EGGD consensus statement
Recommendations for the management of Equine Glandular Gastric Disease

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Tim graduated from Liverpool University in 1988. He then spent 11 years dividing his time between private practice and university teaching hospital jobs in Canada, Liverpool & Edinburgh. He was awarded a PhD from Edinburgh University in 1999 for research into RAO and became a Diplomate of the European College of Equine Internal Medicine in 2005. Since 2004, Tim has run his own mobile equine internal medicine consultancy service (Equine Medicine on the Move) providing diagnostic and second opinion services to equine veterinary practices throughout the UK and Europe and more recently joined The Veterinary Defence Society as a claims consultant.

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Foreword

The European College of Equine Internal Medicine (ECEIM) consensus statement recently made the distinction between disease of the squamous mucosa (Equine Squamous Gastric Disease; ESGD) and of the glandular mucosa (Equine Glandular Gastric Disease; EGGD) (Sykes et al, 2015a). Since its publication, a number of reports have furthered understanding of the pathology and management of EGGD, such that new clinical guidelines for the management of this condition were considered necessary. The following guidelines are the consensus views of subject specialist representing authors of the ECEIM consensus statement, authors of recent clinical research, and clinical specialists active in the management of horses with this condition.

The recommendations were developed using an informal two-round Delphi process, considering published and un-published research relating to EGGD using a round table forum and online discussion. Where research evidence was conflicting or absent, collective expert opinion based on the clinical experience of the group was applied. The opinions expressed are the consensus of views expressed by the authors. The expert group was organised by *UK-Vet Equine* with sponsorship from Luoda Pharma.

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Recommendations for the management of equine glandular gastric disease

While Equine Glandular Gastric Disease (EGGD) is recognised as a disease of the stomach and acid plays an important role in its pathophysiology, EGGD is a separate and distinct disease entity from Equine Squamous Gastric Disease (ESGD) as evidenced by differences in epidemiology, prevalence, risk factors, pathophysiology and response to treatment. Investigations of relationships between the presence of ESGD and EGGD have produced conflicting results (Murray et al, 2001; Beg and O'Sullivan, 2003; Luthersson et al, 2010a; Habershon-Butcher et al, 2012; Hepburn, 2014) and the presence of both conditions concurrently does not indicate that they are associated given the high prevalence of both conditions in domesticated equids. The nutritional, management and pharmaceutical strategies for prevention and treatment of ESGD cannot be extrapolated to EGGD. EGGD should be considered as a distinct entity from ESGD.

Risk factors

Information on the risk factors for EGGD is limited and occasionally contradictory. Risk factors are likely to exist at different levels from individual horse level, through yard level up to population level, with the clinician best placed to identify and reduce exposure to putative risk factors relevant to each individual case. The prevalence of EGGD appears to increase with domestication; however, many of the accepted risk factors for ESGD do not appear to increase the risk of development of EGGD. Warmblood horses have been identified to have a higher prevalence of EGGD (Luthersson et al, 2010b; Monki et al, 2016). In Thoroughbred racehorses, trainer has been identified to be a risk factor independent of other management factors (Habershon-Butcher et al, 2012). Performing exercise more than 4 or 5 days per week was found to be a risk factor for EGGD in racing Thoroughbreds (Habershon-Butcher et al, 2012) and show jumpers (Pedersen, 2015) respectively; however, the intensity of exercise was not. EGGD was inversely correlated to the experience of the horse in both polo ponies (Macleod et al, 2015) and show jumpers (Pedersen, 2015) which may suggest a degree of adaptation, differences in management of elite horses or selection for horses that do not develop EGGD. In endurance horses, the prevalence of EGGD doubled during the competition season compared with the inter-season period (Tamzali et al, 2011). In people, gastric disease is more common in both elite and recreational athletes and this may be related to a reduction in blood supply to the stomach during exercise. A similar relationship between frequency of exercise and gastric blood supply may exist in horses and exercise may be an example of physiological stress on the glandular mucosa. Physiological stresses such as hypotension or ischaemia are implicated in the development of glandular gastric mucosal disease in foals (Furr et al, 1992) and with exercise in rats (Pare. 1975) and man (Perko et al, 1998). The total amount of exercise, and particularly the number of days of exercise per week, are likely to be more relevant to the risk of EGGD than the intensity or duration of exercise.

Stress is an important risk factor in the development of peptic ulcers in people (Levenstein et al, 2015; Melinder et al, 2015; Deding et al, 2016). Horses which crib bite and might be considered stressed were not shown to have an increased prevalence of EGGD in one study (Scott et al, 2017) although this may indicate that stereotypic behaviours are a strategy to manage increased stress. Horses with severe EGGD have been shown to exhibit greater increases in cortisol in response to novel stimuli (Malmkvist et al, 2012) and in response to exogenous ACTH (Scheidegger et al, 2017) indicating that they may be more sensitive to stress. These horses did not have their responses to stress assessed once EGGD had resolved so an alternative explanation for these findings would be an exaggerated response to stress as a result of EGGD. The reduction in prevalence of EGGD that is seen in more experienced polo ponies and show jumpers (Macleod, 2015; Pedersen et al, 2015) may relate to an adaptation to physiological stress as more experienced show or show jumping horses have lower cortisol concentrations than less experienced horses (Covalesky et al, 1992; Cayado et al, 2006). Interestingly, there was an increase in prevalence of EGGD with an increase in the number of people looking after the horse in one study, though the association was not significant statistically (Monki et al, 2016). Although a tentative link appears to be present, whether stress is a contributor to EGGD in the horse remains to be fully elucidated. It is very difficult to provide general recommendations to reduce stress as individual horses respond very differently to different potential stressors. Management should be tailored to the individual and, when suitable, kept consistent.

Historically, non-steroidal anti-inflammatory drugs (NSAIDs) have been considered a risk factor for EGGD. However, there is insufficient evidence to indicate that NSAIDs at standard doses increase the risk of EGGD and it is therefore questionable whether the use of cyclo-oxygenase (COX) selective NSAIDs is protective against the condition. At high doses, NSAIDs will induce lesions of the glandular mucosa (MacAllister et al, 1993); however these lesions are different to those seen in clinical EGGD cases in both their gross and histological appearance. Pathophysiology and management of NSAID-induced gastric disease differs from that of naturally occurring disease.

Although it is often perceived that there is an association between orthopaedic disease

and EGGD, their presence concurrently may just be due to their high prevalence in certain populations. Associations between orthopaedic disease and EGGD have not been identified (Habershon-Butcher et al, 2012), but require further investigation.

There is currently no evidence to indicate an association between diet and EGGD. Access to pasture appears to be protective against the development of EGGD (Bowen, unpublished data). There is limited evidence on which to make recommendations for feeding horses with EGGD; however, it would seem logical to maximise grazing and to ensure exercise is not performed on an empty stomach.

Recommendations for reducing EGGD:
- Provide a minimum of 2 rest days from work per week if possible or provide regular rest periods
- Turn-out where possible provided the horse does not become stressed by turn-out. Some horses that are not accustomed to turn-out may be less stressed in a stable environment
- Minimise management changes and other potential stressors
- Minimise changes in equine companions and human carers
- Feed 2 litres of chaff or an equivalent volume of forage 30 mins prior to exercise.

Aetiopathogenesis

It is unlikely that there is a single aetiopathogenesis for all EGGD lesions. Furthermore, there is no single type of glandular mucosa; the anatomy and physiology of the mucosa of the pyloric, fundic and cardiac regions of the stomach are different and the response to treatment is likely to be different between regions. Although acid injury is not thought to be the primary cause of EGGD, a low pH may perpetuate mucosal damage, to cause clinical signs and to inhibit mucosal healing (Sykes et al, 2015a). Stress may influence gastrin production and blood supply to the glandular mucosa and may therefore be a factor in the perpetuation, if not the initiation, of glandular lesions. Blood supply to different regions of the gastric mucosa may be uneven and may be affected by both exercise and feeding, potentially influencing the occurrence of disease.

The lesions of EGGD are inflammatory in nature and contain a variable mixture of neutrophils, lymphocytes and plasma cells; the condition is therefore best described as a glandular gastritis. The majority of lesions are lymphoplasmacytic with a variable eosinophilic and neutrophilic component (Martineau et al, 2009; Husted et al, 2010; Crumpton et al, 2015). Nodular lesions typically have a lymphoplasmacytic infiltrate. Some lesions have a predominance of neutrophils and these lesions may have a fibrinosuppurative appearance on gastroscopic examination. The presence of neutrophils does not indicate an infectious aetiology. Fibrosis rarely develops, even in chronic cases with gross distortion of the surface of the pyloric antrum. It is rare for the lamina propria to become damaged resulting in ulceration; however, there may be variable erosion or denudation of the superficial mucosa (Martineau et al, 2009). The inflammatory lesions of EGGD have similarities with lesions of idiopathic inflammatory bowel disease (IIBD) and, while there is no evidence to support a link between IIBD and EGGD, it is possible that some EGGD lesions may be part of more generalised inflammatory gastrointestinal disease.

There is no evidence that bacteria are implicated in the pathogenesis of EGGD. Although *Helicobacter pylori* is implicated commonly in human gastric disease, several investigations have failed to consistently identify *Helicobacter*-like organisms in EGGD lesions (Martineau et al, 2009; Husted et al, 2010). Other bacterial species including *Escherichia fergusonii, Streptococcus bovis* and *Enterococcus faecium* are potentially pathogenic and have been identified in association with EGGD lesions; however, their pathogenicity remains unproven. The balance of bacteria within the stomach has been hypothesised to be relevant to the development of EGGD, although there was no difference between the microbiota of horses with EGGD and horses with no gastric disease in one study (Dong et al, 2016). Mucolytic enzymes produced by bacteria as they transit the gastric mucosa can contribute to barrier denudation in other species, but their role is unknown in the horse. Bacteria are unlikely to have a primary role in the development of EGGD although certain species may have the capacity to colonise the damaged mucosa and inhibit healing.

Clinical signs

The clinical signs of EGGD are diverse, non-specific and are often subjective, which can make assessment of the clinical significance of different lesions extremely challenging. This is complicated further by the fact that there is

currently very little epidemiological evidence to support an association between perceived clinical signs of EGGD and the presence or absence of a type of lesion seen on gastroscopy.

The following are considered potential signs of EGGD:
- Changes in temperament including nervousness and aggression
- Changes in rideability including reduced willingness to work and reluctance to go forward
- Unexplained weight loss
- Reduced appetite or altered eating patterns
- Cutaneous sensitivity manifest as biting of the flanks or resentment of girthing, grooming, leg aids or rugging
- Colic — mild and possibly recurrent.

The following signs that have been proposed to be associated with ESGD are considered unlikely to be due to EGGD:
- Changes in coat condition
- Stereotypical behaviour (e.g. crib biting and wind sucking)
- Bruxism
- Diarrhoea.

The sensations of touch and pressure on the flanks or biting at the flanks seem unlikely indicators of gastric disease; however, mechanisms have been identified in other species which provide possible explanations. First, there are common afferent pathways from the abdominal viscera and the 6th to 9th thoracic spinal nerves and by the 'common pool theory' afferent signals from the skin may be affected by input from visceral afferents and misinterpreted within the brain. Second, viscero-somatic reflexes may result in localised visceral stimuli producing patterns of reflex activity and potentially pain and sensitivity in segmentally related somatic structures such as the skin (de La Hunta et al, 2014).

Diagnosis

Gastroscopy is currently the only reliable ante mortem means of diagnosing and monitoring EGGD; and should be considered the gold standard against which all other diagnostic tests are compared (Sykes et al, 2015a). Based on current evidence, the sucrose blood test and tests for protein or haemoglobin in faeces are unreliable and should not be used diagnostically (Sykes et al, 2014a; Hewetson et al, 2017). Biopsies are rarely indicated but if more severe pathological changes are suspected or if cases are refractory to treatment for 3 or more months then biopsies should be considered. Bi-

Figure 1. Collecting a grap biopsy from the pyloric antrum.

Figure 2. Mild raised multi-focal erythematous lesions.

Figure 3. Mild diffuse erythematous lesions.

Figure 4. Moderate diffuse erythema

Figure 5. Focal nodular lesion with associated haemorrhage.

opsies should be collected using as large a grab as possible (*Figure 1*). The following protocol is recommended:

1. Remove the loosely adherent exudate from the surface of the lesion with two or three bites of the grab biopsy forceps. This may be best accomplished by angling the biopsy forceps across the lesion
2. Create an impression smear (or smears) from the first grab(s) on a microscope slide and submit for cytological examination
3. Take at least two deeper bite(s) from the newly exposed mucosa with the biopsy forceps perpendicular to the surface of the stomach
4. Transfer the largest tissue sample into 10% formalin and submit for histology
5. Transfer a further section into a small quantity of saline to prevent desiccation or into a broth culture medium and submit for bacterial culture.

Gastroscopic appearance of EGGD lesions

Lesions of the pyloric antrum are identified most frequently and are assumed to be the most important clinically. However, when pyloric lesions are identified, inflammation is demonstrable though the entire glandular mucosa (Crumpton et al, 2015) and fundic lesions are seen frequently in examinations of the stomach that are performed post mortem when they are not concealed by gastric contents. Lesions of the cardia are uncommon but may be more prevalent in endurance horses (Hepburn, 2014).

The variable appearance of EGGD lesions has been highlighted previously (Sykes et al, 2015a). The inclusion of the terms nodular and hyperaemic is proposed to provide a more accurate description of the full range of lesions which are identified (*Figures 2–11*).

Lesions should therefore be described as:
● Focal, multi-focal or diffuse
● Mild, moderate or severe
● Nodular, raised, flat or depressed
● Erythematous, haemorrhagic or fibrinosuppurative.

Currently there are no means of assigning scores to EGGD lesions as their relative severity and clinical importance is unknown. Anecdotally, nodular and fibrinosuppurative lesions are more difficult to treat than flat or erythematous lesions. The significance of erythematous lesions is hard to determine. Some horses appear to have persistent focal erythema in the peripyloric region in the absence of clinical signs;

however, other horses with mucosal hyperaemia will show a marked clinical improvement in response to treatment. These lesions may also be a precursor or sequel to other lesion types and it is therefore very difficult to assess the clinical significance of mucosal hyperaemia on a single gastroscopic examination. Assessment of the appearance and colour of the mucosa is subjective and may be affected by differences in endoscopy equipment and different light and colour settings. Response to treatment is the best means of assessing the clinical relevance of lesions which are of questionable significance.

Treatment

A number of treatments have been advocated for the management of EGGD. Despite the high prevalence of the condition, evidence for the relative efficacy of different treatments is limited (Sykes et al, 2015a) and interpretation is complicated by the diversity of EGGD lesions.

Although EGGD is unlikely to be caused solely by acid injury, acid suppression is considered important for mucosal repair (Sykes et al, 2015a). The response to omeprazole (and probably other acid suppressants) varies markedly between horses and between different regions of the stomach (Sykes et al, 2017a). Some horses exhibit minimal acid suppression even with doses of PPIs well in excess of those that are used clinically (Sykes, unpublished data). Treatment of EGGD is challenging and this may be exacerbated by the presence of a lower pH in the pyloric antrum, where most lesions are identified, than in more dorsal regions of the stomach, even with acid suppressant therapy.

Omeprazole (oral)

Omeprazole is very effective for the treatment of ESGD and it has been described for the treatment of EGGD. It is the only licensed veterinary medicine for the treatment of gastric ulceration. However, oral omeprazole has a limited effect on pH in the pyloric antrum and rates of healing of EGGD lesions with oral omeprazole monotherapy (4 mg/kg PO SID) are poor, ranging from 9–32% (Sykes et al, 2014b,c; Sykes, 2015b). Higher doses (8 mg/kg PO SID) or increased frequency (4 mg/kg PO BID) of dosing to increase acid suppression do not appear to improve rates of healing (Hepburn, unpublished data; Sykes unpublished data). Given consistent reports of poor acid suppression in the pyloric antrum and low rates of EGGD healing, the use of oral omeprazole as a monotherapy is not appropriate for the management

Figure 6. Moderate focal fibrinosuppurative lesion.

Figure 7. Moderate multi-focal haemorrhagic and fibrinosuppurative lesions.

Figure 8. Moderate raised haemorrhagic and fibrinosuppurative lesions.
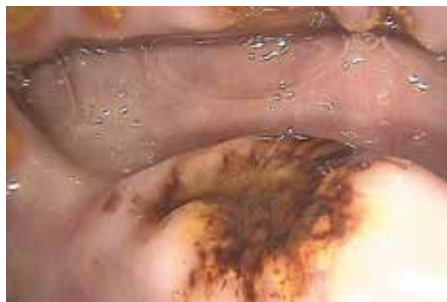

Figure 9. Haemorrhagic EGGD lesions.

Figure 10. Marked multi-focal depressed haemorrhagic and fibrinosuppurative lesions.

Figure 11. Marked diffuse haemorrhage lesions. Courtesy of Paul Smith, Northwest Equine Vets.

of EGGD. Efficacy may be increased if it is used in combination with sucralfate (see below).

> **Recommendations — oral omeprazole:**
> - Is unlikely to be effective as monotherapy for naturally occurring EGGD, especially if lesions are within the pyloric antrum[a]
> - Is licensed for the treatment of ulcerative lesions and should be the first-line treatment in such cases, for example with NSAID overdose.

Sucralfate

Sucralfate is complex salt of polyaluminium hydroxide with a sulphated disaccharide skeleton which adheres to the mucosa and may have a number of beneficial effects:

- Provision of a physical barrier which blocks the diffusion of acid
- Stimulation of mucus secretion which blocks the diffusion of acid
- Inhibition of pepsin and bile acid release
- Promotion of re-epithelialisation by prevention of fibroblast degradation
- Stimulation of epidermal and insulin-like growth factors
- Increased mucosal blood flow via increased production of prostaglandin E (PGE).

In foals, sucralfate was shown to be protective against gastrointestinal injury induced with high doses of NSAIDs (Geor et al, 1989),

but did not provide any greater effect than corn oil in healing naturally occurring gastric lesions (Borne, 1993). There are no published data on the efficacy of sucralfate monotherapy for the treatment of EGGD and its effects on gastric pH are short lived (Clark et al, 1996). Sucralfate does not hold a veterinary license and is therefore used following the prescribing cascade.

> **Recommendations — sucralfate:**
> - Has insufficient evidence to support it use as a monotherapy
> - May have a protective effect in foals
> - Should only be used in combination with an acid suppressant, preferably omeprazole
> - Does not hold a veterinary licence and is therefore used following the prescribing cascade[a].

Omeprazole (oral) and sucralfate combination

Hepburn reported 80% improvement and 63% healing (grade ≤1)[b] of EGGD lesions (grades ≥2) in 204 sport and leisure horses treated with both omeprazole (4 mg/kg PO SID) and sucralfate (12 mg/kg PO BID) (Hepburn, 2014). Improvement in pyloric lesions, which are seen most commonly in practice, was slightly lower at 67.5%. In another report, with much smaller numbers, these rates of healing (grade 0) were not replicated and only 22% of cases

healed with sucralfate and omeprazole (Varley et al, 2016). The discordance may be explained by differences in the definition of healing with Hepburn considering grade 1 as healed to account for the chronic mucosal changes which can be apparent, and Varley et al (2016) aiming for complete resolution of the lesions. Sucralfate does not hold a veterinary licence and is therefore used following the prescribing cascade.

Proton pump inhibitors (PPIs) are prodrugs and require proton pumps to be activated in order for the active drug to bind and inhibit acid production. Feeding stimulates the activation of proton pumps and, in the presence of a proton pump inhibitor, paradoxically results in reduction of acid production. However, the presence of food within the stomach inhibits the absorption of PPIs so it is essential that feeding patterns are modified to maximise bioavailability. Horses should have feed removed at least 8 hours prior to the administration of oral omeprazole and food should not be provided for at least 30 minutes, and ideally 60–90 minutes after treatment. Feed deprivation prior to the administration of omeprazole may seem counter intuitive; however, most horses rest overnight and would eat very little even if they had access to forage. While daytime fasting decreases pH within the stomach, overnight fasting has little effect (Husted et al, 2009).

> **Recommendations — omeprazole and sucralfate:**
> - In combination is a valid first-line treatment option for EGGD
> - Combination therapy should include sucralfate at 12 mg/kg PO BID and omeprazole at 4 mg/kg PO SID. Lower doses of omeprazole are unlikely to be effective for treatment or prevention
> - Should only be used if omeprazole can be administered after 8 hours of feed deprivation and a minimum of 30 (preferably 60–90) minutes prior to feeding
> - Should be administered such that sucralfate is administered at least 30 minutes after omeprazole
> - Is used following the prescribing cascade as sucralfate does not have a veterinary licence[a].

Omeprazole long-acting intramuscular injection

A long-acting preparation of omeprazole that is administered by intramuscular injection at 4 mg/kg has been reported to be more effective than oral formulations in increasing the pH in the ventral stomach (Sykes et al, 2017b). Following intramuscular injection of the long-acting formulation, marked acid suppression occurs for between 4 and 7 days after which pH gradually decreases. The long-acting injection should therefore be administered at 5–7 day intervals. The greater consistency and magnitude of acid suppression achieved with the long-acting injectable formulation may be helpful in determining whether clinical signs are related to EGGD as a clinical response is usually seen within 1–3 days (Rendle unpublished data; Sykes, unpublished data).

Limited investigations have been performed to date, but the rates of healing of EGGD that have been reported with the long-acting injectable formulation of omeprazole are notably higher than the rates reported with the use of oral omeprazole as monotherapy. Sykes et al (2017b) reported 75% healing and 100% improvement in 12 horses at 2 weeks after two injections of long-acting omeprazole in Thoroughbred racehorses with EGGD. In sports and leisure horses, Rendle (unpublished data) reported 64% healing (normal mucosa) and 96% improvement of EGGD in 30 horses with two injections at 7 day intervals and 86% healing and 93% improvement within 4 weeks with ≤ 4 injections. The injection is oil based and in <10% of cases (Rendle, unpub-

lished data) transient, non-painful swelling may develop which resolves spontaneously over a few days. Most reactions are associated with injection into the pectoral muscles and reactions are seen less commonly with injection into the gluteals (which is preferred due to the greater muscle mass) or the neck. Injection is quicker and easier if the vial is warmed to body temperature prior to use. Further investigations of safety and efficacy with larger numbers of horses are warranted. There may be value in combining long-acting omeprazole with sucralfate, although there is currently no evidence to recommend this. The long-acting omeprazole formulation does not hold a veterinary licence and is therefore used following the prescribing cascade.

> **Recommendations — injectable omeprazole[a]:**
> - Is a valid first-line treatment option for EGGD
> - Should be used at 4 mg/kg IM every 5–7 days
> - Does not necessitate manipulation of normal feeding routines
> - Might logically be used in conjunction with sucralfate at 12 mg/kg PO BID, though this combination has not been investigated
> - Is associated with a risk of transient reaction at the injection site, a risk which is minimised by injecting into the gluteals
> - Requires further study as limited efficacy and safety data are available
> - Does not hold a veterinary licence and is used following the prescribing cascade[a].

Intravenous omeprazole is licensed for human use, but in horses its duration of action is too short for the drug to be a practical treatment option (Sykes et al, 2015c). A single clinical study has been performed in which individual responses were inconsistent and there was no improvement in EGGD lesions; treatment was only administered for 5 days (Andrews et al, 2006).

Misoprostol

Misoprostol is a prostaglandin analogue and an increasingly popular treatment for EGGD that has multiple mechanisms of action that may be of benefit. Misoprostol suppresses acid production (Sangiah et al, 1989) and inhibits neutrophilic inflammation (Martin et al, 2017) and is therefore a logical treatment for EGGD. However, there is limited evidence of its efficacy. In a

study of 40 sports horses with clinically significant EGGD, misoprostol at 5 µg/kg PO BID resulted in healing (return to normal appearance) in 73% of horses compared with only 22% healing in horses that were receiving both omeprazole and sucralfate (Varley et al, 2016).

Diarrhoea has been reported in association with high doses of misoprostol but is rare at standard clinical doses and, in the authors' experience, is mild and self limiting. Misoprostol may compromise the acid suppressive effect of proton pump inhibitors and the two treatments should not be used simultaneously. The concurrent use of misoprostol and sucralfate has not been investigated and, although there are no known contraindications to this combination, there is no evidence to recommend it currently.

Misoprostol has the potential to induce abortion in humans and potentially in the horse, although some safety data exist for its use in mares between 100–130 days of pregnancy (Jacobson et al, 2012). While it is licensed for use in humans for the treatment of gastric disease, there is no veterinary licence and mistoprostol is therefore used following the prescribing cascade. Potential benefits have to be balanced against the risks to human handlers of the medicine.

> **Recommendations — misoprostol:**
> - Is a valid first-line treatment option for EGGD
> - Should be used at a dose of 5 µg/kg PO BID
> - Cannot be recommended in breeding mares
> - Should not be used in combination with proton pump inhibitors
> - Requires further study as limited efficacy and safety data are available
> - Is licensed for the treatment of refractive chronic gastric disease in people but does not hold a veterinary licence and is therefore used following the prescribing cascade[a]
> - Should only be used with careful consideration of potential risks to human health.

Antimicrobials

The role of bacteria in the aetiopathogenesis of EGGD is unknown, but they are found occasionally colonising some chronic lesions (Hepburn, unpublished data). *Helicobacter*-like organisms are not identified consistently in EGGD lesions and they are not considered to be an important factor in the development or persistence of EGGD (Sykes et

al, 2015a). Antimicrobials should not be used for the routine management of EGGD and do not improve healing when used as a first-line therapy (Sykes et al, 2014d). Antimicrobials should only be used in refractory cases where there is evidence of neutrophilic inflammation and relevant bacterial species (e.g. *E. fergusonii*, *S. bovis* and *E. faecium*) are identified as a profuse growth on culture of biopsy specimens. Lesions that fulfil these criteria are typically fibrinosuppurative in appearance; however, the majority of fibrinosuppurative lesions will heal without the need for antimicrobials.

Recommendations — antimicrobials:
- Are not indicated as a first-line treatment
- Should only be used in cases that are refractory to initial treatment and with supportive histology and bacteriology findings
- Are very rarely indicated, likely <1% cases, and should be used in accordance with the principles of antimicrobial stewardship including bacterial sensitivity testing.

Glucocorticoids

Glucocorticoids are not indicated as a first-line treatment for EGGD. However, the authors concluded that a small subset of cases heal with glucocorticoid treatment after failure with other treatments, which is logical given the lymphoplasmacytic inflammation that is present in the majority of cases. It is hypothesised that some EGGD cases may have more generalised IBD or represent dietary intolerances hence the improvement with glucocorticoid treatment. There is no evidence to guide selection and dosing of glucocorticoids and they are not licensed for this indication in horses. Prednisolone at 1–2 mg/kg PO SID or dexamethasone at 0.05–0.1 mg/kg PO SID would typically be used by the authors. Glucocorticoids should be administered once daily in the early morning to minimise effects on the hypothalamic pituitary adrenal axis.

Recommendations — glucocorticoids:
- Are not indicated for first-line treatment
- May be indicated in cases that have not improved with first-line treatments
- Are indicated if there is evidence or suspicion of generalised inflammatory gastrointestinal disease
- Are not licensed for the treatment of EGGD[a].

Others

There is no evidence to support the use of the following unlicensed products for the treatment of EGGD:
- Ranitidine
- Aloe vera
- Pectin/lecithin complexes
- Polysaccharides
- Kaolin
- Bismuth subsalicylate
- Sea buckthorn
- Acupuncture
- Homeopathy.

While some of these products/approaches might have merit for the prevention of disease, they are unlikely to be of benefit in treatment and as interactions with other treatments are unknown their use ought to be avoided unless further evidence becomes available.

Summary of treatment recommendations

Based on current evidence the use of one of three first-line treatment protocols[a] is recommended as shown in *Figure 12*:
- Oral omeprazole at 4 mg/kg PO SID with sucralfate at 12 mg/kg PO BID. This option is only appropriate if feed is withheld for a minimum of 8 hours before and 30 minutes after the administration of omeprazole and if sucralfate can be administered at least 30 minutes after the administration of omeprazole.
- Misoprostol at 5 µg/kg PO BID. The risks of misoprostol to human health must be considered carefully and it may not be considered appropriate where there are concerns over human exposure.
- Long-acting omeprazole at 4 mg/kg IM every 5 to 7 days.

While they are different conditions, EGGD and EGSD frequently occur concurrently. EGSD lesions would be expected to resolve using any of these three treatment options and treatment decisions should therefore be focused on finding the most effective treatment for EGGD.

Clinical progression, monitoring and treatment of non-responders

Rates of healing are difficult to predict. Raised, nodular, haemorrhagic and fibrinosuppurative lesions appear to take longer to heal than flat erythematous lesions. Mucosal lesions may heal within 2–4 weeks, but frequently take far longer

to resolve. When there is thickening, nodule formation or metaplasia resolution is likely to take months.

The aim of treatment should be complete resolution and a mucosa that has a normal appearance. If treatment is discontinued when there are still signs that are indicative of the presence of mucosal inflammation, there is a risk that lesions will worsen and clinical signs will recur.

Regardless of the primary treatment, repeat gastroscopic examination at monthly intervals is recommended with continual assessment of the clinical response also being important. It is important that sufficient time is allowed for each treatment to take effect and frequent changes to the treatment regimen should be avoided. If there is improvement then the same treatment regimen should be continued for a further month. If there is no improvement then an alternative treatment regimen should be initiated (*Figure 12*).

If there is no improvement at 3 months, biopsy should be considered. Biopsies enable assessment of bacterial involvement and the elimination of uncommon causes of gastric lesions such as *Habronema* spp. and *Drachsia* spp. Both of these conditions are extremely rare. Investigation of more generalised gastrointestinal disease should also be considered, or the response to glucocorticoids could be assessed.

Once lesions have resolved treatment should be discontinued. Although there can be a rebound increase in acid production following the withdrawal of acid suppressant therapy in man, there is no evidence that this is the case in horses and it is unknown whether a gradual reduction in acid suppressant therapy is of any clinical benefit. Low (1–2 mg/kg) doses of oral omeprazole are unlikely to result in sufficient acid suppression to be of clinical benefit and efficacy will be further impaired by feeding unless the routine of fasting prior to feeding is maintained. The benefits of reduced doses of misoprostol or injectable omeprazole have not been investigated; however, as with oral omeprazole, it is unlikely that low doses will result in sufficient acid suppressive effect to merit their use.

It is important that clinical signs are monitored once treatment is withdrawn. The need for follow-up gastroscopy should be determined on a case-by-case basis. Follow-up gastroscopic examination between 1 and 3 months after the withdrawal of treatment will provide an indication of whether management changes are sufficient to prevent recurrence.
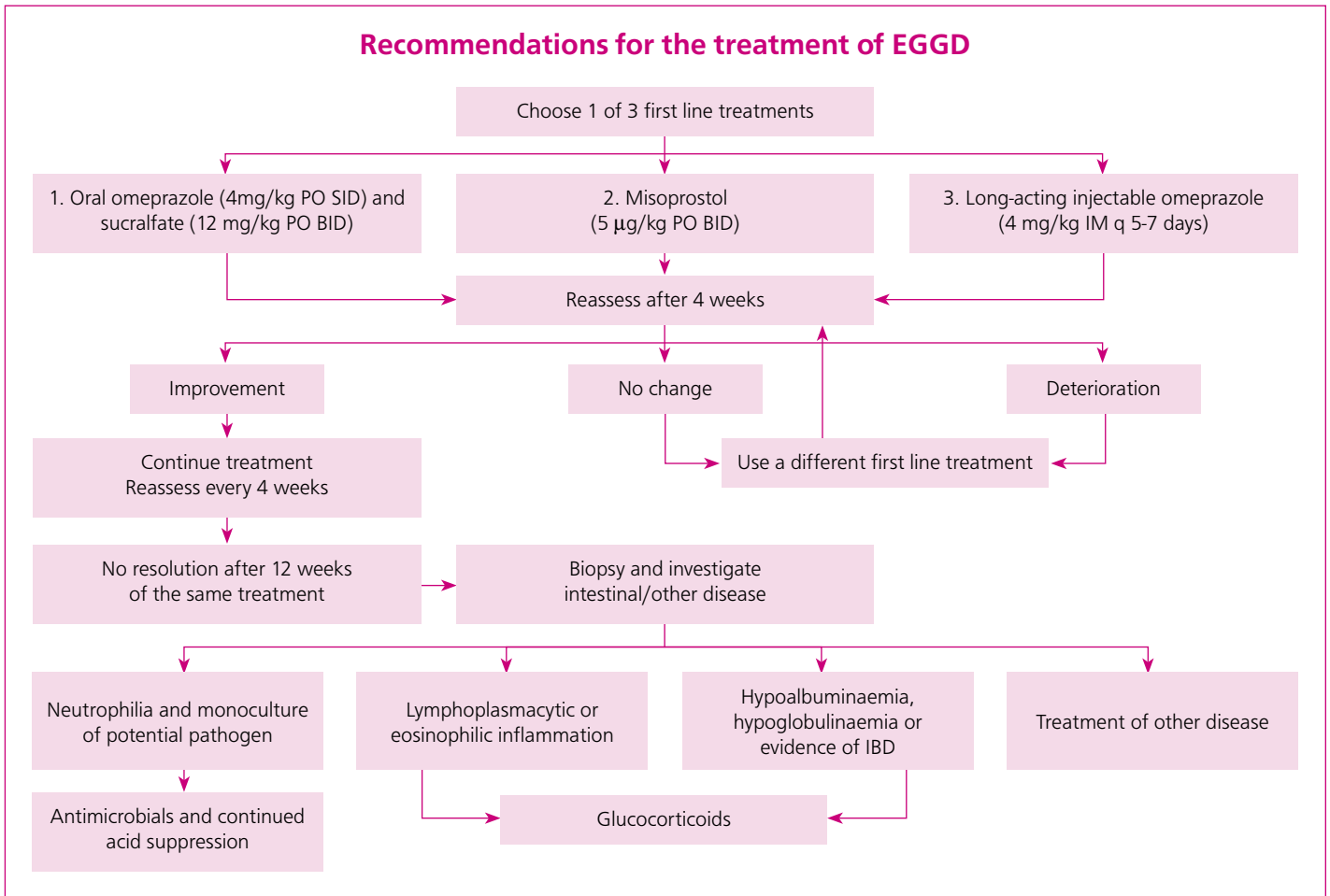
Recommendations for the treatment of EGGD

Choose 1 of 3 first line treatments

1. Oral omeprazole (4mg/kg PO SID) and sucralfate (12 mg/kg PO BID)

2. Misoprostol (5 μg/kg PO BID)

3. Long-acting injectable omeprazole (4 mg/kg IM q 5-7 days)

Reassess after 4 weeks

Improvement

No change

Deterioration

Continue treatment Reassess every 4 weeks

Use a different first line treatment

No resolution after 12 weeks of the same treatment

Biopsy and investigate intestinal/other disease

Neutrophilia and monoculture of potential pathogen

Lymphoplasmacytic or eosinophilic inflammation

Hypoalbuminaemia, hypoglobulinaemia or evidence of IBD

Treatment of other disease

Antimicrobials and continued acid suppression

Glucocorticoids

Figure 12. Recommendations for the treatment of Equine Glandular Gastric Disease (EGGD).

Recommendations for monitoring.
- Gastroscopic examination should be performed at monthly intervals during treatment to assess responses
- Frequent changes to the treatment regimen should be avoided
- If there is no improvement at 3 months, biopsy and investigation of other disease should be considered
- Clinical signs should be monitored carefully during, and following cessation of treatment.

Prevention of EGGD

Omeprazole at 1 mg/kg PO SID has been used as a means of preventing the recurrence of gastric disease. While this regimen may be of some benefit in the prevention of EGSD recent evidence indicates it will be insufficient acid suppression to prevent EGGD. Furthermore, EGGD is not induced by acid injury.

In horses with a history of EGGD, or those considered to be at high risk, the addition of oil and mucosal protectants to feed may be of benefit. Maize oil may be added to feed at 0.1 ml/ kg bwt (Cargile et al, 2004) or at higher doses if additional caloric intake is not contraindicated. Rapeseed oil is a cheaper alternative that is likely to be equally effective and may contain a better balance of omega 3 to omega 6 fatty acids.

Supplemental pectin and lecithin complexes have shown to be of benefit in small numbers of horses (Venner et al, 1999; Ferrucci et al, 2003). Sugar beet is high in pectin and may be fed as a less expensive alternative to proprietary pectin and lecithin products, although no data exist to support its use in this setting.

Conclusions

EGGD is a distinct disease entity from ESGD with differences in epidemiology, prevalence, risk factors, pathophysiology and response to treatment. The nutritional, management and pharmaceutical strategies for prevention and

treatment of ESGD cannot be extrapolated to EGGD. This document has outlined measures that may help to prevent EGGD. Options for treatment are summarised with there being three suggestions for first-line treatment regimens that should be selected on a case-by-case basis and should be used in accordance with the prescribing cascade as all three options necessitate the use of unlicensed medicines. Further treatment options are proposed for cases that are refractory to treatment. The authors acknowledge that many of the recommendations are made based on weak evidence or expert opinion and urge all stakeholders to support future research into EGGD so that more evidence-based recommendations can be made in the future. **EQ**

Footnotes

[a] These recommendations require the use of unlicensed medications which the authors consider justified on the prescribing cascade. Clinicians should satisfy themselves that the

use of unlicensed medicines is necessary on a case-by-case basis and in accordance with professional obligations. Informed and written consent should be obtained and an appropriate advice sheet should be issued with the unlicensed medicine. Further information and suitable advice sheets are available from BEVA: https://www.beva.org.uk/cascade.

[b] According to the grading system that was in use at the time (The Equine Gastric Ulcer Council, 1999) Grade 1 was classified as 'The mucosa is intact, but there are areas of reddening or hyperkeratosis (squamous)'. Grading EGGD lesions is no longer considered appropriate.

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