


Equine Squamous Gastric Disease: Prevalence, Impact and Management

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Abstract: This narrative review explores the etiopathogenesis, clinical signs, diagnosis and treatment of ESGD (equine squamous gastric disease) and discusses the impact of this commonly encountered condition on the equine industry. ESGD refers specifically to peptic injury of the squamous mucosa of the stomach. Prevalence is highest in performance horses, but the disease has been documented across many breeds and ages, including in feral horses and foals. The pathogenesis of ESGD is well understood. Intensive management and exercise are important factors that contribute to a disruption of the normal stratification of gastric pH. This results in exposure of the vulnerable squamous mucosa to acid, leading to ulceration. Clinical signs are variable and there is little evidence to support a direct association between reported signs and the presence or absence of lesions seen on gastroscopy. Management is aimed at acid suppression and mitigation of known risk factors.

Keywords: ulcer, stomach, ESGD, omeprazole, performance

Introduction and Terminology

Equine Gastric Ulcer Syndrome (EGUS) is a term that was first adopted in 1999 to describe erosive and ulcerative diseases of the equine stomach and is comparable to the term peptic ulcer disease in people. The terminology was recently expanded to include the terms Equine Squamous Gastric Disease (ESGD) and Equine Glandular Gastric Disease (EGGD) as it became clear there was a need to distinguish the anatomical region of the stomach affected.^{1,2} Although squamous and glandular gastric diseases can occur concurrently, there are significant differences in prevalence, epidemiology, pathogenesis, and treatment, and they should be seen as distinct disease entities. There is currently no clear relationship between the presence of ESGD and EGGD, and direct extrapolation from one disease to another is therefore inappropriate. ESGD refers specifically to peptic injury of the squamous mucosa of the stomach and is the focus of this review.

Relevant Anatomy and Physiology

The horse is a monogastric animal, and the stomach is comprised of four distinct anatomical regions; the dorsal fundus, the ventral fundus, the cardia and the pylorus (Figure 1). The mucosal lining is divided into a dorsal squamous and a ventral glandular portion by the *margo plicatus*. The dorsal squamous portion has a smooth, glistening surface and is pale yellow to white in color. It is comprised of stratified squamous epithelium and is contiguous with the esophagus at the level of the cardia. Histologically, the squamous epithelium consists of layers of

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Figure 1 The normal equine stomach showing the four distinct anatomical regions. **A**, ventral fundus; **B**, cardia; **C**, pylorus; **D**, dorsal fundus. Image adapted with permission of Equine Veterinary Journal. Martineau H, Thompson H, Taylor D. Pathology of gastritis and gastric ulceration in the horse. Part 1: range of lesions present in 21 mature individuals. *Equine Vet J.* 2009;41(7):638–644.²³

keratinized and non-keratinized epithelial cells, an underlying *lamina propria* and a muscularis mucosa. The epithelium varies in thickness from 309 μ m to 1154 μ m, and is thickest immediately adjacent to the *margo plicatus*, presumably as an adaptation to increased acid exposure in this region.³ There is no inflammatory cell infiltration in the epithelium or the *lamina propria* of healthy equine squamous epithelium.³

The squamous mucosa has no absorptive or secretory capacity and simply acts as a protective barrier. In contrast, the glandular mucosa is comprised of mucus producing cells and gastric glands and is responsible for secreting hydrochloric acid (HCL) in response to gastrin. Horses are basal acid secretion and as such, they secrete acid constantly irrespective of feed consumption.⁴ The pH in the ventral stomach of adult horses is therefore predominately acidic and remains relatively stable, with a median pH of 2.9 over a 24-hour period.⁵ In contrast, pH in the dorsal stomach is less acidic, with a median pH of 6.8, however it is exposed to large diurnal fluctuations, likely due to the natural feeding patterns of horses. Horses consume most of their roughage during the day.⁶ Once ingested, it forms a fibrous mat within the stomach that helps maintain normal pH stratification of gastric content, thereby facilitating buffering of acid in the dorsal stomach.⁷ As a consequence, horses have a significantly higher pH in the dorsal stomach during the day, and this may persist for up to five hours after feeding.⁵ In addition to endogenous acid secretion, gastric pH in the dorsal

stomach is also influenced by saliva, short-chain fatty acids (SCFA), lactic acid and duodenal reflux of biliary secretions.^{8–12}

In contrast to adult horses, gastric pH in the proximal and distal stomach of neonatal foals is highly variable, with a mean pH of 5.5.¹³ The squamous mucosa is thin at birth and becomes progressively thicker as the foal gets older, presumably as an adaptation to increased acid exposure.¹⁴

Gross Pathology and Histopathology

Characteristic lesions associated with ESGD include hyperkeratosis, erosion, and ulceration. Lesions are most commonly seen adjacent to the *margo plicatus* along the lesser curvature and greater curvature of the stomach in both adults and foals; and tend to be more severe at the lesser curvature in the region of the cardia.^{15–22}

Hyperkeratosis

Hyperkeratosis is caused by thickening of the keratinized layers of the squamous epithelium (the stratum corneum) and can be recognized macroscopically as diffuse regions of thickened, corrugated tissue (Figure 2). The affected epithelium is often friable and has a characteristic yellow discoloration. Histologically, these lesions are characterized as parakeratotic or orthokeratotic hyperkeratosis (Figure 3).²³ The exact cause of hyperkeratosis is unclear, however it is likely to be a response to excessive exposure to acid and as such, may be an early manifestation of acid injury.²³



Figure 2 Hyperkeratosis (white arrow). Notice the thickened, corrugated squamous mucosa surrounding the cardia. Regions of hyperkeratosis often have a characteristic yellowish discoloration. Image property of the author.

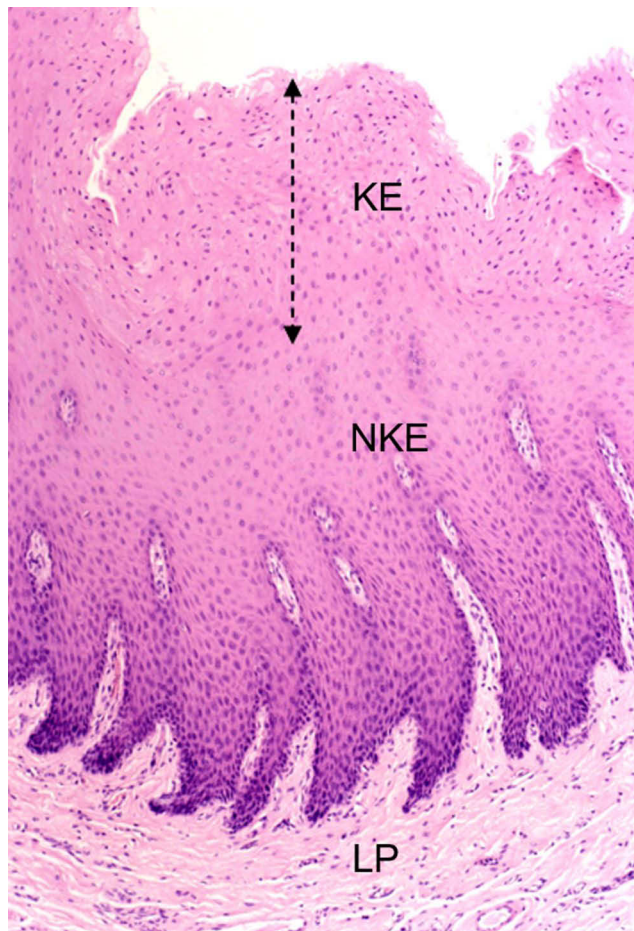


Figure 3 Parakeratotic hyperkeratosis (dashed arrow). Bar = 400 μ m. Image reproduced with permission of Equine Veterinary Journal. Martineau H, Thompson H, Taylor D. Pathology of gastritis and gastric ulceration in the horse. Part I: range of lesions present in 21 mature individuals. *Equine Vet J*. 2009;41(7):638–644.²³

Abbreviations: K, keratinized epithelium; NKE, non-keratinized epithelium; LP, lamina propria.

Erosions

Erosions are superficial defects in the squamous mucosa involving the epithelium and basement membrane, but do not extend beyond the lamina propria. Erosions have a smooth reddish/pink macroscopic appearance and can be focal or diffuse (Figure 4). Histologically, they are characterized by thinning and lifting of the keratinized layer of the epithelium and an influx of polymorphonuclear cells within the epithelium and the lamina propria (Figure 5).^{3,23} Erosions represent a milder form of acid injury and will progress to ulceration with ongoing acid exposure.

Ulceration

Ulcers are deeper defects in the squamous mucosa that extend beyond the lamina propria. Ulcers have a characteristic

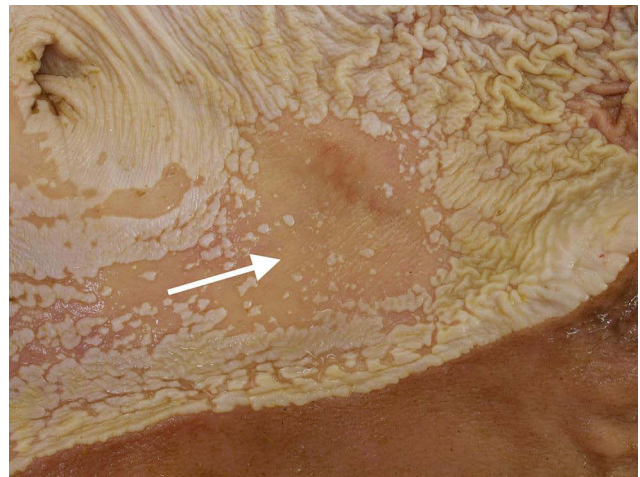


Figure 4 Erosion (white arrow). Notice the focal region of squamous mucosa that is smooth and reddish/pink in appearance. This represents thinning of the squamous epithelium and loss of the keratinized layer. Image courtesy of Henry Martineau.

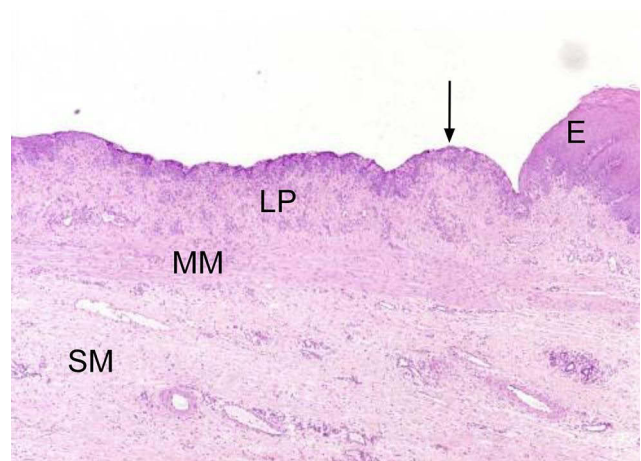


Figure 5 Erosion (black arrow) adjacent to normal squamous epithelium. Bar = 1000 μ m. Notice the dramatic thinning of the affected epithelium. Image reproduced with permission of Equine Veterinary Journal. Martineau H, Thompson H, Taylor D. Pathology of gastritis and gastric ulceration in the horse. Part I: range of lesions present in 21 mature individuals. *Equine Vet J*. 2009;41(7):638–644.²³

Abbreviations: E, epithelium; LP, lamina propria; MM, muscularis mucosa; SM, submucosa.

depressed center surrounded by a prominent margin of tissue and may be associated with active hemorrhage when severe (Figures 6 and 7). Histologically, there is complete epithelial loss, and the underlying muscularis mucosa is exposed (Figure 8).^{3,23} Over time, a bed of granulation tissue develops that is covered with neutrophils, fibrin and necrotic debris, and bacteria can sometimes be seen invading the keratinized epithelium at the edge of the ulcer.^{3,23} The mucosa immediately adjacent to the ulcer responds by developing prominent epithelial projections that extend into the lamina propria and capillaries that extend from the lamina propria into the epithelium. Furthermore, the keratinized and non-keratinized

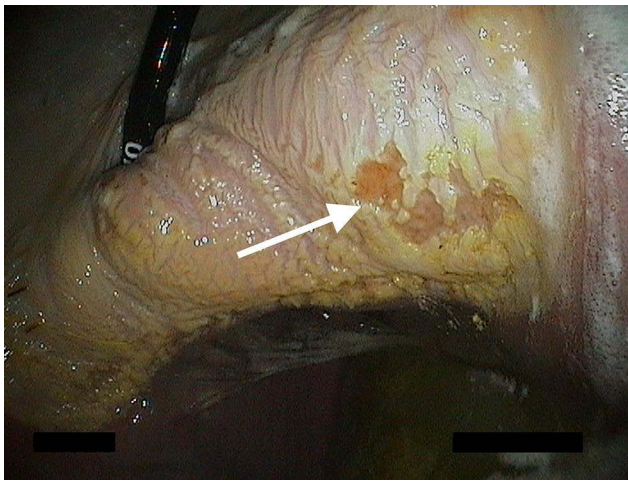


Figure 6 Ulcer (white arrow). Notice the characteristic depressed center surrounded by a prominent margin of tissue. Image property of the author.

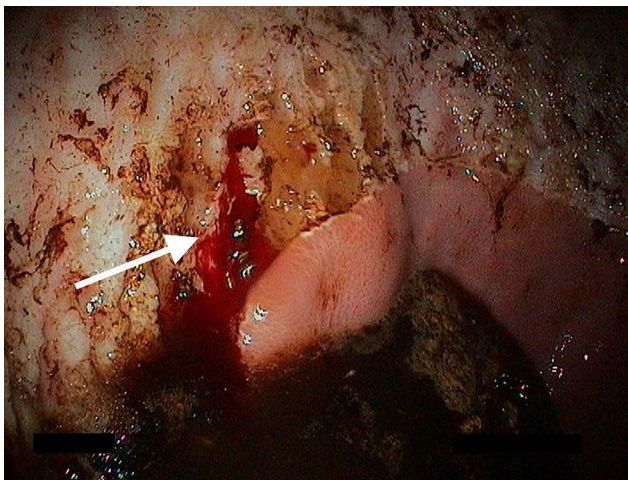


Figure 7 Bleeding ulcer (white arrow). Ulcers may be associated with active hemorrhage when severe. Image property of the author.

epithelium increases in thickness, giving the ulcer margin a characteristic proliferative appearance.³ In rare cases, deep ulcers may perforate the stomach and lead to a fatal septic peritonitis. It is most commonly seen in foals and is extremely uncommon in adult horses.²⁴ Strictures can form as a sequel to ESGD, although this is rarely reported in the squamous portion of the stomach.²⁵ Glandular metaplasia is sometimes seen in horses and should not be mistaken for ulceration. Glandular metaplasia is characterised by the development of islands of glandular mucosa that are interspersed within the stratified squamous epithelium along the *margo plicatus*, particularly in the region of the cardia. The clinical significance of this finding in the horse is unclear at present, however it may represent an adaptation to continual exposure of the squamous epithelium to acid.²³ In people, a similar condition exists

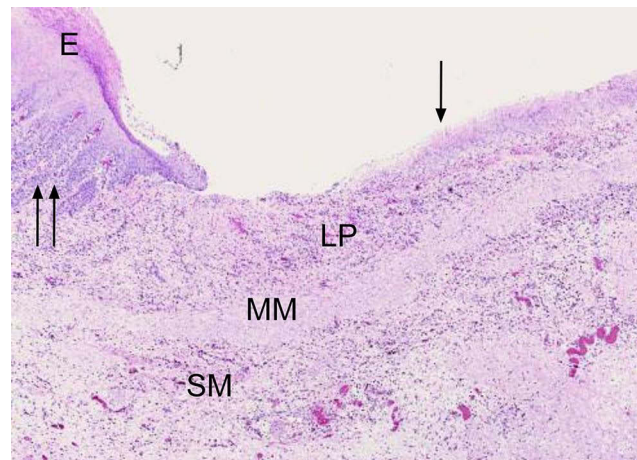


Figure 8 Ulcer (single black arrow) adjacent to normal squamous epithelium. Notice the complete loss of epithelium in the ulcer bed and exposure of the underlying *lamina propria*. Prominent epithelial projections can be seen in the normal mucosa immediately adjacent to the ulcer (double black arrows). Bar = 1000 μ m. Image reproduced with permission of Equine Veterinary Journal. Martineau H, Thompson H, Taylor D. Pathology of gastritis and gastric ulceration in the horse. Part 1: range of lesions present in 21 mature individuals. *Equine Vet J*. 2009;41(7):638–644.²³

Abbreviations: E, epithelium; LP, *lamina propria*; MM, muscularis mucosa; SM, submucosa.

called Barrett's esophagus, which occurs in response to chronic inflammation associated with gastroesophageal reflux disease (GERD) and represents a pre-neoplastic change.²⁶ A potential association between *Equus caballus* papillomavirus type 2 (EcPV-2) infection and a subset of horses with gastric squamous cell carcinoma (SCC) has been recently reported.^{27,28} It is unclear whether squamous epithelial injury might play a role in the development of SCC. Squamous epithelial hyperplasia or metaplasia has been suggested as a precursor of carcinoma development, although further work is needed to characterise the gross appearance of early pre-neoplastic change in the equine stomach and to explore the link between squamous ulceration and SCC.

Pathogenesis

Equine squamous gastric disease is a consequence of sustained exposure of the squamous mucosa to acid and is comparable to gastric ulceration of the *pars esophagea* in pigs and GERD in people. As is the case with other species, the squamous mucosa of the equine stomach is inherently vulnerable to acid injury as it has a poor blood supply and does not possess a mucus-bicarbonate layer in order to protect itself.²⁹ The thick keratinized epithelium together with the presence of high electrical resistance, tight epithelial junctions and an osmophilic phospholipid surfactant-like layer provide some protection, however this

mucosal barrier is rapidly overwhelmed in the presence of acid, with evidence of injury occurring after as little as 30 minutes of exposure.^{7,30,31}

Acid injury is primarily attributable to endogenous HCL, which erodes the outer keratinized layers of the squamous epithelium and results in disruption of the bioelectric properties of the transporting cells, thus compromising barrier function.^{8,10,30} In addition, other gastric constituents, including SCFA, lactic acid and bile salts, have been shown to act synergistically with HCL, thus further attenuating barrier function and ultimately resulting in cellular injury.^{8–12} For example, SCFA have been shown to be relatively harmless to the squamous epithelium at a pH >4, however they become lipid soluble at a pH ≤ 4, and are then able to penetrate cells, causing cellular injury.^{7,10,11} Bile acids have a similar deleterious effect on the squamous mucosa in their unionized lipid soluble state.^{7,12}

The sequence of events following exposure of squamous epithelial cells to acid is the movement of H⁺ ions across the cell membrane, acidification of cellular contents, inhibition of sodium transport, cellular swelling and ultimately cell death.⁷ The squamous epithelium initially reacts by thickening and becoming hyperkeratotic. Sloughing of superficial layers of epithelium result in the development of erosions, and with continued acid exposure, lesions deepen to form ulcers.²³

Equine squamous gastric disease can be either primary or secondary.¹ Primary ESGD occurs in response to risk factors inherent in domestication and intensive management that result in prolonged exposure of the squamous mucosa to acid in horses with an otherwise normal gastrointestinal tract. In contrast, secondary ESGD occurs as a direct consequence of delayed gastric emptying. This causes chronic gastric distension resulting in prolonged exposure of the squamous mucosa to acid. The most common cause of delayed gastric emptying in adult horses and foals is pyloric outflow obstruction secondary to glandular gastric disease.^{24,32–34}

Prevalence and Risk Factors

Prevalence studies can be challenging to interpret as not all reports make a clear distinction between ESGD and EGGD. Interpretation is further complicated by the fact that the prevalence of ESGD within specific subpopulations of horses may vary over time in response to changes in management or the intensity of training. It has also been suggested that the prevalence of ESGD may be

overstated in some populations, as many studies include horses with mild (≤ grade 2/4) lesions that may be of questionable clinical significance.³⁵ Table 1 summarises prevalence data and reported risk factors for ESGD in adult horses and foals.

The prevalence is highest in performance horses and reflects changes in management and intensity of exercise inherent in competition. It has been shown that the risk of ESGD increases with an increase in the intensity of exercise and the duration of time at work.^{36,37} This association is well recognized in Thoroughbred and Standardbred racehorses,^{20,37–41} but has also been shown in elite endurance horses,⁴² show jumping warmbloods³⁸ and other non-racing performance horses.⁴³ Strenuous exercise causes an increase in intraabdominal pressure associated with contraction of the abdominal muscles. This results in gastric compression and exposure of the sensitive squamous mucosa to acidic gastric content.⁴⁴ Strenuous exercise has also been shown to cause an increase in post-prandial gastrin secretion, resulting in an increased production of HCL.⁴⁵

Several additional factors associated with management have also been shown to increase the risk of ESGD, many of which are imposed on horses at the commencement of training or during active competition. These include the trainer, high starch/low roughage diets, fasting, stall confinement, transport, intermittent access to water and administration of hypertonic solutions of electrolytes.^{36,46–49} Exposure to a combination of a high starch diet, stall confinement and strenuous exercise has been shown to induce lesions in as little as 7 days; and intermittent fasting is so effective at inducing lesions that it is used as a model for ESGD in experimental studies.^{50,51} Intermittent fasting disrupts normal pH stratification of gastric content, thereby allowing high concentrations of HCL and refluxed bile to mix in the dorsal stomach.^{7,50} Low roughage diets also disrupt normal pH stratification by causing greater gastric fluidity and mixing of dorsal and ventral gastric contents, but in addition to this, horses chew less, and this results in decreased production of saliva, which is an important buffer of acid in the dorsal stomach.⁷ Ingestion of large quantities of fermentable carbohydrate (starch >1g/kg/meal) exacerbates the situation further by causing rapid production of SCFA, which acts synergistically with HCL in the presence of a low pH to cause acid injury of the squamous epithelium.⁴⁶ High concentrate diets also stimulate secretion of gastrin which results in further acid secretion.⁵²

Table 1 Prevalence of ESGD in Different Populations of Horses and Associated Risk Factors

Population	Prevalence	Risk Factors	Limitations	Ref.
Racehorses				
TB	52–92% Prevalence 92% in symptomatic horses and 52% in asymptomatic horses	Active training		[41]
TB	93%	Active racing within the previous 2 months	Small sample size (n=67)	[53]
TB	82%			[54]
SB	87%	Horses ≥ 3 years old; geldings		[59]
SB	44%	Active racing [OR 9.3]; gait - trotters more likely to have ESGD than pacers [OR 2.2]; poor body condition; horses living at racetracks; increasing age		[39]
TB, SB	86%			[15]
SB	88%	Intensity of training [OR 6.71]; horses in their first 5 months of training with the highest risk at 3 months [OR 6.17]	Small sample size (n=48); limited to 3 training yards	[20]
SB	70%	Horses that have raced in the last month [OR 14.7]		[40]
TB, SB	88%	Horses ≥ 3 years old; no difference in prevalence between horses stabled full time, kept at pasture for part of the day or kept at pasture full time		[60]
TB	72%	Horses with stereotypies [OR 5]; time in work ≤6 weeks [OR 0.3]; aggression towards to humans [OR 0.12]		[37]
Endurance horses				
Arab, other	57%	Age; final ride position; days a week trained; hours a day trained	Small sample size (n=37)	[61]
Arab, Anglo-Arab	48–93% Prevalence 48% during the inter-season period and 93% during the competition season	Longer endurance race distance; high starch diet	Small sample size (n=30)	[42]
Non-racing performance horses				
Mixed breeds	58%	Active competition; nervous disposition; lower RBC counts and hemoglobin concentration	Small sample size (n=50)	[62]
QH Western performance	40%			[63]

(Continued)

Table 1 (Continued).

Population	Prevalence	Risk Factors	Limitations	Ref.
Mixed breeds Dressage, show jumping, western performance, endurance	17–56% Prevalence 17% before competition season and 56% after competition season	Active competition		[43]
WB Show jumpers	25%	Increased exercise intensity [OR 3.8]	Small sample size (n=83); limited to a small geographical radius	[38]
TB, other Polo ponies	37%	Decreasing exercise duration [OR 19.5]	Small sample size (n=63)	[64]
Non-performance horses				
American paint horses	Experimental study	Transport and stall confinement		[47]
Mixed breeds	Experimental study	Repeated administration of oral electrolytes		[48]
Mixed breeds Riding school	11%	Horses aged 2–6 or 18–23 years old	Small sample size (n=80); limited to one riding centre	[65]
TB Broodmares	67–76% Prevalence 67% in pregnant mares and 76% in non-pregnant mares		Small sample size (n=62); limited to one breeding farm	[66]
Mixed breeds Pleasure horses	53%	Straw only available forage [OR 4.2]; ≥ 1 g/ kg BW of starch per meal [OR 2.6]; water not available in the turnout paddock [OR 2.3]; interval between forage feeding >6 h [OR 5.3]		[19, 46]
Mixed breeds Pleasure horses	48–66 Prevalence 66% in symptomatic horses and 48% in asymptomatic horses			[67]
Donkeys and wild equids				
Donkeys	38%		Small sample size (n=39)	[68]
Zebras in captivity	64%		Small sample size (n=55); postmortem study - prevalence may have been influenced by concomitant disease	[69]
Feral horses	22% Prevalence 61% in domestic horses and 22% in feral horses		Abattoir study - prevalence may have been influenced by transport and fasting	[56]
Foals				
TB foals 2–85 days old	47–57% Prevalence 47% in Ireland and 57% in England			[70]

(Continued)

Table I (Continued).

Population	Prevalence	Risk Factors	Limitations	Ref.
WB foals 82–200 days old	7–97% Prevalence 7% before weaning and 97% after weaning		Limited to one breeding farm	[18]
Mixed breeds 1–180 days old	17% Prevalence lowest in neonatal foals	Foals > 1 month old; concomitant gastrointestinal disease	Postmortem study - prevalence may have been influenced by concomitant disease	[58]

Note: Colors denotes different subpopulations of horses.

Abbreviations: OR, odds ratio; QH, Quarter horse; SB, Standardbred; TB, Thoroughbred; WB, Warmblood.

Non-performance horses are also susceptible to ESGD however the prevalence is generally lower, and when lesions occur, they tend to be less severe. This suggests that risk factors other than intense exercise and management may play a role and underscores the multifactorial nature of this disease. There is conflicting evidence for the role that intrinsic risk factors, such as age, gender and breed, may play a role in the development of ESGD and where evidence exists, it is likely to be confounded by other factors such as management and exercise. Feeding of straw has been associated with an increased risk of ESGD, presumably due to the abrasive effect of the coarse roughage, and this may be relevant to other forage with a high lignin content.⁴⁶ Stress and administration of inappropriate doses of non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of EGGD; however, there is currently no conclusive evidence to suggest that a similar association exists with ESGD.^{53–55}

Interestingly, ESGD has also been reported in wild equids and feral horses with no apparent exposure to recognized risk factors, and it poses an interesting (and as yet unanswered) question as to whether some degree of ESGD is “constitutive” in the equine stomach and develops as a normal response to periodic exposure of the squamous mucosa to acid.⁵⁶ This notion is supported by the fact that many horses with ESGD will not demonstrate clinical signs and the fact that mild lesions may heal spontaneously, particularly if the inciting cause has been removed.^{3,57}

In foals, the prevalence of ESGD ranges from 7% to 57% depending upon the age. Older weanling foals appear to be most susceptible, however ESGD has also been reported in foals as young as 24 hours.⁵⁸ Very few risk factors have been reported for ESGD in foals.

Concomitant gastrointestinal disease has been associated with the presence of ESGD at the time of necropsy, however a cause-and-effect relationship has not been demonstrated.⁵⁸

Clinical Signs

Numerous clinical signs have been attributed to ESGD in adult horses and foals, however there is currently very little evidence to support a direct association between any of these signs and the presence or absence of lesions seen on gastroscopy. The evidence that is available is often conflicting and therefore establishing the clinical significance of ESGD can be challenging.¹ Most of the clinical signs are non-specific and are often subjective and owner perceived. This is complicated further by the fact that horses with ESGD may not demonstrate clinical signs and if they do, the signs do not necessarily correlate with the severity of the lesions seen on gastroscopy.^{16,41,54,70} In addition, horses will often present with ESGD and EGGD concurrently; and to date there has been no attempt to differentiate between EGGD and ESGD when reporting clinical symptomatology. Clinical signs suggestive of ESGD should therefore always be interpreted in context, and gastroscopy should always be performed to confirm the disease.

Clinical signs that have been attributed to ESGD in adult horses include inappetence, poor body condition or weight loss, changes in behavior, acute or recurrent colic, bruxism, and stereotypic behavior (crib biting, stall weaving) and poor performance.¹ In light of the disproportionately high prevalence of ESGD in performance horses, poor performance has perhaps received the most attention, yet surprisingly, there are very few studies that have investigated the relationship between poor performance

and ESGD.^{54,71,72} This may be in part due to the difficulties in excluding the many confounding factors that might influence poor performance, including the effects of ESGD on appetite and interruption of training.¹ The exact mechanism by which ESGD may affect performance has not been elucidated but is likely to be related to epigastric pain.⁷³ In people, epigastric pain is defined as pain localized to an area below the sternum and above the umbilicus and is common in athletes with GERD.⁷⁴ Acid reflux onto the sensitive squamous epithelium of the esophagus during exercise causes a “burning sensation” that is proportional to increasing exercise intensity and has been shown to affect performance.⁷⁵ Horses with ESGD have similar lesions to those causing GERD in human athletes, and the problem is likely to be compounded by the fact that the squamous epithelium extends into the proximal one-third of the stomach and is not protected by an esophageal sphincter. Interestingly, a recent study in human athletes suggested that GERD may be associated with increased abdominal pressure during exercise, a mechanism that is all too familiar in the equine athlete.^{44,76} The exact mechanism by which epigastric pain impacts on athletic performance in the horse is a matter of ongoing speculation. One theory is that it may affect stride length, leading to reduced time to fatigue and a lower increase in maximal specific oxygen uptake during peak exercise.⁷²

The clinical signs of ESGD in foals have traditionally been divided into four distinct syndromes, however this classification is historical and should no longer be used.²⁴ Foals and adults share the same underlying pathogenesis and differences in the spectrum of clinical disease in foals can be attributed to differences in diet, behavior and duration and severity of ulceration. As is the case in adult horses, foals will often be asymptomatic.^{18,70} When clinical signs do occur, they tend to manifest as poor body condition, inappetence, ptyalism, bruxism or colic.²⁴ Perhaps, the most important difference in clinical symptomatology between foals and adult horses is that foals are more likely to develop severe disease and this may result in full thickness perforation which is invariably fatal.²⁴ Foals are also more likely to develop chronic secondary ESGD as a consequence of gastric outflow obstruction.³⁴ This may arise from cardiac, antral, pyloric or proximal duodenal strictures, although strictures involving the proximal duodenum appear to be more common than those involving the stomach.²⁴

Diagnosis

At present, the only reliable antemortem test for ESGD is gastroscopy. Other methods such as blood biomarkers have been investigated with variable results. Serum amyloid A concentration was not associated with the presence of ESGD, and no significant correlation was found between fecal albumin and hemoglobin values and gastric ulcer score.^{77,78} Blood sucrose concentration was shown to have poor sensitivity and specificity for the diagnosis of gastric ulceration in adult horses.⁷⁹ The test was shown to have better sensitivity in weanling foals, but specificity remained poor, limiting its use in a screening test to identify foals that may benefit from gastroscopy.¹⁸ Hair cortisol concentrations were lower in horses with ESGD and were negatively correlated with lesion severity, but further work is needed to explore this association.⁸⁰ More recently, proteomic analysis has identified several candidate proteins associated with the presence of ESGD. However, these proteins are not well characterized in the horse and further work is needed to understand their function and relationship to ESGD.⁸¹ Owner questionnaires have also been investigated as a diagnostic tool.^{36,82} A recent study found that a questionnaire was not useful for predicting the presence and the severity of lesions detected during gastroscopic examination.³⁶ However, answers to some of the questions did correlate with the development of gastric lesions. Such questionnaires may be a useful tool to evaluate the risk of ESGD but cannot replace gastroscopic examination to make a definitive diagnosis.

Gastroscopy requires some degree of expertise and specialized equipment; a three-meter videoendoscope is necessary to reach the stomach of an adult horse and visualise the squamous mucosa. Complications associated with the procedure include small intestinal segmental volvulus, which was documented on four horses following gastroscopy.⁸³ A larger study reported colic signs in 0.9% of healthy horses undergoing routine gastroscopy.⁸⁴ Although insufflation of air has not been shown to increase the odds of colic, it appears prudent to deflate the stomach following the procedure.

Multiple scoring systems for ESGD have been described including a number/severity system,⁸⁵ a 0–3 ordinal system,^{39,51,86} and a system based on lesion depth and surface area. A 0–4 scoring system was recommended by the Equine Gastric Ulcer Council in 1999.² This was subsequently shown to perform better than the

number/severity scoring system and remains widely used, both in clinical practice and in research settings.⁸⁷ The 0–4 grading system was recently shown to have substantial inter- and intra-observer agreement (0.69 and 0.80, respectively) and appears to perform well regardless of observer experience.⁸⁸ The same study investigated the use of a visual analog scale, in order to generate continuous data over a 100-point scale based on the severity of ulceration. This had moderate interobserver and intra-observer agreement, which improved with experience, but was found to be inferior to the 0–4 scoring system for ESGD. Endoscopic assessment is subjective to some extent and may under- or overestimate the severity or depth of squamous lesions.⁸⁹ Unlike the glandular mucosa, where a range of lesion types are documented, biopsy is rarely indicated for squamous lesions, which tend to be more homogenous in appearance, and represent true ulceration rather than an inflammatory process.^{3,23} However, biopsy remains the only available method to accurately determine lesion depth.

Because there is currently little evidence to suggest an association between lesion severity and clinical signs, determining the clinical significance of lesions seen on gastroscopy can be difficult. Lesions are therefore typically considered to be clinically significant once there is a breach of the squamous epithelium, ie, \geq grade 2/4. The clinical significance of hyperkeratosis (grade 1/4) remains unclear; however, it may represent an early manifestation of acid injury, and there are anecdotal reports of horses with hyperkeratosis responding to treatment.^{1,23}

In the absence of gastroscopy, it is possible to commence treatment and assess clinical response, bearing in mind that clinical signs are numerous and variable, this approach can be costly, and gastroscopy is still necessary to conclusively rule out ESGD if clinical improvement is not seen with treatment.

Treatment and Management

It is now well established that acid is directly implicated in the development of ESGD and therefore treatment should be aimed at acid suppression. Spontaneous healing of ESGD is variable, with reported healing rates of less than 5% in horses in training and up to 55% in horses at pasture.^{57,86,90} Treatment is therefore recommended for any horse with a clear disruption of squamous epithelial integrity, ie, \geq grade 2. It is important to remember, however, that acid suppression does not initiate healing, but rather, it facilitates healing by providing an optimal

environment for healing to occur.³ Treatment should therefore always be done in conjunction with appropriate management changes that mitigate against recurrence of disease. The efficacy of acid suppressants for the treatment of ESGD can be assessed by demonstrating an increase in pH in the stomach and an improvement in lesion score. In people, it is recommended that the intra-day percentage of time that gastric pH is maintained above 4 should be greater than 66% to facilitate healing,^{91,92} and similar criteria have been used for horses.^{93,94}

Proton Pump Inhibitors (PPIs) Omeprazole

The drug of choice for acid suppression in the horse is omeprazole. It irreversibly inhibits the H⁺/K⁺ ATPase pump on the secretory surface of the gastric parietal cell, taking up to five days to reach steady state concentration.^{86,95} Various formulations of oral omeprazole are available, including plain paste, buffered paste or enteric coated preparations. The oral bioavailability of plain omeprazole paste is approximately 10% in the fasted state.⁹⁶ Enteric coated formulations have higher bioavailability (median 22%), although considerable inter-horse variation appears to exist²⁶ and plasma concentrations of omeprazole do not appear to predict drug pharmacodynamics in horses.^{94,96}

The duration of acid suppression required over a 24-hour period to allow healing of lesions is currently unknown. Doses ranging from 0.5–4mg/kg have been reported (Table 2). A recent study demonstrated that dose does not appear to predict pharmacodynamics of omeprazole, suggesting that lower dose rates (1mg/kg) may be as effective as higher doses.⁹⁴ Administration in the fasted state appears to be an important factor, improving the area under the curve by 300% in one study,⁹⁷ although this difference was not repeatable in subsequent work.⁹⁶ Horses on an *ad libitum* hay were shown to require higher doses of omeprazole to achieve sufficient acid suppression in one study.⁹⁵ When oral omeprazole is administered prior to feeding and before exercise, doses as low as 1 mg/kg bwt may be as effective as higher doses.⁹⁸ It is worth noting that this study used an enteric coated preparation. Lower dose rates have not been investigated with buffered or plain formulations, although another study comparing three commercially available buffered pastes and two enteric coated granule preparations found that the method of protection utilized did not significantly alter the pharmacokinetics of the drug.⁹⁹

Table 2 Reported Dose Rates for Oral Omeprazole for the Treatment or Prophylaxis of ESGD

Dose	Formula	Population	Outcome	Limitations	Ref.
1 mg/kg bwt	Gastrogard® Buffered paste	6 TB horses Experimental	Increased gastric pH Better on low hay diet	Experimental study; small number of horses; outcome measured by change in pH not effect on ulceration	[95]
4 mg/kg bwt	Gastrogard® Buffered paste	6 TB horses Experimental	Increased gastric pH Better on low hay diet	Experimental study; small number of horses; outcome measured by change in pH not effect on ulceration	[95]
4 mg/kg bwt	Gastrogard® Buffered paste	140 horses and foals	Improved: 99% Healed: 87%	Only re-evaluated at 28 days so response to treatment could have occurred sooner; mixed population; some administration intermittent with racehorse withdrawal times	[102]
1 mg/kg bwt Pre-exercise	Gastrozol® Enteric coated paste	18 TB racehorses	Improved: 100% Healed: 89%	Exact period of fasting before medication administered unknown; cannot extrapolate to buffered or plain paste; small number of horses	[98]
2 mg/kg bwt Pre-exercise	Gastrozol® Enteric coated paste	16 TB racehorses	Improved: 100% Healed: 94%	Exact period of fasting before medication administered unknown; cannot extrapolate to buffered or plain paste; small number of horses	[98]
4 mg/kg bwt Pre-exercise	Gastrozol® Enteric coated paste	16 TB racehorses	Improved: 88% Healed: 75%	Exact period of fasting before medication administered unknown; cannot extrapolate to buffered or plain paste; small number of horses	[98]
4 mg/kg bwt Pre-exercise	Abgard® Buffered paste	13 TB race horses in training	Improved: 100% Healed: 92%	Small number of horses	[107]
4 mg/kg bwt Post-exercise	Abgard® Buffered paste	12 TB racehorses in training	Improved: 92% Healed: 67%	Small number of horses	[107]
4 mg/kg bwt	Peptizole® Plain paste OR Gastrogard® Buffered paste	27 mixed breed horses	Improved 89% Healed 67%	Plain and buffered formulations combined into same category; management not standardized	[100]
0.5 mg/kg bwt	Gastrozol® Enteric coated paste	17 TB racehorses in training	Prophylaxis 12% worsened	Small number of horses; limited to racehorse population; cannot extrapolate to buffered or plain paste	[108]
1 mg/kg bwt	Gastrozol® Enteric coated paste	16 TB racehorses in training	Prophylaxis 6% worsened	Small number of horses; limited to racehorse population; cannot extrapolate to buffered or plain paste	[108]

Note: Colors denote different studies.

Abbreviations: bwt, body weight; TB, Thoroughbred.

Rates of healing of ESGD following oral omeprazole treatment have been reported between 67% and 94%.^{86,98,100–102} Differences in dose, diet, management, and duration of treatment between studies may contribute to this variability. The ECEIM consensus statement recommends three weeks of omeprazole treatment for ESGD,¹ on the basis that most healing has occurred by day 21.¹⁰³ However, studies investigating this duration of omeprazole treatment for ESGD are lacking. Healing is generally defined as grade <1/4, indicating the integrity of the squamous mucosa, although care should be taken when comparing studies, as different definitions may be used. The requirement for withdrawal times may influence success rates with omeprazole treatment in racehorses. Kerbyson et al demonstrated ulcer healing (grade <1/4) in 52% of Thoroughbred racehorses following 4 weeks of treatment with 4mg/kg buffered omeprazole paste where horses raced as normal, with five-day withdrawal periods observed prior to each race.¹⁰⁴ This is lower than published figures following treatment with an uninterrupted course but may be more representative of use in clinical practice.

Administration of intravenous omeprazole has been described and has been shown to be effective in increasing gastric pH.¹⁰⁵ However, the short half-life and requirement for daily injections make this a less attractive option in practice. A compounded, long-acting intramuscular preparation has become available in recent years and has been shown to be highly effective for ESGD when used at a dose of 4 mg/kg every 5–7 days.¹⁰⁶ A more recent study found that healing occurred in 97% of horses treated with the intramuscular preparation for four weeks, compared to 67% of those treated with an equivalent dose of oral omeprazole paste.¹⁰⁰ Mild localized swelling was reported in 5% of the injections administered.

Esomeprazole

Esomeprazole, a second-generation proton pump inhibitor, is the *S*-isomer of omeprazole. In people, it is metabolized more slowly than omeprazole, resulting in a higher area under the concentration–time curve after administration of the same dose.¹⁰⁹ It is superior to other proton pump inhibitors for the treatment of reflux esophagitis in people and has been shown to have less variation between patients.^{110,111} Evidence for the use of esomeprazole in the treatment of ESGD is currently limited. Intravenous administration for 14 days caused a significant increase in gastric pH,¹¹² and a preliminary study found that oral

doses of a licensed human preparation of esomeprazole magnesium (Nexium) as small as 40 mg daily in Thoroughbred racehorses resulted in acid suppression when given for five days.¹¹³ More recent studies have showed that enteric coated oral esomeprazole (0.5–2.0mg/kg q24h) increases gastric pH and was as effective as oral omeprazole at increasing gastric pH.^{114,115} Diet appears to have an effect, with horses on a hay only diet requiring a higher dose (2mg/kg q24h) to achieve acid suppression compared to those on a concentrate-based diet.¹¹⁴ Further studies are needed to determine if esomeprazole carries any benefit compared to omeprazole in the horse. It was recently reported to result in resolution of lesions in horses that were refractory to omeprazole treatment,¹¹⁶ however the number of horses in the study was small, and larger comparative trials are needed. At present, there is no licensed product for use in the horse, however it may represent a useful “off-label” alternative for horses with ESGD that are refractory to omeprazole treatment. Intravenous pantoprazole caused a significant increase in the gastric pH of healthy foals, but use has not been described in adult horses and is likely to be cost-prohibitive.¹¹⁷

Side Effects of PPIs

Long-term omeprazole use can cause interstitial nephritis in people, thought to be related to induction of oxidative stress and renal tubular cell death.¹¹⁸ At present, there is no published work examining the potential renal side effects in the horse. Omeprazole did not induce significant major changes in the composition of fecal or gastric glandular microbiota in horses, suggesting it may have fewer effects on the gastrointestinal microbiome compared to other species. It is worth noting, however, that the duration of omeprazole treatment in the horse tends to be significantly shorter than in people, where PPI treatment may continue for decades.

Proton pump inhibitors have also been linked to reduced nutrient digestibility in people.¹¹⁹ In horses, reduced calcium digestibility following omeprazole administration has been demonstrated. This is likely due to an increase in gastric fluid pH causing a reduction in calcium solubility and subsequent digestibility.¹²⁰ This is unlikely to be clinically significant in horses on a diet with normal calcium intake but should be borne in mind. Conversely, another study found that short-term administration (60 days) of oral omeprazole did not significantly affect total and ionized serum calcium concentrations in

healthy horses.¹²¹ Bone density and bone mineral content were also not affected.

The loss of negative feedback from gastric acid during PPI treatment causes an increase in gastrin secretion. In some people, hypergastrinemia has a positive trophic effect on the gastric mucosa and has been linked to the development of gastric carcinoids.¹²² Octreotide acetate, a somatostatin analogue, inhibits gastrin secretion and has been shown to increase the gastric pH in horses,¹²³ but this benefit is unclear, as gastric hypertrophy following prolonged use of PPIs has not been reported in the horse to date.

ESGD may recur following discontinuation of treatment with omeprazole⁸⁶ and rebound acid secretion may be implicated. This phenomenon occurs in people following the discontinuation of PPIs and is again linked to an increase in gastrin that can persist for up to 14 days.¹²⁴ Furthermore, enterochromaffin-like (ECL) cells, which release histamine signaling for gastric acid production, proliferate due to the trophic effects of hypergastrinemia. Together, these factors are responsible for increased gastric acid production when treatment is stopped. Whilst there is currently no direct evidence to suggest that rebound acid secretion occurs in horses, it has been shown that treatment with oral omeprazole results in hypergastrinemia, and further studies are needed to determine the implications of this on acid production following discontinuation of treatment.¹²⁰ Despite the current lack of evidence, many practitioners will taper the dose of omeprazole due to concerns over rebound acid secretion. Unfortunately, there are also no studies that have compared the effect of sudden discontinuation of treatment with a tapering dose on the reoccurrence of ESGD, and therefore it is difficult to determine if there is any benefit to this practice. Other factors may also play a role in recurrence of ESGD, particularly in performance horses that continue to race, and therefore the practice of prophylactic (maintenance) treatment with omeprazole is also common. There is some evidence to suggest that this may have a benefit, as it has been shown in a recent meta-analysis, that prophylactic treatment with 1mg/kg or 2 mg/kg PO SID of oral omeprazole paste is superior to a sham treatment for preventing recurrence of ESGD.¹²⁵ Furthermore, another study found that doses as low as 0.5mg/kg of enteric coated paste prevented development of ESGD in racehorses in training and did not differ in effect from a 1mg/kg dose (Table 2).¹⁰⁸

H2 Receptor Antagonists

H2 receptor antagonists (H2RA) prevent histamine from binding to its receptor on the gastric parietal cell, suppressing acid production. Ranitidine increased the gastric fluid pH > 6 for a longer duration than did famotidine in one study.¹²⁶ Limited acid secretion may continue in the face of H2RA treatment, and ranitidine has been shown to be inferior to omeprazole in adult horses for treatment of ESGD.¹²⁷ Another study found cimetidine (20mg/kg PO q8h) to be less effective than omeprazole for treating ESGD in Thoroughbred racehorses in training.¹²⁸ The requirement for more frequent dosing also makes this class of drug a less appealing option in clinical practice. At present, there is no licensed equine product.

Potassium-Competitive Acid Blockers

In some people, potassium-competitive acid blockers (PCABs) such as vonoprazan and revaprazan provide an attractive alternative to proton pump inhibitors. This class of drug binds reversibly to the potassium-binding site of the H⁺/K⁺ ATPase and accumulates at a higher concentration in the parietal cell than PPIs. Other benefits include a long half-life, efficacy from the first dose, and the ability to administer the drug regardless of fed or fasted state.¹²⁹ PCABs have also been effective at treating PPI refractory GERD in people.¹³⁰ At present, there are no published studies examining the use of PCABs in horses.

Supplements

Numerous supplements are marketed for ESGD, often with limited evidence to support their use in the horse. Demonstrating the benefits of a particular supplement can be difficult as the effect may be too weak to detect in a clinical trial and reported benefits may be influenced by owner perception.¹³¹

Antacids are commonly included in commercial gastric supplements and act by buffering gastric acid. A combination of aluminium hydroxide and magnesium hydroxide increased gastric pH for up to two hours after oral administration; however, the need for such frequent dosing makes this a less practical option for prolonged acid suppression.¹³² Pectin, a gel-forming carbohydrate polymer and lecithin, an amphiphilic phospholipid, have received a good deal of attention due to their suggested ability to form a protective gel barrier within the stomach.¹³³ Their evidence for use in ESGD appears to be contradictory. Early studies showed that a pectin-

lecithin-glycerol complex (Apolectol[®]) had a beneficial effect on the healing of gastric ulcers, with horses receiving this complex showing improvement or resolution of ulceration compared to controls.¹³⁴ However, other work has found that pectin-lecithin complex failed to prevent lesions in the squamous mucosa induced by intermittent feed deprivation.^{133,135} More recent work demonstrated that a combination of Apolectol[®], live yeast and magnesium hydroxide was an effective prophylactic against ESGD.¹³⁶

A supplement containing beta glucan, saccharomyces yeast and amino acids (Succeed digestive conditioning[®]) was inferior to omeprazole when compared over a 30-day period in racehorses in training but when examined over a 90-day period, was found to be non-inferior to omeprazole.¹⁰⁴ A similar supplement containing herbs, polysaccharides, amino acids, antioxidants and probiotics (Smart Gut Ultra Pellet[®]) prevented the number of squamous ulcers from increasing in intermittently fed stabled horses following omeprazole treatment when compared to untreated controls.⁷⁸ Porcine hydrolyzed collagen enhanced the effects of omeprazole on gastric pH, inhibited gastrin secretion after feeding and resulted in fewer squamous ulcers after long term (56 days) in stall-confined horses undergoing omeprazole treatment and feed-deprivation.¹³⁷

Some studies have demonstrated a lack of efficacy of commonly used supplements. A supplement containing sea buckthorn liquid fed to horses did not show efficacy in the treatment or prevention of naturally occurring ESGD in horses.¹³⁸ Aloe vera was shown to be inferior to omeprazole for the treatment of ESGD,¹³⁹ and a Chinese herbal supplement blend (Wei le San) was no more effective than a placebo.¹⁴⁰

Dietary Modifications

The risk of developing ESGD increased when straw was the only forage available, 1 g/kg bwt of starch per meal was exceeded, water was not available in the turnout paddock, and the interval between forage feeding was <6 h.⁴⁶ A high fibre, low-starch diet had a positive outcome on gastric and fecal microbiota and promoted gastric ulcer healing in one study.¹⁴¹ Horses with ulcers were shown to have less microbiota diversity than those without and improvement in ulcer scores was associated with an increase in specific carbohydrate-utilising species and a decrease in lactate-fermenting species. Recent work showed that dietary modification played a significant role

following discontinuation of omeprazole therapy in horses with ESGD.¹⁴² Horses that were maintained on a high fibre, oil based, low starch concentrate feed remained unchanged following discontinuation of omeprazole therapy, while those that did not undergo dietary modification regressed following discontinuation of omeprazole therapy, to the point where ulcer scores did not differ from the start of treatment.

The addition of oil is commonly recommended as part of treatment for ESGD, although there is limited published evidence to support its use. Supplementation with 240 mL of corn oil, refined rice bran oil, or crude rice bran oil (0.5 to 0.6 mL/kg bwt) did not significantly alter the development of gastric ulcers in a feed deprivation model.¹⁴³ In a smaller study of four ponies, 45 mL of corn oil fed daily for five weeks caused decreased acid output and increased PGE2 and sodium output compared to those measured before corn oil supplementation, although gastroscopy was not used to assess the gastric mucosa.¹⁴⁴ A more recent study found that corn oil did not have any effect on healing in the squamous mucosa following phenylbutazone-induced ulceration.¹⁴⁵ The addition of oil may be useful in replacing calories when transitioning away from a high starch diet.

Regular feeding of concentrates using a commercially automated feeder resulted in fewer ulcer scores compared to traditional feeding,¹⁴⁶ although this involved splitting the feed into 20 aliquots over a 24-hour period, which is difficult to replicate in a practical setting. Feeding a small amount of chaff prior to exercise is commonly recommended to reduce acid splashing in the stomach, although there are no published studies investigating the effects of this.

Conclusion

Although ESGD is a common condition in the adult horse, interpretation of prevalence studies is complicated by several factors, making estimation of true prevalence challenging. The clinical significance of mild lesions remains unclear, raising the question as to whether these mild lesions represent a normal response to periodic exposure of the squamous mucosa to acid. It is difficult to define the full extent of the impact of ESGD on the equine industry, partly due to the variable nature of clinical signs and their lack of association with the presence of lesions and partly due to the inherent challenges associated with investigating poor performance in the equine athlete. Recent developments in the management

of ESGD include a long-acting intramuscular omeprazole preparation, with promising results. Evidence for the use of dietary supplements remains limited, but potassium-competitive acid blockers may represent an alternative to proton pump inhibitors in the future.

Disclosure

The authors report no conflicts of interest in this work.

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