Gastroduodenal Ulceration in Foals (16-Dec-2003)

M. J. Murray
Merial Equine Global Enterprise, Duluth, GA, USA.

Summary
Gastric ulcers are highly prevalent in foals, and severe ulcers can develop as early as 2 days of age. Gastric acidity can be very high in foals, particularly between nursing activities. Hydrochloric acid can begin damaging the gastric epithelium within minutes of exposure. Risk factors for ulcers include illness and other conditions that result in decreased nursing and feeding. Foals with severe illness, such as septicemia, may have reduced gastric mucosal blood flow, further predisposing the gastric lining to injury. Clinical signs may not be apparent in foals until ulcers are very severe, and when clinical signs are noted, treatment should be very aggressive. Drugs that block gastric acid secretion are recommended, and the proton pump inhibitors, such as omeprazole, are particularly recommended.

Introduction
Peptic disorders affecting the esophagus, stomach, and duodenum have been recognized as important conditions in foals for many years, and in one of the first reports describing gastric lesions in foals (Rooney 1964) the author suggested that lesions might have resulted from *Gastrophilus intestinalis* larvae, foreign body trauma (stones), or corticosteroid administration. In the late 1970’s and early 1980’s the fatal consequences of severe, perforating gastroduodenal ulcers in foals were reported (Valdez 1979, Rebhun, et al 1982), and for several years thereafter the typical "ulcer" cases were considered to be foals in which either there was sudden death due to gastroduodenal perforation or foals that showed bruxism, pytalism, or dorsal recumbency (Acland et al. 1983, Becht and Byars 1986). With the introduction of endoscopic equipment designed for use in foals and horses in the late 1980’s the number of foals examined for gastroduodenal lesions greatly increased, and an expanded spectrum of gastroduodenal lesions and clinical syndromes was described (Murray et al. 1987, Murray et al. 1989, Murray et al. 1990a). This has led to improved recognition, treatment, and prevention of ulcers in foals.

Developmental Gastric Anatomy and Physiology
The stratified squamous epithelium and the glandular epithelium of the equine stomach differ structurally and functionally, and these mucosae undergo substantial development during late gestation and the neonatal period (Murray and Mahaffey 1993). Within the first two weeks of life the gastric squamous epithelium undergoes vigorous epithelial hyperplasia, including increased epithelial cell layers, thickening of the keratinized layers, and pronounced epithelial projections extending into the lamina propria. This mucosal hyperplasia probably results from increasing exposure to an acidic environment (De Backer et al. 1985), in conjunction with responses to local and possibly milk-derived growth factor effects (Murray et al. 1992). Physiologic events associated with gastric development occur within the first few days of life in foals (Murray and Luba 1993, Sanchez et al. 1998). The maturation of mucosal defenses parallels the onset of hydrochloric acid secretion. Mucosal defense development has not been studied in foals, but mucus-bicarbonate secretion by the gastric glandular mucosa appears to be intact in very young foals (Murray and Grodinsky 1989). Foals are capable of substantial gastric acidification at an early age (Baker and Gerring 1993a, Sanchez et al. 1998) and earlier than in other animals (Takeuchi et al. 1981) and in human beings (Euler et al. 1979). One day-old foals tended to have a relatively high gastric pH and had few pH recordings less than 4.0 (Baker and Gerring 1993a). In foals two days of age, more highly acidic pH values were recorded, and by 1 week of age, gastric pH recordings were frequently less than 2.0 (Baker and Gerring 1993a, Sanchez et al. 1998). Nursing was associated with an abrupt increase in gastric pH, and conversely, gastric pH became highly acidic when foals remained recumbent and did not nurse for more than 20 minutes (Sanchez et al. 1998).
Ulcer Pathophysiology

Because hydrochloric acid is secreted at a very early age, foals are susceptible to developing gastric lesions within a few days of birth. The author has not seen gastric lesions in aborted fetuses or in term foals that died from dystocia, but gastric lesions have been found in foals as young as two days old in the hospital, as well as in foals treated for several days in the intensive care unit that that were born as much as 45 days prematurely. The gastric squamous epithelium is inherently more susceptible to peptic injury than the glandular mucosa, because it has little resistance to HCl (Widenhouse et al 2002). Mucosal protection of the gastric glandular mucosa includes a hydrophobic mucus layer into which bicarbonate ion is secreted, blood flow characteristics that rapidly remove hydrogen ion that diffuses through the mucus-bicarbonate barrier, and the ability to rapidly replace damaged superficial mucosal cells (Hojgaard et al. 1996).

Stress, as a general term, is often cited as a risk factor for foals to develop gastric lesions. Physiologic stresses, in particular illness, can impair mucosal defenses and render the glandular mucosa more susceptible to peptic injury in human beings and in foals (Furr et al. 1992). Any factor that results in decreased nursing or feed consumption is likely to promote increased gastric acidity, and if the foal also is ill, lesions in both the gastric squamous and glandular mucosae can be expected. An important cause of peptic disease in human beings is Helicobacter pylori (Mertz and Walsh 1991). Several Helicobacter species have been identified in animals, and recently Helicobacter DNA was identified in equine gastric mucosa (Scott and Murray, unpublished data). An Helicobacter organism has not been cultured form an equine stomach at this writing, it the role of such an organism in the pathophysiology of ulcer disease in foals or adult horses would remain to be determined.

Duodenal ulcer disease in foals is classically considered to be a peptic disease, one in which damage to the duodenal mucosa results from excessive exposure to hydrochloric acid and pepsin. This concept may require revision. This is no longer considered to be the case in human beings, in whom most cases of duodenal ulcer disease are associated with Helicobacter pylori infection (Mertz and Walsh 1991, McColl et al. 1997). We have recognized cases of duodenal ulceration and inflammation in which cases were clustered geographically (same farm) and temporally. These foals all had moderate to severe gastric ulceration, and they had extensive inflammation with varying degrees of erosion or ulceration in the proximal duodenum. These findings seem inconsistent with a purely peptic insult as the cause for the ulcerative duodenitis. An infectious cause seems likely, but has not been identified.

Gastroduodenal Ulcer Syndromes

Gastric ulcers that cause clinical signs occur in both the squamous and glandular portions of the stomach, and there is no association between clinical signs and location. The classic clinical presentation of foals with gastroduodenal ulceration includes bruxism, ptyalism, and dorsal recumbency (Becht and Byars 1986). In one retrospective report, diarrhea was the most frequent clinical finding in symptomatic foals with gastric lesions (Murray 1989). Bruxism and dorsal recumbency presumably reflect abdominal discomfort, and are not be specific for gastroduodenal ulceration. Ptyalism is directly associated with esophagitis, which often results from gastroesophageal reflux that occurs secondary to severe gastroduodenal ulceration and either functional or anatomic gastric outlet obstruction. A cause and effect association between diarrhea and gastroduodenal ulceration has not been proven, but in many cases in which another causative agent or condition was not determined there has been rapid (24 hour) temporal association between initiation of acid suppressive therapy and cessation of diarrhea.

Gastric erosions and ulcers form in a high proportion of clinically normal foals, with foals younger than 30 days old most susceptible (Murray et al. 1987, Murray et al. 1990a, Murray et al. 1990b). Erosions in the squamous mucosa along the greater curvature have been found in up to 50% of young foals, which probably results from exposure of the relatively thin mucosa to substantial hydrochloric acid secretion early in life. Fortunately, most such lesions heal without treatment or apparent clinical problem (Murray et al. 1990b). There has been no observed association between foal heat diarrhea and endoscopically-observed gastric lesions in foals. Superficial erosions in the gastric glandular mucosa have been observed by the author in up to 40% of normal foals less than 14 days old, which also resolved without treatment or incident. Because gastric erosions and ulcers develop so easily in foals, anything that accentuates gastric acidity or disrupts normal healing can cause severe, clinical ulcer disease in a very short time. Clinically important gastroduodenal ulceration can occur in foals of all ages. Foals presented to the hospital with duodenal ulcer disease have typically been 3 to 7 months old. Unlike gastric ulceration, subclinical duodenal ulceration probably is uncommon. Lesions occur primarily in the proximal duodenum, and range from diffuse inflammation to focal, bleeding ulcers. Signs of duodenal ulcer disease include those described as "classic gastric ulcer" signs, and they often appear to develop suddenly. Many signs attributed to duodenal ulcer actually are signs of the sequelae of duodenal ulcers. Foals may present because of abdominal discomfort or may, instead, be depressed. Fever is a frequent finding, and this sign may be accompanied by changes in the leukogram, including leukopenia or leukocytosis and hyperfibrinogenemia.
Complications of Gastroduodenal Ulceration

Gastric and duodenal ulcers in young foals (< 1 month old) may result in significant blood loss, resulting in anemia and hypoproteinemia. In all foals, delayed gastric emptying is a common complication to gastroduodenal ulceration, particularly when lesions occur in the duodenum or pylorus. Impaired gastric emptying causes accumulation of acidic gastric secretions, with resultant severe ulceration of the gastric mucosa, particularly the squamous mucosa. Gastroesophageal reflux and esophagitis with signs of ptyalism may occur.

Perforation is a dramatic, although infrequent, sequel to gastric ulceration. In many cases, perforation is not preceded by typical gastric ulcer signs and foals are found acutely depressed, or dead. Most foals presented with perforation have significant peritonitis which can have a tremendous fibrinous component. In such cases it is possible for peritoneal fluid cell count and protein to be normal, because of sequestration of cells and protein in fibrin clots within the omentum. Careful inspection of a Wright's or gram-stained slide for bacteria may confirm a perforated viscus. Occasionally, a small perforation in the stomach or in the duodenal ampulla will be sealed by the greater omentum. Foals with perforated ulcers will be febrile and often will have signs of shock.

In general, the sequelae to duodenal ulceration are more severe than gastric ulceration. These include severe gastric emptying dysfunction, duodenal perforation with peritonitis and/or adhesions, duodenal stricture with complete or partial obstruction, and ascending cholangitis and hepatitis (Campbell-Thompson et al. 1986).

Diagnosis

The gold standard for diagnosis of gastroduodenal lesions in foals remains endoscopy. This is the only method that permits direct examination of the lesions, and therefore proper assessment as to the presence and severity of gastroduodenal lesions. Other means of increasing the index of suspicion for gastroduodenal ulceration include thorough assessment of relevant clinical signs, examining for gastric or fecal blood, contrast radiography, and abdominal ultrasonography and paracentesis. Unfortunately, gastroduodenal ulceration will be usually very severe before these procedures are likely to reveal an abnormality. In foals with extensive bleeding ulcers, gastric fluid will appear dark brown. Fecal occult blood may be detected in foals with immature hindgut fermentation, but in older foals and in horses hemoglobin from gastric bleeding will be excessively degraded by the time digesta has completed its passage through the colon (Pearson et al. 1987). Abdominal ultrasonography and paracentesis can be useful when gastric or duodenal perforation is suspected. Ultrasonography may reveal gastric or small bowel distension with fluid or free fluid in the peritoneal cavity. Paracentesis may reveal an inflammatory reaction with gastric or duodenal perforation, but in some cases peritoneal fluid analysis can be misleading because inflammatory cells may be sequestered in fibrinous exudate.

Treatment and Prevention

The key to treating ulcers in foals successfully is to recognize that by the time clinical signs are apparent, ulcers can be severe, and they can deteriorate rapidly. This calls for aggressive treatment measures. Blocking gastric acid secretion is the most important therapeutic goal, using the histamine type-2 receptor antagonists (H₂ blockers) (Murray and Grodinsky 1992, Sanchez et al. 1998) or the proton-pump blocker omeprazole (Andrews et al. 1999, MacAllister et al 1999). The author's clinical experiences have tended to favor the use of ranitidine and omeprazole. It is crucial to use recommended dosages (Table 1), because at lower dosages there may be no effect. Also, with gastroduodenal disease in foals, stomach emptying is often impaired, resulting in poor delivery of drug to the intestine and poor absorption into the blood. Clinical responses can be misleading, because clinical improvement may be noted but substantial ulceration may persist and even worsen!

| Table 1. Therapeutic agents for use in treating gastric and duodenal ulcers in foals |
|---------------------------------|---------------------------------|
| **Histamine type 2 receptor antagonists** | **Proton pump inhibitor** |
| Ranitidine: 6.6 mg/kg, p.o., q 8 hr; 1.5 mg/kg, i.v., q 8 hr | Omeprazole |
| Cimetidine: 6.6 mg/kg, i.v., q 6 hr | Gastrogard®: 4 mg/kg, p.o., once daily |
| Proton pump inhibitor | Losec: 1.0 - 1.5 mg/kg, once daily, p.o. or by nasogastric tube |
| **Mucosal protectants** | **Sucralfate** |
| Sucralfate: 20 mg/kg, p.o., every 6 to 8 hours | |

Omeprazole (Losec, Gastrogard) is a potent suppressor of gastric acidity, because whereas the H₂ blockers function by
competitive inhibition of receptor sites, omeprazole inactivates the parietal cell H\textsubscript{+}K\textsubscript{−}ATPase, or "proton pump", that secretes hydrogen ion into the gastric lumen (Wallmark 1989). Several reports in horses have demonstrated that omeprazole is highly effective in suppressing gastric acidity in horses (Andrews et al. 1992, Daurio et al 1999) and facilitating gastric ulcer healing in foals and horses (MacAllister et al 1999). Omeprazole paste (Gastrogard ®) appears to rapidly increase gastric pH in foals (Merritt, personal communication 2003).

Sucralfate (Carafate, Marion Merrill Dow Laboratories, Kansas City, MO), sucrose octasulfate and aluminum hydroxide, binds to ulcerated glandular mucosa and appears to promote healing by inhibition of pepsin, enhancement of the mucus-bicarbonate gastric mucosal barrier, local enhancement of mucosal prostaglandins and blood flow, and binding and concentration of epidermal growth factor (McCarthy 1991). Sucralfate may be used as an adjunct treatment to ranitidine or omeprazole, but it should not be used as the only ulcer treatment in a foal, because it is unlikely to be effective.

Gastric emptying is typically delayed due to inflammation in the gastric antrum or pylorus, or the duodenum. Also, lower esophageal sphincter tone appears to be impaired in these foals, permitting gastroesophageal reflux. Improving gastric emptying is important in removing acidic secretions, but also is essential to the delivery into and absorption of therapeutic agents from the small intestine. Treatment failure of orally administered acid-suppressive agents can be a result of poor gastric emptying. We have had success using bethanecol, a cholinergic agonist. Bethanecol enhances gastric emptying in horses (Ringger et al. 1996), and in human beings bethanecol appears to enhance lower esophageal sphincter tone (Robinson 1995). In our hospital, foals with severe gastroduodenal ulceration are initially treated with parenterally administered H\textsubscript{2} blockers and bethanecol. When clinical signs and/or endoscopic findings have improved, administration changes to the oral route.

References

Murray MJ and Luba NK. Plasma gastrin, somatostatin, and serum thyroxine (T4), triiodothyronine (T3), reverse triiodothyronine (rT3), and cortisol in foals from birth to 28 days of age. Equine Vet J 1993; 25:237-239.

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