Literature Review

rccp Revista Colombiana de Ciencias Pecuarias

Equine gastric ulcer syndrome: risk factors and therapeutic aspects¤

Síndrome de úlcera gástrica equina: factores predisponentes y aspectos terapéuticos

Síndrome de úlcera gástrica equina: fatores predisponentes e aspectos terapêuticos

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(Received: February 25, 2013; accepted: December 11, 2013)

Summary

The equine gastric ulcer syndrome (EGUS) involves a complex of diseases associated with ulceration of the esophageal, stomach and duodenum mucosa of horses. EGUS occurs frequently due to multiple and overlapping risk factors (activity, food management, anti-inflammatory therapies, among others) and anatomo-physiological peculiarities of horses. The combination of therapeutic strategies and management and environmental shifts are important in both the preventive and the curative approach to this syndrome. However, further studies on the epidemiological and clinical aspects of EGUS and low-cost therapeutic alternatives are required.

Key words: *glandular and nonglandular mucosa, gastroscopy, horse, hydrochloric acid, stomach, treatment.*

Resumen

El síndrome de úlcera gástrica equina (EGUS) implica un complejo de enfermedades asociadas con ulceración de la mucosa esofágica, gástrica y duodenal en animales con diferente edad. EGUS es altamente frecuente por la naturaleza multifactorial de los factores de riesgos (tipo de actividad, manejo alimentario, terapias anti-inflamatorias, entre otros) y particularidades anatomo-fisiológicas de estos animales que son sometidos excesivamente en los diferentes sistemas de explotación. La combinación de estrategias terapéuticas, de manejo y de adecuación de ambiente son de importancia en las conductas preventivas y curativas de este síndrome. Sin embargo se requieren más estudios de prevalencia y de caracterización de los factores predisponentes de EGUS; así como también, más investigación para generar alternativas terapéuticas de bajo costo.

Palabras clave: *ácido clorhídrico, caballo, estómago, gastroscopia, mucosa glandular y no glandular, tratamiento.*

¤ To cite this article: Martinez JR, Silveira GE. Equine gastric ulcer syndrome: risk factors and therapeutic aspects. Rev Colomb Cienc Pecu 2014; 27:157-169.

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Resumo

A síndrome de úlcera gástrica equina (EGUS) envolve o complexo de doenças associadas com úlcera da mucosa esofágica, gástrica e duodenal em animais de diferentes faixas etárias. EGUS tem elevada frequência pela natureza multifatorial dos fatores de risco (tipo de trabalho, manejo alimentar, terapias anti-inflamatórias, entre outros) e peculiaridades anatomo-fisiológicas destes animais sometidos em excesso nos sistemas de exploração. A combinação de estratégias terapêuticas, de manejo e de adequação de ambiente é de importância nas condutas preventiva e curativa desta síndrome. Porem se requer mais estudos de prevalência e de caraterização dos fatores predisponentes de EGUS, assim como também, mais pesquisas na geração de alternativas terapêuticas de baixo custo.

Palavras chave*: ácido clorídrico, cavalo, estômago, gastroscopia, mucosa glandular e não glandular, tratamento.*

Introduction

Equine gastric ulcer syndrome (EGUS) negatively impacts the equine industry by causing weight loss, unresponsive training, poor performance in the affected animals (Nieto *et al.*, 2009) and incurring a high cost associated with the treatment. Additionally, EGUS causes discomfort and colic that may also lead to other gastrointestinal complications. EGUS affects horses of all breeds and ages. EGUS prevalence between 25 to 50% in foals and 80 to 90% in adult horses has been reported (Murray, 2009). Prevalence depends upon the stress level, welfare status related to sport or work activity, and food quality. Prevalence greater than 50% has been also reported in non-competing equines with normal clinical appearance (McClure *et al.*, 2005; Videla and Andrews, 2009; Luthersson *et al.,* 2009a). Due to the complexity, pathophysiology and triggering factors of EGUS, the treatment requires many strategies and long term care, both preventive and curative, thereby increasing treatment cost (Aranzales and Alves, 2013). Furthermore, the pharmacological approach and feeding and environmental alterations are important for avoiding EGUS recurrence. Given these facts, the current study aims to describe the factors involved in the gastric ulcerative process, as well as to present preventative therapeutic treatments to reverse or avoid the progression of the disease.

General aspects of EGUS

EGUS involves a complex of diseases associated with mucosa ulcers of the esophagus, stomach and duodenum (Andrews *et al.*, 1999a). This concept applies specifically to horses, since peptic ulcer in humans is not similar to aglandular mucosa lesions in equines. However, gastroesophageal reflux disease (GERD) of humans presents similar histological lesions to those found in horses. Merritt (2009) recently recommended proper usage of the term "EGUS" because of the excess of publications referring only to ulcers in the aglandular mucosa. This same author also proposed this condition as a primary squamous disease, still held within the concept of EGUS. However, a recent collaborative study reported high prevalence of ulcerative lesions in the glandular mucosa of horses managed under several nutritional and environmental conditions (Luthersson *et al.*, 2011). These findings were useful for recommending more attention to individual assessment of gastric mucosa to improve the quality of EGUS prevalence studies.

Risk factors for EGUS

Although acid causticization is accepted as one of the primary causes of EGUS, several other risk factors have been described. Risk factors inherent to the animal and the husbandry system, such as intense exercise, inappropriate feeding management, stress, confinement, and non-steroidal, anti-inflammatory drugs therapies are considered gastritis and gastric ulcer triggers (Lorenzo-Figueras *et al.*, 2002; Videla and Andrews, 2009). Some metabolites produced by certain bacteria populations have also been recently associated with EGUS.

Intrinsic factors

Results indicating predisposition towards EGUS due to gender, breed, age, and temperament are

controversial. Most studies have been conducted in distinctive equine populations with mixed intensity factors, such as type of work, training, and physical activity. Geldings are seemingly more predisposed due to a decrease in salivary epidermal growth factor concentration, stimulated by reproductive hormones (Rabuffo *et al.*, 2002). However, studies conducted in active racehorses did not find any association between prevalence and intensity of EGUS and gender (Bell *et al.*, 2007; Luthersson *et al.*, 2009b; Tamzali *et al.*, 2011).

Standardbred horses seem to be less affected by EGUS than Warmbloods, which might also indicate possible differences in the husbandry conditions or management of both breeds (Sandin *et al.*, 2000). However, Luthersson *et al.* (2009a) did not identify breed as a risk factor for EGUS. On the other hand, studies conducted in training Standardbred and English Thoroughbred horses determined both a similar and increased prevalence and severity of gastric ulcers. This situation was potentially associated with the horse management system, because both breeds were designed for sport activities (Ferruci *et al.*, 2003; Orsini *et al.*, 2009).

Age has been also associated with increased quantity and intensity of ulcers. Ulcers in geriatric horses are apparently bigger, affecting the aglandular and glandular areas of the gastric mucosa (Rabuffo *et al.*, 2002). Chameroy *et al.* (2006) and Jonsson and Egenvall (2006) determined increased prevalence in animals older than three years of age compared to those younger than two years, which was related to the beginning of the racing training. On the contrary, Luthersson *et al.* (2009b) found no association between age and degree of gastric ulceration.

Equine temperament is related to stress predisposition. This has been considered a risk factor for developing gastric ulcers, especially in the glandular mucosa (Malmkvist *et al.,* 2012), which may lead to neuroendocrine imbalances, including increased gastrin and histamine production. In murine models, this results in increased hydrochloric acid secretion. However, the relationship between temperament and gastric ulcers in equines is still controversial (Vatistas *et al.*, 1999).

Intensity of exercise

Active Thoroughbred racing horses present higher EGUS prevalence in the aglandular mucosa (Orsini *et al.*, 2009). This has been attributed to physiologic and mechanic events. Exercise decreases gastric motility and increases intragastric pressure due to activation of abdominal muscles and breathing effort, which changes the pH gradient in the dorsoventral area of the stomach (Bell *et al.*, 2007). The increase of abdominal pressure during exercise pushes the liquid phase of the gastric content containing hydrochloric acid, short-chain fatty acids and bile to the aglandular proximal area of the gastric mucosa (Lorenzo-Figueras *et al.*, 2002).

Human athletes exposed to ischemic conditions under strenuous tests have presented gastric and intestinal mucosa alterations (Oktedalen *et al.*, 1992). This has not been reported in horses; however, Barton *et al.* (2003) described signals of subclinical endotoxemia in endurance horses, which may indicate permeability changes of the gastrointestinal mucosa. Intensity of physical activity is directly related to the prevalence of EGUS.

A relationship between training and gastrin concentration has been reported in horses. Gastrin is the main endogenous secretagogue of hydrochloric acid. Thus, a gastrin secretion increase implies increased caustic effects on the aglandular area of gastric mucosa. Equine athletes are exposed to different stressors that may result in neuroendocrine imbalances that increase gastric mucosal vulnerability.

Inappropriate feeding

Intermittent food deprivation is associated to increased acidity in the gastric lumen and decreased amounts of saliva in the gastric liquid content, which compromises the buffering effect of stomach environment (Argenzio, 1999). Furthermore, fasting periods produce changes in the physical properties of gastric content (Varloud *et al.*, 2007). Proximal gastric pH during fasting is lesser in early mornings (Husted *et al.*, 2009). For this reason, intermittent fasting periods have been established in research protocols for inducing gastric ulcers, mainly in the aglandular mucosa.

Feeding frequency, ration amount, and type of food processing have been considered risk factors for EGUS (Flores *et al.*, 2011). Luthersson *et al.* (2009b) reported that starchy diets increased the risk of EGUS and the effect was dose-dependent. High amounts of starch per kg BW per day or per meal, as well as feeding intervals longer than six hours were also associated with EGUS. Grain-rich diets increase soluble carbohydrate concentration, leading to increased fermentation and stimulating short-chain fatty acids and lactic acid production (Nadeau *et al.*, 2000). This affects mucosa's bioelectrical properties, changing its permeability (Andrews *et al.*, 2006). It is known that carbohydrate-rich diets also increase gastrin concentration.

Apparently, fiber concentration helps horses to maintain a healthy gastric mucosa. Therefore, to prevent horses from suffering EGUS, greater amount of forage or longer time spent grazing is a strategy. Grazing allows for a continuous flow of saliva and ingesta that helps buffer the stomach acid environment throughout the day. However, studies have not shown this in all breeds and found similar prevalence in both free pasture and confined horses (Bell *et al.,* 2007; Le June *et al.,* 2009). These findings were possibly related with the multifactorial nature of ulcers in the horse stomach. Current equine husbandry in urban centers does not allow horses to remain in free grazing because it is not practical or feasible for owners and trainers. Faced with this problem, they should adopt other management strategies (meals, frequency, type of feeding, supplementation, etc.) to minimize the impact on animal health.

Water deprivation periods longer than four hours are also a risk factor for EGUS. Drinking water dilutes the gastric content, subsequently raising the pH (Andrews *et al.*, 2006; Luthersson *et al.*, 2009b). Frequent transportation of sport horses produces changes in water and food consumption, which facilitates the risk of gastric ulcers (McClure *et al.*, 2005). Administration of hypertonic electrolytic pastes to prevent dehydration during competitions has been related to appearance or permanency of gastric ulcers in endure horses (Holbrook *et al.*, 2005). These authors proposed a feasible interaction between hypertonic solutions and hydrogen ion activity in the gastric content.

Confinement

Long confinement periods are related to gastric ulcer prevalence. Periods in stalls longer than 19 hours per day increased the risk of gastric ulcer onset (Murray and Eichorn, 1996; Bell *et al.*, 2007), although other studies did not show any difference in gastric lesions intensity when comparing full-time with part-time confinement or permanent grazing. This suggests the involvement of other factors in the pathophysiology of ulcer. Husted *et al.* (2009) determined significant changes in the gastric pH of horses in lairage or picketing.

Confined horses experience changes in feeding management in relation to the amount, frequency, and type of food. In addition, confinement, contrary to the gregarious and social nature of equines, induces stressors and behavioral, neuroendocrine and metabolic changes that impact different organic systems.

Horses confined in a hospital environment due to medical or surgical conditions have increased risk for developing or exacerbating EGUS lesions due to stress, where eating interruption, administering of analgesic and support medicines, as well as changes in management schemes are common (Rabuffo *et al.*, 2009).

Flora and bacterial metabolites

The importance of bacteria in the predisposition to EGUS is still controversial. However, *Helicobacter pylori* (Scott *et al.*, 2001) and *Helicobacter equorum* (Moyaert *et al.*, 2009) have been isolated from the aglandular and glandular areas in both adult and young horses, as well as in both sick and healthy animals. Genus *Helicobacter* is well adapted to survive in the acidic stomach environment because of the urease enzyme, bacterial motility and efficient bacterial mechanism of adhesion to gastric epithelium (Krakowka, 2007).

Helicobacter pylori infection in humans is more common in poor and developing countries, with prevalence ranging from 37.5 to 84.7% in Latin America, and 77.2% in Colombia (Pounder, 1995; Campuzano *et al.*, 2007). Epidemiology of gastric

infections produced by this bacterium in Colombian horses could be similar to that in people of this country. This may explain the low prevalence of the bacterium in the United States and Europe, where its importance and involvement in EGUS has been questioned. Considering the scarcity of information regarding Colombian equine population, it is possible for this bacterium to be related to EGUS in horses, which could be associated with a zoonosis and consequently present a public health problem. For this reason, it is necessary to diagnose the impact of this bacterium in the gastric mucosa of horses and their caretakers.

Other acid resistant bacteria as well as lactic acid and short-chain fatty acid producing bacteria from starch fermentation have been involved in the origin of aglandular mucosa ulcers (Nadeau *et al.*, 2003; Andrews *et al.*, 2006). Patton *et al.* (2009) reported a case of gastritis in a horse associated with *Clostridium perfringens* type A isolated from the submucosa, indicating a possible involvement of this bacterium in gastric lesions. Liguori *et al.* (2008) reported a clinical case of botulism from the invasion of *Clostridium botulinum* type B in gastric ulcers. Bacterial colonization in gastric ulcers retards healing. In this case, antibiotics are recommended (Videla and Andrews, 2009).

Therapies with nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used in human and veterinary medicine because of their analgesic, anti-inflammatory and antipyretic effects. In horses, NSAIDs are used mainly to treat pain and inflammation in the musculoskeletal and gastrointestinal systems. There is evidence of overuse of these drugs in veterinary medicine. A study by Anon (2009) showed 82% frequency of NSAIDs use without veterinary prescription. A similar situation could be true for Colombia, where phenylbutazone, flunixin meglumine, ketoprofen, and others are indiscriminately used without veterinary criteria, accompanied by an absence of a monitoring policy and control studies of these drugs in this country.

Inhibition of cytoprotective prostaglandins (PGs) by cyclooxygenase (COX) blockage has been associated with NSAID side effects on the gastric mucosa. Despite evidence of adverse effects by depletion of PGs, a recent study concluded that there is no change in COX1-2 gene expression following oral administration of phenylbutazone (PBZ) (Nieto *et al.*, 2012); which could suggest other possible routes for gastric mucosal lesions associated with the use of these drugs (Naito *et al.,* 1998; Polat *et al.,* 2010). The oxidative stress pathway may participate in EGUS, by changing the antioxidant-oxidant balance (Naito *et al.,* 1998). These authors have observed changes in nitric oxide, catalase, superoxide dismutase, malondialdehyde, N-acetylglucosaminidase, and myeloperoxidase concentration in the gastric mucosa of horses treated with PBZ (Aranzales JRM, 2012).

On the other hand, local lesions derive from the inhibition of mitochondrial oxidative phosphorylation in mucus producing cells, which changes hydrophobicity, and inhibition of kinases. Such direct cytotoxic effects, apoptosis and necrosis were demonstrated *in vitro* and *in vivo* in murine models (Tomisato *et al.*, 2004). Although not yet fully demonstrated, it is possible that a similar situation also occurs in horses. The most traditional NSAIDs are weak acids, which are transformed into non-ionized molecules under the acidic conditions of stomach, facilitating the entry into the cell where they are ionized at a neutral pH, causing retention and release of hydrogen ions with the potential to change cell function (Tomlinson and Blikslager, 2003).

Colombian Creole horses are used in different sport activities and their temperament influence the intensity and performance of this athletes. Therefore, several predisposing factors described for EGUS in other breeds could be identified as predisposing risks for the onset of this illness in these horses. Studies on the prevalence of this syndrome and correlations with triggers in Colombian Creole horses should be conducted. Specific information on this breed would contribute to the varying information in the literature.

EGUS prevalence

EGUS prevalence is variable among equine populations due to its multifactorial nature. The presence of gastric ulcers in horses has been widely described and characterized in breeds involved in high

performance competitions. Prevalence in sport horses ranges from 20 to 90%, depending on physical intensity of exercise (Bezdekova *et al.*, 2005). Studies on lesion dynamics showed 17.4% pre-competition prevalence and 56.5% post-competition in non-racing performance horses for modalities as such endurance riding, show jumping, and dressage (Hartmann and Frankeny, 2003), and 48 against 93% in high level endurance horses (Tamzali *et al.*, 2010). This demonstrates that physical effort or exercise level could affect EGUS incidence and progression in this population (Murray and Eichorn, 1996; Chameroy *et al.*, 2006).

Active racing horses have shown EGUS prevalence between 51 and 90% (Murray *et al.*, 1996; Rabuffo *et al.*, 2002; Jonsson and Egenvall, 2006). EGUS prevalence reaches 80% for sport horses in training (Hammond *et al.*, 1986) compared to 52% for inactive or retired racing horses (Vatistas *et al.*, 1999). Some authors reported EGUS prevalence under 19% for athlete horses (Sandin *et al.*, 2000), which suggests variability in animal conditions or differences in evaluation criteria and classification of gastric lesions.

Prevalence between 31 and 58% has been described for leisure and exhibition horses (Murray and Grodinsky, 1989; Bezdekova *et al.*, 2005; Luthersson *et al.*, 2009a; Aranzales JRM *et al.,* 2012). Murray *et al.* (1996) reported 81, 32, 22 and 16% EGUS prevalence in aglandular mucosa, glandular mucosa, duodenum, and esophagus, respectively, in foals. Rabuffo *et al.* (2009) determined 68% EGUS prevalence in horses hospitalized due to emergencies caused by acute abdomen crisis, where gastroscopic evaluation was recommended for such patients. Another study reported 49% prevalence in animals with abdominal pain, and prevalence was higher in animals needing medical treatment compared with those who needed surgery. An increase in EGUS prevalence in horses with anterior enteritis was also reported (Dukti *et al.*, 2006).

There are no studies of EGUS prevalence in Colombia, though there are reports for this problem in Brazil. Prevalence between 47.6 and 77.91% in asymptomatic adult horses under stabling and grazing conditions was reported in Brazil for different breeds (Fernandes *et al.*, 2003; Aranzales JR *et al.*, 2012). There are also reports in horses managed at hospital settings (Belli *et al.,* 2005) and in equines performing various physical activities, showing a significant association between presence of gastric injury and type of activity (Berger *et al.*, 2009). A gastric lesion incidence of 43.3% was reported in Quarter Horse foals aged 1 to 120 days (Dearo *et al.*, 1998). Goloubeff (2006) determined 45 and 100% prevalence of gastric mucosal changes in *Brasileiros de Hipismo* foals before and after weaning, respectively. Studies in Venezuela and Chile reported 58 and 69% presentation frequencies, respectively (Morales *et al.,* 2008; Cardona *et al.,* 2009), with differences in classification and measurement of relevant lesions, as well as type of activity and handling of the animals tested.

Clinical signs and diagnosis of EGUS

Most horses suffering EGUS do not show characteristic clinical signs. When clinical signs related to gastric ulcer appear, they include colic, bruxism, hypersalivation, decreased appetite, weight loss, changes in behavior and athletic or reproductive performance. Episodes of mild and intermittent colic during and after feeding may be related to EGUS (Videla and Andrews, 2009). Aerophagia was recently associated to increased production of saliva in horses with gastrointestinal irritation (Moeller *et al.*, 2008). Correlation between clinical signs and intensity of ulcers proved to be variable (Murray and Grodinsky, 1989).

Sandin *et al.* (2000) reported an association between EGUS and abdominal discomfort, but a recent study did not determine significant correlation between gastric ulcer in horses hospitalized with colic and animals hospitalized for different reasons (Rabuffo *et al.*, 2009). Generally, ulcers in the aglandular mucosa must be intense to cause abdominal pain. Meanwhile, ulcers in the glandular mucosa can be moderate to intense—and especially near the pylorus—to cause colic (Videla and Andrews *et al.*, 2009).

Medical record, clinical examination, and identification of risk factors, together with complementary tests, such as blood in stool, can help detect EGUS. Hematological and biochemical exams have not been very relevant for diagnosis, but a reduction of red blood cells, hemoglobin and

hematocrit has been observed in gastric ulcers cases (McClure *et al.*, 1999; Rabuffo *et al.*, 2009). Urine sucrose test is recommended for ulcer detection, with 83 and 90% sensitivity and specificity, respectively (O´connor *et al.*, 2004). However, difficulties to collect urine limit the practicality of the test, so it has been recommended to assess sucrose in serum, which is highly effective to detect gastric ulcers in equine patients (Hewetson *et al.*, 2006).

Occult blood detection in stools has been used in diagnoses of gastrointestinal ulcers, but it has low sensitivity and specificity for EGUS, especially for negative predictive values. Due this technical problem, Pellegrine (2009) developed a quick test using monoclonal antibodies against albumin and hemoglobin in stools, finding a positive correlation between albumin detection and colonic ulcers, and between hemoglobin and gastrointestinal lesion, which improved the negative predictive values in EGUS diagnosis.

Definitive diagnosis of EGUS is confirmed by gastroscopy or necropsy. Visualization of the lesion allows not only the diagnosis, but also the classification and determination of the lesion level, as well as monitoring the response to treatment (Andrews *et al.*, 1999a). In the absence of gastroscopy, response to the treatment is also important in confirming EGUS (Videla and Andrews, 2009).

Gastroscopic exams in adult horses require the use of a 3-meter videoendoscope to inspect the gastric mucosa and to reach the duodenum. The availability of this equipment has facilitated diagnosis as well as monitoring the prevalence of gastric ulcers. Researchers initially described limitations of horse gastroscopy, such as poor visualization due to remaining feed contents and difficulties in accessing some areas of the stomach (Murray *et al.*, 2001). Gastroscopy procedures are currently more effective; they include a fasting preparation for increased gastric lumen visualization. However, it is possible to observe some gastric contents remaining in the fundus area after fasting periods exceeding 14 hours. This is possibly due to periodic retrograde reflux of duodenal contents into the stomach and the volume of saliva (Merritt, 2003). These limitations may result in underestimation of ulcer presence in both mucosae (glandular and aglandular), when compared to findings during necropsy (Andrews *et al.*, 2002).

Several systems are used to assess gastroscopy findings, such as the EGUS council system, which scores mucosal lesions in numbers (from 0 to 4) and severity (from 0 to 5), and systems that combine both criteria (from 0 to 6). Score systems help to determine a lesion's extension, intensity, and characteristics in the different areas of gastric mucosa. Some systems detail and describe gastric mucosal lesions, while others are less detailed. The most specific system to score ulcers according to number or intensity (degree of severity) was described by McAllister *et al.* (1997). This consensus was reached after evaluating comparative studies between these systems (Luthersson *et al.*, 2009a). The main differences between the EGUS council system and the McAllister *et al.* (1997) system are more evident in lower scores. This may influence the prevalence report and determination of clinically relevant ulcers. Luthersson *et al.* (2009a) recommended consolidating the score or determining equivalence ranks between categories to improve the objectivity of gastroscopy evaluations.

Rodrigues *et al.* (2009) studied the efficiency of histological evaluation of biopsies obtained by endoscopy. They suggested histological evaluation of the entire gastric surface could be improved by taking six or more tissue samples from difficult-to-reach areas or poor quality material from the aglandular mucosa. Hyperkeratosis, scarring, diffuse erosions and lesions in the *margo plicatus*, hyperemia in the glandular mucosa, focal erosions and ulcers have been the most common histological lesions described in the equine stomach (Martineau *et al.*, 2009a).

The classification score of histological findings in gastric tissue of horses has been adapted from the Sidney system used in humans. Histologically, erosion refers to superficial loss of mucosa; meanwhile, ulcer refers to deep loss of mucosa with muscular mucosal exposure, so during evaluation it is important to characterize the inflammatory processes subsequent to the lesions (Martineau *et al.*, 2009b).

A study that compared gastroscopy histologic evaluation and expression of gastric mucosal cytokines

found a high correlation between EGUS presence and proinflammatory markers TNF-α and IL-13. These findings suggest that both qualitative and quantitative PCR are accurate methods for evaluating equine patients suffering this syndrome (Pietra *et al.*, 2010).

Treatment of EGUS

Therapeutic management of EGUS focuses on determining the possible causes, controlling the environment, adjusting the diet, and intervening pharmacologically, since its etiology is multifactorial. Thus, the treatment aims to block gastric acidity, stimulate healing, control pain, and prevent recurrences. To do this, neutralizing agents (antacids), antisecretories antagonists (H_2), prostaglandin analogues, proton-pump inhibitors (PPIs), mucosa protectors (sucralfate), gastric emptying accelerators (bethanechol, mosapride citrate, domperidone) could be used (Blikslager, 2004; Murray, 2009; Okamura *et al.*, 2009). Considering that corrosion is the main cause of ulcers, acid secretion blockage and pH rising could be the most important strategy for improving the healing process and controlling pain associated with ulcers (Videla and Andrews, 2009).

Proton-pump inhibitors are part of the antacid specific therapy used in horses, in which the use of enteral (1-4 mg/kg sid) and parenteral (0.5-1.0 mg/kg sid) omeprazole represents prophylactic and therapeutic benefits in EGUS cases (Andrews *et al.*, 1999b; McClure *et al.*, 2005; Andrews *et al.*, 2006), although, S isomer esomeprazole oral (40-80 mg sid) (Pereira *et al.*, 2009) and intravenous (0.5 mg/kg sid) (Videla *et al.*, 2011) have shown pharmacological advantages over omeprazole S and R isomers.

Although side effects of prolonged PPI use in horses have not yet been described, its use in humans was associated with mucosal hyperplasia by hypergastrinemia generated by blocking hydrochloric acid secretion and hypochlorhydria with subsequent bacterial growth and formation of N-nitrose compounds, which are carcinogenic (Carcelen *et al.*, 2005) and could induce hepatitis, interstitial nephritis and ocular changes (Stedman and Barclay, 2000). This situation highlights the need for studies to determine the adverse effects of these drugs in horses, since there is a tendency for the massive use of PPIs by equine practitioners and caretakers around the world.

Competitive antagonists of H_2 receptors (anti-H_2), such as oral (6.6 mg/kg qid) and intravenous (1.5 mg/kg qid) ranitidine reversibly block the action of histamine. Nevertheless, these drugs do not inhibit the direct action of acetylcholine and gastrin in inducing acid production (Sangiah *et al*., 1988). Other drugs of the same group (i.e., cimetidine and famotidine) have been used in horses; however, their high cost and short plasma life discourage its use (Videla and Andrews, 2009). Mucosal protectants, such as oral sucralfate (22 mg/kg tid) and bismuth subsalicylate (26.25 g), have been used in both foals and adult horses with poor clinical success when used as unique therapy (Borne *et al.*, 1993).

Combination of PPIs, anti-H_2, and mucosal protectants is commonly used to reduce the undesirable effects of NSAIDs on the gastric mucosa, whether they are administered alone or associated. The use of ranitidine and sucralfate at recommended doses has proven to be effective in phenylbutazone toxicosis (Geor *et al.*, 1989). However, in a preliminary study, Delboni *et al.* (2009) described similar prophylactic effects of omeprazole and sucralfate in horses treated with the same NSAID.

Recently, antibiotics (i.e., penicillin, streptomycin and sulfa-trimethoprim) and probiotics containing *Lactobacillus spp*. and *Streptococcus* spp. have been promising in the treatment of chronic and non-responsive EGUS, since acid-resistant bacteria complicate healing of ulcers (Al Jassim and Andrews, 2009). However, bacterial participation in EGUS genesis and the most predisposed anatomical region for EGUS have not been clearly established; although, Al Jassim *et al.* (2005) reported an important involvement of resident stomach bacteria in the maintenance and progression of nonglandular gastric ulcers.

Phytotherapeutic resources are being used with promising results for treating peptic ulcers in humans. Some herbal compounds, such as *Maytenus ilicifolia* leaves, reduce basal hydrochloric acid secretion and induce cytoprotective and healing effects by creating

a layer on the ulcerated mucosa (Oliveira *et al.*, 1991; Santos *et al.,* 2007). The use of *Hippophae rhamnoides* in equine medicine proved to be efficient preventing ulcers in the aglandular mucosa during stress episodes (Lans *et al.*, 2006; Reese and Andrews, 2009). Huff *et al.* (2012) recently tested a commercially available *Hippophae rhamnoides* formulation (Sea Buck SBT Gastro-Plus) finding that it was effective in preventing ulcer formation in the glandular mucosa of stabled horses under intermittent fasting periods. Additionally, Fialho *et al.* (2010) described antiulcerogenic gastric effects of *Casearia sylvestris* extracts in horses.

According to empirical observations, some nutraceuticals and dietary additives could help to control EGUS. Calcium carbonate may offer advantages to preserve gastric mucosal integrity by recovering sodium transport and increasing pH (Videla and Andrews, 2009). Alfalfa hay also increases pH due to its high calcium contents (Nadeau *et al.*, 2000; Craig, 2007; Reese and Andrews, 2009). Antiulcerogenic effects of rice and corn oil have also been described (Cargile *et al.,* 2004; Frank *et al.*, 2005; Aranzales JRM, 2012). These substances present a positive effect only on the glandular mucosa and are suitable as coadjutants in patients treated with NSAIDs.

The balance between Omega-3 and Omega-6 fatty acids is important in inflammatory diseases of the gastrointestinal tract because of their anti-inflammatory properties, influence on mucosal circulation, and cytoprotective effects (Tillotson and Traub-dargatz, 2003). Commercially available supplements high in Omega-3 and Omega-6 such as corn oil, which provides a better ratio of these two essential fatty acids, can be administered for preventing and curing EGUS (Aranzales JRM, 2012).

The therapeutic arsenal for EGUS is broad and efficient depending on the severity and complication of the gastric lesion. However, changes in external risk factors are important to obtain fast and positive results. For example, implementation of free grazing along with adequate drug therapy improves physiological condition for tissue recovery with optimal healing of the ulcers (Alves *et al.*, 2010). Furthermore, nutrition changes such as a reduction of starch and an increase of digestible fiber could be a key factor in preventing EGUS.

Finally, duration of EGUS treatment depends on recognizing the syndrome as a complex problem with multiple causes, and determining the extent and intensity of early lesions. Moreover, gastric mucosa is highly capable of healing and regenerating if the gastric environment is favorable. Generally, the treatment period can be shortened by decreasing exposure to risk factors and using the best therapeutic options according to the patient type and clinical problem. Pharmacological therapy during 28 days has been effective to achieve complete healing and prevent recurrence of ulcers (Andrews *et al.,* 1999b). Re-epithelialization of the glandular mucosa requires more time for severe and larger lesions (Geor *et al.,* 2013). Gastroscopy monitoring is ideal for evaluating the response to treatment in horses with poor clinical evidence of EGUS.

Conclusion

There are no studies on gastric mucosal lesions and predisposing factors for equine breeds in Colombia. Due to EGUS complexity, it is necessary to associate the specific pharmacological arsenal with drugs effectively used on guinea pigs and humans. It is important to study possible adverse effects in horses receiving prolonged treatments. More clinical research is required to find alternative, effective, and low-cost therapies for gastric lesions in equines.

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