Gastric Ulcers in Horses: Equine Gastric Ulcer Syndrome (EGUS)

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Equine gastric ulcer syndrome (EGUS) is common in performance horses and in foals.[1-12] Diagnosis of EGUS is based on history, clinical signs, endoscopic examination, and response to treatment. All ages and breeds of horses are susceptible to EGUS and current therapeutic strategies focus on blocking gastric acid secretion and raising stomach pH. Two approved drugs exist to treat EGUS in Australia and they are Gastroshield® (Merial Australia Pty, Ltd, Paramatta, Australia) and Ulcerguard® (Ranvet Pty Ltd, Beaconsfield, Australia). However, a more comprehensive approach to EGUS includes determining and correcting of the underlying cause, environmental management, dietary manipulation and pharmacologic intervention. These proceedings focus on a comprehensive approach to treatment of EGUS and briefly cover basic anatomy and physiology of the equine stomach, multiple etiologies and risk factors for EGUS, and preventative management strategies.

Anatomy and Physiology of the Equine Stomach

The proximal third of the equine stomach is lined with non-glandular stratified squamous epithelium, an extension of the esophagus. The majority (80%) of ulcers are found in this region. The distal two-thirds of the stomach is covered by glandular mucosa, which is responsible for secretion of mucus, hydrochloric acid (HCl), and Pepsinogen.[13] Ulcer development in these regions is thought to be an imbalance between protective and aggressive factors (Table 1).

<table>
<thead>
<tr>
<th>AGGRESSIVE FACTORS</th>
<th>NON-GLANDULAR MUCOSA</th>
<th>GLANDULAR MUCOSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric acid secretion</td>
<td>Epithelial restitution</td>
<td>Epithelial restitution</td>
</tr>
<tr>
<td>Organic acid production</td>
<td>Intracellular bicarbonate</td>
<td>Bicarbonate-mucus layer</td>
</tr>
<tr>
<td>Pepsin conversion from</td>
<td>Mucosal blood flow</td>
<td>Mucosal blood flow pepsinogen</td>
</tr>
<tr>
<td>Duodenal reflux of bile acid</td>
<td></td>
<td>Prostaglandin E production</td>
</tr>
</tbody>
</table>

The nonglandular squamous mucosa is predisposed to acid injury because it lacks the protective and buffering capacity provided by the bicarbonate-rich mucus found in the glandular region.[14, 15] The glandular region, on the other hand, has extensive protective mechanisms, including a bicarbonate-rich mucus layer, an extensive capillary network, and rapid restitution of epithelium when injured. Ulcers in this region are less common and heal rapidly.

Etiology for EGUS in Adult Horses

Horses are continuous gastric HCl secretors, and acid exposure is thought to be the primary cause of EGUS.[16] Several acids (HCl, volatile fatty acids (VFAs),
and bile acids) have been shown to cause damage to the non-glandular region of the equine stomach. [17, 18, 19] In a recent report, HCl alone and in combination with VFAs caused inhibition of cellular sodium transport, cell swelling, and eventual ulceration, when exposed to the non-glandular squamous mucosa at pH ≤ 4.0. Ulcerogenic effects of the VFAs in combination with HCl were dose dependent and the intensity of damage varied between the VFAs studied.[18] Bile acids were shown to increase the non-glandular mucosal cell permeability to hydrogen ions, which eventually lead to ulceration.[17] However the effects of bile acids in EGUS is questionable because they usually come from less acidic duodenal reflux and are non-ulcerogenic at a pH >4.[20, 17] Pepsinogen, which is cleaved to pepsin at a pH<4, has a role in the development of EGUS. This proteolytic digestive enzyme may act synergistically with HCl to result in acid damage. While HCl and stomach pH have been incriminated as the main culprits causing EGUS, it is likely that a combination of HCl, organic acids, and pepsin act synergistically to cause EGUS.

**Risk Factors in Adult Horses**

While acid injury has been implicated in the cause of EGUS, several risk factors for its development have been identified (Table 2).[2, 3, 14]

**Table 2: Clinical Signs and Risk Factors of EGUS**

<table>
<thead>
<tr>
<th>Clinical Signs in Adults</th>
<th>Clinical Signs in Foals</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute colic</td>
<td>Diarrhea</td>
<td>Stress</td>
</tr>
<tr>
<td>Recurring colic</td>
<td>Abdominal pain</td>
<td>Transportation</td>
</tr>
<tr>
<td>Excessive recumbency</td>
<td>Restlessness</td>
<td>High-grain diet</td>
</tr>
<tr>
<td>Poor body condition</td>
<td>Rolling</td>
<td>Stall confinement</td>
</tr>
<tr>
<td>Partial anorexia</td>
<td>Lying in dorsal recumbency</td>
<td>Intermittent feeding</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>Excessive salivation</td>
<td>Intense exercise</td>
</tr>
<tr>
<td>Poor performance/training</td>
<td>Bruxism</td>
<td>Racing</td>
</tr>
<tr>
<td>Attitude changes</td>
<td>Intermittent nursing</td>
<td>Illness</td>
</tr>
<tr>
<td>Stretching often to urinate</td>
<td>Poor appetite</td>
<td>NSAID use</td>
</tr>
<tr>
<td>Inadequate energy</td>
<td></td>
<td>Management changes</td>
</tr>
<tr>
<td>Chronic diarrhea.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exercise Intensity**

Horses involved in training and racing are at high risk to develop EGUS.[21] Current prevalence figures show that 60 to 90% of performance horses have EGUS. Recently it has been shown that horses running on a high-speed treadmill have increased abdominal pressure and decreased stomach volume. The authors speculated that contraction of the stomach allowed acid from the glandular mucosa to reflux up into the non-glandular mucosa leading to acid injury.[22] Daily exercise may increase the exposure of the non-glandular mucosa to acid explaining the increased prevalence of gastric ulcers in horses in training. Furthermore, an increase in serum gastrin concentration has been shown to occur in exercising horses.[23] This increase in serum gastrin may increase glandular HCl secretion that may lead to acid damage.
**Intermittent vs. Continuous Feeding**

Horses grazing at pasture have a decreased prevalence of EGUS. During grazing, there is a continuous flow of saliva and ingesta that buffers stomach acid, keeping stomach pH $\geq 4$ for a large portion of the day. On the other hand, when feed is withheld from horses, before racing or in managed feeding stables, gastric pH drops rapidly and the non-glandular mucosa is exposed to an acid environment. Intermittent feeding has been shown to cause and increase the severity of gastric ulcers in horses and this technique has been developed as a model to consistently produce EGUS.[24-26] The non-glandular mucosa is the most susceptible to ulceration in horses subjected to intermittent feeding due to its lack of mucosal protective factors.

**Diet**

Diet has been implicated as a risk factor for EGUS. Serum gastrin concentrations are high in horses fed high concentrate diets. Also, high concentrate diets are high in digestible carbohydrates. Digestible carbohydrates are fermented by resident bacteria, resulting in the production of VFAs, which in the presence of low stomach pH ($\leq 4$), cause acid damage to the non-glandular squamous mucosa.[18] Furthermore, a recent study in horses fed a high protein and calcium diet (alfalfa hay/grain) showed higher stomach pH than horses fed a low protein and calcium (brome grass hay) diet. The high protein and calcium diet had fewer and less severe gastric ulcers. Thus feeding alfalfa hay may have some protective effect on the non-glandular mucosa in horses.

**Transport Stress**

Transporting horses has been implicated as risk factor for EGUS. Transportation of horses has been associated with dehydration, increased threat of respiratory illness (pleuritis, pleuropneumonia), and immune suppression.[27] When horses are being transported, water and feed consumption is usually decreased which may cause an increased incidence of EGUS. Transportation has been shown to increase the severity of gastric ulcers in horses.[28] However, a recent endoscopic study in western performance Quarter horses subject to frequent travel and intensive training had a lower prevalence (40%) of gastric ulcers than horses in race training, calling into question the effect of these factors on the development of EGUS in western performance horses. The authors' speculated that demeanor played a role in the lower prevalence of ulcers in this breed of horse. Quarter horses are typically calm compared to Thoroughbred racehorse, which may explain the higher prevalence of EGUS (93%) in Thoroughbreds.

**Stall Confinement**

Stall confinement has been implicated as a risk factor for EGUS. Horses that are housed in pastures have a decreased prevalence of gastric ulcers, compared to horses that are housed in stall. The reason for this may be multifactorial, as horses that are stalled may be fed intermittently and housed without exposure to other horses.[26]
Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), phenylbutazone and flunixin meglumine, have been shown to induce gastric ulcers in horses.[29] However, the use of NSAIDs in race horses has not been shown to be a risk factor for EGUS in multiple epidemiologic studies.[1-3, 5,9] In one study NSAIDs did cause ulcers in the glandular mucosa and increased the severity of ulcers in the non-glandular squamous mucosa.[30] NSAIDs are thought to cause more severe ulcers in the glandular stomach mucosa because of their effect on prostaglandin inhibition. Prostaglandin inhibition by NSAIDs results in decreased mucosal blood flow, decreased mucus production, and increased HCl secretion. While prostaglandins are also important in the regulation of acid production and sodium transport, it may be their effect on mucosal blood flow that is the most important.[31, 32] Adequate blood flow is necessary to remove the hydrogen ions that diffuse through the mucus layer covering the glandular mucosa. Gastric mucosal ischemia may lead to a hypoxia induced cellular acidosis, release of oxygen free radicals, phospholipase, and proteases, which may damage the cell membrane leading to necrosis.[33]

Helicobacter spp.

While Helicobacter spp. is an important cause of ulcers in other species, it has not been cultured from the horse. However, Helicobacter-specific DNA was isolated from glandular and non-glandular mucosa of seven horses.[34] The importance of this discovery is unknown and the role of Helicobacter spp. in EGUS remains speculative, in light of other reports in which no organisms were seen in necropsy specimens from the stomach of horses with and without EGUS.[9] More studies are necessary to define the role of Helicobacter spp. in EGUS. However, horses with chronic recurring gastric ulcers may benefit from antibiotic and antacid treatment much like people with Helicobacter pylori infections.

Etiology and Risk Factors for EGUS in Foals

The assumption that the etiology of EGUS in neonatal foals is the same as adult horses is being challenged. Age and recent illness are two risk factors of EGUS in foals, but others have not been well defined.[12] Acid and mucus secretion occurs as early as 2 days of age in foals.[7] However, the role of gastric HCl in ulcer pathogenesis in foals has recently been questioned and may impact treatment.[32, 37, 38]

Clinical Signs of EGUS

Adult Horse

Clinical signs associated with EGUS are numerous, and often vague. Ulcers are more common in horses showing clinical signs (Table 2).[7, 14, 35, 39, 40] In Thoroughbred horses in race training, gastric ulcers were associated with poor performance, poor hair coat, picky eating, and colic.[1] Of horses with a client complaint of conditions associated with gastric ulcers, or showing subtle signs of poor health, gastric ulcers were identified in 88-92% compared to 37-52% identified in horses not showing clinical signs.[1, 4, 7] In addition to an increased prevalence of ulcers in clinically affected horses, the severity of ulceration may be correlated with the severity of the symptoms.[7, 1, 39]
Foals

Clinical signs in foal differ from adults. Classically, EGUS in foals has been divided into 4 clinical syndromes, subclinical, clinical, perforating, and gastric outflow obstruction secondary pyloric stricture.[41] Clinical signs of foals suffering from clinically active ulcers are listed in table 2.[14, 32, 42] Typically foals showing clinical signs of disease (e.g. salivation, and bruxism) have severe gastric lesions when present, but the clinical signs may also indicate other gastrointestinal disease such as: small intestinal intussusceptions, small intestinal volvulus, peritonitis, impaction, diaphragmatic hernia, enterocolitis, and gastric outflow obstruction.[43]

Diagnosis

While an appreciation of the basic anatomy and physiology of acid production is important, it is equally important to be able to identify horses which would benefit from anti-ulcer therapy (Figure 1). Gastroscopy is the only definitive diagnosis of gastric ulcers currently available. The procedure for gastroscopy has been described in detail elsewhere, but requires at least a 2 meter endoscope to visualize the non-glandular mucosa and Margo plicatus and a 2.5m to 3m to visualize the pylorus and proximal duodenum in most adult horses.[6, 44] Once visualized, ulcers should be scored for severity.[14] Use of a scoring system allows the clinician to monitoring healing and evaluate efficacy of treatment.

Currently there are no hematologic or biochemical markers to diagnose EGUS. However, O’Connor et al. recently evaluated the potential of a sucrose absorption test to diagnose gastric ulcers.[45] Sucrose is a large carbohydrate broken down in the brush border of the intestine to glucose and fructose. If absorbed by the body, it must be absorbed across damaged gastric mucosa. It is not metabolized by the body, and is excreted in the urine. Concentrations of sucrose rose in the urine of horses with experimentally induced gastric ulcers. Initial evaluation of this test suggested that it holds promise to diagnosis EGUS, without the expense and expertise of gastroscopy, but more research is needed to further refine this technique.

Because of the lack of any additional laboratory diagnosis, in situations where ulcers are strongly suspected, but gastroscopy is not available, it may be worthwhile to start empirical treatment and observe for resolution of clinical signs. If the horse does not respond to treatment, referral to a facility with a gastroscope is indicated.

Treatment of EGUS

The goals of antiulcer therapy are to relieve pain, eliminate clinical signs, promote healing, prevent secondary complications, and prevent recurrence. The mainstay of EGUS treatment is increasing the stomach pH and suppression of stomach HCl acid secretion. Because of the high recurrence rate, effective acid control should be followed by altered management strategies and/or long-term treatment to prevent ulcer recurrence.

Pharmacologic Therapy

Once EGUS is diagnosed, therapy should be initiated to achieve the above outlined goals. Some ulcers heal spontaneously, but the majority need
pharmacologic therapy to achieve healing, especially while horses remain in athletic training.[3, 46] There are many approaches to treating EGUS but the mainstay is acid suppressive therapy, which sets up a permissive environment in the stomach to allow ulcer healing. Many pharmacologic agents are available to treat gastric ulcers in man but few have been shown to be effective in treatment and prevention of EGUS. Of these products, only Gastrogard® is approved by the FDA for treatment and prevention of recurrence of EGUS. However, other therapies have been used to treat EGUS with mixed success and their advantages, disadvantages, and evidence are presented below. Doses for these pharmacologic agents are listed in Table 3.

Acid Suppression Therapy

Antacids

Antacids neutralize stomach HCl, however aluminum containing antacids may have mucosal protective effects by stimulating prostaglandin production. Their usefulness in controlling stomach pH in the horse is questionable.[47] A liquid mixture containing aluminum hydroxide (30 g) and magnesium hydroxide (15 g) (Maalox TC®, 250 ml, PO) increased stomach pH in horses for 2 hours after administration.[48] Another study found that magnesium hydroxide (7.2 g) and aluminum hydroxide (8.1 g) had a moderate and short-lived effect on pH.[49] It would appear from this data that every two hour dosing of large volumes of an antacid is needed to treat EGUS. Their prolonged use may interfere with the absorption of electrolytes (e.g. calcium, magnesium, and phosphorus). Thus, antacids such as aluminum hydroxide/magnesium hydroxide may relieve clinical signs of EGUS, but are probably not effective in healing gastric ulcers.

Recently, an equine neutraceutical antacid was developed containing aluminum phosphate, calcium carbonate, dihydroxy-aluminum sodium carbonate, (Neigh-Lox®, Kentucky Equine Research) and is sold as a pelleted feed additive to relieve heartburn in horses.[50]

To the authors’ knowledge, there are no published scientific studies proving efficacy of this compound in the treatment or prevention of EGUS.

Histamine Type-2 Receptor Antagonists

Histamine stimulates acid secretion from the parietal cells.[51] Histamine type-2 receptor antagonists decrease acid secretion by competitively binding to the histamine receptor, thus blocking histamine attachment and stimulation of gastric acid secretion. Additionally, these agents may inhibit acid secretions stimulated by gastrin and acetylcholine.[52] Cimetidine and ranitidine have been used extensively to treat EGUS.

Cimetidine

Cimetidine has been used since the early 1980s to treat and prevent ulcers in horses and foals.[53] Cimetidine (20-25 mg/kg, PO, 6-8 hrs; 6.6 mg/kg, IM/IV, q6h) is currently recommended for treatment of EGUS, although doses vary among clinicians.[14] Cimetidine is less potent than ranitidine, with a variable oral absorption.[53, 54] It may inhibit the hepatic microsomal enzyme system and prolong half-life of drugs with high first pass hepatic metabolism.[55] When compared to omeprazole (4mg/kg and 2mg/kg PO SID), cimetidine (20mg/kg PO TID) is not as
effective healing EGUS of horses in race training.[56] Although cimetidine is effective in treatment of gastric ulcers in man, there is little scientific evidence in the veterinary literature showing that cimetidine has efficacy in the treatment of EGUS.

**Ranitidine**

Ranitidine hydrochloride (Gastroguard®, Ranvet Pty Ltd, Beaconsfield, Australia) is 4 times more potent than cimetidine.[53] When given orally (6.6mg/kg, PO, q8h), it suppresses acid output and maintains a median stomach pH of 4.6.[57] At a dose of 6.6 mg/kg given orally every 8 hours, ranitidine is able to successfully limit ulcer development in a feed deprivation model.[58] Lower doses (4.4 mg/kg, PO, q8h) given orally are ineffective for treatment of EGUS.[60, 61] The recent availability of the generic ranitidine has made this drug popular and effective in treating EGUS.[59] Ranitidine (6.6 mg/kg, orally, q8h) has efficacy and is recommended for treatment of EGUS, but owner compliance is difficult.

While ranitidine and cimetidine have been the most studied, other H2 antagonists have been evaluated experimentally and may allow for less frequent dosing and more effective acid suppression.[30, 62, 63] Bioavailability and pharmacodynamic studies with famotidine (2.8 mg/kg, PO, q12h; 0.3 mg/kg, iv, q12h) in horses suggest that it can be used for treatment of EGUS, but may be cost prohibitive.[64]

**Proton Pump Inhibitors (PPIs)**

The use of proton pump inhibitors offers many advantages over H2 antagonists. Once daily administration and ability to block gastric acid secretion regardless of stimulus is the advantage of these drugs.

**Omeprazole**

Omeprazole, a substituted benzimidazole, is the only approved drug for the treatment of EGUS. Omeprazole oral paste (Gastroshield® Merial Australia Pty, Ltd, Paramatta, Australia; GastroGard®, Merial Limited, Decatur, GA; 4mg/kg, PO, q24h) inhibits gastric acid secretion for 24 hours in horses.[65] In an acid environment omeprazole is activated to a sulphenamide derivative and binds reversibly to the H+/K+ ATPase in parietal cells and inhibits transport of hydrogen ions into the stomach.[55] Because of its effect on the cell, omeprazole is often called a proton-pump blocker. The effect on gastric acid secretion is dose and time dependent. Omeprazole in a gel suspension suppresses basal acid secretion by 83.7% 5 hours after a single dose of 1.5 mg/kg. After 5 days of once daily dosing at 1.5 mg/kg, acid secretion was suppressed 93%.[66] Omeprazole is metabolized in the liver and excreted in urine and bile, and significant liver disease may affect the metabolism of the drug. Long-term administration in dogs, did not cause any clinical, hematological, or biochemical alterations, but did cause a reversible gastric mucosal hypertrophy.[67] Long-term administration of high doses causes hyperplasia of ECL cells and gastric carcinoid tumors in rats.[68] No significant side effects have been reported in horses treated for up to 90 days.

Omeprazole has been shown to be an effective treatment for EGUS at a dose of 4 mg/kg orally once daily.[46, 56, 59, 69] A recent study of 565 horses in race...
training found that 96% of the 147 horses being administered H2 antagonists had gastric ulcers, with 61% considered to be severely affected.[59] Of the horses not receiving H2 antagonists, 88% had gastric ulcers, with 58% considered severe. All of the horses in the study were put on a 28-day course of omeprazole. There was a statistical improvement in performance, weight gain, attitude, appetite, and appearance after treatment. Endoscopically 65% of the horses with gastric ulcers that were treated were healed and 94% were improved. The primary reason for the failure of treatment with H2 antagonists was owner compliance and incorrect dosing. A second study found that 99% of spontaneous ulcers in adult horses and foals over 4 weeks of age were improved with 86.7% healed with omeprazole treatment.[70] Effectiveness of omeprazole was also shown to increase the rate of healing in horses with ulcers removed from race training.[69]

**Coating or Binding agents**

Sucralfate and bismuth subsalicylate are two compounds that bind to stomach ulcers and promote healing. Sucralfate is a hydroxyl aluminum salt of sucrose octasulfate and binds to the negatively charged particles in the ulcer bed, buffering HCl by increasing bicarbonate secretion, stimulating prostaglandins production, and adhering to the ulcer bed.[73] In the stomach, sucralfate is converted to a sticky amorphous mass, thought to prevent diffusion of hydrogen into the ulcer. In a clinical trial in horses, sucralfate (22 mg/kg, PO, q8h) did not improve subclinical ulcer healing in 6 and 7 month old foals.[73] In a rat model sucralfate successfully prevented gastric ulceration in a dose dependent manner after an ischemia reperfusion injury.[74] Recently, GastrafateTM (20-30 ml, PO, q12h; MFP, Ltd, Sterling CT), an emulsion (10% Sucralfate, Calcium Carbonate, DASC, Magnesium Hydroxide, Carboxylate, Apple Flavor, Methyl & Propyl Parabens, and Water) has been advertised as a treatment for EGUS. This quantity of Gastrafate would provide 3 g of sucralfate to a patient, which is significantly less than the 9-18 g currently recommended for treatment of EGUS. Currently, there is no published scientific data on the efficacy of this product in treating EGUS. Therefore, sucralfate alone may not be beneficial in treatment of EGUS, but can be used in conjunction with acid suppressive therapy and may be more suited for treatment of Right Dorsal Colitis (colonic ulcers) at a dose of 22 mg/kg, PO, q6-8h.

Bismuth containing compounds may have a coating effect similar to sucralfate. Additionally it will inhibit the activation of pepsin and increase mucosal secretion.[75] A compound containing 26.25 g of bismuth failed to raise the pH in 5 horses.[48] Bismuth subsalicylate may be converted to sodium subsalicylate in the gastrointestinal tract, which may cause gastric irritation. Also, salicylates, similar to aspirin, decrease prostaglandin secretion and may further compromise an already damaged mucosa.[76] Thus, compounds containing bismuth are not recommended for treatment of EGUS. However, bismuth is used as part of the therapy in humans with *Helicobacter pylori* induced gastric ulcers and may be used in horses with chronic recurring gastric ulcers in which Helicobacter is suspected.

**Synthetic hormones**

Misoprostol, a synthetic PGE1 analogue, is effective in the treatment of gastric and duodenal ulcers in man. Acid suppression, increased mucosal blood
flow, increased bicarbonate secretion, and increased mucosal restitution are mechanisms of misoprostol. In one study, misoprostol (5 mcg/kg, PO) increased stomach pH and inhibited gastric acid secretion for 8 hours. Misoprostol is contraindicated in pregnant and nursing horses due to its effect on increasing uterine contractions. Although no reports of side effects have been reported in horses, side effects reported in other species include: diarrhea, cramping, flatulence, and uterine contraction. Side effects are dose dependent.[55]

A somatostatin analogue, octreotide acetate, has also been evaluated in horses.[77] Octreotide (0.5 to 5.0 mcg/kg) raised the gastric pH > 4 for approximately 5 hours, with no adverse effects noted. While octreotide appears to be very safe in human patients, it requires multiple daily dosing and is cost-prohibitive in horses. The benefit of using a somatostatin analogue is the prevention of hypergastrinemia associated with long-term use of acid suppressive drugs. The hypergastrinemia has a positive tropic effect on gastric cells and may result in proliferation.[68] Because somatostatin inhibits gastrin secretion, this hypertrophy is avoided, however no case of gastric hypertrophy has been reported in horses following long term use of acid suppressive drug therapy.

**Prokinetic Agents**

Prokinetics agents may be valuable as an adjunct therapy in the treatment of EGUS and when there is adynamic ileus and gastroduodenal reflux. Bethanechol (0.25 mg/kg, IV) and erythromycin lactobionate (0.1 and 1.0 mg/kg, IV) increased solid phase gastric emptying time in horses.[78] No adverse effects were seen in healthy patients, however other forms of erythromycin can cause fatal colitis in adult horses at antimicrobial doses. Both prokinetics increase gastric emptying versus saline, but bethanechol appeared to be superior. It increased gastric emptying rate of solid food versus erythromycin and increased gastric emptying rate of liquid versus saline. Bethanechol is a synthetic muscarinic cholinergic agent that is not degraded by acetylcholinesterases. The only side effect of the bethanechol administration was increased salivation. Other authors have recommended a dose of 0.025 – 0.030 mg/kg subcutaneously every 3-4 hours followed by oral maintenance therapy of 0.3 – 0.45 mg/kg 3-4 time daily.[79] It is also possible that gastroduodenal reflux may worsen after treatment in patients with a proximal small intestinal obstruction.[78]

**Antibiotics (Helicobacter spp.)**

Treatment of *Helicobacter pylori* infection in humans greatly accelerates ulcer healing, and eradication reduces the risk of reoccurrence.[35] In people combination therapy is the treatment of choice and includes acid suppressive therapy (PPIs or H2 antagonists) and antibiotics. Several examples include: 1) omeprazole or ranitidine, clarithromycin, and amoxicillin or metronidazole, 2) omeprazole or ranitidine, bismuth, tetracycline, and metronidazole, 3) omeprazole or ranitidine, bismuth, tetracycline, and furazolidone. A 10-14 days treatment period is successful in 65% to 80% of clinical cases. This is less than the 95%-99% seen in clinical trials, which is likely due to poor patient compliance. These same combination therapies have been proposed for treating dogs and cats with Helicobacter infections.[36] Extrapolating from other species, a oral combination therapy in horses with chronic active, non-healing ulcers (caused by a Helicobacter species), would be omeprazole (4 mg/kg
q24hr), metronidazole (15 mg/kg q6hrs) and/or trimethoprim/sulfa (25 mg/kg q 12 hrs), and bismuth subsalicylate (3.8 mg/kg q6hrs). An initial 14-day treatment period could be prescribed, which should be followed by gastroscopy. Omeprazole therapy should be continued for the full 28 day if needed.

**Other treatments**

Other treatments including, furosemide, fenbendazole, G.U.T, and Nutrient Buffer® have been suggested for treatment of EGUS, but efficacy has not been reported in scientific literature. Furosemide showed a strong correlation to reduced severity of ulcers in Thoroughbred horses in race training.[40] However, this same correlation has not been found in any other studies. It was theorized that furosemide might modify gastric mucosal blood flow.

Fenbendazole (6g, PO, q24h for 5 days), because of its chemical similarity to omeprazole, has been suggested to be an effective treatment of EGUS. However, in one study gastric ulcer scores were significantly improved after 2 weeks of fenbendazole treatment, but after 4 weeks of treatment gastric ulcer scores were no different than controls.[80] Thus, fenbendazole is not effective in treatment of EGUS.

Other neutraceuticals such as G.U.T. and Nutrient Buffer® claim to be useful in horses with EGUS but no data has been published to show that these compounds have any effect in horses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Dosing Interval</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>1.0 mg/kg</td>
<td>Intravenously</td>
<td>Q 24 hrs</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>4 mg/kg</td>
<td>Orally</td>
<td>Q 24 hrs</td>
</tr>
<tr>
<td>Omeprazole (prevention)</td>
<td>1 mg/kg</td>
<td>Orally</td>
<td>Q 24 hrs</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1.5 mg/kg</td>
<td>Intravenously</td>
<td>Q 6 hrs</td>
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<tr>
<td>Ranitidine</td>
<td>6.6 mg/kg</td>
<td>Orally</td>
<td>Q 8 hrs</td>
</tr>
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<td>Famotidine</td>
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<td>Intravenously</td>
<td>Q 12 hrs</td>
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<td>Famotidine</td>
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<td>Orally</td>
<td>Q 12 hrs</td>
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<tr>
<td>Misoprostol</td>
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<td>Orally</td>
<td>Q 8 hrs</td>
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<td>Sucralfate</td>
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<td>Q 8 hrs</td>
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<td>Q 2hrs</td>
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<td>Subcutaneous</td>
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<td>Orally</td>
<td>Q6-8 hrs</td>
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<tr>
<td>Erythromycin lactobionate</td>
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</tbody>
</table>

*Cimetidine: Not effective for treatment of EGUS

**Duration of Treatment**

It is difficult to predict how long a gastric ulcer will take to heal, so treatment duration must be tailored for the individual horse. In a feed deprivation model of ulcer induction, ulcers were healed or almost healed in the horses after 9 days of pasture turnout.[25] Omeprazole treatment in Thoroughbred horses in training resulted in healing in 57%, 67%, and 77% of horses treated for 14 days, 21 days, and 28 days, respectively.[81] Horses with spontaneous occurring ulcers in a field trial treated with omeprazole showed 86% healing after 28 days of treatment.[59, 70] We recommend endoscopic examination after 14 days of omeprazole therapy to determine if the ulcers are healed. If the gastric ulcers are healed then the horse...
can be put on omeprazole (2 mg/kg, PO, q24h) to prevent recurrence of ulcers while
the horse is in training. If the ulcers are still present then the full 28-day course of
omeprazole should be followed and the horse further evaluated after that time.
When endoscopy is not available, horses should be treated for at least 28 days. It
should be noted that clinical signs might resolve before complete healing has taken
place. Signs of poor appetite, colic or diarrhea will usually resolve soon after initiating
treatment, and the horse is expected to make improvements in body condition and
attitude within two to three weeks.[79] H2 antagonist therapy should be continued for
at least 14-21 days, but healing has taken over 40 days in some studies.[79]

In general it may take longer to treat large ulcers, more severe ulcers, and
ulcers in the non-glandular mucosa.[75] In cases where clinical signs have resolved
and the risk factors for ulcer development are low, spontaneous healing of ulcers
may occur without further treatment. However, spontaneous healing will not occur in
horses that continue intensive training, and ulcers may re-occur in those successfully
treated if therapy is discontinued.[81] If clinical signs attributed to EGUS have not
resolved after 48 hours of treatment, the diagnosis or therapy should be re-
considered.

Dietary Management
In conjunction with pharmacological therapy, environmental and dietary
management may be helpful to facilitate ulcer healing. In man ingestion of a high
protein meal is a stimulus for the release of gastrin and subsequently gastric
acid.[57,82] In the horse, the ingestion of a grain meal resulted in a higher gastrin
stimulus than grass hay. Horses fed hay versus withholding feed had similar acid
output, but higher gastric pH. It was theorized that the salivary bicarbonate and the
buffering effect of the hay were responsible for the higher pH.[83] Providing constant
access to alfalfa or good quality hay will also help to raise the pH.[58] In addition to
providing constant access to feed to buffer gastric acidity, modifying the diet may
help prevent ulcers. Although the VFA concentrations were higher, an alfalfa/grain
diet had a higher pH and less ulcers than a plain bromegrass hay diet.[19] In that
study no gastric hormones were measured, and it was hypothesized that the calcium
could have a direct effect on gastric secretions or the protein was acting as a buffer
for the pH. In a rat model a diet of 2% calcium inhibited basal gastric secretion, but
not secretions in response to histamine stimulation.[84]

Pasture turnout is the best dietary method of controlling gastric ulcers. One
study found that simply putting a horse in a stall with ad lib grass hay created ulcers,
while horses maintained on pasture rarely have gastric ulcers.[57,58] Management
of the diet fed to stalled horses can be modified to decrease the risk of ulcer. Current
dietary recommendations include providing continuous feeding of good quality grass
and/or alfalfa hay. Sweet feed should be kept to a minimum and grains like barley or
oats can be substituted to decrease its fermentation to VFAs.

Prevention in Adult Horses
Treatment strategy may vary on an individual basis. While acid suppression is
the cornerstone of therapy, preventative therapy must be continued unless risk
factors are eliminated. Because of difference in training/management requirements, several courses of therapy may be pursued.

**Pharmacotherapy**

Omeprazole and the H2 antagonists can be used at their standard doses in hopes of preventing ulcers. There are no published studies evaluating the preventative effects of H2 antagonists, but omeprazole at 2mg/kg has been shown to prevent ulcer recurrence after treatment in horses in race training.[56, 81]

**Management and Feeding Strategies**

Different combinations of preventative and therapeutic treatments may be employed in differing situations (Table 4).

*Race training*

There is limited opportunity to modify the management of horses that are in race training. Due to the high prevalence of EGUS in this population, preventative therapy is strongly encouraged. Horses treated successfully will have reoccurrence of ulcers if appropriate therapy is not instituted. The best strategy for managing horses in race training includes feeding free choice alfalfa, providing GastroGard®, (4mg/kg, PO, q24h, for 28 days) for treatment and GastroGard®, (2 mg/kg, PO, q24h) for prevention of recurrence until the horse is removed from race training (Table 4, Strategy 1). A second option would be to feed alfalfa free choice and treat with ranitidine (6.6 mg/kg, PO, q8h) until the ulcers are healed (via gastroscopy) and then maintain on GastroGard®, at 2.2 mg/kg orally once daily (Table 4, Strategy 2). A final option to consider would be to treat the horses with 30 g AIOH and 15 g MgOH (approximately 250 mls Maalox TC, PO) after the horse has finished its evening meal and within two hours of an intensive work (Table 4, Strategy 3). The horses could be kept on a GastroGard®, (2 mg/kg, PO, q24h) during this time.

*Show training*

Horses that are in show training do not have as high an incidence of EGUS as horses in race training, but still have a high prevalence and preventative therapy is strongly encouraged. Show horses can be managed with treatment strategies one and two discussed above. Additionally the ability of most show horses to have pasture turnout is more flexible than that of horses on a race track, and management should be altered to pasture turnout as often as possible. An additional therapy for show horses would consist of treatment with GastroGard (4 mg/kg, PO, q24h) or ranitidine (6.6 mg/kg, PO, q8h) for 3 to 4 days before transporting to a show, during the show, and for a 3 to 4 days after returning home (Table 4, Strategy 4). In such a situation the horse should be maintained on pasture while at home, or fed free choice alfalfa hay when stalled.

*Trail horses, Brood mares, Pleasure horses*

For the low maintenance non-show horse kept on pasture, no prevention is necessary. For those horses diagnosed with EGUS based on clinical signs and gastroscopy, appropriate therapy with omeprazole or ranitidine should be instituted (Table 3). Patients should be rechecked at 14 days and therapy discontinued if the ulcers are healed. Otherwise therapy should be continued for the full 28 days (Table 4, Strategy 5). In situations where horses maintained on pasture develop non-
glandular ulcers, a careful evaluation of the management and husbandry is indicated.

Table 4 – Treatment/Preventative Strategies

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Exercise Regimen</th>
<th>Hay type</th>
<th>Husbandry</th>
<th>Intermittent vs Free choice feeding</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 1</td>
<td>Race training /</td>
<td>Alfalfa</td>
<td>Stall confinement</td>
<td>Free Choice</td>
<td>Gastroguard 4mg/kg 28 days then 2mg/kg maintenance</td>
</tr>
<tr>
<td></td>
<td>Intensive training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Race training /</td>
<td>Alfalfa</td>
<td>Stall confinement</td>
<td>Free Choice</td>
<td>Ranitidine 6.6 mg/kg PO TID for treatment and</td>
</tr>
<tr>
<td></td>
<td>Intensive training</td>
<td></td>
<td></td>
<td></td>
<td>maintenance</td>
</tr>
<tr>
<td>Strategy 3</td>
<td>Race training /</td>
<td>Alfalfa</td>
<td>Stall confinement</td>
<td>Free Choice</td>
<td>Antacid 30/15 g Al/Mg before exercise and in evening</td>
</tr>
<tr>
<td></td>
<td>Intensive training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 4</td>
<td>Moderate training,</td>
<td>Alfalfa</td>
<td>Stall confinement with limited pasture turnout</td>
<td>Free choice when in stall</td>
<td>Same as 1 &amp; 2, or treat with omeprazole or ranitidine 3 days before and throughout show</td>
</tr>
<tr>
<td></td>
<td>Show/performance</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>horses</td>
<td></td>
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</tr>
<tr>
<td>Strategy 5</td>
<td>Brood mare, trail</td>
<td>Either</td>
<td>Maintained on pasture</td>
<td>On pasture</td>
<td>Not necessary except when diagnosed with ulcers. Treat for 14 days and reevaluate ulcers</td>
</tr>
<tr>
<td></td>
<td>horse, pleasure</td>
<td>alfalfa</td>
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<tr>
<td></td>
<td>horse</td>
<td>or grass</td>
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<tr>
<td></td>
<td>hay</td>
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</tbody>
</table>

Treatment Strategies in Foals

For several years it has been the standard practice to put sick neonatal foals on prophylactic ulcer treatment due to the fear of gastric perforation, and bacterial or fungal colonization of the ulcer.[6, 32] In contrast to this practice, Barr reported a decrease in the incidence of gastric ulcers in foals examined at necropsy despite not treating foals with acid-suppressive medications.[32, 37] The reduced prevalence was credited to improved management of the critical patients including: early treatment of sepsis, sufficient oxygenation, improved monitoring, institution of enteral feedings, and improved nursing care.[32] Additionally, Sanchez showed that critically ill neonatal foals can have an atypical gastric pH, and may not respond to the administration of ranitidine in the same manner as healthy foals.[38, 85] In this study foals with acidic pH values survived while those with alkaline or fluctuating values were more likely to die. While no specific cause was identified for the increased pH, alterations in mucosal blood flow and duodenal reflux were suggested as possibilities.

More evidence against the prophylaxis use of acid-suppressive therapy in critically ill patients can be found in human literature. Increased mortality, and the incidence of pneumonia were indirectly correlated to gastric pH in a small population of human patients during ventilation therapy. A retrograde colonization of the
Oropharynx from microaspiration was suggested as the cause of the pneumonia, and higher numbers of bacteria were found in patients treated with acid-suppressive therapy vs. treatment with sucralfate. In a separate study, increased translocation of bacteria from the stomach to the spleen, liver, and mesenteric lymph nodes was significantly increased in neonatal rabbits treated with acid-suppressive therapy. This study would indicate a acidic environment in the stomach may be an important barrier to intestinal colonization and translocation of bacteria. How these studies apply to neonatal foals is not known, but does indicate that the use of acid-suppressive therapy in neonatal foals should be re-evaluated. It may be that the gastric ulcers of sick neonatal foals is more similar to gastric stress ulcers in man, while EGUS is more similar to reflux esophagitis.
Figure 1 – Diagnosis and Treatment of EGUS

References

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