

# Gastric ulcers in horses<sup>1</sup>

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**ABSTRACT:** Gastric ulcers are common in horses resulting in decreased performance and economic loss to the industry. Ulcers usually occur in the nonglandular mucosa of the stomach, which lacks adequate protection against the harmful effect of stomach acids. Also, performance horses are fed high hydrolyzable carbohydrate (grain) diets, which lower stomach pH and serve

as substrates for resident fermentative bacteria, such as *Lactobacillus spp.* By-products of these bacteria include organic acids (VFA and lactic acid) that cause injury to the mucosa. This manuscript reviews the anatomy and barrier function of the stomach, and the causes and risk factors for development of gastric ulcers in horses.

Key Words: Gastric Ulcers, Horses, Hydrolyzable Carbohydrate

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## Introduction

Gastric ulcers are common in horses, with prevalence estimated from 53 to 93%, depending on populations surveyed and type of athletic activity (Vastistas et al., 1994; Hammond et al., 1996; Murray et al., 1996). The gastric ulcers in horses are caused by many factors including, anatomy of the stomach, diet, restricted feed intake, exercise, stress (stall or transport), and the use of non-steroidal antiinflammatory agents. Because many factors are involved in the cause of ulcers, the term equine gastric ulcer syndrome (**EGUS**) has been coined to describe the condition of erosions and ulcerations occurring in the distal esophagus, nonglandular and glandular stomach, and proximal duodenum of horses (Andrews et al., 1999). This paper reviews the anatomy and barrier function of the equine stomach, causes and risk factors for EGUS, and current studies aimed at determining the pathogenesis of EGUS.

## Anatomy and Barrier Function of the Equine Stomach

The proximal half of the equine stomach is covered by stratified squamous epithelium or mucosa (an extension of the esophagus) and approximately 80% of ulcers

occur in this region (Andrews and Nadeau, 1999). Histologically, the nonglandular squamous mucosa consists of four distinct zones or cell layers; the outermost cell layer (stratum corneum) functions as a barrier to diffusion of strong electrolytes, such as sodium and HCl. The cells of the middle (stratum transitionale) and deeper (stratum spinosum) layers contain sodium-potassium ATPase, which functions in the transcellular transport of Na (Schnorr et al., 1971; Argenzio, 1999). The principle barrier to the diffusion of strong acids in the deeper layers consists of glycoconjugate substances containing bicarbonate, which is secreted by the superficial cells in the stratum spinosum. A minimal barrier of tight junctions between cells exists in the stratum corneum. The last layer is the stratum basale, which is one cell thick and presents no barrier to diffusion. These epithelial layers present a minimal physical barrier to acid (HCl and organic acids) diffusion compared with the glandular mucosa. Despite this minimal barrier function, in a recent study, a 30 mmol/L concentration of HCl (pH 1.5) exposed for 60 min was required to disrupt the barrier function in the horse squamous mucosa (Nadeau et al., 2003a,b). Thus, due to the mucosa's relative resistance to HCl damage, other acids in gastric fluid may act synergistically with HCl to disrupt this physical barrier.

The distal half of the stomach is covered by glandular mucosa, which is responsible for secreting mucus, bicarbonate, hydrochloric acid (HCl), and pepsinogen (Murray, 1991). Approximately, 20% of gastric ulcers occur in this region of the stomach. This region of the equine stomach has extensive protective mechanisms consisting of a bicarbonate-rich mucus layer, an extensive capillary network, and a rapid ability for restitution or

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healing. Gastric ulcers occurring in this region are likely due to the breakdown of this barrier function from a stress-induced release of endogenous cortisol or the administration of nonsteroidal antiinflammatory agents. These agents cause a reduction in prostaglandins, which are important in maintaining mucosal mucus and bicarbonate secretion and maintaining blood flow to the epithelium.

### Cause of Gastric Ulcers in Horses

Horses are continuous gastric HCl secretors, and acid exposure is thought to be the primary cause of gastric ulcers in horses. Also, performance horses are usually fed relatively low-roughage, high hydrolyzable carbohydrate diets and have a higher prevalence of gastric ulcers compared with pastured horses. Diets high in hydrolyzable carbohydrates provide substrates for gastric fermentation by resident bacteria. Gastric fermentation by-products, such as volatile fatty acids (VFA), alcohol, and lactic acid, may damage the squamous mucosa. Recently, several species of *Lactobacillus* were isolated from the stomach of horses, adding credence to this theory (Scott et al., 2003). Previously, an in vivo study in cannulated horses showed that an alfalfa hay/grain diet produced high VFA concentrations in the stomach (Nadeau et al., 2000). A stepwise model generated from those data showed that the presence of VFA (butyric, propionic, and valeric acids) and low stomach pH were important predictors of ulcer severity. Furthermore, an in vitro study with Ussing chambers showed that a 60 mmol/L concentration of VFA (acetic, propionic, butyric, and valeric acids) led to decreased chloride-dependent Na transport across the squamous mucosa and histologic changes of cell swelling (Nadeau et al., 2003a,b). In addition, Ca- and protein-rich diets, such as alfalfa hay, may protect nonglandular mucosa against acid injury (Nadeau et al., 2000).

In a recent report, HCl alone and in combination with VFA caused inhibition of cellular chloride-dependent Na transport, cell swelling, and eventual ulceration when exposed to the nonglandular squamous mucosa at pH  $\leq$  4.0. The ulcerogenic effects of the VFA in combination with HCl were pH, dose and chain-length dependent (Nadeau et al., 2003a,b). Bile acids were also shown to increase the nonglandular mucosal cell permeability to hydrogen ions, which eventually lead to ulceration (Berschneider et al., 1999). 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 (Argenzio, 1999; Berschneider et al., 1999). Pepsinogen, which is cleaved to pepsin at a pH  $<$  4, may have a role in the development of EGUS. This proteolytic enzyme may act with HCl to result in acid damage, but not synergistically (Widenhouse et al., 2002). Although HCl and stomach pH have been implicated as causes of EGUS, it is likely that a combination of HCl, organic acids, and pepsin act synergistically to cause EGUS.

### Risk Factors in Horses

Although acid injury has been implicated in the cause of EGUS, several risk factors for its development have been identified (Murray et al., 1996; Andrews et al., 1999; Rabuffo et al., 2002).

#### *Exercise Intensity*

Horses in training and racing are at high risk of developing EGUS (Vatistas et al., 1999). Recently, it was shown that horses running on a high-speed treadmill have increased abdominal pressure and decreased stomach volume (Lorenzo-Figueras and Merritt, 2002). The authors speculated that stomach contractions allowed acid from the glandular mucosa to reflux into the nonglandular mucosa, leading to acid injury. Daily exercise may increase the exposure of the nonglandular mucosa to acid, explaining the increased prevalence of gastric ulcers in horses in race training. Furthermore, an increase in serum gastrin concentration has been shown to occur in exercising horses (Furr et al., 1994). This increase in serum gastrin may stimulate an increase in HCl secretion and lower stomach pH.

#### *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, with stomach pH  $>$  4 for a large portion of the day. Conversely, when feed is withheld from horses, before racing or in managed stables, gastric pH drops rapidly and the nonglandular mucosa is exposed to an acid environment. Intermittent feeding has been shown to cause and to increase the severity of gastric ulcers in horses, and an alternating feed deprivation model was developed to produce EGUS experimentally (Murray and Schusser, 1993; Murray, 1994; Feige et al., 2002). The nonglandular mucosa is the most susceptible to ulceration in horses subjected to intermittent feeding due to its lack of mucosal protective factors. Studies have shown that stomach pH drops 6 h after feeding (Nadeau et al., 2000) and DM content decreases 12 h after feeding a mixed-feed diet compared with horses fed a hay diet (Coenen, 1990). Thus, horses should be fed hay continuously or every 5 to 6 h to buffer stomach pH.

#### *Diet*

Diet has been implicated as a risk factor for EGUS. Serum gastrin concentrations are high in horses fed high-concentrate diets. In addition, as noted previously, concentrate diets are high in hydrolyzable carbohydrates and are fermented by resident bacteria, resulting in the production of VFA, which, in the presence of low stomach pH ( $\leq$ 4), cause damage to the nonglandular squamous mucosa (Nadeau et al., 2003a,b). In another recent study in horses fed a high-protein and high-

calcium diet (alfalfa hay/grain) showed higher stomach pH than horses fed a low protein and high-Ca (brome grass hay) diet. The high-protein, high-Ca diet had fewer and less severe gastric ulcers (Nadeau et al., 2000). Thus, feeding alfalfa hay may have some protective effect on the nonglandular mucosa in horses. Furthermore, horses fed mixed feed (128 g of CP and 175 g of crude fiber/kg of DM) for at least 14 d showed increased gastric ulcers in the nonglandular mucosa localized along the margo plicatus compared with horses fed a hay diet (Coenen, 1990). Thus, diets high in carbohydrates and protein have been implicated in causing gastric ulcers in horses.

### *Transport Stress*

Transporting horses has been implicated as a risk factor for EGUS. Transportation of horses has been associated with dehydration, increased threat of respiratory illness (pleuritis, pleuropneumonia), and immune suppression (Watson, 2002). During transport, 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 (MacAllister and Sangiah, 1993). However, a recent endoscopic study in Western performance quarter horses subjected to frequent travel and intensive training had a lower prevalence (40%) of EGUS than did horses in race training, calling into question the effect of transport on the development of EGUS (Bertone et al., 2000).

### *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 with horses that are housed in stalls. The reason for this may be multifactorial, as horses that are stalled may be fed intermittently and housed without exposure to other horses (Feige et al., 2002).

### *Nonsteroidal Antiinflammatory Drugs*

The nonsteroidal antiinflammatory drugs (NSAID), phenylbutazone and flunixin meglumine, have been shown to induce gastric ulcers in horses (MacAllister et al., 1993). However, the use of NSAID in racehorses has not been shown to be a risk factor for EGUS in multiple epidemiologic studies (Johnson et al., 1994; Murray et al., 1996; McClure et al., 1999; Vatistas et al., 1999; Rabuffo et al., 2002). However, in one study, NSAID caused ulcers in the glandular mucosa and increased the severity of ulcers in the nonglandular squamous mucosa (Murray, 1991). Thus, NSAID are thought to cause more severe ulcers in the glandular stomach mucosa because of their effect on prostaglandin inhibition. Prostaglandin inhibition by NSAID results in decreased mucosal blood flow, decreased mucus production, and increased HCl secretion. Although

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 (Navab and Steingrub, 1995; Barr, 2000). Adequate blood flow is necessary to remove 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.

### *Helicobacter Species*

Although *Helicobacter* species are an important cause of ulcers in other species, it has not been cultured from the horse. However, *Helicobacter*-specific DNA was isolated from the glandular and nonglandular mucosa of seven horses (Scott et al., 2001). 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 (Johnson et al., 1994). However, horses with chronic recurring gastric ulcers may benefit from antibiotic and antacid treatment in much the same way people with *Helicobacter pylori* infections have.

## Conclusions and Future Studies

Equine gastric ulcer syndrome is caused by exposure of the stomach to inorganic and organic acids. Many factors including feeding, management, and stress allow increased production of these stomach acids that act synergistically to produce gastric ulcers. Volatile fatty acids (fermentation by-products of resident stomach bacteria), because of their high lipid solubility at stomach pH  $\leq 4.0$ , enter into the nonglandular mucosal cells, acidifying the cell and damaging chloride-dependent Na transport, which results in cell swelling, necrosis, and ultimately, ulceration.

Future studies should be directed at evaluating diets and dietary supplements that decrease or buffer secreted or fermented stomach acids. A recent study in ponies with chronic gastric cannulas showed that corn oil supplementation (45 mL/d orally) significantly decreased gastric acid production and increased prostaglandin concentration in gastric juice (Cargile et al., 2004). The authors speculated that corn oil added to the diet might impart protection to the stomach and prevent gastric ulcers. Furthermore, diets or supplements high in Ca and protein may buffer stomach contents and increase stomach pH, thereby preventing the damaging effects of HCl and organic acids.

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