Rethinking equine gastric ulcer syndrome: Part 2 – Equine squamous gastric ulcer syndrome (ESGUS)

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Summary
It has recently been highlighted that significant differences in prevalence, risk factors and the response to treatment exist between ulceration of the squamous gastric mucosa and ulceration of the glandular gastric mucosa in the horse. In the first article in the series, the term equine squamous gastric ulcer syndrome (ESGUS) was used to describe disease of the squamous gastric mucosa with clinical signs and diagnosis discussed. The purpose of this article is to review the pathophysiology, risk factors, prevalence, treatment and prevention of ESGUS.

Introduction
Ulceration of the squamous mucosa of the horse has been recognised as a highly prevalent condition for nearly 30 years (Hammond et al. 1986) and numerous studies have investigated the factors that contribute to the development of disease, its prevalence, risk factors, treatment and prevention. The term equine squamous gastric ulcer syndrome (ESGUS) was proposed in the first article of this series to describe disease of the squamous mucosa (Sykes and Jokisalo 2014). It is recognised that, under the term ESGUS, further distinction into primary and secondary squamous disease is warranted as discussed below.

Pathophysiology
Horses are constant secretors of gastric acid (Campbell-Thompson and Merritt 1987) and the median pH of the ventral stomach of 3.0 over a normal 24 h period reflects this (Husted et al. 2008). Under normal conditions the consumption of roughage creates a basketball-sized bolus of feed in the stomach that acts as a buffer to absorb gastric acidity. As a result the gastric pH at the level of cardia has a median value of approximately 7.0 (Husted et al. 2008).

Squamous ulceration occurs, fundamentally, as a result of increased exposure of a tissue with limited defence mechanisms to highly acidic gastric contents (Lorenzo-Figueras and Merritt 2002). Endogenous production of hydrochloric acid is likely the dominant aggressive agent, as discussed below, although duodenal bile salts may also play a role (Berschneider et al. 1999). Any disruption of the normal stratification of gastric pH results in an increased risk of ESGUS and damage occurs rapidly with evidence of acid injury evident within 30 min of exposure in vitro (Widenhouse et al. 2002). The fermentation of short-chain fatty acids consumed in the diet are likely also to contribute to squamous mucosal injury (Nadeau et al. 2003). However, the high rate of ESGUS healing observed with omeprazole treatment, and in the absence of risk factor reduction, (Murray et al. 1997; Andrews et al. 1999b; MacAllister et al. 1999; Doucet et al. 2003; Lester et al. 2005; Sykes et al. 2014b, 2014d) provides indirect evidence that gastric acid is the dominant erosive agent and that the role of short-chain fatty acids and duodenal bile salts are likely to be less important.

Equine squamous gastric ulcer syndrome can occur as a primary disease in otherwise healthy animals, primarily associated with management impositions as discussed below, or as a secondary disease consequent to the delayed gastric outflow. While both ESGUS and EGGUS (equine glandular gastric ulcer syndrome) are common in certain populations, such as Thoroughbred racehorses, (Begg and O’Sullivan 2003; Sykes et al. 2014b), no relationship exists between the presence of ESGUS and EGGUS within affected animals at a population level (Murray et al. 2001; Begg and O’Sullivan 2003) and the majority of ESGUS is primary in origin. However, the authors have occasionally observed severe ESGUS in horses with concurrent severe EGGUS in animals that otherwise would be considered to be at low risk of ESGUS. As such, the authors believe that, although a link is not demonstrable at a population level, the possibility that EGGUS can cause ESGUS in certain animals should not be discounted. For the purposes of this article the discussion will focus on primary ESGUS recognising that management of secondary ESGUS is dependent on appropriate treatment of any underlying disease as well as addressing any ulceration that may be present.

Prevalence and risk factors
The prevalence of ESGUS mirrors exercise intensity with the risk of disease increasing as the intensity of work increases. The highest prevalences have been reported in Thoroughbred racehorses, with >70% of animals affected across a wide range of studies (Murray et al. 1996; Vatistas et al. 1999b; Begg and O’Sullivan 2003; Bell et al. 2007) and in competing endurance horses with 93% of animals affected (Tamzali et al. 2011). Standardbred racehorses are also commonly affected (63–87% of animals [Rabuffo et al. 2002; Dionne et al. 2003]). However, ESGUS is not solely a disease of high performance horses and it is seen across a wide range of other horse types with 69% of horses used for a variety of purposes affected in a recent Danish study (Luthersson et al. 2009a). Prevalences of ESGUS of 58 and 40% have also been reported in show horses and it is seen across a wide range of other horse types. The authors generally consider grades 1–2/4
lesions unlikely to cause clinical signs in contrast to grades 3–4/4 lesions, although strong evidence to support this opinion is lacking. In line with this, only 10% of Standardbred racehorses had lesions ≥grade 3/4, despite an overall ESGUS prevalence of 44% [Dionne et al. 2003] and only 36 and 48% of Thoroughbred racehorses had lesions ≥grade 3/4, despite overall ESGUS prevalences of 74 and 78%, respectively [Begg and O'Sullivan 2003; Marqués et al. 2011]. As such, the authors believe that prevalences stated above should be interpreted with caution as they may not truly reflect the prevalence of animals with potentially clinically significant disease.

The prevalence of ESGUS in horses at rest is variable but it is typically lower and when observed tends to be less severe. However, the authors have observed severe (grades 3–4/4) ESGUS in some individual horses at pasture and consider that ESGUS should not be discounted as a differential diagnosis simply because a horse does not meet the ‘typical’ risk profile.

A large number of management changes are imposed upon horses with the commencement of training, many of which have been documented to increase the risk of ESGUS. These include exercise [Lorenzo-Figueras and Merritt 2002], high concentrate/low roughage diets [Nadeau et al. 2000], fasting [Murray and Eichorn 1996], transport [McClure et al. 2005a], stall confinement [Murray and Eichorn 1996], the administration of hypertonic electrolytes [Holbrook et al. 2005] and intermittent access to water [Luthersson et al. 2009b]. Induction of ESGUS can be rapid occurring within 7 days in some studies [Valtis et al. 1999a; McClure et al. 2005a] and the risk of disease increases with time in work [Habershon-Butcher et al. 2012].

Management and treatment

Given the central role that management plays in the development of ESGUS, it is logical that removing or at least reducing the impact of various risk factors should reduce the risk of disease. This is supported by a study in endurance horses where the prevalence of ESGUS was 48% during the inter-season period compared with 93% during the competition season [Tamzali et al. 2011]. The provision of access to hay, or alternative forms of roughage, should restore the normal pH stratification of the stomach; however, straw on its own is an unsuitable candidate as the provision of straw as the sole roughage source has been demonstrated to be a risk factor for disease [Luthersson et al. 2009b]. It has been further suggested that including multiple forage sites may be beneficial as it may increase the time spent grazing [Hepburn 2011]. A reduction in the soluble carbohydrate content of meals should reduce the impact of secondary volatile fatty acid injury, while the addition of corn oil appears to have the dual benefit of increasing caloric intake (allowing a reduction in carbohydrate content) and directly decreasing gastric acid production [Cargile et al. 2004]. Based on the identified risk factors other specific management measures that may be beneficial include increasing the availability of turnout, ensuring ad libitum access to water and the feeding of a small, roughage based meal 30–60 min prior to exercise.

The authors’ knowledge, the efficacy of management changes have not been specifically documented in the peer reviewed literature and the high prevalence (48%) of ESGUS observed in endurance horses during the noncompetition season [Tamzali et al. 2011] suggests that a reduction in work alone is not enough to prevent the disease. Theoretically, removal of the horse from the risk factors that caused disease in the first place and re-establishment of a normal pH gradient in the stomach should result in healing. However, anecdotally it appears that even when removal from the risk factors is possible, acid suppression therapy is often required to restore a normal appetite so that enough roughage is consumed to re-establish the pH gradient in the stomach allowing healing to occur, especially in horses with weight loss and/or decreased appetite. Further, the ability to remove risk factors, such as exercise and concentrate diets, is often limited thus the use of acid suppression therapy remains a cornerstone in the management of ESGUS.

Pharmaceutical treatment of ESGUS focuses on suppression of acid production. A variety of drugs have been used for this purpose but omeprazole remains the most effective [Lester et al. 2003] and best studied. In a study comparing the likelihood of ESGUS being present only commercial omeprazole decreased the risk below that of a placebo, in contrast to buffers, sucralfate, H₂-receptor antagonists (ranitidine and cimetidine) and compounded omeprazole, none of which had any demonstrable benefit [Orsini et al. 2003]. Omeprazole impairs the H+ K+ ATPase (proton) pump that secretes HCl [Fellenius et al. 1981] and does not directly contribute to healing. Instead the squamous mucosa has an enormous proliferative capacity and the removal of ongoing insult is sufficient for the tissues to heal in the majority of cases. Several factors warrant consideration in regards to the response to omeprazole therapy including the formulation and dose used and the timing of administration.

To date, little attention has been given to the effect of formulation with Gastrogard [Merial, Duluth, GA, USA], the formulation predominately used globally, due to it being patent protected in most markets. However, the patent has recently expired and interest in different formulations has increased. Omeprazole is acid labile and it is generally regarded that some form of protection is necessary to prevent degradation of the drug within the acidic environment of the stomach [Meritt et al. 2003]. Gastrogard utilises a buffered paste formulation to achieve this protection [Meritt et al. 2003] compared with other formulations that utilise enteric-coated granules suspended within a paste to achieve the same objective [Sykes et al. 2014b]. The manufacturers of enteric-coated formulations claim superior bioavailability and it appears that a modest benefit may be present with the bioavailability of a commercially available enteric-coated formulation [Gastrozol, Virbac, Milperra, NSW, Australia] reported to be 1.26 times greater than that of Gastrogard [Birkmann et al. 2014]. Recently, a plain, unbuffered formulation of omeprazole has been released onto the European market with a claim of bioequivalence to Gastrogard1 [Morgan 2010]. Further work into the relative bioavailability of different formulations is ongoing but preliminary results suggest that modest effects of formulation are present [Sykes et al., unpublished data].

Gastrogard is the best studied at its registered dose of 4 mg/kg bwt per os s.i.d. for 28 days as recommended by the 1999 EGUS Council [Andrews et al. 1999a] with ESGUS healing rates of 70–77% consistently reported [Murray et al. 1997; Andrews et al. 1999b; MacAllister et al. 1999; Doucet et al. 2003; Lester et al. 2005]. Recently, the use of lower doses of an enteric-coated formulation [Gastrozol] has been evaluated and, under certain conditions, doses as low as 1 mg/kg bwt have been shown to be as efficacious as 4 mg/kg bwt in the treatment of ESGUS [Sykes et al. 2014b]. Similarly, Gastrozol at
1 mg/kg bwt per os s.i.d. was equally effective as Gastrogard at 4 mg/kg bwt per os s.i.d. in a recent clinical trial, despite an only modest increase in bioavailability (Birkmann et al. 2014). Considering this, the authors’ consider that the use of lower doses of buffered formulations warrants further investigation and the authors routinely use 2 mg/kg bwt per os s.i.d. as a treatment dose when using buffered formulations. In a study using another buffered formulation, a reduction below this dose to 1.6 mg/kg bwt was associated with a decreased response rate (Sykes et al. 2014c) and, as such, a reduction below 2 mg/kg per os s.i.d. is not recommended. In the authors’ opinion, a reduction in the dose of plain omeprazole below the label dose of 4 mg/kg bwt is not recommended until the relative pharmacokinetics of this formulation are further defined.

Based on experimental studies (Andrews and Jenkins 1992; Jenkins et al. 1992a, b; Dauroio et al. 1999; Haven et al. 1999; Sandin et al. 1999; Andrews et al. 2006), it is widely believed that once daily administration of omeprazole results in 24 h of acid suppression. However, the methodology used to measure gastric acidity in those studies may not be true reflective of mucosal pH (Merritt et al. 2003). A study using pH probes inserted in ponies with an indwelling gastric cannula, which the authors believe offers the most reliable model of intra-gastric pH measurement, has suggested that the duration of acid suppression following dosing at 4 mg/kg bwt may be as short as 12 h (Merritt et al. 2003). Considering this, the timing of administration may be important with exercise considered to be the peak risk period for EGSUS development (Lorenzo-Figueras and Merritt 2002). A recent study in Thoroughbred racehorses found no clear advantage of administration of omeprazole 1–4 h prior to exercise compared with administration post exercise but the results suggested that an effect may be present and that a small, no cost management change may improve efficacy (Sykes et al. 2014d).

Regardless of the formulation or dose used it is important to recognise that at best only approximately 80% of animals will heal within a 28 days treatment period (Murray et al. 1997; Andrews et al. 1999b; Doucet et al. 2003; Sykes et al. 2014d). As such, repeat gastroscopy is recommended prior to the cessation of therapy to ensure that healing has occurred. The factors contributing to nonresponders are poorly described but potentially include the failure to reduce associated risk factors and individual variation in the absorption of omeprazole. It has recently been reported that a wide range of interindividual variation is present in the oral bioavailability of omeprazole with 3/12 horses in one study being poor absorbers regardless of the conditions studied (Sykes et al. 2014e). As such, it is tempting to speculate that the animals that fail to respond to conventional dose omeprazole therapy may simply be poor absorbers of the drug and the authors consider the presence of severe, persistent EGSUS at follow-up examinations to be highly suggestive of a failure of omeprazole to achieve acid suppression in that animal. Under such conditions (i.e. in individuals that appear refractory to treatment with omeprazole) alternative therapeutic agents should be considered.

A variety of other drugs have been used in the treatment of EGSUS, most commonly the H$_2$ receptor antagonists ranitidine and cimetidine. Both drugs work via competitively blocking the H$_2$ receptor on the parietal cell and their efficacy is dependent on maintaining plasma concentrations. Ranitidine, most commonly used at 6.6 mg/kg bwt per os t.i.d., has been shown to effectively suppress gastric acidity in experimental studies (Campbell-Thompson and Merritt 1987; Sangiah et al. 1988; Murray and Grodinsky 1992; Murray and Schusser 1993) and provides an option for acid suppressor therapy where omeprazole is not available or ineffective as discussed above. Cimetidine is relatively poorly studied and its use is not justified in the authors’ opinion.

Nonpharmaceutical methods, such as feed supplements and antacids, of treating EGSUS are popular amongst owners, typically because of low cost and availability. Although antacids can effectively reduce gastric acidity, their effect is short-lived (≤2 h) (Murray and Grodinsky 1992; Clark et al. 1996) and, as such, their use beyond short term symptomatic control is not recommended. Mucosal protectants, such as pectin-lecithin complexes, may play a role in providing a physical barrier between the mucosa and acid, and symptomatic relief with their use is often reported anecdotally. To date their efficacy as a therapeutic agent is unproven with 2 studies failing to demonstrate a protective effect in a fasting model of EGSUS (Murray and Grady 2002; Sanz et al. 2014) despite initially promising results in clinical patients (Venner and Laufts 1999). Whether the fed/fasted model often used to study such products is representative of the clinical setting is, in the authors’ opinion, disputable and studies in clinical patients may yield more relevant results. Recently, it has been demonstrated in a clinical study that a feed supplement consisting of salts of organic acids (SOC) in combination with B vitamins may be beneficial in the treatment of EGSUS (Hellings and Larsen 2014) and the authors believe that further investigation of nutraceuticals under clinical conditions is warranted.

Prevention

The approach to prevention of EGSUS is similar to treatment. In many cases a significant reduction in risk factors is not possible and the risk of recurrence is typically moderate to high. Prevention should be approached on a case by case basis, wherein the greater the ability to impact on risk factors, the lower the need for additional therapy. Although ineffective in feed deprivation models (Murray and Grady 2002; Sanz et al. 2014), the use of mucosal protectants such as the pectin-lecithin complexes may be adequate in low–moderate risk environments, especially when used in combination with antacids where they have been shown to be beneficial (Sykes et al. 2013). In contrast, a formulation containing seabuckthorn berries failed to demonstrate a protective effect for EGSUS in a fed/fasted model (Huff et al. 2012) although, as previously mentioned, the authors question the validity of this model. Omeprazole is indicated in cases where the risk of recurrence is deemed to be high. It is typically used at 1.0 mg/kg bwt per os s.i.d. using buffered formulations (McClore et al. 2005b; Endo et al. 2012), although 0.5 mg/kg bwt per os s.i.d. of an enteric-coated formulation (Gastrozol) has recently been shown to be as effective under specific conditions (Sykes et al. 2014a).

Summary

The risk of EGSUS increases with increased intensity of management with a high prevalence of animals potentially affected in high risk populations. Risk factors are well described and the ability to reduce exposure to risk factors, where possible, should reduce the risk of disease. However, EGSUS
remains common in some populations and the use of specific therapeutics is warranted in affected animals. Omeprazole remains the best studied of these with recent work suggesting that lower doses than traditionally used may be efficacious. Conversely, a small subset of the population appear refractory to omeprazole treatment and other therapeutic modalities such as ranitidine and/or specific nutraceutical complexes warrant consideration in selected cases.

Authors’ declaration of interests
One of the authors (BWS) is employed as a consultant by Boehringer Ingelheim, the manufacturers of Pronutrin. The manufacturer’s of Gastrozol have previously sponsored research by one of the authors (BWS). Neither company was involved in the development of this manuscript.

References


