Proceedings of the
18th Annual Meeting of the
Italian Association of Equine Veterinarians
SIVE

Feb. 3-5, 2012 - Bologna, Italy

Next SIVE Meeting:

Feb. 1-3, 2013 – Arezzo, Italy

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Equine gastric ulcer syndrome (EGUS) encompasses a variety of pathological conditions including the presence of focal or multi-focal lesions in the squamous or glandular mucosal lining of the stomach, generalized gastritis, gastric emptying disorder, gastro-esophageal reflux disorder and duodenal obstructive disorder.

**PREVALENCE**

Estimates of EGUS in foals range from 25%, based upon necropsies of foals examined at a veterinary teaching hospital, to 51%, based upon an endoscopic survey of 183 foals (ages 1-310 days) examined at a veterinary teaching hospital. In that study, most lesions were found in the squamous mucosa adjacent to the margo plicatus along the greater curvature of the stomach. Lesions in the glandular and duodenal mucosa (occurring in 26 and in 5 of the 183 foals, respectively) existed primarily in foals with concurrent medical disorders. In another survey of asymptomatic Thoroughbred foals (2-85 days of age) in Ireland and England, prevalence rates of gastric ulcer formation were 47% and 57%, respectively with lesions noted primarily in the squamous mucosa adjacent to the margo plicatus. Nine percent of those foals had glandular lesions as well as a previous medical disorder such as diarrhea.

**PATHOPHYSIOLOGY OF ULCER DISEASE IN FOALS**

Although the causes of EGUS remains to be firmly established, it is thought that EGUS results from an imbalance between intrinsic protective factors and ulcerogenic factors. Protective factors include mucosal blood flow (considered to be the most important), mucous-bicarbonate secretion, mucosal epidermal growth factor, epithelial cell restitution, prostaglandin E (PGE, PGE,) and gastroduodenal motility. Since mucosal protective factors are more developed in the glandular mucosa as compared to the squamous mucosa, different causative mechanisms are hypothesized to cause ulceration such as prolonged acid exposure in the squamous region versus altered blood flow in the glandular region. Intrinsic ulcerogenic factors include hydrochloric acid, pepsin, bile salts, lactic acid and volatile fatty acids while extrinsic ulcerogenic factors entail nonsteroidal anti-inflammatory drug (NSAID) administration, stress (related to diet, management or disease) and the presence of gastrointestinal disorders that impact on motility.

In the stomach, the squamous mucosa provides a critical physical barrier against the intrinsic ulcerogenic factors. In the neonatal foal, the superficial cornified epithelium and its overlying keratin layer is much thinner than that found in the adult perhaps increasing this region’s susceptibility to acid destruction. Desquamation or “shedding” of the squamous mucosa occurs in 80% of foals up to 35 days age and this process may increase epithelial susceptibility to acid injury. Acid injury delays re-epithelialization propagating the ulcerogenic cycle. In healthy, newborn pony foals, the mean gastric fluid pH is 4.1, a value which decreases to a pH of 2.3 by seven days of age with no further change noted by 2- to 3-months of age. Sanchez et al (1998)
reported mean intragastric pH values of 3.2-3.7 in healthy 2-day old foals. The percentage of time that the intragastric pH was > 4 ranged from 15 to 40% of the day. Milk ingestion in neonates or in older foals (2-3 months of age) results in an immediate and profound rise in intragastric pH, an effect that lasts for several minutes to hours. Fasting or interrupted milk feedings markedly decrease gastric pH.\textsuperscript{8} In neonatal foals that are septic, premature or suffering from hypoxic ischemic encephalopathy, the intragastric profiles are highly variable with nearly 50% of the foals exhibiting alkaline intragastric profiles (pH > 5) in the absence of ulcer treatment. The investigators attributed the alkaline profiles to the effects of recumbency, ileus and entero-gastric reflux.\textsuperscript{9}

Mucosal blood flow is considered to be the most important protective defense against ulcer formation, especially in the glandular region of the stomach or in the duodenum. Nitric oxide (NO) may be the primary regulator of gastric mucosal blood flow along with prostaglandin E\textsubscript{1} and E\textsubscript{2}.\textsuperscript{10} Prostaglandins also regulate bicarbonate and mucus secretion, stimulate surface-active protective phospholipid release and facilitate mucosal repair.\textsuperscript{6} Decreased prostaglandin syntheses has been implicated as the cause of glandular gastric ulcers in foals since these are induced with NSAID (phenylbutazone; flunixin meglumine) administration.\textsuperscript{11,12} Stress and endogenous cortisol release may induce ulcer formation by inhibiting prostaglandin E synthesis.\textsuperscript{13} Gastric blood flow is also decreased by serotonin (5-hydroxytryptamine, 5-HT): In a immunohistochemical study of the equine gastrointestinal tract, significantly more 5-HT containing cells were detected in the pyloric region and near the margo plicatus compared to adults but it remains to be determined how this anatomical difference contributes to ulcer formation.\textsuperscript{14} Lastly, as evident from the epidemiological studies, neonatal foals with sepsis, pneumonia, hypoxic-ischemic encephalopathy, enterocolitis or painful orthopedic conditions, are at risk of glandular ulcer formation. This is attributed to reductions in tissue perfusion (gastric blood flow) and gastrointestinal motility. In summary, in the stomach, protection from squamous mucosal ulceration is dependent upon limiting exposure of this region to acids while glandular ulcer prevention is dependent upon maintaining gastric blood flow, mucus and bicarbonate production.

EGUS lesions also occur in the duodenum and the esophagus. Duodenal ulcers occur less frequently than gastric lesions and are often associated with enteritis or duodenitis.\textsuperscript{15} The protective factors in the duodenum are the presence of submucosal glands that secrete mucins; the intestinal motility patterns that promote aborad movement of gastric effluent and extrinsic factors such a water, sodium, chloride and bicarbonate secretions that dilute and/or neutralize acid from stomach.\textsuperscript{16} In the esophagus, mucosal protection from acid injury is dependent on the lower esophageal sphincter tone preventing reflux of gastric contents into the esophagus, the neutralizing effect of saliva that washes away gastric contents and the ability of salivary mucins to form a thin protective layer on the esophageal mucosal surface. In outflow disorders, gastric distention and acid reflux induce erosive lesions.

**Clinical syndromes** that have been described in foals include: \textsuperscript{6,16}

1. **Subclinical or “silent” gastric ulceration** is the most common clinical scenario in foals less than 4 months of age. As previously noted, lesions occur in the squamous mucosa along the greater curvature adjacent to the margo plicatus. “Silent” glandular or duodenal ulcers are occasionally found in foals with concurrent medical problems, stress or NSAID administration. “Silent” ulcers may resolve without treatment or may produce clinical signs including perforation.

2. **Clinical or active gastric ulcers** probably reflect an increase in the size or the extent of subclinical ulcers as they are typically found in the squamous mucosa along the margo plicatus. Some clinical ulcers develop in the glandular mucosal. Affected foals exhibit poor appetite, interrupted nursing patterns, poor growth and hair coat, a pot-bellied appear-
ance, bruxism, colic (dorsal recumbency) and ptyalism due to reflux of gastric contents into esophagus and mouth. Some foals may be painful on abdominal palpation caudal to the xiphoid process.

3. Perforating ulcers with secondary fatal peritonitis or hemorrhage is an infrequent sequel. Most involve the squamous regions but can occur with glandular gastric or duodenal ulcers. Small perforations may heal spontaneously by adhesions although abscessation can ensue. Affected foals (a few days of age to 5-months of age) exhibit depression, tachycardia, colic, abdominal distention and prolonged capillary refill time. Early diagnosis is essential as surgical intervention may reduce mortality.

4. Gastric outflow obstruction secondary to pyloric or duodenal ulceration is also rare most frequently occurs in foals 2-5 months of age. Pyloric stenosis develops secondary to chronic ulceration and inflammation. A segmental ulcerative duodenitis rather than a discrete duodenal ulcer has been reported in some foals. Clinical signs are related to the ulceration, the outflow obstruction that causes gastro-esophageal reflux and erosive esophagitis. Clinical sign include milk drooling, bruxism, excessive salivation, post-prandial colic, reduced manure production or diarrhea and aspiration pneumonia. Duodenal lesions may cause cholangiohepatitis and pancreatitis.

**Diagnosis of EGUS:**

1. Gastroscopy, using a 2-meter scope with an outside diameter (OD) < 9 mm, is necessary to confirm the diagnosis. (In foals less than 1 month of age, a 1 meter scope may be sufficient for the gastric exam). Young foals on a milk diet do not require a prolonged fast prior to the exam as the stomach is usually free of liquid within 4 hours of milk ingestion unless an outflow obstruction exists. In older foals consuming roughage, a 12-hour fast is usually necessary. In the sedated foal, endoscopic evaluation of the esophagus is conducted to rule out the presence of linear ulcers, erosive esophagitis, a dilated esophagus or a flaccid esophageal sphincter. Once in the stomach, use caution in inflating it due to small size and remember to deflate it by suction when the exam is completed. In neonatal foals the squamous mucosa is thin and light pink but becomes hyperplastic and parakeratotic within a few days. Identify the location, the extent and the severity of lesions using a scoring system, an example of which is shown below from Murray and co-workers (2001).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Intact epithelium with no apparent mucosal changes.</td>
</tr>
<tr>
<td>1</td>
<td>Mucosal reddening or hyperkeratosis (squamous).</td>
</tr>
<tr>
<td>2</td>
<td>Small single or multifocal lesions.</td>
</tr>
<tr>
<td>3</td>
<td>Large single or multifocal lesions or extensive superficial lesions.</td>
</tr>
<tr>
<td>4</td>
<td>Extensive lesions with areas of apparent deep ulceration.</td>
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A scoring system based upon histological examination of biopsies obtained from squamous and glandular regions has also been developed and used in adult horses. Once the gastric exam is completed, the scope is maneuvered into the duodenum where the mucosal color, contour and presence of motility is evaluated. Difficulty in passing the scope through the gastric antrum into the duodenum suggests the presence of a stricture.

2. Ultrasound examination of the gastrointestinal tract (and thoracic cavity if aspiration pneumonia is a concern in cases gastrointestinal reflux) is useful in evaluating motility and wall thickness. On the left side, the stomach is scanned to detect evidence of dilation or enlargement. In the caudal right abdomen, the wall thickness and luminal diameter of the duodenum, as well as evidence of peristalsis throughout the intestinal tract, is assessed.

3. Radiographs and a barium study. In survey radiographs, the presence of a dilated esophagus and an enlarged stomach are suggestive of outflow obstructions. Following administration of barium by nasogastric tube (10 mL/kg), serial radiographs are taken 30 minutes post barium administration for 2-3 hours. Barium should be detected in the duodenum within 10 minutes of its administration in healthy foals. Delay in gastric emptying suggests either a functional (inflammation that al-
ters myoelectric activity) or mechanical (pyloric/duodenal stricture) obstruction. Following gastric decompression, medical management may initially be tried to determine if gastric emptying can occur and a repeat barium study may be warranted.

4. Sucrose permeability test has been described as a non-invasive method for screening and monitoring horses with gastric ulceration. In adult horses which have been fasted for 20 hours, 250 g of sucrose (10% solution) is administered by nasogastric tube and blood samples, obtained every 15-30 minutes, are assayed for sucrose using high performance liquid chromatography-mass spectroscopy. In adult horses with grade 3 and 4 ulcer scores, serum sucrose was detected within 15 minutes of sucrose administration. Serum sucrose was not detected in healthy horses or those with mild lesions. This test has not been conducted in foals and currently requires sophisticated instrumentation.

5. Fecal occult blood testing might be helpful in detecting ulcers in young foals that have not yet established colonic microflora that normally digest hemoglobin. One newer commercial test utilizes monoclonal antibodies to detect albumin and hemoglobin. The manufacturers of the test purport a 77% positive predictive value and a 72% negative predictive value.

6. Alpha-1 antitrypsin serum concentrations. Taharaguchi and co-workers (2007) reported that the serum α-1 antitrypsin concentrations were elevated in 44 of 47 foals with clinical and endoscopic evidence of EGUS. In contrast only 3 of 22 healthy, ulcer-free foals exhibited elevations of this serum protein. It remains to be determined if the increase in this inflammatory protein correlates with endoscopic scores of ulceration.

**Treatment of EGUS** is somewhat dependent the constellation of clinical problems and the region affected.

1. Foals lacking evidence of gastroduodenal outflow obstruction. Medical therapy is directed at promoting ulcer healing by reducing exposure to an acid environment, enhancing the production of intrinsic protective factors; managing pain; providing nutrient support (milk, total parenteral nutrition if necessary) and ensuring gastrointestinal motility.

H-2 Receptor Antagonists – Ranitidine, on a molar basis is 5-12 times more potent than cimetidine, in preventing gastric acid release from the parietal cells. In healthy neonatal foals, administration of ranitidine (2 mg/kg q 4h IV or 6.6 mg/kg q 8h PO) increased gastric pH to 6-8 for approximately 4 to 8 hours but failed to consistently increase gastric pH in critically ill neonatal foals even when administered intravenously. In a study of flunixin-induced ulcers in young ponies, MacAllister and Sangiah (1993) reported that oral administration of ranitidine (4.4 mg/kg q 8h) for 40 days failed to enhance ulcer healing compared to placebo (corn syrup). They attributed their lack of response to the short duration of acid suppression by the ranitidine. Cimetidine has been used to treat ulcers at a dose of 15-20 mg/kg PO q 4h or 6.6 mg/kg IV q 4h but has a short duration of acid suppression.

Proton pump inhibitors (PPI) used in veterinary medicine include omeprazole, pantoprazole and more recently esomeprazole. These drugs work by irreversibly binding H⁺/K⁺ ATPase on the parietal cell surface but for this inhibition to occur, the PPI must be absorbed and distributed to the parietal cell via the systemic circulation. Omeprazole when administered to healthy neonatal foals at 4 mg/kg PO q 24h increased intragastric pH > 4.0 for up to 23 hours. In critically ill neonatal foals, a single dose of omeprazole (4 mg/kg PO q 24h) increased intragastric pH between 5.2 and 7.8 for at least 12 hours. In a toxicity study conducted in 2-4 month old foals given omeprazole at 5 times the recommended dose of 4 mg/kg PO q 24h, no adverse clinical effects were found. Hematological and serum biochemistry data were not reported in that study.

In a multi-center study examining the efficacy of a 28-day omeprazole treatment regimen on the healing of spontaneous gastric ulcers (scores > 1) in 4-12 week old foals, investigators reported that 99% of the treated foals showed an improvement in ulcer score and that 87% were completely healed after 28 days of therapy. The efficacy of intrarectally
administered omeprazole on gastric pH profiles in adult horses (but not foals) was recently reported: The bioavailability was poor and absorption was erratic with only 2 of the 6 treated horses have intragastric pH values > 4.0. A similar study has not been conducted in foals. Pantoprazole (1.5 mg/kg IV) was evaluated in healthy neonatal foals and shown to increase intragastric pH within 2 hours of its administration, and to maintain intragastric pH > 5 for 22 h. In that same study, oral administration of pantoprazole increased intragastric pH similar to that of IV administration. Esomeprazole was recently evaluated in adult horses following intravenous dosing of 0.5 mg/kg q 24 hours and found to increase intragastric pH > 6.4. Studies of esomeprazole have not been conducted in foals.

Cytoprotective agents that can be used to treat ulcers include sucralfate, a basic aluminum salt of sulfated sucrose. This agent adheres to the ulcerated mucosa, deters further destruction of the epithelium by acid and pepsin, and reduces colonization of pathogenic bacteria. Sucralfate also stimulates mucus-bicarbonate secretion, enhances prostaglandin and epidermal growth factor production and promotes gastric blood flow. Sucralfate is also used in the treatment of duodenal ulcers/duodenitis in foals. Doses of 10-20 mg/kg PO q 6h are administered prior to treatment with alkalinizing agents since sucralfate adheres best in an acidic environment. Misoprostol, a synthetic prostaglandin E₁ analogue, is another cytoprotectant that is used to promote gastrointestinal blood flow in foals with glandular and duodenal ulcers. It is administered at a dose of 2-5 µg /kg q 8-12h PO and may cause abdominal pain and/or diarrhea.

Prokinetics. Drugs that enhance gastric/duodenal motility aid in removing acidic secretions and in delivering medications to the small intestine. Bethanacol is the drug of choice for promoting gastric motility (0.35 mg/kg PO q 8h) but can produce diarrhea, inappetence, salivation and colic. Metoclopramide is a derivative of procainamide and increases myogenic tone of lower esophageal sphincter (decreasing reflux) and accelerates gastric emptying. Recommended doses are 0.1 to 0.25 mg/kg PO q6 or 8h although a constant infusion rate of 0.04 mg/kg/hr may be more effective in stimulating motility. Neurological side effects (excitement, tachycardia, sweating) have been reported with its administration. In cases in which delayed gastric emptying is associated with distention, mechanical decompression of the stomach is indicated.

Antimicrobials. Little is known about the change in gastric and duodenal microbial flora that occurs with EGUS. Prophylactic administration of broad spectrum antimicrobials is recommended to reduce colonization of ulcerated areas by pathogenic bacteria and secondary bacterial translocation.

Analgesics. Controlling the pain associated with EGUS (clinically active ulcers; erosive esophagitis, gastro-esophageal reflux) is a challenge since most clinicians would prefer not to use NSAIDs. Theoretically, firocoxib a “selective” COX-2 inhibitor, might be less detrimental to ulcer healing but its efficacy at ameliorating visceral pain in foals has not been reported. Alternative pain management approaches include lidocaine constant rate infusions or intermittent intramuscular butorphanol administration.

2. Foals with gastroduodenal outflow obstruction (mechanical) often require surgical intervention. The decision to operate is usually made after medical management (including gastric decompression) for 24 or 36 hours is unsuccessful. The specific surgical bypass procedure elected depends upon the location of the obstruction. Procedures used include pyloromyotomy (pyloric stenosis); gastroduodenostomy (to bypass duodenum) and gastrojejunostomy (to bypass duodenal stricture). Potential complications are re-obstruction, perforation, post-operative ileus, obstruction of the major duodenal papilla (cholangitis, cholangiohepatitis or pancreatitis), adhesions and incisional infection. In a retrospective study of 16 Thoroughbred foals (mean age of 65 days) that had a gastrojejunostomy to resolved duodenal outflow obstruction, Coleman (2009) reported that 50% of the foals survived to 3 years of age and that 7 of the 8 surviving horses entered race training. Three raced successfully. Post-mortem evaluations
of the non-survivors revealed ulcer perforation near the gastric incisional site; small intestinal constriction at the outlet of bypass; severe cholangiohepatitis due to bile duct obstruction and persistent gastric ulceration. The authors concluded that the long-term prognosis of surgically treated cases is fair.

Prophylactic therapy of the high risk neonatal foal is somewhat controversial because prolonged periods of gastric alkalinity could allow for alterations of bacterial flora within the gastrointestinal tract and increase the risk of bacterial translocation across a compromised gastrointestinal mucosal barrier. In severely compromised recumbent neonates, supportive care to ensure adequate tissue perfusion provides more protection against ulcer formation than any medication directed at the suppression of acid production. Recommendations are to hydrate foal, monitor its blood pressure and tissue perfusion. In ambulatory foals receiving repeated doses of NSAIDs (for musculoskeletal problems) or those foals with diarrhea, prophylactic ulcer treatment may still be recommended.

References