seen in horses > 1 year of age. What is seen from time to time is the rather acute onset of gastric outflow obstruction caused by the formation of proximal duodenal strictures that have progressed to a critical point. It would be interesting to examine the medical history of these cases to see if they had shown classical signs of gastric duodenal ulceration when they were sucklings or weanlings, but this has not yet been done. Surgical correction of the stricture can be attempted but the prognosis for a successful outcome to surgery is guarded at best.

Since 1979, it has been well-known that non-steroidal anti-inflammatory drugs (NSAIDs) can, if given in excess to horses, cause severe ulceration of the glandular mucosa, especially in the pyloric region (18). These gastric ulcers are now categorized as **primary glandular or upper duodenal mucosal ulcerations that disrupt outflow**. NSAIDs are considered to be ulcerogenic by causing down-regulation of prostaglandin E₂ (PGE₂) production within the glandular mucosa (19). Interestingly, corn oil can significantly increase PGE₂ and reduce gastric acid output. Thus, the corn oil supplementation of horses that need to be on long-term NSAID therapy because of a chronic musculoskeletal problem, for example, is worth contemplating. If the recommended dosages for the NSAIDs are followed, however, it is highly unlikely that this problem will occur, although certain horses appear to be overly sensitive to the gastric effects of NSAIDs and will develop lesions even when given recommended doses. It should be stressed that the primary gastric lesions of NSAIDs toxicity in the horse occur within the glandular mucosa.

With the availability of longer endoscopes combined with extra effort to remove all contents from the stomach during endoscopy, a form of EGUS in the horse that manifests as a primary ulceration of the pyloric glandular mucosa has been seen in adult horses (20). In these cases, the squamous mucosa is usually free of lesions. Clinical signs of the acute form of this problem can be as varied as those seen with primary squamous disease. Furthermore, if untreated in their early stages, lesions near or around the pyloric outflow may induce sufficient scarring to interfere with gastric emptying, which can end up causing secondary squamous ulcerations and severe postprandial distress to afflicted animals. The cause is still unknown in the horse. Searching for possible answers, we look to the human model of this disease. While there is little doubt that medications (H₂ blocker and proton pump inhibitors) suppress acid production and induce healing in humans, there is an alarming rate of recurrence (50% over six months, 95% over two years). Reports in humans indicate that *Helicobacter pylori* plays a pivotal role in the disease process. This led to antibiotic therapies and to the use of antibiotics in combination with acid-suppression therapies in people. When compared to acid suppression alone, these combination therapies demonstrate greater short-term efficacy and recurrence rates that were reduced by 80%. In addition to its superior acid-suppression properties, the proton pump inhibitor omeprazole (Prilosec^R, Gastrogard^R) has been shown to have a bacteriostatic effect on *H. pylori*. Omeprazole and amoxicillin have been shown to be the most effective and produce few side effects in human medicine. Numerous attempts to identify, isolate, or culture *H. pylori* in the horse have been unsuccessful. It is generally agreed that *Helicobacter* infection is not a factor in the equine gastric ulcer syndrome. (6)

By far the most common manifestation of EGUS in adult horses under intensive training programs, irrespective of breed or program, is **primary squamous (non-glandular) ulcerations not associated with any problem with gastric emptying**. This was most likely the type of ulcer being discovered in those early endoscopic studies, although obviously not always defined as such. Recently, a study demonstrated that activities typical for the recreational use of horses and generally not considered to be stressful resulted in gastric ulcer development (21). Ten young horses were exposed over five days to conditions that simulated activities that are typical for the recreational use of horses, including transportation to a stable facility, twice daily feeding and light exercise (lunge line) and return transportation to the premises of origin. Ten age-matched herd-mates remained on the premises of origin during the trial. Gastroscopy was performed at the beginning (day 1) and the end of the trial (day 5). The appearance of all horse's stomachs was

normal at the beginning of the trial. Two control horses and seven transported horses developed ulcers in the squamous mucosa of the stomach by day 5. These results demonstrate how readily gastric ulcers can develop in horses in training.

Because the squamous portion of the equine stomach is not responsible for acid production, the ulcerations are thought to be 'reflux' in nature, similar to erosive esophagitis in humans. In view of the predilection of training-related squamous ulcerations in horses, the question arises concerning the similarity between this problem and gastric-esophageal reflux disease (GERD) in humans. That is, are these horses suffering from what humans would complain of as "heartburn"? Numerous theories have been presented that might explain the relationship between training and the high occurrence of gastric squamous lesions in horses. The "stress" of training has been raised more than once, and has been reinforced by the fact that the lesions quickly decrease in severity and often disappear, when the animal is taken out of training (22). Gastric acid (as in humans) has to be the number one cause, especially because treatment with acid-suppressing drugs results in lesion regression, even in the face of continued training (23).

Certain foods are notorious for causing "heartburn" in humans, although the actual mechanism for this is still not well understood. Accordingly, Nadeau *et al.* explored the possible etiologic role of volatile fatty acids (VFAs) derived from intra-gastric fermentation of ingested soluble carbohydrate feedstuffs as the cause of squamous gastritis in horses (24). This idea takes into account the common practice of feeding horses in training large amounts of feedstuffs that are high in soluble carbohydrates. They found a significant positive relationship between the presence of squamous lesions and the concentration of some of the longer chain VFAs, within the gastric contents of their horses. VFAs can add to the corrosive potential of acidic gastric contents, especially as their chain length increases (25). They found that feeding alfalfa hay resulted in an increased, rather than the expected decrease, in post-feeding intra-gastric pH, which was attributed to the buffering effect of constituent calcium salts and protein. Thus, alfalfa-fed animals had fewer squamous lesions, in spite of more VFA production, than did horses fed brome grass hay. Interestingly, a study performed in 2000 compared the prevalence of gastric ulcers in elite Western performance horses to the published statistic in racing Thoroughbreds (90% at the time). Only 36 of 156 of this population of horses had gastric ulcerations (95% of which were in the squamous mucosa, 5% in gastric mucosa), an incident rate that matches resting horses, yet these horses keep a very intense schedule as well. Coincidentally, the major roughage source was alfalfa hay, which is significantly different from Thoroughbred diet of grass hay, pellet diets and high concentrate rations (26). While the role of diet in the pathogenesis of primary squamous ulceration cannot be ignored, there remains a great deal of work to be performed to elucidate what parts of the diet may be critical to the production of potentially corrosive properties.

What about the composition of gastric contents? Certain bile acids refluxed from the duodenum into the stomach have been shown to have corrosive potential for the sensitive esophageal squamous mucosa in people (27). Studies with equine gastric tissue have produced mixed results (28). Thus, while duodeno-gastric reflux can easily occur in the horse, especially when the stomach is not very full (29), the actual ulcerogenic potential of this activity remains to be determined.

Since GERD is more common in human athletes, especially runners and cyclers, a number of studies were devised to look at some of the effects of treadmill exercise on equine intra-gastric status. A study using inflatable balloons suggested that during movement at a gait faster than a walk, either the gastric wall of the horse becomes more rigid or some external pressure is exerted on the stomach. To investigate the latter, intra-abdominal pressure was measured during exercise while at the same time monitoring intra-gastric pressure. Changes in pressure were parallel (presumed due to tensing of the abdominal muscles during exercise). From the above results it was deduced that the increase in intra-abdominal pressure during exercise pushes gastric contents up into the squamous-lined proximal region of the stomach, exposing that mucosa to corrosive agents, most notably acid, within those contents (the proximal portion of the equine stomach is not normally filled). To test this hypothesis, electrodes were placed distal to the esophagus and the pH was monitored during exercise. While standing or walking, the pH remained in the 5-6 range, but as the horse moved into a trot or faster, the pH began to drop rapidly, as far down as a pH of 1 in some cases, and remained very low until the animal was brought back to a halt. The most profound drops in pH during exercise were in fasted rather than fed animals. It was concluded that the high incidence of squamous mucosal gastric ulcers in horses in training is primarily a mechanical phenomenon, due to an increased exposure of that region of the stomach to acidic gastric contents during the exercise session (6). This discovery was *HUGE* and contributes now to our evolved understanding of this syndrome in the horse. So in essence, our equine athletes have squamous mucosal ulcerations because they are athletes, and our recreational horses have squamous mucosal ulcerations because they are athletic!

There are several therapeutic agents available to treat gastric ulcerations in people, and until omeprazole (Prilosec^R, Gastrogard^R, Ulcergard^R) was FDA approved for use in the horse in 1999, veterinarians would reach for these human medications in attempt to heal their equine patient's gastric ulcers. These medications included cimetidine (Tagamet^R), ranitidine (Zantac^R), sucralfate (Carafate^R), and aluminum-magnesium antacids (Maalox^R). Maybe not surprising, these medications all exert their major activity at the level of the glandular mucosa: cimetidine increases gastric pH by binding with histamine to prevent its binding to the H₂ receptor, ranitidine decreases HCl by binding at the H₂ receptor, and sucralfate creates a protein bandage of mucus over the ulceration. Studies always demonstrated variable response in the horse. A recent study from the University of California at Davis indicates that cimetidine at 20 mg/kg TID per os is not effective in controlling squamous ulcer disease in horses in training (30). Sanchez *et al.* at the University of Florida showed that ranitidine is effective in suppressing gastric acid secretion in normal neonates (31). In critically ill neonates, however, they found that the response to intravenous ranitidine was highly variable, with some responding as expected, but also with a significant group of others not responding at all (32). Sucralfate can be helpful in controlling the severity of glandular gastric ulcer disease, with rationale for its use in its putative ability to induce mucosal protection by activating PGE₂ synthesis (33). However, clinical trials of its efficacy in treatment have not been very convincing (34). Since we now

understand that the majority of gastric ulcerations in horses in training are within the squamous mucosa, it is obvious why response to treatment was not predictable and often frustrating for this group. Without being overly dramatic, omeprazole was a breakthrough therapy for the treatment of squamous mucosal gastric ulcers in the horse.

Omeprazole acts as a proton pump inhibitor. It binds irreversibly to the enzyme hydrogen-potassium adenosine triphosphate needed for secretion of hydrogen ions from parietal cells into the gastric lumen. The proton pump is the final pathway in gastric acid (HCl) secretion. Maximum control of acid production is achieved regardless of the stimulus to the parietal cell and acid secretion is blocked for as long as 24 hours (35). However, in order to reach the parietal cell, omeprazole must be protected from stomach acid. This is somewhat of a paradox in that every effort must be made to protect omeprazole from exposure to gastric acid before its absorption. Such exposure, followed by alkalization within the small intestine, will otherwise render the compounds inactive (36). This is why it requires the special formulation of approved veterinary product. Recent studies performed at the University of California at Davis have found that, in general, compounded preparations of omeprazole were distinctly inferior to Gastrogard^R with regard to the duration of maintenance of a satisfactorily high pH and to the efficacy in controlling development of squamous lesions (37, 38). Omeprazole efficacy data would also suggest that the best time to train would be somewhere between 2-8 hours after giving the drug. Furthermore, it is recommended that a small grain meal be given right after treatment to maximize the drug's absorption, because it is more rapidly taken up by parietal cells that have been stimulated to secrete acid.

Finally, with our modern understanding, attempts have been made to link squamous gastric ulcerations to poor performance in racehorses. Only anecdotal evidence existed in the literature that EGUS caused poor performance, and previous studies relied on trainer's expectation and did not examine objective measurements of performance. Interestingly, a recent study in human runners addressed the effect of GERD and treatment on poor performance (39). In that study, runners with frequent GERD had a significantly decreased time to exhaustion compared to runners without reflux disease. However, treatment did not improve performance in the runners with GERD. In a recent veterinary report, 80 racehorses underwent comprehensive performance evaluations, and 4 were identified that had no significant abnormalities except for the presence of a squamous gastric ulcer. The author offered two suggestions on the mechanisms by which EGUS could cause poor performance: gastric pain and anemia. There was no evidence of abdominal pain in these horses, but signs of gastric disease are often vague and go unnoticed by observers. Anemia could explain the poor performance, for 3 of the 4 identified horses had hemoglobin concentrations below the reference range, and this correlation had been demonstrated in an earlier study (40). All horses in the study were treated with omeprazole paste (Gastrogard^R) and returned to racing. Improvement in Raceform ratings and increased earnings were noted and this was attributed to resolution of the gastric lesions (since omeprazole has no performance-enhancing properties). The results of this study are quite interesting and give some objective evidence that gastric ulcers can lead to poor performance and that successful treatment with omeprazole can improve performance (41).

What about gastric ulcer recurrence? Ulcers may develop within a few days after treatment is discontinued. In one study, squamous gastric ulcers returned within 8 days after cessation of treatment with omeprazole in horses engaged in both light and heavy training regimens (42). A low dose of omeprazole can be used to prevent recurrence (1 mg/kg/day). However, prophylactic use of omeprazole results in a significant economic cost to owners and trainers, therefore management changes may be more cost effective.

To reduce gastric acidity, alter management practices, including daily pasture access, feeding plenty of forage, providing smaller and more frequent concentrate feedings, and feeding a higher fat diet. Horses only require 1-1.5% of their body weight in roughage, so this recommendation isn't a "free-pass" to gorge on pasture. Remember that it takes 14 hours for roughage to exit the equine stomach, so just a bit of hay or grass will have lingering effects. Saliva is high in bicarbonate, which act as a buffering agent, and is released with chewing, so choose long-stem forage over hay-stretchers or cubes when you can. Feed hay before grain meals whenever possible; this also acts to increase the pH of the stomach contents and slow transit time from the stomach. Another dietary strategy is feeding alfalfa hay. Because of its superior buffering capacity, alfalfa protects the squamous mucosa from acid damage and has been shown to decrease gastric ulcers in horses. Horses fed alfalfa hay and exercised showed decreased gastric ulcer scores compared to horses fed a coastal hay diet (43). One flake of alfalfa hay buffers the stomach for 6 hours. Also, a general rule for feeding grain is to limit grain to less than 5 pounds at any single feeding. The interval between grain feeding should be at least 5-6 hours to prevent reaching a threshold whereby VFAs and acid pH could increase the risk of ulcer development. Lastly, consider a higher fat diet. Information on oil and high-fat diets seems conflicting until you appreciate that oils are meant to help the glandular portion of the stomach (not the squamous portion, as we were just discussing). In fact, a comparison of rice bran oil and corn oil showed no difference for treatment and prevention of squamous ulcers. Yet another study found that 8 ounces (1 cup) of corn oil given twice a day with some grain decreased total acid production in the stomach and increased protective prostaglandin E₂ production in the glandular portion of the stomach. In other words, corn oil helps protect against glandular mucosal ulcers related to NSAIDs use, but may not have an effect on the squamous mucosa.

In summary, gastric ulceration is common in horses, even more common in our equine athletes, and now we have objective evidence that it leads to poor performance. Omeprazole treatment appeared to help improve performance as indicated by an increase in Raceform ratings and earnings in these horses. Since ulcers will likely return after treatment is discontinued, a low dose of omeprazole can be used to prevent recurrence, but long-term management changes are more likely to be cost effective. However, more research is needed to determine which management strategies are effective and which ones are of greatest benefit to the horse, while still maintaining a level of performance.

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