CHAPTER 48

Gastrointestinal diseases of performance horses

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Equine gastric ulcer syndrome

- Spontaneous erosion or ulceration of the gastric mucosa represents the most important gastrointestinal disease of the athletic horse, both in terms of prevalence and economic impact. The latter is influenced not only by reduced earnings due to diminished performance, but also by the high costs associated with therapeutic and prophylactic medication.
- The pathophysiologic basis of gastric squamous ulceration in horses is multifactorial.
- The history and clinical signs of gastric ulceration in adult horses are often vague and not specific.
- The most effective treatment strategies are those that reduce gastric acidity. These include administration of antacids, H_2 receptor antagonists, or proton pump blockers.

Gastric anatomy

The horse is a hindgut fermenter with an extensive and complex cecum and large colon, but has a simple stomach similar in shape to that of domestic carnivores and omnivores. The nonglandular, squamous mucosal lining of the distal esophagus spreads through the cardia and covers the proximal half of the stomach. The margo plicatus defines the lower border of the squamous mucosa with the glandular mucosa. The glandular mucosa covers the remainder of the stomach through the antrum and down to the pylorus. Histologically the glandular mucosa is divided into three areas: the cardiac, fundic and pyloric regions. The cardiac gland region is a narrow strip of mucosa that lies immediately beneath the margo plicatus. The natural bend to the stomach permits further anatomic classification into greater and lesser curvatures.

Recognition of the disease

Equine gastric ulcer syndrome (EGUS) is not a single disease entity, but rather a term that embraces a group of distinct disorders that can affect horses of all ages.[1] These disorders include not only primary gastric disorders, but also related diseases of the distal esophagus and proximal duodenum. Many of these diseases share aspects of pathology, but likely differ widely in terms of primary pathophysiology.

1. *Neonatal gastric ulceration*. As the name indicates this syndrome is usually limited to diseased or otherwise highly stressed newborn foals. Ulceration and occasional perforation frequently, but not exclusively, occur in the cardiac gland region of the stomach. This syndrome is often clinically silent due to the coexistence of severe primary diseases such as systemic sepsis or peripartum asphyxia syndromes. The first signs may not be apparent until fatal perforation has occurred. Attenuated mucosal protection through reduced blood flow is a likely key component of the pathophysiology of neonatal gastric ulceration.
2. *Gastroduodenal ulcer disease (GDUD)*. This form of EGUS occurs primarily in suckling foals and in its most severe form involves the proximal duodenum, pylorus, stomach, and distal esophagus.[2,3] It is highly likely that the initial lesion in affected foals is a diffuse duodenitis. This initially results in a functional delay to gastric emptying with secondary gastric and esophageal irritation, probably due to prolonged exposure of susceptible mucosa to acidic luminal contents. During the healing process strictures may form in the duodenum and/or pylorus which result in a mechanical obstruction to emptying, again leading to gastric distension and secondary gastric and esophageal erosion. Of all of the forms of EGUS this syndrome is the one most likely to have a precipitating infectious

component. This is further supported by the observation that cases frequently occur in clusters and are often preceded by episodes of diarrhea. Acid suppression is a key component in the management of GDUD when delayed gastric emptying (either functional or mechanical) is present, but does not have a role in prophylaxis.

3. *Glandular ulceration*. Experimental induction of glandular ulceration is easily achieved using repeated high doses of non-steroidal anti-inflammatory drugs, such as phenylbutazone.[4] Lesions in the glandular mucosa also occur spontaneously in both athletic and non-athletic horses and often coexist with squamous mucosal lesions. They are usually seen in response to some form of stress, such as training or concurrent diseases. Glandular lesions are often associated with the most overt clinical signs of EGUS, such as postprandial abdominal pain and inappetence.
4. *Squamous mucosal ulceration*. Most discussion of ulcer disease in performance horses refers to erosion or ulceration of the squamous mucosa, the most common form of EGUS in this type of horse. The regions adjacent to the margo plicatus are most frequently diseased and are usually more prominent on the lesser curvature between the cardia and the margo plicatus.[5]

This discussion focuses on the glandular and squamous ulceration syndromes of performance horses. Readers are directed to other more general equine medicine texts for further information on neonatal cardiac gland disease and GDUD.

Clinical signs

In sharp contrast to young foals with GDUD, the history and clinical signs of gastric ulceration in adult horses are often vague and not specific. Only since the release of the 3-m endoscope has an association between signs and disease evolved. This has however been complicated by the frequent disparity between clinical signs and disease severity. It is not uncommon to observe horses with severe endoscopic lesions with no reported abnormal clinical signs. Conversely, there are horses with typical signs that have minimal changes on gastroscopy.

Probably the most common and consistent findings associated with gastric squamous ulceration are related to consumption of feed. Affected animals will typically take a longer than expected time to consume a concentrate feed and owners or trainers often report problems in achieving or maintaining body condition. More overt signs may include colic, particularly after eating. Anecdotally, horses with moderate signs of pain due to gastric ulceration commonly have glandular lesions, often around the pylorus, with or without squamous disease. This reinforces the importance of a complete endoscopic examination in animals presenting with colic in the absence of other abnormal findings.

Other reported signs consistent with ulcer disease include a rough hair coat, aggressive or nervous attitude, intermittent diarrhea, and poor performance. It is the latter sign that is most difficult to directly ascribe to gastric disease, but trainers will often report improved performance when horses are placed on antiulcer therapy.

Diagnosis

Endoscopy of the stomach is the most accurate method for establishing a diagnosis of gastric ulcer disease. This is best achieved using a 2.5- to 3-m flexible endoscope in the standing, sedated horse. The duration of fasting prior to endoscopy varies with the type of examination required. Examination of the antrum, pylorus and duodenum usually necessitates an overnight fast of 12–16 hours and withdrawal of water 1–2 hours prior to the procedure. The fasting period can be shortened to 6–8 hours if the examination is limited to the squamous mucosa. Adding air to the stomach will make the procedure easier to perform, but care should be taken not to overdistend the stomach particularly in foals and young horses. A suction system aids not only in evacuation of air at the completion of the procedure, but also to remove any excess fluid in the antrum.

A 2.5-m endoscope may not permit complete examination of the margo plicatus in large horses. This may be problematic as squamous ulceration tends to be more severe at the lesser curvature due to the greater exposure of this region to acidic fluid. The gastric squamous mucosa is scored using a simplified system that ranges from 0 to 3.[1] Examples are included in Fig. 48.1. Lesions are graded as follows: Grade 0, intact mucosal epithelium with or without reddening or hyperkeratosis; Grade 1, single or multiple small ulcers; Grade 2, single or multiple large ulcers; and Grade 3, extensive ulceration with coalescing of ulcerated areas. A modified system was recently published to categorize lesions of the squamous mucosa, glandular body of the stomach, antrum, pylorus, and duodenum.[6] The authors used the following 0–4 scoring system: Grade 0, intact epithelium with no apparent mucosal changes; Grade 1, mucosal reddening or squamous hyperkeratosis; Grade 2, small single or multifocal lesions; Grade 3, large single or multifocal lesions or extensive superficial lesions; and Grade 4, extensive lesions with apparent deep ulceration.

In other species, elevations in the serum concentration of pepsinogen have been observed in association with ulcerative diseases of the stomach and duodenum. Pepsinogen is converted to pepsin by autocatalytic activation under acidic conditions. Although equine pepsinogen has been isolated and appropriate assays developed, no such association has been published to date in adult horses.[7,8] Serum levels in foals with confirmed or suspected gastric or duodenal ulcers were significantly greater than serum pepsinogen levels in apparently healthy age-matched foals.[9]

Indirect methods of diagnosis include recognition based on clinical signs, although the vague nature of these signs can be problematic, and through response to treatment. Given the expense of treatment and the difficulty in evaluating improvement associated with therapy it is often more economical to perform gastroscopy.

Treatment

As discussed below, the pathophysiologic basis of gastric ulceration is likely multifactorial. Despite the apparent complexity of the disease the role of gastric acidity appears to be

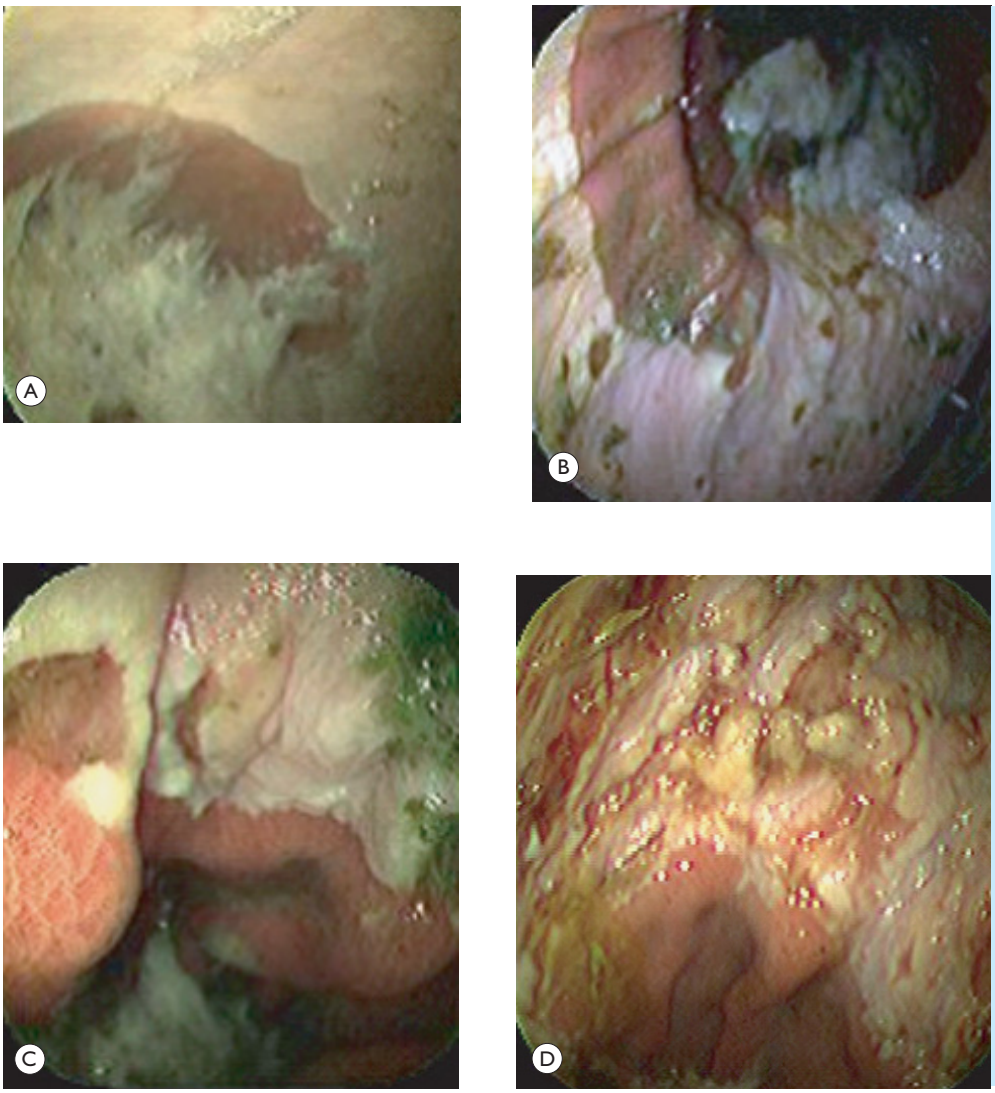

Fig. 48.1
Gastric ulcer scoring system.(A) Grade 0: Intact mucosal epithelium with or without reddening or hyperkeratosis. (B) Grade 1: Single or multiple small ulcers. (C) Grade 2: Single or multiple large ulcers. (D) Grade 3: Extensive ulceration with coalescing of ulcerated areas.

pivotal. Consequently, the most effective treatment strategies are those that reduce gastric acidity. These include administration of antacids, H_2 receptor antagonists, or proton pump blockers.

Antacids are most commonly used to provide temporary symptomatic relief from ulcer disease. They are used in relatively large volumes (240–360 mL) to improve appetite, feed consumption, and athletic performance in affected horses. Unfortunately, the effect of antacids is short-lived necessitating frequent treatment (q 2–6 hours) if ulcer healing is required. The oral administration of 30 g of aluminum hydroxide and 15 g of magnesium hydroxide resulted in a mean hourly gastric pH ≥ 4.0 for at least 120 minutes in one study.[10] A cautionary note: antacids reduce the bioavailability of many concurrently administered oral medications.

Histamine type-2 receptor antagonists have been widely used in equine practice to successfully treat and prevent gastric ulceration.[11,12] These drugs block histamine binding to receptors on the parietal cell. The duration of action is dependent on plasma levels, but is generally between 2 and 8 hours. Bioavailability of H_2 receptor antagonists is relatively poor and variable between animals; approximately 27% for ranitidine in adult horses[13] and between 7 and 22% for cimetidine.[14] The recommended oral dose for ranitidine is 6.6 mg/kg q 8 hours in the adult horse. Response data derived from healthy neonatal foals indicates that a dosing interval of 12 hours may be adequate in that age group.[15] The reported recommended dose of oral cimetidine in the literature is highly variable. Most veterinarians are using a total daily dose of 60–100 mg/kg divided and administered three to four times daily. Famotidine has been evaluated in adult horses, but further studies are required in order to characterize an optimal dose rate for acid control.[16] A dose of 2 mg/kg bodyweight was effective at significantly elevating the intragastric pH.

Proton pump blockers are effective at increasing intragastric pH and healing gastric ulcers in adult horses.[17–22] These drugs irreversibly bind parietal cell H^+-K^+-ATPase, the 'proton pump' responsible for H^+ secretion. Omeprazole is the most commonly prescribed proton pump blocking agent in

horses. The drug is well absorbed and at recommended doses will suppress acid production for approximately 24 hours. The recommended therapeutic dose rate of commercial omeprazole paste (GastroGard (USA) and GastroShield (Australia), Merial, Ltd) is 4 mg/kg bodyweight once daily. A dose of 1 mg/kg bodyweight daily has been recommended for the human preparation of omeprazole, a 20-mg capsule of enteric-coated granules.[23] Omeprazole paste has been shown to not only heal squamous mucosal ulcers, but also to maintain healing in Thoroughbred race horses maintained in active training.[19]

The effect of H_2 receptor antagonists and proton pump blockers on gastrin levels requires further investigation in horses. The secretion of gastrin is inhibited by gastric acid, therefore treatments that reduce acid secretory responses increase gastrin release and increase enterochromaffin-like (ECL) cell numbers. The prolonged usage of acid-suppressing drugs has been linked to the development of ECL cell tumors, although direct causal data are lacking.[24] Of more practical concern is the possibility of rebound hypersecretion of acid after withdrawal of acid-suppressing therapy.

Additional strategies involved in antiulcer therapy include coating of the ulcer with an acid-resistant compound and simulating or supplementing protective prostaglandins. The use of sucralfate – a polysulfated sugar (sucrose octasulfate) combined with aluminum hydroxide – in horses is controversial.[25,26] Anecdotal evidence suggests that sucralfate can be an important adjunct in the management of glandular ulcers. Sucralfate has a number of potentially beneficial properties, including binding to exposed gastric mucosa, stimulating mucus production and local prostaglandin synthesis, and improving mucosal blood flow. An effective dose rate has not been determined; commonly quoted dose rates range between 10 and 20 mg/kg bodyweight given orally every 6–8 hours. Additional problems associated with sucralfate administration include interference with the absorption of other drugs (e.g. certain antibiotics and H_2 receptor antagonists) and the requirement for an acid medium for maximum efficacy. As a result of the latter problem, most clinicians dose the drug 60 minutes prior to the administration of acid-suppressing agents.

Prostaglandin replacement therapy is often considered in animals undergoing prolonged therapy with non-steroidal anti-inflammatory agents and in those experiencing high levels of physiologic stress. Direct replacement with a PGE_2 analog, such as misoprostol, is costly and has been associated with undesirable gastrointestinal side effects (diarrhea and colic). Reported dose rates range between 1.5 and 2.5 μg/kg bodyweight every 8 hours. An indirect method of supplementing PGE_2 centers on feeding linoleic acid in the form of corn oil. Supplementation at a rate of 20 mL/100 kg bodyweight significantly increased PGE levels in the gastric fluid of cannulated ponies (AM Merritt, personal communication).

Etiology and pathophysiology

The pathophysiologic basis of squamous ulceration is likely multifactorial. A simplistic approach is to conclude that erosions or ulcers occur when there is an imbalance between ulcerogenic factors, such as the presence of hydrochloric acid, pepsin, or bile salts, and mucosal defense mechanisms. The glandular mucosa requires an extensive defense system because it is constantly exposed to acidic luminal contents. Prostaglandins, particularly PGE_2, play a key role in glandular mucosal defense through a number of mechanisms, including promotion of effective mucosal blood flow, increased mucus and bicarbonate secretion, supporting epithelial cell restitution, and by reducing acid output. The importance of homeostatic prostaglandins is clearly demonstrated through the experimental induction of glandular ulcers using NSAIDs.

The stomach is covered by a continuous layer of viscoelastic mucus.[27,28] This layer acts as the primary physical barrier to luminal contents. The gastric mucus covering the glandular stomach is actually made up of overlapping layers of mucin secreted by highly specialized cells of the glandular mucosa. Luminal acid, bradykinin and PGE_2 all increase the thickness of the mucus layer.[27] Within the mucus barrier is a pH gradient that varies from around 1.0 at the luminal surface to 7.0 pH units at the mucosal junction. Active mucosal secretion and entrapment of bicarbonate (HCO_3^-) within the mucus barrier is the primary factor responsible for the gradient. Bicarbonate secretion is enhanced during acid secretion through a process referred to as the 'alkaline tide'.[28] Briefly, within the parietal cell 1 mole of HCO_3^- is produced for each mole of H^+. The HCO_3^- is transported across the basolateral surface of the parietal cell in exchange for Cl^-. The HCO_3^- is subsequently transported via the local vascular supply to the epithelial cells where it is excreted. Acidic luminal contents provide the primary stimulus for bicarbonate secretion.[27] Sympathetic stimulation, mediated primarily through α_2-adrenoreceptors, is inhibitory to gastric and duodenal bicarbonate secretion.[28] This may be an important mechanism whereby stress can lead to reduced mucosal defense and ulceration.

Acid secretion

The horse stomach is similar to that of most other mammals in that it is capable of secreting large volumes of 0.16 N hydrochloric acid.[29] The acid is produced by gastric parietal cells located in the oxyntic glands of the glandular mucosa. The mucus layer that prevents the luminal contents from coming into direct contact with the epithelial surface does not impede the transport of acid or pepsin from the crypts into the gastric lumen.[28] The secreted hydrogen ions travel through small channels within the mucus gel created by hydrostatic pressure with the glands.

Acid secretion is regulated both centrally and peripherally, but it is the latter that has been the primary focus for pharmacologic control. The key local stimuli of acid secretion are acetylcholine, histamine, and gastrin. Acetylcholine release from postganglionic fibers at the level of the fundic mucosa directly binds to muscarinic receptors of the M_3 subtype.[30] Equally or more importantly acetylcholine also stimulates local ECL cells to release histamine, which subsequently bind

with histamine type 2 (H_2) receptors on the parietal cell, causing acid release.[29] Acetylcholine can also indirectly stimulate ECL cells through augmentation of gastrin release from G-cells. It does this by directly acting on G-cells and also by inhibiting the release of somatostatin from D-cells.[29]

ECL cells are small cells that lie subepithelially, and are therefore not directly exposed to luminal contents. The cells contain numerous cytoplasmic vesicles and function to synthesize, store and release histamine. Histamine release from ECL cells is stimulated by gastrin, acetylcholine, and β-adrenergic agonists. Release is inhibited by somatostatin and by histamine itself, through an autocrine feedback mechanism. Gastrin is a long-recognized acid secretagog and acts directly on the ECL cells by binding to the cholecystokinin B subtype (CCK_B) receptor to cause histamine release. Gastrin also has a hypertrophic and hyperplastic effect on ECL cells, as well as a key role in regulating the relative proportions of different gastric epithelial cell types, including stimulation of parietal cell differentiation.[31] In contrast to ECL cells, the gastrin-producing G-cells do have direct contact with gastric contents. A number of factors are known to regulate gastrin release, acting at either the luminal or basolateral surfaces of the G-cell. These include acetylcholine, gastrin-releasing peptide, somatostatin, and the chemical effects of luminal contents. The known luminal stimuli of gastrin release include amino acids (particularly aromatic amino acids), dietary amines, and calcium.[31] Gastrin is also released in response to sham feeding, oropharyngeal stimulation, and gastric distension. The pH of gastric contents has an important effect on gastrin, such that release is inhibited when the luminal pH is less than 3. This probably occurs indirectly through the paracrine release of somatostatin and provides an important feedback mechanism for parietal cells. Gastrin is considered to be a true peptide hormone in that it travels to target tissues via the blood. The hormone can therefore be measured in peripheral blood. The application of kits used to measure human gastrin in horses has been questioned as antisera raised against human gastrin binds poorly to equine gastrin.[32,33] Consistent with data derived from other species, serum gastrin levels in horses were increased after meal feeding.[34,35] The magnitude of the postprandial increase was also greater in treadmill-conditioned animals. These factors could provide a basis for the increased prevalence of squamous ulcers in Thoroughbreds in race training. Gastric distension in response to abdominal disease in horses also resulted in a significant increase in serum gastrin levels.[36]

Somatostatin is released from enteric fibers as well as fundic and antral D-cells. Somatostatin has a variety of functions in the stomach, one of which is inhibition of gastrin release from G-cells. Administration of the somatostatin analog, octreotide, at doses between 0.1 and 5 μg/kg bodyweight to healthy ponies resulted in a significant increase in intragastric pH that was sustained for between 2.4 and 5.4 hours.[37]

On the cellular level acid secretion from the parietal cell involves an elevation of intracellular calcium and cAMP, followed by activation of protein kinase cascades, which in turn trigger the translocation and insertion of the proton pump enzyme, H^+-K^+-ATPase, into the apical membrane of the cell.[38] After insertion the apical membrane opens up potassium and chloride ion conductance pathways. The H^+-K^+-ATPase enzyme catalyzes the electroneutral exchange of intracellular protons for extracellular potassium ions, thereby generating the proton gradient associated with HCl secretion.[38]

The parietal cell has a number of probable receptors, including those for histamine (H_2 receptor), acetylcholine (M_3 receptor), gastrin (CCK-B receptor), somatostatin, prostaglandins, and epidermal growth factor.[29,38] The latter three are thought to be inhibitory to the parietal cell.

Enterogastric reflux

Evidence exists to support a role of enterogastric reflux in gastric homeostasis. Visual inspection of the pylorus during routine gastroscopy in fasted horses frequently reveals entry of bile-colored fluid from the duodenum into the antrum. Bile salt concentrations obtained from the stomach of fasted horses with gastric cannulas averaged 0.23–0.44 mmol/L with some samples approaching 1.0 mmol/L.[39] Other investigators have measured intragastric concentrations of bile acids up to 2–3 mmol/L (AM Merritt, personal communication). Concentrations in fed animals are lower, usually less than 0.2 mmol/L.[39]

The importance of enterogastric reflux in the pathogenesis of squamous ulcer disease is not clear. Bile salts, such as taurodeoxycholate, have been incriminated in the pathophysiology of gastro-esophageal reflux disease (GERD) in people.[40] Several groups have demonstrated a harmful effect of bile acids on squamous mucosa in the presence of a low pH.[39–42] At a pH below their p*K*a bile acids are mostly non-ionized and insoluble, permitting mucosal uptake and damage. At a low pH (1.7 pH units) high concentrations of taurocholate (2.5 mmol) failed to cause additional damage to equine squamous mucosa above that induced by acid alone.[43] At a neutral intragastric pH bile acids are predominately ionized and remain in the gastric lumen. In vitro experiments have confirmed that bile acids at a neutral pH have no deleterious effect on the bioelectric properties of equine gastric squamous mucosa.[39,43]

Alternatively, the frequent refluxing of duodenal contents into the stomach may provide protection against mucosal ulceration or erosion by acting as a buffer. The continuous measurement of intragastric pH from healthy horses often reveals periodic and sudden elevations in pH. These pH shifts often occur at 15- to 30-minute intervals and are seen in both fed and fasted states. It is likely that these increases reflect enterogastric reflux of bicarbonate-rich fluid, rather than any abrupt cessation to local acid production.

Epidemiology

There is little doubt that the importance of gastric squamous ulceration has increased with the advent of 2.5-m and 3-m flexible videoendoscopes. These endoscopes have given us a

clear understanding of the prevalence of ulceration across a variety of horse types and activities. A number of important, albeit unexpected, observations have been made with respect to the prevalence of equine gastric squamous ulceration. For example, squamous ulceration occurs commonly (up to 50%) in young suckling foals in the absence of clinical signs and heals spontaneously without medication.[2]

Squamous mucosal ulceration has also been frequently reported in adult horses but the prevalence is dependent on a range of factors that include activity type and level, feed intake, management (diet, housing), and the presence of clinical signs compatible with ulcer disease.[5,6] Reported rates of disease frequently range between 50 and 90%, with horses in race training carrying the greatest risk of squamous mucosal ulcer disease (80–90%).[5,6,44] In this group the severity of disease usually increases as the intensity of training increases. By contrast, horses that are pastured and have limited controlled exercise are usually free of squamous ulcers.

The prevalence of gastric glandular ulceration is also greater in exercising horses, but the frequency of lesions is usually less than that reported in the squamous mucosa. In a retrospective study of 162 horses squamous ulceration was observed in 58% of animals.[6] By contrast, erosions and ulcers in the body of the glandular region were seen in only 8% of animals. Interestingly, antral and pyloric lesions were again noted in 58% of horses, but the authors could not find any association between sites with respect to either the presence or severity of lesions.

Role of feed and diet composition

The association between race training and gastric squamous ulceration has frequently led to speculation that diet may be a critical factor in the development of ulcer disease. Animals in race condition commonly receive high caloric diets, rich in concentrates and low in roughage.[5] Potentially ulcerogenic short chain volatile fatty acids (VFAs) are produced in the stomach from fermentable carbohydrates through the action of resident bacteria.[45] In the acidic conditions of the equine stomach these VFAs often exist in non-ionized forms and consequently are likely to penetrate and damage squamous epithelial cells.[46] The addition of the short chain fatty acid, acetate, to the mucosal side of isolated porcine gastric squamous epithelium in the presence of a low pH, resulted in reduced tissue electrical resistance consistent with damage to the mucosa.[41]

In a study using similar methodology on harvested equine gastric squamous mucosa the authors concluded that butyric, propionic, and valeric acid, but not acetic acid, were identified as potential ulcerogenic VFAs in that species.[47] This finding prompted the same group of investigators to examine the effect of diet on gastric squamous epithelium ulceration using healthy mixed breed horses with surgically implanted gastric cannulas.[46] The two diets contrasted in the experiment were a grass hay (bromegrass) diet and a combination of legume hay (alfalfa) and grain. In an unanticipated outcome, the number and severity of squamous ulcers were greater in horses that received the grass hay only diet. This was associated with a lower postprandial intragastric pH, and lower concentrations of acetic, propionic, valeric and isovaleric acid, and higher concentrations of butyric acid in animals that received the bromegrass hay. The authors suggested that the high calcium and/or protein content of the alfalfa and grain diet could have provided a protective buffer to the gastric contents. Alternatively, the transient postprandial increase in butyric acid with the grass hay diet may have been injurious to the squamous mucosa, particularly in light of the group's in vivo finding and documentation of a falling postprandial intragastric pH. These results further support the contention that gastric acidity may be a critical factor in the development of gastric ulceration.

Feeding frequency has an important impact on gastric squamous ulceration. Murray and Eichorn demonstrated that squamous ulceration could be induced in normal adult horses by alternating 24-hour periods of feed deprivation and ad libitum access to hay over an 8-day period.[11] Changes occurred rapidly and were usually apparent within 24–48 hours of cumulative feed deprivation. Feed deprivation results in increased gastric acidity.[48] The median intragastric pH during a 24-hour period with ad libitum access to grass hay was 3.1 pH units. Feed deprivation in the same group of healthy horses was associated with a lower median intragastric pH of 1.6. The common conclusion of these studies is that gastric acidity is the primary mechanism responsible for squamous ulcer disease.

The feed deprivation model for induction of squamous ulcer disease does not appear to result in glandular lesions.[6] This is not an unexpected finding in that the glandular mucosa is better suited to acid resistance, through a variety of mechanisms including secretion and maintenance of mucus-bicarbonate layer and mucosal blood flow.

Exercise

The prevalence data support a strong link between exercise and gastric ulceration. Using a barostat system, investigators recently measured the change in gastric volume in response to feeding and exercise.[49,50] Gastric volume was abruptly and significantly reduced during treadmill exercise in healthy horses. The authors concurrently measured intra-abdominal pressure and concluded that exercise-induced increases in intra-abdominal pressure were likely responsible for the observed reduction in gastric volume. The decrease in volume resulted in greater exposure of the squamous mucosa to the acidic contents of the ventral or dependent area of the gastric lumen.[49] The significance of these findings with respect to ulcer development is yet to be fully elucidated, particularly as the duration of exercise is often limited to minutes each day.

A further consideration is the effect of exercise on antroduodenal motility and gastric emptying. Data derived from human athletes indicated that exercise can delay gastric emptying.[51] Similar data are not available from horses, but it would not be unreasonable to assume that upper gastrointestinal tract motility was attenuated in exercising horses.

Stress

Diminished mucosal defenses associated with physiologic stress are thought to play an important role in the development of glandular lesions in humans. Similar mechanisms are likely responsible for glandular lesions in sick adult horses and newborn foals. It is highly unlikely that physiologic stress has a direct negative effect on squamous mucosa. By contrast, the role of psychologic stress in EGUS is not clear. Several studies have reported a higher prevalence of ulceration in horses that appeared to be more anxious or nervous, though differences were not great.[44,52] It has been hypothesized that horses of a nervous disposition may have reduced gastric volume in response to persistent tension of their abdominal muscles. This presumptive elevation in intra-abdominal pressure may force acidic contents into the dorsal region of the stomach (see above).

Housing

Simply relocating horses from pasture to a stall environment can induce gastric squamous ulcer disease.[11] Lesions are apparent within 7 days of the change. This occurs despite allowing free and continual access to grass hay. There could be a number of factors responsible for the increased incidence after confinement, including changes in diet and exercise, and induction of psychologic stress.

Right dorsal colitis

- An ulcerative syndrome of right dorsal colitis (RDC) that is associated with non-steroidal anti-inflammatory drug use, most commonly phenylbutazone.
- The clinical signs of RDC are variable depending on the duration and severity of the underlying colonic lesion, but include colic, weight loss, poor hair coat, diarrhea, reduced feed intake, and dependent edema.
- Both surgical and medical treatments have been utilized in the management of RDC. Surgery is usually performed on horses with narrowing of the right dorsal colon and correction involves surgical bypass or resection of affected tissue. Conservative medical management includes dietary control, medications, and avoidance of NSAIDs.

Recognition of the disease

Clinical signs

The clinical signs of RDC are variable depending on the duration and severity of the underlying colonic lesion. Commonly reported clinical signs include colic, weight loss, poor hair coat, diarrhea, reduced feed intake, and dependent edema. Signs of abdominal pain are often mild, but recurrent. The exception is horses where colonic stricture has occurred as a chronic response to persistent inflammation.[53] These horses often present with moderate and persistent pain due to impaction of proximal colonic segments and require surgical exploration or euthanasia. The diarrhea is highly variable in terms of volume and consistency, but is often of normal volume and soft, but formed consistency. The edema is due to hypoproteinemia secondary to loss across the inflamed and ulcerated colonic mucosa. The edema is most prominent in dependent regions including the ventrum, prepuce, distal limbs, and muzzle. In most horses with RDC dependent edema is absent or mild.

It is not uncommon for persistently affected animals to have flare ups of clinical signs. During these episodes horses may be febrile and colicky with diarrhea. The fever is likely due to the absorption of luminal toxins across the compromised mucosa.

Diagnosis

The diagnosis of right dorsal colitis is most commonly based on clinical signs, laboratory data, and a history of non-steroidal anti-inflammatory usage. Hypoproteinemia, specifically hypoalbuminemia, is the most characteristic laboratory finding in horses with RDC. Peripheral leukocyte changes are variable, and total white cell counts may be decreased, normal, or elevated. The count reflects the stage and severity of colitis at the time of sampling, and frequently, during acute exacerbations of the disease, there may be endotoxemia with resultant leukopenia with neutropenia, left shifting, and toxic neutrophil changes. As the disease progresses the total white cell count is commonly in the upper normal range or is mildly increased. Mild hyperfibrinogenemia is a common feature of RDC.[53] There may be a range of other biochemical and electrolyte abnormalities, but none is specific for RDC. Commonly reported derangements include hypocalcemia, hypophosphatemia, hyperbilirubinemia, and azotemia. Many abnormalities are attributable to a combination of mild dehydration and reduced feed intake.

Ultrasound may be a useful diagnostic aid although sensitivity and to a lesser extent specificity data are lacking. The colon on the right side of the abdomen may appear thickened with a distinctive hypoechoic line caused by edema formation. In some cases ultrasound is also used to assess disease progression and response to therapy. Recently, the use of ^{99m}Tc-HMPAO-labeled white blood cells in establishment of a diagnosis of RDC was described.[54] The authors reported linear uptake of radiolabeled white cells in the right craniioventral abdomen at 20 hours postinjection in two horses with RDC. The technique is clearly limited to referral practices with access to appropriate nuclear medicine facilities.

Treatment

A range of surgical and medical methods have been utilized in the management of RDC.[53,55–57] Surgery is usually performed on horses with narrowing of the right dorsal colon and correction involves surgical bypass or resection of affected tissue. Many cases have been successfully managed

conservatively, through a combination of dietary control, medications, and avoidance of NSAIDs.

Dietary management of RDC is aimed at minimizing the mechanical load on the colon.[55,57] This is achieved primarily by reducing the volume of long-stem roughage. Successful management often involves feeding of a complete pelleted ration, that is, a processed feed that contains both concentrates and fiber (roughage). If such a feed is not available or is not readily eaten then roughage is best provided in the form of frequent but brief access to pasture. Supplemented concentrates should be offered as frequent, small feeds. Psyllium mucilloid (30–100 g daily) has been fed to horses with RDC to aid in mucosal healing. The theoretic basis of psyllium supplementation is as a prebiotic, to promote the numbers of healthy bacteria that may facilitate mucosal healing, and to alter the concentration of luminal short chain acids to favor a ratio of acids that accelerate mucosal healing.[55,58] Feeding of psyllium is usually recommended for a minimum of 12 weeks after the diagnosis has been established.

The addition of linoleic acid, usually in the form of corn oil, to the diet of affected animals has been commonly advocated as a preventative strategy against gastric glandular ulceration in animals maintained on high doses of NSAIDs. Linoleic acid is a precursor of eicosanoids, such as PGE_2, and therefore may promote mucosal defensive mechanisms and aid in healing. An additional benefit of oil is the provision of calories, absorbed predominately in the small intestine.

Drug therapy in the management of RDC is controversial. Metronidazole has been used in many cases based on data derived from other species where certain intestinal obligate anaerobic bacteria, such as *Bacteroides vulgatus*, perpetuated the development of colitis.[59] Metronidazole also has anti-inflammatory effects and protects against the uncoupling of mitochondrial oxidative phosphorylation caused by NSAIDs.[60]

Sucralfate has been used in the management of RDC despite very little supportive data. Justification for use in colonic disease is based on limited cost, oral administration, an apparent absence of side effects, and limited efficacy data derived from humans.

There are a number of other drugs that have theoretical use in the management of RDC in horses, based on efficacy in the management of inflammatory bowel disease (IBD) in humans.[61] Pentoxifylline and thalidomide have anti-tumor necrosis factor alpha (TNF-α) effects that are of benefit, given the pivotal role of TNF-α in IBD. It is not known whether this cytokine plays a role in perpetuating the inflammation in RDC.

The avoidance of NSAIDs is often highly problematic in horses with RDC. This is particularly true for those with intermittent abdominal pain associated with the disease. If necessary, attending veterinarians should aim to minimize dosing and maximize interval times between doses. Preference is usually given to flunixin over phenylbutazone, but all drugs of this type should ideally be avoided. The other common circumstance of continued use involves persistent skeletal problems. Phenylbutazone is particularly attractive to horse owners because it is cheap, easy to administer, and effective. The development of RDC appears to be an idiosyncratic response to phenylbutazone in many horses, and as such, even infrequently administered small doses of the drug may be detrimental.

It has also been recommended to reduce physical and physiological 'stress' in animals to facilitate healing.[57] It is particularly important to ensure that rehabilitating animals are not exposed to episodes of dehydration. This means avoidance of forced exercise and unnecessary transportation.

A positive response to treatment can be gauged by an improvement in clinical signs, normalization of circulating protein concentrations, and a reduction in bowel wall thickness on ultrasound. Improvement is gradual, usually over 4–8 weeks, and it may take months to normalize many of these parameters. Animals are at risk of relapse, particularly in response to dietary changes and/or administration of NSAIDs.

Pathophysiology

The pathophysiologic basis of RDC remains to be fully elucidated. The adverse effects of NSAIDs on the gastrointestinal tract are however well described across a wide range of species.[62] Most of these are ascribed to the suppression of protective endogenous prostanoids, particularly PGE_2, and result in mucosal erosion or ulceration. Excessive doses of NSAIDs reliably produce gastric glandular ulceration in normal horses, but member drugs do so with differing potencies.[63,64] The variability between drugs with respect to adverse side effects is likely due to their relative inhibition of cyclooxygenase I or cyclooxygenase II isoenzymes.[65] Ulcerative lesions involving the right dorsal colon have also been induced experimentally in normal horses by giving 6 g of phenylbutazone daily for 5 days in the face of reduced access to water.[56] The susceptibility of the right dorsal colon over other regions of the colon has been the focus of much discussion. An inflammatory disease of the colon has also been described in humans associated with the administration of NSAIDs.[66]

Both phenylbutazone and indometacin influence in vitro ion transport in tissues collected from the right dorsal colon.[67] The primary effect is likely mediated by prostaglandins as changes were reversed when PGE_2 was added to the bathing media. There was a strong association between prostaglandin supplementation and chloride and bicarbonate secretion. The authors reported that the major histologic lesion induced by phenylbutazone was consistent with the induction of apoptosis.[67]

Salmonella species have been isolated from the feces of animals with RDC, raising the possibility of a direct causal relationship. Given that the recovery of *Salmonella* is uncommon in horses with suspected RDC, and that the organism is often shed by small numbers of healthy animals, this association remains doubtful.[57]

Epidemiology

The ulcerative syndrome of right dorsal colitis (RDC) is associated with non-steroidal anti-inflammatory drug use, most com-

monly phenylbutazone. Most cases are reported to occur after prolonged or excessive courses of the drug, but some have occurred in horses that have received appropriate doses of phenylbutazone for as little as 3–5 days.[55,56] Although uncommon, RDC has been reported after the administration of other anti-inflammatory drugs, such as flunixin meglumine.

Cecal emptying defect

- Cecal emptying defect (CED) is a primary motility disease involving the cecum or ileocecocolic region.
- The pathophysiology of CED is not known, but the syndrome may best mimic postoperative ileus in humans, which is considered a large intestinal disorder.
- Clinical signs are often subtle unless cecal perforation has occurred.
- Management of CED includes fluid therapy in combination with lubricants or laxatives, such as mineral oil or magnesium sulfate, and careful use of anti-inflammatory drugs.

Recognition of the disease

Clinical signs

Clinical signs are often subtle unless cecal perforation has occurred. In horses with CED after anesthesia evident signs are usually apparent 3–5 days after the procedure; early signs include depression and a reduction in both feed intake and fecal output. Ineffective emptying results in overfilling of the cecum with moist contents, which is manifest by signs of mild to moderate colic. Cecal distension with digesta can be palpated rectally in horses with advanced cecal dysfunction. If recognized late or untreated the cecum may rupture resulting in fatal peritonitis.

Treatment

Fluid therapy is an important component in the management of CED, usually in combination with lubricants or laxatives, such as mineral oil or magnesium sulfate, and with careful use of anti-inflammatory drugs. Horses with primary cecal impaction or impaction secondary to an emptying defect frequently require surgery in order to prevent fatal rupture. The surgical management of these cases is controversial and may include typhlotomy alone, typhlotomy with a bypass procedure such as ileocolic or jejunocolic anastomosis, or a bypass without typhlotomy.[68] Most horses that undergo simple typhlotomy have an uneventful recovery,[69] although a small number will reimpact and require a second laparotomy. The use of prokinetics in the prevention and treatment of CED is also controversial. Intravenously administered erythromycin lactobionate (1.0 mg/kg i.v.) hastens cecal emptying in normal animals and induces colonic MMC-like activity across the colon.[70] Administration is often associated with defecation and abdominal discomfort. The drug may be helpful at preventing cecal impaction in horses after anesthesia, though its effectiveness on cecal motility in the immediate postoperative period may be reduced.[71] High doses, constant infusion or prolonged use of erythromycin induces receptor downregulation and inhibition of activity. Erythromycin can induce diarrhea in adults therefore dosing over many days should be avoided. Other drugs that may be useful include bethanechol, lidocaine (lignocaine), or yohimbine, although efficacy data are lacking.[72]

Pathophysiology

The pathophysiology of CED is not known, but the syndrome may best mimic postoperative ileus in humans, which is considered a large intestinal disorder. An important difference in horses is that laparotomy is a rare predisposing factor, and most cases occur in horses undergoing routine extra-abdominal surgical procedures. General anesthesia itself is a potent inhibitor of gastrointestinal motility in horses, but these effects are short-lived and reversible within hours of anesthetic withdrawal.[73] The return of normal motility in horses after experimental ileus was most delayed in the cecum, suggesting that this may be a common site of ileus in horses.[71] A link between routine postoperative medications, such as phenylbutazone and aminoglycoside antibiotics, has been suspected but not established. An inhibitory effect of NSAIDs on large colon contractility has been demonstrated using in vitro techniques.[74] Primary sympathetic overstimulation could be involved as many of the affected animals are young, male horses, or animals with painful diseases. The development of small intestinal postoperative ileus but not cecal emptying dysfunction, is influenced by the duration of surgery.[75,76]

Epidemiology

Cecal emptying defect (CED) is a primary motility disease involving the cecum or ileocecocolic region.[76–78] The syndrome occurs sporadically, but anecdotally appears to be more prevalent in young athletic horses. Most cases are reported after general anesthesia and extra-abdominal surgery, particularly orthopedic and upper airway procedures. Others occur spontaneously, often in animals with painful primary conditions such as uveitis or septic tenosynovitis.

Stress-associated diarrhea

Diarrhea occurs commonly in certain animals when placed under stressful conditions. These include transportation, placement into a foreign environment, exposure to unknown animals, or associated with moderate to heavy exercise. The intermittent nature of the diarrhea, coupled with an absence of abnormal clinical findings, likely reflect a physiologic rather than pathologic basis. In any animal exposure to hostile condi-

tions initiates a stress response that comprises alterations in behavior, autonomic function, and the secretion of multiple hormones.[79] The latter includes increased secretion of epinephrine (adrenaline) and norepinephrine (noradrenaline), the release of corticotropin-releasing factor (CRF) and vasopressin, and the secretion of adrenocorticotrophin (ACTH).

Corticotropin-releasing factor is the neurohormonal factor of greatest interest with respect to stress-induced alterations in colonic motility. The central release of CRF acts in the brain to inhibit gastric emptying; while CRF-induced modulation of parasympathetic outflow stimulates colonic motility and fecal excretion in response to psychologic stress.[80] Hypersecretion of CRF may contribute to stress-related exacerbation of irritable bowel syndrome in man.[80] Similar neurohormonal responses to stress have not been reported in horses, although exercise in conditioned horses was not associated with significant increases in CRF levels collected from pituitary venous blood.[81]

Treatment is rarely indicated in horses with stress-associated diarrhea as the volume of diarrhea rarely results in clinical dehydration. Novel treatments for irritable bowel syndrome in humans include tachykinin receptor antagonists, 5-HT_3 receptor antagonists, and 5-HT_4 agonists, but none of these agents has been evaluated clinically in horses.

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