Review Article

Rethinking equine gastric ulcer syndrome: Part 3 – Equine glandular gastric ulcer syndrome (EGGUS)

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Summary
It has recently been highlighted that significant differences exist between ulceration of the squamous gastric mucosa and ulceration of the glandular gastric mucosa in the horse. The first article in this series discussed terminology, clinical signs and diagnosis and the second reviewed ulceration of the squamous gastric mucosa in detail. The purpose of this article, the third and last in the series, is to review the pathophysiology, risk factors, prevalence, treatment and prevention of ulceration of the glandular gastric mucosa.

Introduction
Gastroscopy has been in widespread use in the horse for over 20 years and factors associated with disease of the squamous mucosa (ESGUS) have been well described. However, to date, the factors associated with disease of the glandular mucosa (EGGUS) remain poorly understood. A key reason for this is that the early gastroscopes used were only 2.5 m in length, which, as discussed in the first article in this series (Sykes and Jokisalo 2014a), meant that the entire glandular mucosa was rarely observed; in particular, the pyloric antrum, where the majority of glandular ulceration occurs (Begg and O’Sullivan 2003; Lutherson et al. 2009a; Husted et al. 2010; Habershon-Butcher et al. 2012; Hepburn and Proudman 2014; Sykes et al. 2014a,b,c,d), was rarely observed in clinical cases. The implications of this historical bias towards squamous disease are significant as it has biased the EGGUS discussion towards ESGUS.

The importance of distinguishing ESGUS and EGGUS has recently been highlighted (Merritt 2009) and a series of recent studies have clearly demonstrated that the risk factors for (Habershon-Butcher et al. 2012), and response to treatment (Hepburn and Proudman 2014; Sykes et al. 2014a,b,c,d), of EGGUS differ dramatically from that of ESGUS. This is not surprising given the differences in the anatomy of the glandular mucosa and pathophysiology of the conditions. Considering this, it is important to recognise that EGGUS should be considered as a separate disease condition to ESGUS and that extrapolation of factors known to be associated with disease from ESGUS to EGGUS is inappropriate. Instead, EGGUS should be considered as a separate entity that warrants consideration in its own right and, given the paucity of information available, specific further investigation.

Pathophysiology
The glandular mucosa differs fundamentally from the squamous mucosa in that under normal physiological conditions it is exposed to highly acidic gastric contents with the pH in the ventral portion of the stomach relatively stable at around 3 (Husted et al. 2008). In contrast to ESGUS, which occurs as a result of increased acid exposure in a region with limited defence mechanisms, EGGUS is believed to result from a breakdown of the normal defence mechanisms that protect the mucosa from acidic gastric contents, although the specific mechanism by which this occurs has yet to be elucidated. Bacterial agents and nonsteroidal anti-inflammatory drugs (NSAIDs), which are the predominant causes of gastric ulceration in man (Malfertheiner et al. 2009; Iijima et al. 2014), have both been proposed as likely aetiologies in the horse although, to date, evidence supporting either as a cause of disease at a population level is weak at best. Non-Helicobacter pylori, non-NSAID ulceration, otherwise known as idiopathic peptic ulcer disease, does occur in man and until recently has been considered rare (Malfertheiner et al. 2009). However, more recent publications have suggested that between 10% and 30% of peptic ulcers in certain populations of human patients may be idiopathic in nature (Iijima et al. 2014). Interestingly, largely mirroring our current state of knowledge in the horse, the aetiology of idiopathic ulceration in man is unknown and treatment is empirically with proton pump inhibitors (Iijima et al. 2014). Further, the efficacy of acid suppression in the prevention of reoccurrence is questionable (Wong et al. 2012).

The role of bacteria in EGGUS is controversial and a recent study demonstrated that both gastric-adapted bacteria and opportunistic pathogens may play a role in squamous ulceration (Al Jassim et al. 2008). Whether the situation is similar in the glandular mucosa is unknown but Helicobacter-like organisms have been identified in horses affected with EGGUS in some studies (Fox 2002; Contreras et al. 2007; Morales et al. 2010). However, other studies have failed to identify such organisms (Martineau et al. 2009; Husted et al. 2010) and it appears, based on current knowledge, that it is unlikely that H. pylori is the primary causative agent of EGGUS. The role of secondary bacterial infection in the worsening or perpetuation of EGGUS is unclear and warrants further investigation. However, in the authors’ opinion, the role of bacteria has not been sufficiently established to warrant the widespread use of antimicrobials in the treatment of EGGUS.

Equally controversial is the role of NSAIDs in the development of EGGUS. A variety of NSAIDs, namely flunixin, phenylbutazone and ketoprofen, have been shown to have ulcerogenic potential at doses only 50% higher than typically recommended (MacAllister et al. 1993). However, at clinical doses phenylbutazone and sulbuxzone did not induce gastric ulceration when administered for 15 days (Andrews et al. 2009) and the administration of NSAIDs was not identified as a risk factor in a recent study (Habershon-Butcher et al. 2012). Further, in the authors’ experience, the use of NSAIDs is rarely
Prevalence and risk factors

The prevalence of EGGUS is less well described than ESGUS but it has been reported in a number of studies as shown in Table 1. In contrast to the prevalence of ESGUS, which increases as the intensity of exercise and management increases, the prevalence of EGGUS is more variable between populations. This suggests that other factors may be more significant than the intensity of exercise and management imposed during training. This concept is supported by a Danish study that found that horses in work were no more likely to have EGGUS than young horses, breeding mares or mature horses at pasture (Luthersson et al. 2009b). Further, a 2012 report demonstrated that the risk of EGGUS increased with time in work, while the risk of EGGUS did not (Habershon-Butcher et al. 2012).

To date, the risk factors for EGGUS have been poorly described. In a study on Thoroughbred racehorses risk factors identified for EGGUS were sex (colts are at reduced risk), trainer, no grass turnout, horses in direct contact with each other, horses not fed haylage, horses fed unprocessed grain, horses that were infrequently fed a complete diet, horses that underwent fast exercise on fewer days of the week and horses that went swimming (Habershon-Butcher et al. 2012). The wide geographical variation observed within this study (see Table 1) is interesting although its meaning is unknown. In contrast to the wide range of factors identified in Thoroughbred racehorses, no effect of age, sex, use or month of presentation was found on ulcer location or type in a large study of UK leisure and sport horses (Hepburn 2014). Further work identifying risk factors for EGGUS in a range of populations is needed.

Together the results of these studies suggest that diet may influence the risk of EGGUS in a manner similar to ESGUS, with high concentrate/low roughage diets increasing the risk of disease. However, the relatively direct relationship between intensity of, and duration in, work and the prevalence that is observed in of ESGUS is not observed in EGGUS.

Management and treatment

Evidence-based treatment guidelines for EGGUS are difficult to formulate due to the paucity of information available and, as such, current treatment recommendations are largely empirical. However, recent studies in which only 25% of glandular ulcers healed with 28–35 days of omeprazole therapy at 4.0 mg/kg per os s.i.d. in direct contrast to an ESGUS healing rate of 78% (Sykes et al. 2014a,b,c) suggest clearly that specific treatment recommendations for EGGUS are needed and that direct extrapolation of ESGUS treatment recommendations are inappropriate.

The use of dietary modification, as per ESGUS, is logical given that diet has been identified as a risk factor for EGGUS as discussed above. The addition of corn oil at 0.3–0.5 ml/kg bwt/day (150–250 ml/day for a 500 kg horse) has been shown to decrease gastric acid output and increase prostaglandin E2 production (Cargile et al. 2004) both of which are, in theory, beneficial for the treatment and prevention of EGGUS. Whether dietary management is efficacious in the management of EGGUS is debatable and, in the authors’ experience, the majority of sport and leisure horses afflicted with EGGUS have management that would already be considered low-risk.

In man, the use of acid suppressors, specifically proton pump inhibitors, is considered a cornerstone of treatment, regardless of the inciting cause and the duration of treatment and use of adjunctive agents depends on the primary cause (Malfertheiner et al. 2009). Complicating treatment recommendations in the horse is the fact that, while it is commonly believed that administration of omeprazole results in 24 h of acid suppression, one study suggested that the duration of acid suppression achieved with once daily administration of omeprazole may be <12 h in the horse (Merritt et al. 2003). Further, a wide degree of variation is observed in the individual absorption of omeprazole (Sykes et al. 2014e). Further investigation into the duration of acid suppression achieved with a variety of dosing regimens is ongoing; however, in the meantime the authors dose omeprazole in a manner similar to their recommendations for ESGUS (Sykes and Jokisalo 2014b), accepting that such recommendations are likely to change as more information becomes available. Given the slow response to treatment, the authors routinely treat EGGUS for a minimum of 6 weeks prior to repeating gastroscopy. As discussed above, the role of bacteria in the pathogenesis is controversial although antimicrobial therapy is commonly recommended as an adjunct to acid suppression therapy in refractory EGGUS (Nadeau and Andrews 2009; Hepburn 2011). However, no direct evidence supports the use of antimicrobials, and in a recent study the addition of trimethoprim-sulfadimidine at 30 mg/kg bwt per os s.i.d. to omeprazole at 4.0 mg/kg bwt per os s.i.d. failed to improve the healing rate of 78% (Sykes 2010).

Table 1: The prevalences of ESGUS and EGGUS in different populations of horses

<table>
<thead>
<tr>
<th>Population</th>
<th>ESGUS prevalence</th>
<th>EGGUS prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian TB racehorses</td>
<td>86%</td>
<td>47%</td>
<td>(Begg and O’Sullivan 2003)</td>
</tr>
<tr>
<td>Australian TB racehorses</td>
<td>76%</td>
<td>63%</td>
<td>(Habershon-Butcher et al. 2012)</td>
</tr>
<tr>
<td>UK TB racehorses</td>
<td>64%</td>
<td>8%</td>
<td>(Habershon-Butcher et al. 2012)</td>
</tr>
<tr>
<td>Denmark – mixed</td>
<td>86%</td>
<td>57%</td>
<td>(Luthersson et al. 2009a)</td>
</tr>
<tr>
<td>USA – endurance</td>
<td>67%</td>
<td>27%</td>
<td>(Nieto et al. 2004)</td>
</tr>
<tr>
<td>France – endurance</td>
<td>93%</td>
<td>33%</td>
<td>(Tamzali et al. 2011)</td>
</tr>
<tr>
<td>UK – leisure</td>
<td>50%</td>
<td>55%</td>
<td>(Hepburn 2014)</td>
</tr>
<tr>
<td>UK – sport</td>
<td>50%</td>
<td>62%</td>
<td>(Hepburn 2014)</td>
</tr>
<tr>
<td>Denmark – mixed</td>
<td>Not reported</td>
<td>57%</td>
<td>(Husted et al. 2010)</td>
</tr>
</tbody>
</table>
treatment response over omeprazole therapy alone (Sykes et al. 2014e). As such, and in line with the principles of responsible use of antimicrobials, the authors do not believe that their use in the routine treatment of EGGUS is justified.

An alternative approach is the use of mucosal barrier protectants which is logical given the proposed failure of mucosal defence mechanisms in the pathogenesis of EGGUS and although it is unlikely that mucosal protectants alone will result in significant healing, they may serve as an important adjunct to omeprazole therapy. Sucralfate has recently been reported in a UK sport and leisure horse population at a dose of 20 mg/kg bwt per os b.i.d. in addition to omeprazole at 4 mg/kg bwt per os s.i.d. (Hepburn and Proudman 2014). Its mechanism of action is likely to be a combination of adherence to ulcerated mucosa, stimulation of mucous secretion, prostaglandin E synthesis and enhanced blood flow (Murray 2009). The healing response rate observed in this study (63.2%) was higher than previously reported for the omeprazole alone in an Australian Thoroughbred racehorse population (25%) (Sykes et al. 2014a,b,c). Given the marked differences in the populations studied, care should be taken in drawing firm conclusions, although the results provide preliminary evidence to justify the routine use of sucralfate as an adjunctive treatment for EGGUS.

Prevention

Prevention of EGGUS, either as primary disease or recurrence, is problematic. The rate of recurrence following discontinuation of therapy has not been reported and the failure to date to identify clear risk factors makes effective management changes difficult to recommend. Further, the efficacy of omeprazole as a prophylactic is unclear with 23% of horses experiencing worsening of their EGGUS grade in a series of recent studies despite omeprazole therapy at doses ranging from 1 to 4 mg/kg bwt per os s.i.d. (Sykes et al. 2014a,b,c). Interestingly, in man, the efficacy of long-term acid suppression therapy in the prevention of non-H. pylori, non-NSAID associated ulceration has also been questioned (Wong et al. 2012). At the time of writing, the exact role of omeprazole for prevention of EGGUS is unclear; however, use as per the recommendations for EGGUS is logical until further defined.

Alternatively, the use of neutriceuticals is appealing in principle. Apoelctol, a unique pectin-lecithin complex, has been shown to increase the total mucus concentration in gastric juice (Koller et al. 2010), whilst another study suggested that it may have a role in the treatment of EGUS in clinical cases (Venner and Lauffs 1999). Although straight pectin-lecithin complexes have been shown not to be effective in the prevention of EGGUS in fasting models of disease (Murray and Grady 2002; Sanz et al. 2014), the combination of a pectin-lecithin complex, an antioxidant and live yeast (Saccharomyces cerevisiae) has recently shown promise in a trial studying naturally occurring disease of both the squamous and glandular mucosa in a high risk population (Sykes et al. 2014f). Similarly, a preparation containing sea buckthorn berries appeared to have protective effects against the development of EGGUS in a fasting model of disease (Huff et al. 2012). Considering this the authors currently recommend the use of such complexes alongside management changes and the addition of corn oil to the diet in the prevention of EGGUS development or recurrence, especially where long-term pharmaceutical intervention (omeprazole) is inappropriate or ineffective. However, it is recognised that further studies determining the efficacy and ideal composition of neutriceuticals is required to strengthen this recommendation.

Conclusion

The pathogenesis and risk factors reported for EGGUS differ from those reported for ESGUS with the role of high intensity exercise and its associated management less clear. As a result the prevalence of EGGUS differs from the prevalence of ESGUS. Similarly, management of EGGUS differs from management of ESGUS with acid suppressive therapy less effective as a stand-alone therapy. Instead the use of adjunctive treatment appears beneficial, in particular sucralfate, while the use of pectin-lecithin based neutriceuticals may play a role in the prevention of disease.

Authors’ declaration of interests

B.W. Sykes is employed as a consultant to Boehinger Ingelheim, the manufacturers of Pronutrin. J.M. Jokisalo has no conflicts of interest to declare.

References


