UNIVERSIDADE DE LISBOA

Faculdade de Medicina Veterinária

THE USE OF GASTROSCOPY IN THE EVALUATION OF TREATMENT RESPONSE OF EQUINE GASTRIC ULCER SYNDROME (EGUS)

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DISSERTAÇÃO DE MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

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LISBOA

“My mother, is the bone of my spine, keeping me straight and true.
She is my blood, making sure it runs rich and strong.
She is the beating of my heart.
I cannot imagine a life without here.”

Kristin Hannah

I wish to dedicate this thesis to my late mother,
for always nursing me with love and strength while I pursue my purpose in life.

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Abstract

Title: The use of gastroscopy in the evaluation of treatment response of Equine Gastric Ulcer Syndrome (EGUS)

Despite the existence of effective treatment (Omeprazole) for EGUS, given the high cost and recurrence rate, it is essential to take preventive management and dietetic measures.

The purpose of this retrospective study was to evaluate the treatment response with omeprazole using gastroscopy, identify risk factors associated with the appearance of gastric lesions and evaluate the effect of management changes in the prevention of recurrence, between the years of 2010 and 2015.

69 horses with suspected EGUS were evaluated by physical examination, gastroscopic examination and measurement of gastric fluid pH values. The final sample group were the 22 horses with confirmed lesion grade≥1 in the first gastroscopy, then treated with omeprazole 4mg/kg bwt, PO, SID, for 28 days, followed by 2mg/kg bwt, SID, PO, for another 28 days, and recommended management and nutritional measures. After this period, all horses were re-evaluated. Information was gathered from the horse's owners using two questionnaires regarding clinical complaints at both examinations and regarding treatment follow-up.

The occurrence of EGUS was confirmed in 100% (n=69). Clinically relevant symptomatology was identified, were signs of colic in the last year was the most frequent clinical complaint (59,10%) and was significantly associated with higher numeric scores (p=0,029) whereas the coat condition was significantly associated with severity score (p=0,038). After treatment, there was a general improvement of the lesions and clinical signs, with total remission of the lesions in 4,5% (n=2/22). Owner's responses on signs of colic (p=0,031) and body weight (p=0,008) and body weight registered at physical examination (p=0,011) were statistically different, along with an increase in mean pH values show evidence of a certain level of efficacy of treatment with omeprazole. None of the presumable risk factors were found significantly associated with the presence or degree of gastric ulceration (p>0,05). Still, exercise and administration of NSAIDs may have determined a lower treatment response. No significant changes in ulcer scores were identified for any levels of implementation of management measures. Nevertheless, decreased ulcer scores were identified in 45,5% (n=10/22) in those who implemented the management changes in some way.

Keywords: Equine Gastric Ulcer Syndrome, gastroscopy, omeprazole, management, treatment.

Resumo

Título: Utilização de gastroscopia na avaliação da evolução do tratamento de Síndrome de Úlcera Gástrica Equina (SUGE)

Apesar da existência de tratamento eficaz (Omeprazol) para SUGE, dado o elevado custo e taxa de recorrência, é essencial tomar medidas preventivas de maneio ambiental e dietética.
O objetivo deste estudo retrospectivo foi avaliar a resposta ao tratamento com Omeprazol utilizando gastroscopia, identificar fatores de risco associados ao aparecimento de lesões gástricas e avaliar o efeito das alterações de maneio na prevenção de recorrência, entre os anos de 2010 e 2015.
Foram avaliados 69 equinos com suspeita de SUGE por exame físico, exame gastroscópico e medição dos valores de pH gástrico. A amostra final foi de 22 equinos com lesões grau≥1 confirmados na primeira gastroscopia, tratados com Omeprazol 4 mg/kg PV, PO, SID, por 28 dias, seguido de 2mg/kg BWT, SID, PO, por mais 28 dias, e recomendado alterações de maneio ambiental e dietético. Após esse período, todos os equinos foram reavaliados. Informação a respeito das queixas clínicas em ambos os exames e do seguimento do tratamento foi recolhida dos proprietários dos cavalos usando dois questionários.
A ocorrência de EGUS foi confirmada em 100% (n=69). Foi identificado sintomatologia clinicamente relevante, tendo sido a queixa clínica mais frequente sinais de cólica no último ano (59,10%, n=13/22) estando associada significativamente com o grau numérico (p=0029), enquanto a condição de pelagem foi significativamente associada ao grau de gravidade (p=0038). Após o tratamento, verificou-se uma melhoria geral das lesões e dos sinais clínicos, com remissão total das lesões em 4,5% (n=2/22). As respostas dos proprietários sobre sinais de cólica (p=0,031) e peso corporal (p=0,008) e peso corporal registados no exame físico (p=0,011) foram estatisticamente diferentes, juntamente com um aumento nos valores médios de pH mostram evidências de um certo nível de eficácia do tratamento com Omeprazol. Nenhum dos fatores de risco foram encontrados significativamente associados à presença ou grau de ulceração gástrica (p > 0,05). No entanto, o exercício e a administração de AINEs podem ter determinado uma resposta de tratamento mais baixa. Não foram identificadas alterações significativas nos graus de úlcera tendo em conta níveis de implementação das medidas de maneio diferentes. No entanto, foi identificada a diminuição do grau de ulceração em 45,5% (n=10/22) naqueles que implementaram as mudanças de maneio de alguma forma.

Palavras-chave: Síndrome de Úlcera Gástrica Equina, gastroscopia, omeprazol, maneio, tratamento.

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List of Abbreviations and Symbols

% - Percentage

& - And

+ - Plus

< - Less than

> - More than

= – Equal to

± – Plus or minus

® – Registered trademark

AINEs – Anti-inflamatórios não esteróides

BID - *bis in die*

bwt - Body weight

CI95% - Confidence Interval of 95 per cent

Cl^- - Chloride ion

cm – Centimetre

CRT - Capillary refill time

DM – Dry matter

DGEE – Doença Gástrica Escamosa Equina

DGGE – Doença Gástrica Glandular Equina

e.g. – exempli gratia

ECL - Enterochromaffin-like cells

EGUS – Equine Gastric Ulcer Syndrome

EGF - Epithelial growth factor

EGFr - Epithelial growth factor receptor

ESGD - Equine Squamous Gastric Disease

EGGD - Equine Glandular Gastric Disease

EP3 - Prostaglandin E2 receptor 3

FOBT – Faecal Occult Blood Test

FVM-ULisboa - Faculdade de Medicina Veterinária – Universidade de Lisboa

g - Gram

h - Hour

H^+ - Hydrogen ion

i.v - Intravenous

mg/kg - Milligram per kilogram

ml - Millilitre

mmol/l - Millimoles per litre

MR – Mean rank

n - Total sample number

n/a – Not applicable

NSAIDs - Nonsteroidal anti-inflammatory drugs

NSC - Nonstructural carbohydrates

NTA - Nothing to add

p - p-value

PGE2 - Prostaglandin E2

PO – *per os*

SB - Standardbred

SC - Subcutaneous

SD – Standard deviation

SID - *semel in die*

SUGE – Síndrome de Úlcera Gástrica

TB – Thoroughbred

™ - Trademark

$\chi 2$ - Pearson's chi-squared test

kg - Kilogram

I. Report on the activities developed during the curricular internship

This report concerns the curricular internship from the integrated master's degree in veterinary medicine. The internship took place at the Equine Unit of the Teaching Hospital, Faculdade de Medicina Veterinária, Universidade de Lisboa (FMV-ULisboa).

In the last two years of her integrated Masters, the author took an on and off training period starting in September 2013, while finishing her studies, working under the guidance of Professor Paula Tilley, and under the supervision of Dr Joana Simões, Professor Rita Garcia da Fonseca, and Professor Luis Lamas. Following this period, she started the curricular internship *per se* in 2016 for seven months, between March and September. Overall, the author summed a total of 1500 hours of training.

During this time, she collaborated in several services of the hospital, such as internal medicine, imaging services, surgical services and postoperative care, as well as accompanying Professor Tilley on house calls.

The Equine Unit of the FMV-ULisboa is considered a referral hospital, but also provides primary and preventive health care programs, as well as a wide range of medical, surgical and dental services, as well as an emergency service 24hours a day, 365 days a year.

In the internal medicine service, she observed several cases of prophylactic care, namely vaccination and wellness care, preventive dental care, equine identification, blood sampling for identification purposes, microchipping, deworming, and prepurchase examination. Besides prophylactic care, there were other consultations with appointments of different departments such as dermatology, gastroenterology, odontology, orthopaedics, trauma, neurology, ophthalmology, oncology, cardiology, pneumology, andrology, gynaecology and obstetrics, neonatology, intensive care and parasitology.

While in the internal medicine service, a variety of cases were observed, from physical examinations of patients to assisting the responsible physician with any medical acts and diagnostic techniques. These included a wide range of minimally-invasive procedures, in particular, digital radiology, ultrasound (musculoskeletal, cardiac, pulmonary, abdominal and obstetric) and endoscopy (gastroscopy, vaginoscopy, rectoscopy, static and dynamic upper and lower respiratory endoscopy). The author assisted the physician in charge by preparing the patient for the exam, preparing and placing of the necessary equipment, as well as the cleaning and disinfection of the equipment (ultrasound probe and endoscope).

While in the surgery service she was involved in several procedures, starting with the preparation of the operating room, next in the preoperative care of the surgical patient, performing a physical examination of the surgical patient, administering the proper medication prescribed by the surgeon, as well as the anaesthesiologist, and postoperative care.

The author had the opportunity to assist in small procedures such as skin suturing, drainage and removal of abcesses, as well as large procedures such as castration, tenotomy, exerisis of tumours, rectum and perineum reconstruction.

The surgeries that were observed took place in the operating room of the hospital or in the field. During postoperative care, the author was responsible for monitoring vital signs of recovering patients and administering the medication prescribed by the supervising physicians.

During this period the author also collaborated in a few courses that took place at the teaching hospital of FMV-ULisboa, such as the XXXIX Jornadas Médico-Veterinárias (Dynamic Endoscopy Workshop) which took place in October of 2015, and the "Avaliação cardio-respiratória, endoscopia no cavalo e ecografia do aparelho musculo-esquelético" in November of 2015.

The necessary information was gathered for this study during this time frame, namely the chart information of suspected patients of Equine Gastric Ulcer Syndrome (EGUS), such as their physical examination, weight, gastroscopy examination, gastric pH level, and epidemiological questionnaire. The development of this work was accepted to be presented as a poster at the IV Jornadas do Grupo de Trabalho de Investigação em Equídeos, Golegã (November 2015) (available in Annexe 1).

II. Literature review

1. Introduction

Equine gastric ulcer syndrome (EGUS) is a wide-reaching and common disorder in the horse regardless of age, gender, or breed. It has been considered a conundrum for several decades by practitioners, horse owners, riders and trainers for its economic impact and clinical importance, due to its high prevalence, unspecific clinical signs and negative impact on performance (Nadeau & Andrews, 2009).

Many risk factors have been implicated in the aetiology of this syndrome, such as stress, diet and feeding routine, type and intensity of exercise, stall-confinement and the administration of non-steroidal anti-inflammatory drugs (NSAIDs) (Sykes & Jokisalo, 2015). Despite many efforts, due to the nonspecific nature of the symptomology and the absence of specific biochemical and haematological parameters, endoscopic examination remains the only reliable method to determine a definite diagnosis (Sykes, Hewetsen, Hepburn, Luthersson & Tamzali, 2015).

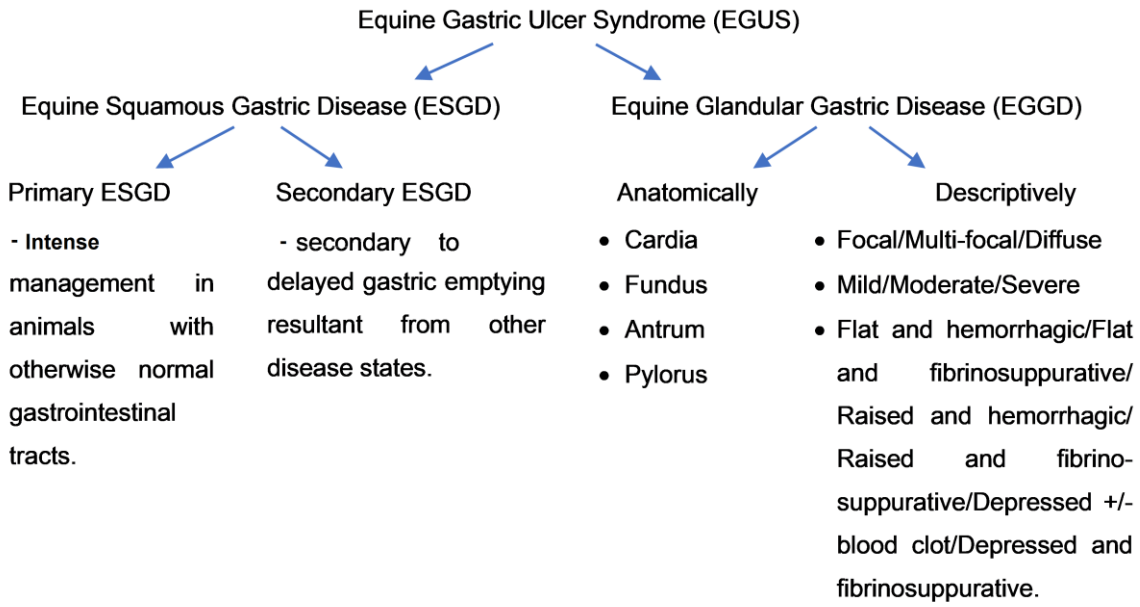
2. Terminology

The term EGUS was first recognised in a consensus compiled by the Council in 1999 to describe gastric ulceration in the horse (Andrews, Bernard,et al., 1999). However, since then, the term has been misused, and therefore, an effort has been made to define and elucidate the terminology appropriately (Merritt, 2009). Similarly, in Human Medicine, the term peptic ulcer disease (PUD) is considered a hypernym to define ulcerative lesions in the oesophagus, stomach and duodenal mucosa (Malfertheiner, Chan, & McColl, 2009).

Recently the terminology has been polished, recognising EGUS as the blanket term to describe gastric ulceration, while distinguishing Equine Squamous Gastric Disease (ESGD) and Equine Gastric Disease (EGGD) separately according to the affected anatomic region (Sykes, Hewetson, et al., 2015). Therefore, it is unfitting to extrapolate the knowledge of one syndrome to the other. Furthermore, collection of information is required for each condition due to the stated differences between the squamous and glandular mucosae, which include differences in prevalence within a population (Begg & O'sullivan, 2003; Habershon-Butcher, Hallowell, Bowen & Sykes, 2012; Luthersson, Hou Nielsen, Harris & Parkin, 2009b; Murray Nout & Ward, 2001b; Tamzali, Marguet, Priymenko & Lyazrhi, 2011), risk factors (Habershon-Butcher et al., 2012), response to treatment with omeprazole and prevention (Sykes, Sykes, & Hallowell, 2014d, 2014a, 2015). However, the presence of squamous and glandular ulceration within an individual was found unrelated (Begg & O'sullivan, 2003; Luthersson et al., 2009b; Murray, Nout, et al.,

2001b). A synopsis of the reinforced and recommended terminology of EGUS is displayed in Figure 1.

Figure 1 – An overview of the recommended terminology for describing equine gastric erosive and ulcerative diseases (Adapted from Sykes et al., 2015).



3. Anatomy of the equine stomach and gastric acid secretion

The horse's stomach consists of a single composite large chamber interposed between the oesophagus and small intestine (König & Liebich, 2004). The oesophagus joins the stomach through the cardia in the right median plane of the abdomen, while the pylorus continues into the duodenum more to the left, both of which are controlled by sphincters (König & Liebich, 2004). The cardiac sphincter in the horse is very well developed, and this, together with the oblique entrance of the oesophagus is believed to be responsible for the presumed inability of the horse to vomit. Although vomiting and regurgitation are considered rare, it may occur (König & Liebich, 2004).

It possesses visceral and parietal surfaces and greater and lesser curvatures (König & Liebich, 2004). The lesser curvature is very short, compared to the greater curvature, causing the cardia and pylorus to have a nearby location (Sisson, 1986).

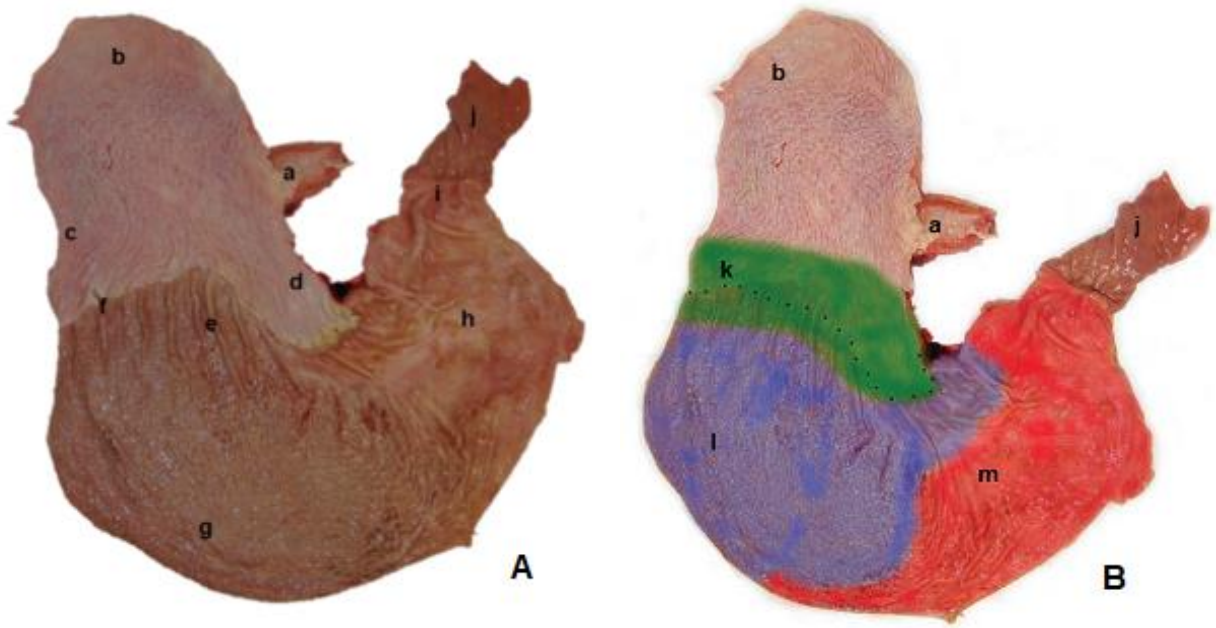
The stomach's position is closely related to the development of the greater omentum and the lesser omentum (König & Liebich, 2004). Also, the exact shape and position depend on the degree of filling (König & Liebich, 2004). Still, the physiological capacity varies between 5 and 15 litres, which is smaller compared to the size of the animal and the volume of forage it consumes

(Dyce, Sack & Wensing, 2004). This fact should be considered when administering fluids via a nasogastric tube to avoid overdistension (König & Liebich, 2004).

The structure of the gastric wall is the same as that of the oesophagus and consists of the following layers, inward to outward: mucosa, submucosa, muscular layer and serosa (König & Liebich, 2004).

The mucosa can be divided into two core regions: the non-glandular region and the glandular region (Figure 2). The squamous non-glandular region includes the dorsal third of the stomach (orad), which is covered with stratified squamous epithelium, identical to the one found lining the oesophagus, as well as the entrance to the stomach via the cardia (Hepburn, 2011). Histologically, no glandular structures of any kind are found within it that could establish assumed digestive or mucosal protective mechanisms. Further, it was found that in an Ussing chamber it maintains no short circuit current, demonstrating the absence of active transport processes (Merritt, 1999). The functional role of this region is yet to be determined (Hepburn, 2011). However, it is believed that since it is not generally exposed to acid, it allows fermentative digestion processes to occur (Klein, 2013).

Figure 2 - A *post mortem* specimen of the equine stomach illustrating the anatomical regions of the stomach (Addapted from Hepburn (2011)).



Legend: A–Equine gastric mucosal anatomy; B–Illustration of gastric pH and content stratification.
a-Oesophagus; b-Squamous fundus; c-Greater curvature; d-Lesser curvature; e-Cardia; f-Margo plicatus; g-Glandular fundus; h-Pylorus region; i-Pylorus; j-Duodenum; k-Low density matter (pH 5-7); l-Medium density matter (pH 4-5); m-High density matter (pH 1-2).

The *margo plicatus* is the delineation region between the squamous and glandular regions of the stomach that lines the distal half of the equine stomach (Hepburn, 2011). Some authors have considered the *margo plicatus* as part of the non-glandular mucosa, while others found that, due to its distinct and complex capillary network and susceptibility to ischemic lesions, it should be seen as an independent region in the transition between the two mucous membranes (Staszyk, Jackowiak, Godynicki, & Gasse, 2001).

The distal two-thirds of the stomach is covered with glandular mucosa, which can then be divided into three regions: glandular fundus (body), pyloric antrum and cardiac glandular region. The glandular fundus (body) occupies the mid third of the stomach, the pyloric antrum occupies the most distal third, and the cardiac glandular region is the narrow strip of glandular mucosa adjacent to the *margo plicatus* (Hepburn, 2011). All these areas contain similarly structured glands, but each has particular cell types with different functions (Klein, 2013; König & Liebich, 2004).

The glandular mucosa of the stomach is comprised in part of simple columnar epithelium, which contains gastric pits, forming the entrance into the gastric glands (König & Liebich, 2004). These epithelial cells, known as surface mucous cells, excrete a thick alkaline mucus that protects the mucosa from the highly acidic gastric fluid (Klein, 2013).

Within the parietal region of the gastric fundus are parietal cells, zymogen (or chief) cells and enterochromaffin-like cells (ECL) that make up the gastric glands (Merritt, 1999). The parietal cells are clustered in the neck of the gland and have the primary function of secreting hydrochloric acid, under the stimulation of histamine, which is produced in a paracrine mechanism by the ECL cells. These cells also modulate gastric mucosal blood flow via the action of serotonin (5-HT) (Klein, 2013). While, in the base of the gland, the chief cells secrete pepsinogen, the precursor to the digestive enzyme pepsin (Klein, 2013). Also, among the parietal cells are neck mucus cells that secrete a thin mucus, less viscous than that of the surface mucous cells. Besides their secretory function, they secondarily function as replacement epithelial cells (Klein, 2013).

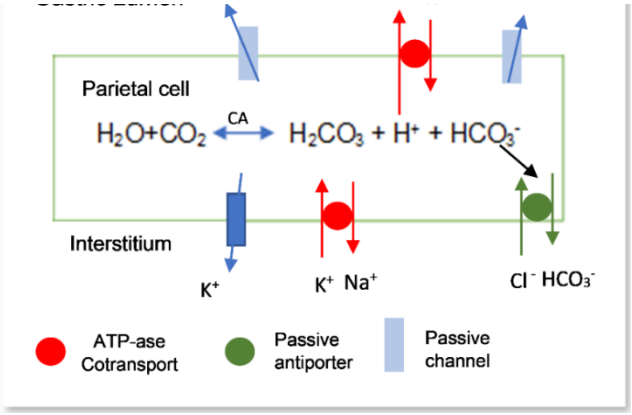
The cardiac and pylorus region resemble parietal region in structure, however, contain different cell types (Klein, 2013). The gastric antrum and pylorus have no parietal cells, but their ramified glands contain gastrin-producing G-cells (Klein, 2013). Also, a large number of somatostatin-immunoreactive cells have been shown in this region of the equine stomach. Along with other functions, somatostatin has been shown to be involved in the endogenous control of gastric acid secretion, while sampling intragastric pH and modulating G-cell gastrin release (Merritt, 1999; Hepburn, 2004). These regions can be incidentally parasitised with larvae of *gastrophilus intestinalis* and may be marked by scars left after their removal (Dyce et al., 2004).

The cardiac mucosa, in the horse and most species, forms a narrow band around the gastric opening of the oesophagus, while in swine it covers a more substantial portion of the proximal stomach (Klein, 2013). Little is known about its function in the horse, but it is thought that the primary secretion is sodium bicarbonate, which may protect the adjacent oesophageal mucosa from the stomach's acid secretion (Klein, 2013).

The horse secretes gastric acid in a continuous, variable manner (Murray, 1994), and the median pH of the ventral stomach of 3.0 over a normal 24h period reflects this (Husted, Sanchez, Olsen, Baptiste, & Merritt, 2008). The acid secretion is predominantly triggered by paracrine, endocrine, and neural stimuli (Yao & Forte, 2003), stimulated by the gastrin, histamine and acetylcholine, a neurotransmitter from the Vagus nerve (Campbell-Thompson & Merritt, 1990).

The hydrogen and chloride ions are secreted by different cellular mechanisms (Klein, 2013). However, the ability of the parietal cell to secrete acid is dependent on active transport, through the H+/K+ ATPase pump (Figure 3), otherwise known as proton pump enzyme, in the cell membrane (Yao & Forte, 2003). This acid secretion occurs against both a concentration and electric gradient, higher than 3 million-fold (Yao & Forte, 2003). Within the parietal cell, H^+ ions are formed from the dissociation of water, then the hydration of CO2 leads to the formation of bicarbonate ion (HCO_3^-), a reaction catalysed by carbonic anhydrase. The bicarbonate is then transported out of the basolateral membrane in exchange for chloride (Yao & Forte, 2003). The discharge of bicarbonate into the blood leads to a small elevation of blood pH (alkaline tide), which serves to maintain intracellular pH in the parietal cell (Yao & Forte, 2003). Hydrogen ions are driven out of the cell, into the lumen, in exchange for potassium through the action of the proton pump (Forte & Zhu, 2010).

Figure 3 - Schematic illustration of the parietal cell transport mechanism (Adapted from Hepburn (2004)).



The bicarbonate trapped in the mucous barrier adhering to the stomach wall forms a pH gradient that allows a physiological pH at the mucosal surface and a pH similar to that of stomach acid at the luminal surface (Andrews et al., 1999).

The horse's stomach presents a dorsoventral gradient (Figure 2B), starting with the squamous mucosa of the fundus (pH 5.46±1.82), followed by the squamous mucosa of the *margo plicatus*

(pH 4.12±1.62), then the glandular mucosa of the pylorus (pH3.09±1.9), being the gastric fluid the most acidic (2.72±1.86) (Murray, Grodinsky, Anderson, Rague, & Schmidt, 1989).

The gastric contents of an adult equid with a regular hay/grain diet, where the roughage is available on a free-choice basis, also have a similar dorsoventral layering. The roughage component of the diet determines this fact seeing that the dense acid liquid is trapped ventrally by the lower density/larger particle size components found dorsally, which is vital to normal gastric function (Hepburn, 2011; Merritt, 2013). Gastric emptying is continuous at a speed that according to the type of content, where liquid contents take only 30 minutes to reduce in half the volume, while solid contents take about 1·5 hours (Hepburn, 2011).

Adult horses may secrete up to 35-40 litres of saliva per day, the majority of which is parotid in origin, with a pH of approximately 7.4 (Eckersall, Aitchison, & Colquhoun, 1985). Saliva secretion has the core function of buffering gastric pH (Bell, Mogg, & Kingston, 2007), consequently, feeding has the buffering effect on gastric pH through effects of increased production of saliva with an increase of mean intragastric pH by one to two units (Murray, Nout, et al., 2001a). The fasting state was shown to increase the acidity of the gastric fluid from a median pH of 3.1 to 1.55 (Murray, Nout, et al., 2001a). Still, evidence was found that the greater the dry matter content of the feed, the greater the amount of saliva secreted due in part to the physical composition of the meal and in part to the time needed for adequate mastication (Merritt, 2013).

Hourly recordings regarding proximal gastric pH displayed a clear circadian pattern, and that the pH decreased during the night. This pattern was thought to be involved with the horses feeding behaviour during the night, associated to the fact that the horse consumes most of the daily food intake during the day (Husted et al., 2008).

4. Gastric mucosal defence mechanisms

The mucosal defence system is a complex and dynamic process. It is composed of numerous factors that permit the mucosa to remain intact despite its frequent exposure to substances with a wide range of temperature, pH, and osmolarity, as well as to cytotoxic substances (acids, bile salts, pepsin and digestive enzymes), and bacterial products capable of causing local and systemic inflammatory reactions (Andrews, Bernard, et al., 1999).

The squamous nonglandular mucosa is limited in defence mechanisms, relying mainly on acid repulsion and intracellular buffering (Murray, 1994). Mucopolysaccharides and intercellular tight junctions in the superficial epithelium are the only defences against H^+ entry, however minimal buffering capacity if still offered by the intercellular secretion of $HCO3^-$ and by intracellular buffers (Hepburn, 2004). The initial response of squamous tissues exposed to the acid is

mucosal thickening, whereas prolonged exposure to increased acidity is likely to cause hyperkeratosis, erosion, and ulceration (Murray, 1994).

Gastric glandular epithelium, on the other hand, has several mechanisms to prevent injury by acid secretion, which include secretion of mucus, EGF, bicarbonate buffering, mucosal blood flow, cellular repair, and prostaglandins (Andrews, Bernard, et al., 1999).

Of these, mucosal blood flow is considered to be the most important as it provides the mucosa with the oxygen and nutrients necessary to produce the mucus-bicarbonate layer and allow rapid turnover of epithelial cells (Wallace, 2008). It is also required for removal of VFAs produced by intragastric carbohydrate fermentation, and to prevent the epithelial damage to progress to necrosis of deeper layers of the mucosa (Wallace, 2008).

Epidermal growth factors, which are found in salivary gland secretions, are known to promote mucosal protection, by inhibition of gastric acid secretion, the proliferation of gastric mucosal cells, and also interfere in prostaglandin synthesis process (Andrews, Bernard, et al., 1999). Although earlier studies regarding observation of the EGF receptor (EGFr) in gastric mucosa have focused on the glandular stomach of laboratory animals as an extrapolation for the human glandular stomach, Jeffrey, Murray and Eichorn (2001) found significant evidence that EGFr is also induced in peptic-injured equine gastric squamous epithelium and its involvement in the healing of gastric squamous mucosal ulcers in horses.

The mucus secreted by neck cells acts as both a protective physical barrier and lubricant against physical damage from ingesta, maintaining a neutral pH environment for the mucosal cells, besides being implicated in resisting the diffusion of protons (Andrews, Bernard, et al., 1999). Although the importance of the mucus layer thickness remains unknown, there is evidence that a change in the mucus layer may cause damage to the mucosa, and eventually ulceration (Wallace, 2008). In response, epithelial cells, with the help of bicarbonate secreted by the mucosal cells at the luminal surface, form a mucoid cap in order to maintain a high pH environment. The resulting inflammatory response includes an increase in mucosal blood flow, which helps with the mucoid cap and facilitates leukocyte recruitment and plasma exudation. If this response is weakened, then mucosal repair is slowed or halted, resulting in gastritis or ulceration (Wallace, 2008).

The prostaglandins (PGE1 and PGE2) promote numerous protective functions within the gastric mucosa (Murray, 2010). These substances promote gastric mucosal blood flow, maintain intercellular tight junctions, stimulate bicarbonate and mucus secretion leading to suppression of HCl secretion and gastric acid production. They also facilitate basal cell migration towards the lumen for repairing the mucosa and maintaining the integrity of nonglandular and glandular

mucosa; this takes place by stimulation of active surface-protecting phospholipid production (Andrews & Nadeau, 1999; Murray, 2010; Murray, Schusser, Pipers, & Gross, 1996).

5. Pathophysiology of ESGD and EGGD

Gastric ulceration occurs whenever there is an increase in acid exposure (pH <4). Squamous ulceration occurs rapidly due to minimal defences and reflects increased mobility of acidic gastric fluid, while glandular ulceration forms more slowly after the breakdown of the mucous and bicarbonate barrier (Hepburn, 2011).

In short, as discussed previously, there are three types of EGUS: (1) primary squamous ulceration, (2) primary glandular ulceration, and (3) secondary squamous ulceration (Sykes & Jokisalo, 2014). Primary squamous ulceration occurs when increased acid exposure arises due to a change in the normal gastric pH gradient and content stratification. The primary glandular ulceration is defined when acid exposure occurs due to a failure of the mucosal defences. Finally, the secondary squamous ulceration, in which delayed gastric emptying (typically pyloric disease) increases the residual gastric fluid volume and, later, results in dorsal movement of acid (Sykes, Hewetson, et al., 2015).

5.1. Equine Squamous Gastric Disease (ESGD)

The pathogenesis of ESGD is well described as a result of increased exposure of tissue with limited defence mechanisms to highly acidic gastric contents (pH of <4) (Lorenzo-Figueras & Merritt, 2002). Any disruption of the normal stratification of gastric pH results in an increased risk of ESGD (Lorenzo-Figueras & Merritt, 2002). Mucosal injury was identified within 30 minutes of exposure to solutions of hydrochloric acid using in vitro models (Nadeau et al., 2003; Widenhouse, Lester & Merritt, 2002). Other known factors considered to contribute to the development of the disease are volatile fatty acids (acetic, butyric and propionic acids), the by-products of carbohydrate fermentation by gastric bacteria (Andrews, Buchanan, Smith, Elliott & Saxton, 2006; Nadeau et al., 2003), associated with grain feeding (Luthersson, Hou Nielsen, Harris & Parkin, 2009a). Also, a longer carbon chained fatty acid (5 carbons), known as valeric acid, was found to have a more profound effect on function of the nonglandular mucosal barrier and is thought to be the reason that some cases of ESGD persist despite adequate acid control (Andrews, Buchanan, et al., 2006).

Concentrations of duodenal bile salts may also play a part and can be found in the gastric contents of horses deprived of feed for as little as 14 h (Berschneider, Blikslager, & Roberts, 2010).

Numerous studies (MacAllister et al., 1999; Sykes, 2019; Sykes, Sykes, et al., 2014d; Sykes, Underwood, Greer, McGowan, & Mills, 2017; Sykes, Underwood, McGowan, & Mills, 2015) demonstrated evidence of ESGD healing with effective antacid omeprazole therapy, in the absence of risk factor reduction. Therefore, there is a clear indication that gastric acid is the foremost erosive agent and that the role of short-chain fatty acids and duodenal bile salts are likely to be less critical (Sykes and Jokisalo, 2015).

Exercise and the increase in intra-abdominal pressure are considered an essential factor in the disruption of the pH gradient (Lorenzo-Figueras & Merritt, 2002).

Feed deprivation has also been shown to cause ulcers in the squamous mucosa of horses (Murray, 1994), which is due to repeated exposure of the squamous mucosa to high acidity (Murray, 2010).

Various experimental and epidemiological studies have identified risk factors, while focusing primarily on feeding and exercise practices, for ESGD which influence the management of clinical cases (Bell, Kingston, Mogg, & Perkins, 2007; Dionne, Vrins, Doucet, & Paré, 2003; Husted, Sanchez, Baptiste, & Olsen, 2009; Husted et al., 2008; Luthersson et al., 2009a; Pedersen, 2017).

5.2. Equine Glandular Gastric Disease (EGGD)

The pathogenesis of EGGD has not yet been identified (Sykes, Hewetson, et al., 2015). The normal physiological conditions of glandular mucosa are to be exposed to extremely acidic gastric contents with the pH in the ventral portion of the stomach fairly stable at around 3 (Husted et al., 2008). Thus, it is believed that EGGD results from a failure of the normal defence mechanisms that protect the mucosa from acidic gastric contents (Sykes and Jokisalo 2015). Moreover, the glandular mucosae anatomy and physiology differs according to the different regions (pyloric, fundic and cardiac regions) and the response to treatment is likely to be different between these regions (Rendle et al., 2018).

The factors believed to have a role in the disruption of the defence mechanisms in horses are bacterial agents and nonsteroidal anti-inflammatory drugs (NSAIDs), which are the predominant causes of gastric ulceration in man (Malfertheiner et al, 2009), and will be discussed further in more detail.

6. Prevalence

The prevalence of gastric ulceration varies between ESGD and EGGD and according to breed, purpose or level of training (Sykes, Hewetson, et al., 2015).

The high-risk horse populations have been the main focus of many authors over the last years, such as racehorses in training, which revealed the highest prevalence of between 80 and 100% within the squamous mucosa (Bell, Kingston, Mogg, et al., 2007; Habershon-Butcher et al., 2012; Hammond, Mason, & Watkins, 1986; Rabuffo et al., 2002; Roy, Vrins, Beauchamp, & Doucet, 2005; Vatistas, Snyder, Carlson, et al., 1999). Other horse populations were shown to also be at risk, reaching between 40 and 58%, such as endurance horses (Nieto et al., 2004; Tamzali et al., 2011), show horses (McClure, Glickman, & Glickman, 1999; Murray et al., 1989) and elite western performance horses (Bertone, 2000).

The prevalence of EGGD is less well described than ESGD (Sykes and Jokisalo, 2015), but it has been reported in several studies, ranging from 8% (Sykes and Jokisalo 2015b) to 70% in various populations (Sykes, Bowen, Habershon-Butcher, Green, & Hallowell, 2019; Ward, Sykes, Brown, Bishop, & Penaluna, 2015).

7. Epidemiology

Despite the many factors implicated in the cause of EGUS discussed above, several risk factors for its development have been identified (Videla & Andrews, 2009).

While the notion of distinguishing EGGD and ESGD is a somewhat a recent one, the few studies that have considered these two syndromes independently found that the risk factors have been mostly different. However, the information on risk factors specifically associated with EGGD is still lacking (Sykes, Hewetson, et al., 2015).

Nevertheless, the generally known risk factors for EGUS (not differentiating EGGD and ESGD) are intense exercise (Lorenzo-Figueras & Merritt, 2002; Nieto et al. 2004), a high grain-low roughage diet (Luthersson et al., 2009; Nadeau et al., 2000), water deprivation (Luthersson et al., 2009a), feed deprivation (Husted et al., 2009; Murray & Eichorn, 1996), hospitalization, and use of NSAIDs (MacAllister, Morgan, Borne, & Pollet, 1993; Rabuffo, Hackett, Grenager, Boston, & Orsini, 2009). Other risk factors include stress, transportation (McClure, White, et al., 2005), stall confinement (Bell, Mogg, et al., 2007; Murray & Eichorn, 1996) and the administration of hypertonic electrolytes (Holbrook, Simmons, Payton, & MacAllister, 2005).

Development of EGUS can be as brisk as arising within seven days in some studies (MacAllister et al., 1999; McClure, White, et al., 2005) and the risk of disease increases with time in work (Habershon-Butcher et al., 2012).

7.1. Intrinsic factors: age, gender, temperament and breed

Results suggesting a higher susceptibility towards developing EGUS due to intrinsic factors such as gender, breed, age, and temperament remains debatable (Martínez & Silveira, 2013).

Different associations have been suggested between the age of the horse and the prevalence of gastric ulceration. Vatistas et al. (1999) found that the incidence of gastric ulceration was lowest in 2-year-old horses (70%) and highest in 6-year-old horses (100%). In other studies (Murray et al., 1996; Orsini, Hackett, & Grenager, 2009; Rabuffo et al., 2002), despite little association between age and prevalence of ulcers, there was a significant association between age and severity of ulcers, where young horses (2-year-olds) had the lowest mean ulcer scores, compared with older horses. Several authors (Bell, Kingston, Mogg, et al., 2007; Dionne et al., 2003; Roy et al., 2005) stated that the presence or severity of ulceration did not vary significantly with the horse's age or location within the stomach. On the other hand, Luthersson et al. (2009b) found evidence of older horses being more prone to have lesions in both the glandular and nonglandular regions despite not presenting a higher risk of developing clinically significant EGUS.

In various published studies (Bell, Kingston, Mogg, et al., 2007; Cate, Nielsen, Spooner, O'Connor-Robison, & Schott II, 2012; Dionne et al., 2003; Marqués et al., 2011), sex did not arise as a significant risk factor for gastric ulceration in active racehorses. A few studies (Rabuffo et al., 2002; Vatistas, Snyder, Carlson, et al., 1999) distinguish between castrated and sexually intact males, rather than grouping stallions, colts, and geldings together as males, describing a higher prevalence in geldings. The cause of these findings is thought to associated with a decrease in salivary epidermal growth factor concentration, stimulated by reproductive hormones (Rabuffo et al., 2002). Another study (Chameroy et al., 2006) reported the opposite, where the majority of horses were mare.

McClure et al. (1999) conducted a prevalence study on show-horses which identified the horses' temperament as a possible risk factor, where horses with a nervous character were more likely to have ulceration than quiet or behaviourally normal horses whereas Jonsson and Egenvall (2006) found no influence of temperament over gastric ulceration scores. In a more recent study (Malmkvist et al., 2012), horses with severe glandular ulcers were found to have a higher stress hormone response to novelty, hence more stress sensitive.

Regarding the importance of breed, as previously mentioned, most prevalence studies of gastric ulceration in adult horses have been conducted on Thoroughbreds with the highest incidence, and less on Standardbreds (Begg & O'sullivan, 2003; Dionne et al. 2003; Jonsson & Egenvall, 2006; Luthersson et al., 2009b, 2009a). Both breeds of racehorses are submitted to demanding training requirements and management; however, genetic, behavioural, and gait differences

should be considered (Dionne et al., 2003). Warmbloods were also found to be predisposed to EGGD with a moderate prevalence, along with increased risk associated with multiple handlers/riders (Mönki, Hewetson, & Virtala, 2016).

Prevalence studies on endurance horses are less frequent then racehorses, nevertheless no relationship has been found to date between age, breed or gender on gastric ulcer scores (Tamzali et al., 2011).

7.2. Intense exercise

Once initiating training, several management changes are enforced upon horses, many of which have been proven to increase the risk of EGUS, one of which includes exercise (Vatistas, Snyder, Carlson, et al., 1999).

There are still many contradictory results regarding exercise as a possible risk factor of gastric ulceration. Luthersson et al. (2009a) found no relationship between the level of exercise and EGUS. Numerous other studies conducted in racehorses (Bezděková, Jahn, Vyskočil, & Plachý, 2005; Murray et al., 1996; Orsini et al., 2009; Roy et al., 2005; Sykes et al., 2019) have been comparable with results reported by Hammond et al. (1986), which show that an increase of prevalence and lesion grades of specific anatomical lesion sites within the squamous mucosa were significantly associated with the increasing intensity of long-duration training. Evidence showed that horses in light to heavy training for as short as eight days were at risk of developing gastric ulcers (White et al., 2007).

However, Roy et al. (2005) suggested that seasonality may also have been an influencing factor on EGUS prevalence results because horses did not have access to pasture nor free access to pasture throughout the study period, which has been reported to decrease the prevalence of squamous ulcers in horses. On the other hand, another publication reports a high prevalence of EGUS in reproductive mares kept in pasture (Le Jeune, Nieto, Dechant, & Snyder, 2009).

There are several proposed mechanisms in order to explain the influence of exercise in the development of EGUS. The best described is the previously mentioned relationship between exposure of squamous mucosa to acidic content and training, demonstrated by a study which used an intermittent feed deprivation model (Murray, Eichorn, & Jeffrey, 2001). The acidic gastric contents are pushed dorsally into the squamous portion of the stomach by increased intra-abdominal pressure and gastric compression associated with gaits faster than walk (Lorenzo-Figueras & Merritt, 2002). McClure et al. (2005) suggested that the tensing of abdominal muscles may also occur during any other activity that is typical in recreational use of horses, such as trailer transport, and ESGD can develop within five days. This process is heightened by the fact that physical stress, hence intensive training, has been found associated

with an increase in gastrin plasmatic concentration, which promotes glandular secretion of HCl production within the gastric lumen (Furr, Taylor, & Kronfeld, 1994; Mills, 1996), thus predisposing the mucosa to acid damage (Mönki et al., 2016).

Authors (Vatistas, Snyder, Carlson, et al., 1999) have also proposed that horses may become excited before a race, which could yet again decrease the gastric pH. Another possible cause is that before any event horses are feed deprived, which could induce a loss of buffering effect by reducing feed content and therefore increase acidity in the stomach (Vatistas, Snyder, Carlson, et al., 1999). Squamous ulceration may occur secondary to delayed gastric emptying, caused by lesions within the distal stomach and/or duodenum, which cause abnormal reflux of acidic contents into the proximal stomach (Merritt, 2012). Lorenzo-Figueras and Merritt (2002) also described a decrease in saliva secretion during exercise, which usually buffers gastric fluid, thus contributing to more prolonged acid exposure.

7.3. Feeding routine (intermittent versus continuous feeding, feed deprivation), water deprivation and stall confinement

Feeding practices, along with stall confinement, have been identified as significant risk factors for developing EGUS (Murray & Eichorn, 1996).

When horses initiate training, they are stabled, fed intermittently, and many times have no access to grazing. Grazing causes a constant secretion of saliva and flow of feed material into the stomach, having a buffering effect against the constant gastric acid secretion in the horse (Murray, Nout, et al., 2001a).

Vatistas, Snyder, Carlson, et al. (1999) were able to show evidence of the development of EGUS in all the horses within 14 days of being stabled and initiating a training regimen.

It has been suggested that horses in training fed *ad libitum* may have a lower risk of developing gastric ulcers (Husted et al., 2009; Murray, 1994). Though, even when offered with feed *ad libitum*, they may spend less time eating when stabled, which may decrease this important salivary buffering mechanism (Buchanan & Andrews, 2003).

Horses grazing at pasture, in most cases, have shown a decreased prevalence of ESGD (Murray & Eichorn, 1996). However, other studies presented conflicting results regarding intermittent feed deprivation. Bell, Kingston, Mogg et al. (2007) reported that pasture turnout did not show evidence of having a protective effect. Husted et al. (2008) described a decreased proximal gastric pH in horses apparent after as little as four hours of feed deprivation. This result was only significant during the day, describing the presence of a nocturnal pH gradient in the fed horses. Feeding routines with intervals longer than 6 hours were found to increase the risk of nonglandular lesions (grade ≥2/5) by 3.9 times (95% confidence interval = 1.5 – 10.4) in Danish

pleasure horses (Luthersson et al., 2009a). Pedersen et al. (2015) showed that horses fed forage once daily were at a higher risk of developing ESGD (grade ≥2/4) than horses fed twice daily or more repeatedly.

Conversely, a prevalence study showed that both pastured pregnant and non-pregnant mares had a high prevalence of ESGD (Le Jeune et al., 2009). The authors acknowledged the hypotheses of grain and hay supplementation of these mares as a possible cause of increased gastric VFA concentration and therefore squamous ulceration (Andrews et al., 2017; Nadeau et al., 2000). Another assumption to explain the high prevalence of squamous ulcers in these pastured mares might have been due to the horses consuming less forage during evening hours than during daytime hours, which may result in less saliva production and a low pH environment in the proximal stomach (Husted et al., 2008).

Water deprivation in pasture turnout has also been associated with both ESGD ≥2 and EGGD ≥2. Despite the number of hours not being a significant factor, the risk increased when a horse is deprived of water for 4 hours, without increasing past this period (Luthersson et al., 2009a). Water intake is thought to cause dilution of gastric fluid (Andrews, Frank, et al. 2006) and thus pH, although the passage of water through the stomach may depend on the nature of the gastric contents (Luthersson et al., 2009a).

7.4. Diet type – Starch content and forage type

Size and composition of complementary grain meal are believed to be a critical factor associated with developing ESGD (Andrews et al., 2017; Reese & Andrews, 2009).

High starch diets are rich in digestible carbohydrates, resulting in higher production of VFA in the upper part of the stomach (Nadeau et al., 2000). The extensive fermentation in this area, due to a higher dry matter content and a slower mixture of stomach matter and gastric fluid, associated to higher lactic acid production in the lower gastric layers, causes a rapid decrease in gastric fluid pH (Harris, Coenen, Frape, Jeffcott, & Meyer, 2006). This low pH (<4) of gastric matter causes acid damage to the nonglandular squamous mucosa (Andrews, Buchanan, et al., 2006; Nadeau et al., 2000, 2003), similar to gastroesophageal reflux disease (GERD) in Humans (Lorenzo-Figueras & Merritt, 2002).

Feeding practices of 0,5 kg of grain-based concentrates (40% NSC) per 100 kg bwt have been proven to produce in general 20 mmol/l of VFAs concentration in the stomach up to 5 h after feeding (Nadeau et al., 2000). The high VFAs concentration leads to a decrease in sodium transport accompanied by a loss of tissue resistance and an increase in tissue permeability in the squamous mucosa in an in vitro Ussing system (Andrews, Buchanan, et al., 2006). Andrews, Buchanan, et al. (2006) reported valeric acid to have the most profound impact on mucosal

barrier function in comparison with acetic, propionic, or butyric acids while Nadeau et al. (2000) reported 78% of acetic acid out of the VFA in the gastric contents of the horses.

Luthersson et al. (2009a) emphasised the fact that the grain (starch) volume of starch fed per day or per meal, over a certain amount, increased the risk of EGUS ≥2 or NG ≥2.

Moreover, a high-grain diet resulted in a higher serum gastrin concentration, hormone known to stimulate secretion of HCl (Sandin, Skidell, Häggström, & Nilsson, 2000) and, is generally ingested quicker in horses with squamous (Malmkvist et al., 2012). Additionally, it may reduce hay uptake, restricting the production of buffering saliva (Nadeau et al., 2000, 2003).

Cereals deliver low levels of calcium (Harris et al., 2006) and, perhaps, other buffering agents, therefore, contributing to increased risk (Nadeau et al., 2000). Contrary to feeding alfalfa hay with grain, which provides a high calcium content (14.4 mg/g of dry weight) and high concentrations of crude protein, contributing with buffering effects on gastric contents (Nadeau et al., 2000).

Another study in horses showed evidence that a high starch-low forage diet increased squamous gastric ulcer scores in the horses compared to horses on a low starch diet (Al Jassim, McGowan, Andrews, & McGowan, 2008).

Horses that were fed straw as the only forage also increased the risk of EGUS ≥2 or NG ≥2, presumably due to the low protein and calcium content and, thus, lacking the buffering aid (Luthersson et al., 2009a).

7.5. Stress

Stress may be the primary cause of glandular gastric ulcers in foals and horses, and stress minimisation could be beneficial in reducing the risk of EGGD in some animals (Sykes et al., 2019). Authors identified trainer as a risk factor for EGGD (Sykes et al. 2019), which aligns with results of a previous Finnish study that identified an increased number of caretakers and riders as possible risk factors (Mönki et al., 2016).

It has been suggested that stress-induced release of endogenous cortisol increases the risk of developing gastric ulceration; e.g. stress of parturition in foals and stress of training and confinement in horses, by inhibition of prostaglandin synthesis, and therefore a failure in mucosal protective factors (Andrews & Nadeau, 1999). Horses with EGGD have augmented cortisol response to exogenous ACTH administration (Scheidegger et al., 2017) and were found to be more stress sensitive presenting in average a 26% higher cortisol concentration in response to novel stimuli (Malmkvist et al., 2012). Still, the authors reported a possible paternal influence (three stallions fathering 89%) on the risk of having gastric ulceration, justifying specific characteristics such as fearfulness and stress-sensitivity as having a genetic component.

In foals, stress was found to be implicated in the development of gastric glandular lesions but not in squamous lesions (Furr, Murray, & Ferguson, 1992).

The stress of hospitalisation for horses with the complaint of colic and those with non-colic complaints may also induce gastric mucosal lesions (Rabuffo et al., 2009). Additionally, as previously mentioned, the physical stress of high performance in thoroughbred and standardbred racehorses may also play a role in the higher occurrence of gastric ulcers in the non-colic patients (Orsini et al., 2009).

7.6. Transportation

The increase in equestrian sports recently has led to a rapid increase in the transportation of horses (Friend, 2001). Activities that are typical in recreational use of horses, besides transportation, but also housing off-site, were found to be ulcerogenic, with development of squamous lesions within five days under these conditions (McClure, Carithers, et al., 2005).

The stressful impact of transportation on the horse has been proven by repeated increases in plasma cortisol concentrations (Möstl et al., 2009). Additionally, the cortisol concentration during transport has been reported to be positively correlated with transport time (Fazio, Medica, Aronica, Grasso, & Ferlazzo, 2008).

The increased risk of EGUS associated with transportation may be associated with temporary disturbances in the feed as well as water intake (Luthersson et al., 2009a; Möstl et al., 2009).

7.7. Nonsteroidal anti-inflammatory agents

The role of NSAIDs in the development of EGGD is also debatable. The NSAIDs are commonly used in equine clinical practice to treat acute abdominal pain and chronic inflammatory conditions, particularly of the locomotor system (Videla & Andrews, 2009). In most cases, horses are given either phenylbutazone or flunixin meglumine intravenously for pain control. These agents, especially flunixin meglumine are very effective in decreasing abdominal pain associated with acute colic; nevertheless, several side effects have been reported that assigns an increased risk associated to their use in horses with EGUS (MacAllister et al., 1993).

Administration of high doses or prolonged treatments of NSAIDs has been proven to be the cause of ulcers in the glandular portion of the stomach (MacAllister et al., 1993; Martínez Aranzales, Cândido de Andrade, & Silveira Alves, 2015). However, studies where the squamous mucosa was the primary focus, the same association was not evident (Hammond et al., 1986; McClure et al., 1999; Murray et al., 1989, 1996; Rabuffo et al., 2002; Vatistas, Snyder, Carlson, et al., 1999). Therefore, it is still unclear if NSAIDs at therapeutic doses increase the risk of EGUS (Rendle et al., 2018).

Additionally, colonic ulcers and renal failure are other frequent side effects of these drugs, regardless of whether the drugs are administered at therapeutic doses or overdoses in horses (Andrews, Reinemeyer, & Longhofer, 2009; MacAllister et al., 1993).

The generally accepted theory to explain the association between NSAIDs and gastric ulcers is cyclooxygenase inhibition, in which conversion of arachidonic acid into prostaglandins is blocked (MacAllister et al., 1993; Murray, 2010). Consequently, the physiologic vasodilating effect of prostaglandins (in particular PGE2) on the stomach mucosa which creates a bicarbonate buffering complex and diminishes the corrosive effect of hydrochloric acid contained in gastric secretions (Andrews & Nadeau, 1999; Morrissey, Bellenger, & Baird, 2008) is inhibited, therefore generating the ideal conditions for development of ulcers in the gastrointestinal tract (Andrews & Nadeau, 1999; Murray et al., 1996). Martínez Aranzales et al. (2015) described another mechanism of injury in the horse stomach, using an EGUS induction model based on a phenylbutazone protocol, which showed the ability to induce oxidative stress in glandular mucosa of horses by changing the antioxidant-oxidant balance.

Evidence from laboratory animals supports the hypothesis of decreased prostanoids and oxidative stress in gastric alterations caused by NSAIDs in humans (Berenguer, Alarcón de la Lastra, Moreno, & Martín, 2002; Tomisato et al., 2004). Mitochondrial oxidative phosphorylation inhibition in mucus-producing cells was shown to alter the hydrophobic characteristics and exhibit direct cytotoxic effects, including necrosis and apoptosis (Tomisato et al., 2004). However, only effects dependent on the inhibition of PGs have been previously reported in horses (Martínez Aranzales et al., 2015).

According to Andrews et al. (2005), gastric mucosal ischemia may lead to hypoxia-induced cellular acidosis, and release of oxygen-free radicals, phospholipases and proteases, which may damage the cell membrane and result in necrosis. Furthermore, the interaction between the chemical properties of most NSAIDs and the acidic conditions of the stomach enhances the cellular changes in the gastric mucosa (Martínez Aranzales et al., 2015).

Nonetheless, at clinical doses, phenylbutazone and suxibuzone did not cause gastric ulceration when administered during 15 days (Andrews et al., 2009). Neither did a maximum recommended dosage of phenylbutazone affect cyclooxygenase-1 or -2 gene expression for seven days (Nieto, Aleman, Anderson, Fiack, & Snyder, 2012). Additionally, authors stated the administration of NSAIDs was not found to be a probable risk factor for EGUS (Habershon-Butcher et al., 2012), suggesting the possibility of existing mechanisms other than impaired prostaglandin synthesis involved in the formation of glandular gastric ulcers (Pedersen, 2017).

As such, despite the conflicting evidence regarding the influence of NSAIDs on the development of EGUS, the Council considers the high prevalence reported in many populations in need of

further investigation and concludes that is unlikely a possible risk factor in the greater number of patients (Sykes, Hewetson, et al., 2015).

7.8. Parasites

Many organisms are known to parasite the equine stomach. Nine species of larvae of flies belonging to the genus *Gasterophilus* (Diptera, Oestridae) are commonly found causing myiasis in the gastrointestinal tract of equine (Cogley, 1999). The third larval stage (L3) in all Gasterophilus species can remain attached to the gastric mucosa for periods of 8–9 months, during which time may cause nonspecific clinical signs characterized by difficulties in swallowing, gastrointestinal ulcerations, gastrointestinal obstructions or volvulus, anaemia, diarrhoea and many other digestive disorders (Cogley, 1989). Bot larvae were found consistently gathered together on the non-glandular mucosa adjacent to the *margo plicatus* (75%) (Agneessens et al. 1998). A. Niedźwiedź, Borowicz, and Nicpoń (2013) detected only *Gasterophilus intestinalis* and *Gasterophilus nasalis* in 47% of cases in a prevalence study conducted in eastern Poland.

Additionally, gastric habronemosis in horses occurs with a worldwide distribution, caused by both adult and larval stages of *Habronema microstoma* and *Habronema muscae* (Nematoda, Spirurida), transmitted by muscid flies (e.g. *Stomoxys calcitrans* and *Musca domestica*) (Anderson, 2000). *Habronema spp*. inhabit either in the stomach wall or on the mucosal surface near to the *margo plicatus*, the fundus or the pyloric valve, causing chronic catarrhal gastritis with symptoms of varying degrees of severity, such as anorexia, digestive disorders, diarrhoea, progressive weight loss, ulcers and postprandial colics (Anderson, 2000; Traversa et al., 2006).

Fernandes, Belli, and Silva (2003) reported a high occurrence of *Habronema spp*. (28.6%) mainly in the region of the *margo plicatus* in horses with chronic catarrhal gastritis while Traversa et al. (2006) reported a prevalence infection by *Habronema spp.* of 53,6%.

Recently, Cardona, Álvarez, and Paredes (2016) found a significative association between the high occurrence of cavitary gastric myiasis with the severity degree of squamous ulcers secondary to abnormal gastric emptying.

Nonetheless, there were authors (Chameroy et al., 2006) who stated the absence of parasites on examinations of horses with gastric ulcers. Nadeau and Andrews (2009) considered that the parasites did not play a substantial role in the development of ulcers, because only 9 out of 169 racehorses in one study presented parasites in the stomach at the examination.

7.9. Bacteria

The function of bacteria in the pathogenesis of EGGD is controversial. *Helicobacter pylori* are commonly implicated for the onset of gastritis and PUD in man (Collier & Stoneham, 1997; Malfertheiner et al., 2009). Although many species of Helicobacter have been identified and associated with ulcers and non-ulcerative gastritis in other animals (Fox, 2002), *Helicobacter pylori* and other *Helicobacter spp*. have not been proven to cause EGGD or ESGD in horses (Rendle et al., 2018).

Numerous attempts have been made to explain the microbial aetiology of EGGD remaining still conflicting results. Belli et al. (2003) reported identifying urease enzyme in a gastric sample from one horse examined suffering from gastric lesions, suggesting the presence of Helicobacter urease-positive species. Morales, Garcia, and Bermudez (2010) stated that thirty-eight per cent (n=52/136) of the horses infected by Helicobacter examined showed gastric mucosal lesions, and all horses with Helicobacter were urease positive. Furthermore, two pieces of research identified Helicobacter specific-DNA from the squamous and glandular mucosa of horses, thought to be less pathogenic than the human form, demanding still further studies on the matter. Hepburn (2004) identified Helicobacter genus-specific DNA by PCR in biopsy samples of asymptomatic horses, having found grade 1/2 glandular ulceration in 42% of horses. Contreras et al. (2007) detected Helicobacter-like DNA in the gastric mucosa of asymptomatic Thoroughbred horses, even though H. pylori-specific PCR detection was unsuccessful.

Additionally, a new enterohepatic Helicobacter species were isolated from faecal samples of two clinically healthy horses - *Helicobacter equorum* (Hilde Moyaert et al., 2007). H. Moyaert, Haesebrouck, et al. (2007) then determined a low zoonotic potential of *H. equorum*, reinforcing the need for more research on the newly discovered organism.

These bacteria were found colonising the distal gastrointestinal tract (H. Moyaert, Decostere, et al., 2007). This finding, along with Bezdekova and Futas (2009) negative results for *H. equorum* DNA detection from gastric biopsies in horses, confirmed that any possible role of this species in EGUS etiopathogenesis should be excluded.

The microbial composition and balance within the stomach have been theorised to be related to the development of EGGD (Vatistas, Snyder, Carlson, et al., 1999), although there was no significant difference between the microbiota of horses with EGGD and healthy horses in two different studies (Dong et al., 2016; Perkins et al., 2012).

Nonetheless, several studies have failed to identify Helicobacter organisms in association with ulcers in horses (Husted, Jensen, Olsen, & Mølbak, 2010; Martineau, Thompson, & Taylor, 2009).

Evidence was found of involvement of a diverse mucosal bacteria population consisting of Lactobacillus and Streptococcus species and Escherichia coli in the pathogenesis of gastric ulceration, and the importance of modification of this population for future treatment outcome (Al Jassim et al., 2008). Authors reported information that corroborated with both gastric-adapted bacteria and opportunistic pathogens possible role in squamous ulceration (Al Jassim et al., 2008) but whether the situation is similar in the glandular mucosa is unknown.

Overall, based on the weak historical evidence of Helicobacter infection in association with ulcers in horses, indicates that Helicobacter spp. are possibly not a prevalent asymptomatic inhabitant of the equine stomach, and their function in gastric ulceration in the horse is until now to be determined (Perkins et al., 2012). Helicobacter pylori is believed to be an unlikely primary contributing factor in the development of EGGD (Perkins et al., 2012; Rendle et al., 2018; Sykes, Hewetson, et al., 2015; Sykes & Jokisalo, 2015) although certain species may have the capacity to colonize the damaged mucosa and prevent healing (Rendle et al., 2018). Also, the role of secondary bacterial infection has not been sufficiently established to justify the general use of antimicrobials in the treatment of EGUS (Sykes & Jokisalo, 2015)

8. Clinical signs of EGUS

Gastric ulceration can cause a wide variety of clinical signs, such as abdominal discomfort, colic, lack of appetite, poor body condition and weight loss, dullness of coat, decrease in performance, diarrhoea, and stereotypic behaviour (Collier & Stoneham, 1997; Murray et al., 1989; Sandin et al., 2000; Vatistas, Snyder, Carlson, et al., 1999). Other signs may include, particularly in foals, a loss of vitality, dorsal recumbency, and bruxism (Nadeau & Andrews, 2009; Sandin et al., 2000; Vatistas, Snyder, Carlson, et al., 1999).

Unfortunately, these clinical signs are non-specific, and horses presenting with clinical signs suggestive of EGUS may have no gastroscopic evidence of gastric ulceration. A Swedish study of 80 Standardbred racehorses, trained by nine different trainers, suggested that changes in performance, behaviour, and eating habits provided only weak clues that an individual horse might have EGUS (Jonsson & Egenvall, 2006). Dionne et al. (2003) suggested that a poor body condition was the only clinical sign distinctly associated with the presence of gastric ulcers and high lesion scores in Standardbreds, whereas recent studies failed to confirm this cause-and-effect relationship (Cate et al., 2012; Poulsen, Sondergaard, Luthersson, & Malmkvist, 2011).

Poulsen et al. (2011) also suggested that a history of eating slowly, which is believed to be associated to a lack of appetite, cannot be assumed as a sign that ulcers are present.

Decreased performance is a commonly referred complaint in racehorses with suspected EGUS (Bell, Mogg, et al., 2007; Franklin, Brazil, & Allen, 2008). However, Cate et al. (2012) ran a study

where trainers assessed the horses' performance as to predict the presence of gastric ulcers using an ordinal scale, which presented many limitations and failed to do so. The authors, however, were not surprised with the results, pointing to the fact that performance can be influenced by many other factors such as physical ability, mental state, and soundness.

Crib-biting and other types of abnormal behaviour have been identified as a sign of frustration and/or stress in situations with stimulation, such as feeding periods (Nagy, Bodó, Bárdos, Harnos, & Kabai, 2009). However, Malmkvist et al. (2012) failed to demonstrate an association between traditional abnormal behaviour (crib-biting, weaving), excessive licking, and glandular ulceration in adult horses. Wickens et al. (2013) found no significant differences in the ulcer scores, the prevalence of hyperkeratosis, or baseline gastric pH between crib-biting horses and non-crib-biting horses. Though, the serum gastrin concentration at 60 and 120 minutes was greater ($P < .05$) and tended to be higher ($P < .06$), respectively, in CB than in NCB horses following concentrate feeding, which possibly led to a greater increase in gastric acid secretion. Nonetheless, stomachs from CB horses do not differ anatomically nor physiologically from NCB horses and are rather a clinical response to environmental and cellular stress (Daniels, Scott, De Lavis, Linekar, & Hemmings, 2018).

Horses with simple obstruction or ulceration often present mild, intermittent abdominal pain that often resolves with appropriate medical treatment (Moore, 2006). Gastric ulceration was found in 68% (n=76/112) of horses with a history of recurrent episodes of abdominal pain, and 72% of horses with non-colic complaints (Rabuffo et al., 2009). In this report, Rabuffo et al. (2009) referred gastric ulceration as the sole complaint in only 12% (13/112), whereas nearly 28% (31/111) of horses in Murray's study had gastric ulceration as the primary cause of colic (Murray 1992). Also, Dukti et al. (2010) reported results which showed that fewer horses presented to a referral hospital for surgically-managed colic (32%) had gastric ulcers than horses that presented for medically-managed colic (49%).

However, none of the reports cited determined whether the severity of clinical signs correlated with the severity, number or location of gastric ulcers.

Even so, studies have reported a large number of asymptomatic horses with gastric ulcerations (Cate et al., 2012; Fernandes et al., 2003; Malmkvist et al., 2012; Niedźwiedź, Kubiak, & Nicpoń, 2013) which reinforces the importance of random sampling to achieve an accurate estimate of the prevalence of EGUS in a population (Bell, Kingston, Mogg et al., 2007).

9. Diagnosis of EGUS

Diagnosis of EGUS is complicated since the clinical signs demonstrated by the horse are nonspecific, as discussed above. Gastroscopy is considered the only steady antemortem method for precise identification of gastric ulceration in the horse (Bell, Mogg, et al., 2007; Sykes, Hewetson, et al., 2015). However, a detailed clinical history, a systematic physical examination and the identification of risk factors that may be associated in each case can help predict the presence of gastric ulceration (Reese & Andrews, 2009).

In the absence of gastroscopy, empiric treatment may be employed, to use the response to treatment as a means of indirectly diagnosing EGUS (Bell, Mogg, et al., 2007). Though, given the high cost of treatment and the importance of distinguishing ESGD from EGGD, the initiation of treatment without previous gastroscopy is not recommended (Sykes, Hewetson, et al., 2015). In cases where empirical treatment is attempted, and the horse does not respond to treatment, gastroscopy should still be carried out to definitively eliminate the gastric disease as a suspicion, as some animals maintain the clinical complaints while complete healing of lesions has not occurred.

9.1. Blood analysis - haematological and biochemical changes

There are currently no consistent haematological or biomechanical markers available to support in the diagnosis of gastric ulceration. Although, show horses with chronic gastric ulceration were found to have anaemia and hypoalbuminaemia (McClure et al., 1999; Reese & Andrews, 2009). Still, according to Videla and Andrews (2009), despite the low erythrocyte number and haemoglobin concentration, they are hardly ever lower than the limits of reference values. Another study conducted by Dezfouli et al. (2009) in Persian Arab horses stated a decrease in the number of monocytes and increased potassium concentration in horses with EGUS. Cate et al. (2012) failed to determine the existence of gastric bleeding ulcers by evaluating packed cell volume (PCV) and total solids confirming the inexistence of pathognomonic clinical signs for EGUS and reinforcing the importance of a complete endoscopic examination for a clinical diagnosis.

Recently, investigators identified ten serum proteins, using electrophoresis and mass spectrometry, which may be used as presumed markers for ESGD, though future investigation is required to fully comprehend the role and association of these proteins to ESGD (Tesena et al., 2019).

9.2. Faecal occult blood test

Horses may manifest melena as a clinical sign suggestive of gastric ulceration. Therefore, a guaiac acid-based faecal occult blood test has been found to improve both the accuracy and speed of diagnosis of EGUS (Pellegrini, 2005). Though, results of this test indicate a poor sensitivity, low specificity and predisposition for interference, with a positive predictive value of 90% and a negative predictive value of only 17%. In order to improve the negative predictive value of the FOBT, investigators developed another test (Succeed® Equine Faecal Blood Test™, Freedom Health LLC[1]) that uses specific equine monoclonal antibodies to both albumin and haemoglobin in an easy-to-use kit (Freedom Health LLC 2011). Recently, the Succeed® test which is currently on the market has been tested for its diagnostic accuracy against gastroscopy in a population of Thoroughbred racehorses and demonstrated high specificity and low sensitivity and high false-negative results for the diagnosis of EGUS (Sykes, Jokisalo, & Hallowell, 2014). Therefore, its use to diagnose EGUS is limited but might be a helpful tool to diagnose and document healing in horses with another gastrointestinal disease, such as colitis (Camacho-Luna, Buchanan, & Andrews, 2018).

9.3. Endoscopic examination

Gastroscopy is currently considered the gold standard method for antemortem diagnosis and monitorization of EGUS (Sykes, Hewetson, et al., 2015). Standing gastroscopy procedures have been described in detail in many reports, using scopes of <3m long allowing visualisation of the nonglandular mucosa and *margo plicatus* (Murray, 1992; Murray et al., 1989, 1996). However, the gastroscopes cited in the earlier literature are insufficient in length to allow examination of the entire stomach in most adult horses (Murray, Nout, et al., 2001b), lacking in particular, the examination of the pylorus antrum and proximal duodenum, essential regions where the majority of glandular disease occurs (Begg & O'sullivan, 2003; Luthersson et al., 2009b; Tamzali et al., 2011). Therefore, to overcome this limitation, a relatively simple clinical procedure has been described which recommends the use of scopes with an insertion length of at least 3 m and an outer diameter of approximately 12.8 mm to (Sykes & Jokisalo, 2014).

Case preparation prior examination is necessary to allow the best visibility and facilitate the entry into the pyloric antrum. The required fasting period may be dependent on the horse's use and diet, ranging from a minimum of 6-8 hours to 16 hours (Sykes, Sykes, & Hallowell, 2014b). Nonetheless, the owner/trainer is told to feed the horse their normal grain meal while only a

[1]Freedom Health LLC, 65 Aurora Industrial Pkwy, Aurora, OH 44202, EUA.

small amount of hay the night before and to remove all remaining feed first thing in the morning (Sykes & Jokisalo, 2014).

Generally, horses are given moderate sedation with an alpha-2 agonist and tolerate the procedure very well. The endoscope is introduced via one nostril, progresses through the oesophagus until it reaches the stomach. The main areas of examination are the greater curvature, the lesser curvature and the pyloric antrum (Sykes & Jokisalo, 2014).

When severe pathological changes are suspected or if cases are refractory to treatment for 3 or more months then transendoscopic biopsies associated to the gastroscopy procedure should be considered; otherwise, biopsies are seldom indicated (Rendle et al., 2018).

9.3.1. Scoring system for gastric ulcers in the horse

Lesions visualised using gastroscopy should be subjectively graded according to their number and severity. Ideally, objective measurements of the size and depth of the lesions should be taken as a factor of severity, yet ambitious due to the irregularity of the lesions (Macallister, Andrews, Deegan, Ruoff & Olovson, 1997).

Many different scoring systems have been published over the years, and the lack of standardised scoring system restricts the clinical case comparison between different prevalence studies (Bell, Mogg, & Kingston, 2007; Collier & Stoneham, 1997). The reported scoring systems vary from a 0-3 scale reported by MacAllister (Dionne et al., 2003; MacAllister et al., 1999; Vatistas, Snyder, Carlson, et al., 1999), 0-4 (Andrews et al., 2002; Furr & Murray, 1989), 0-5 ((Bell, Kingston, & Mogg, 2007; Vatistas, Snyder, Nieto, et al., 1999), 0-6 (McClure et al., 1999) and even 0-10 (Murray & Eichorn, 1996). The assortment of scoring systems described in the literature is such that even separate studies by the same investigators have used different scoring systems (Murray & Eichorn, 1996; Murray et al., 1989, 1996; Vatistas, Snyder, Carlson, et al., 1999; Vatistas, Snyder, Nieto, et al., 1999). A study by Bell et al. (2007) showed that the generally used 0-4 scale was repeatable and reliable between operators and was also more accessible and faster than the Number/Severity scoring system reported by MacAllister et al. (1997).

Opportunely, in recent years, the European College of Equine Internal Medicine recommended the use of a standard, easy and accurate scoring system in a consensus statement (Sykes, Hewetson, et al., 2015).

Endoscopic grading of ulcers, even though not foolproof, offers a foundation for severity scoring and monitoring response to treatment (Pedersen, 2017).

9.3.2. Complications and disadvantages

The technique of gastroscopic examination is quite unambiguous, although, in order to reach a complete examination of the stomach, it requires a certain level of expertise to perform and interpret (Sykes & Jokisalo, 2014). Disadvantages of endoscopic examination include the condition of the horse to be sedated, it is not promptly available to most clinicians, and it is an inefficient expenditure of time.

Additionally, complications may occur during the procedure. Although rare, oesophagal rupture may occur due to iatrogenic perforation during repeated nasogastric tube insertion (or scope), which can be fatal (Bezdekova, 2012). Also, if the gastroscope is removed without removing the air from the stomach, due to the characteristics of the horse's cardia sphincter, the only way to expel it will be gradually through the pylorus (Kihurani, Carstens, Saulez, & Donnellan, 2009). Thus, removal of the air by suction is recommended at the end of the procedure, since gastric distension increases the risk of colic (Sykes, Hewetson, et al., 2015).

9.4. Other diagnostic methods

A sucrose permeability test has shown the potential for non-invasive detection of gastric ulcers as a simple and economical alternative to gastroscopy for screening purposes (Hewetson et al., 2006; O'Conner et al., 2004). However, this method involves sophisticated equipment and therefore, may not be available in clinical practice (Reese & Andrews, 2009).

Nonetheless, in recent publications, results showed that blood sucrose was neither a sensitive nor specific test for detecting EGUS in mature horses, therefore inept as a screening test for EGUS nor will it be expectable to replace gastroscopy in this study population (Hewetson, 2018; Hewetson et al., 2018). In contrast, the same studies concluded that blood sucrose seems to be a sensitive test for detecting EGUS in foals and may represent a clinically useful screening test to identify foals that may benefit from gastroscopy.

10. Management of EGUS

10.1. Pharmacological treatment

The purpose of EGUS therapy is to eliminate clinical signs, promote the healing of lesions and prevent a recurrence. Thus, the primary strategy is to increase gastric pH by suppressing HCL secretion (MacAllister et al., 1999). Several treatments have been promoted for the management of both ESGD and EGGD. Evidence for the relative efficacy of acid suppression treatment to reduce the prevalence and promote healing of gastric ulcers in horses is well documented for ESGD, though limited for EGGD. Although EGGD is improbable to be caused solely by acid injury, acid suppression is still recommended regardless of failure to identify an underlying

cause, as it is considered essential for mucosal repair but a longer treatment period may be vital (Sykes, Hewetson, et al., 2015).

Nonetheless, gastric ulcers often heal without medical intervention, and authors have theorised that medications that reduce gastric acidity do not initiate healing, but rather facilitate ulcer healing by providing a microenvironment that is optimal for healing to proceed (Murray, Eichorn, et al., 2001)**.**

10.1.1. Proton pump inhibitors

10.1.1.1. Omeprazole

- Pharmacokinetics

Oral omeprazole, a substituted benzimidazole, is the preferred drug for the prevention and treatment of EGUS associated with the squamous mucosa (Sykes, 2019). It is absorbed in the small intestine and acts systemically as a proton pump inhibitor, binding irreversibly to the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) enzyme system on the secretory surface of parietal cells, blocking it and therefore inhibiting gastric acid secretion and increasing gastric pH (Hepburn, 2011; Mason, Moroney, & Mason, 2019; McClure, White, et al., 2005).

As an acid labile crystalline powder, it is quickly degraded in the acid environment during its passage through the stomach. The remaining intact fraction of omeprazole is then absorbed in the small intestine and afterwards transported via the bloodstream to the basal side of the parietal cells where it exerts its effect (Andrews, Sifferman, et al., 1999; MacAllister et al., 1999; Nieto et al., 2002).

- Presentation

Omeprazole is used in an enteric-coated encapsulated formulation in humans, available in the form of granules of 10, 20 or 40mg (Prontuário terapêutico on-line 2019) or in the form of a specific oral powder paste formulation for horses (e.g. GastroGard®, Boehringer Ingelheim[2]), is that each dose-adjustable syringe contains 2.28g of Omeprazole (Direção Geral de Alimentação e Veterinária 2018).

In order to increase acid stability of this acid labile drug, it has been recommended that the formulation requires the incorporation of some form of protection because exposure to acid in the stomach followed by alkalinisation in the small intestine causes the drug to become inactive before absorption can occur (Merritt, Sanchez, Burrow, Church, & Ludzia, 2003). Thus, most commercial products are formulated to include buffering with a highly alkaline medium, or the

[2] Boehringer Ingelheim Animal Health Portugal Unipessoal Lda., Av. de Pádua, nº 11 1800-294 Lisboa.

use of enteric-coated granules suspended in a paste (Sykes, Underwood, Greer, & Mills, 2015). The encapsulated formulation used in humans protects the agent during the passage through the acidic environment in the stomach, then once it reaches the alkaline setting of the small intestine, the acid-stable coating is degraded and the active ingredients are released (Haven et al., 2010; Nieto et al., 2002). In a recent study, Sykes, Underwood, McGowan, et al. (2015) reported the bioavailability of an enteric-coated granule formulation (Gastrozol®, Virbac[3]) to be nearly twice that of a plain, unprotected oral omeprazole (Sykes, Underwood, McGowan, et al., 2015) supporting this recommendation.

The efficacies of the different methods of protection are, however poorly investigated to date. Nonetheless, studies have shown that the method of protection, either enteric coating or buffering of the formulation, appears to have no effect on pharmacokinetics (Birkmann, Junge, Maischberger, Wehrli Eser, & Schwarzwald, 2014; Sykes, Underwood, Greer, et al., 2015). Authors stated that dose linear pharmacokinetics had not been demonstrated for omeprazole in the horse, and therefore it cannot be assumed that the pharmacokinetics of the two doses are equivalent, and the direct comparison of different doses is not appropriate (Sykes, Underwood, McGowan, et al., 2015).

Due to the relatively high cost of GastroGard® (Merial[4]), some veterinary physicians choose to prescribe cheaper magistral preparations of omeprazole that are formulated in several private pharmacies, or even opt for preparations available for Human medicine (Merritt et al., 2003).

Intravenous administration of omeprazole is another option in the treatment of SUGE in cases displaying dysphagia, gastric reflux, or another disease that restricts the oral administration of omeprazole in the paste form (Andrews, Frank, et al., 2006; Hepburn, 2011). Despite a fast and potent onset of action, authors (Sykes, Underwood, McGowan, et al., 2015) have reported a shorter half-life compared to oral formulations. Although not yet available on the market, a recent preliminary investigation has been reported on a new, long-acting, injectable, intramuscular formulation of omeprazole in the horse (Sykes, Kathawala, et al., 2017).

- Dosage

The oral omeprazole paste, developed for usage in horses, is the most effective formulation with the most extensive investigation, initially recommended by the EGUS Council (Andrews et al., 1999). Reports of administration of the reference dose of 4 mg/kg orally, SID, significantly suppresses gastric acidity for 24 hours, with EGUS healing rates of 77%-86% and significant

[3] Virbac (Australia) Pty Ltd, 361 Horsley Road, Milperra NSW 2214.

[4] Merial Ltd., Duluth, Georgia, USA.

improvement rates of over 90% (Doucet, Vrins, Dionne, Alva, & Ericsson, 2003; Lester, Smith, & Robertson, 2005; MacAllister et al., 1999; McClure, White, et al., 2005; Murray et al., 1997).

However, based on currently available evidence, the committee suggests that the use of buffered formulations at 2 mg/kg PO once daily warrants further review (Sykes et al., 2015). Similarly, based on reported studies (Birkmann et al., 2014; Sykes, Sykes, et al., 2015) the use of enteric coated granule formulations at 1.0 mg/kg PO, SID, seems acceptable (Sykes, Hewetson, et al., 2015).

Current treatment recommendations are of a minimum of 4 weeks duration (28 days) based principally on existing recommendations for ESGD and clinical experience (Sykes, Hewetson, et al., 2015). Though, duration of treatment also warrants further consideration, since the duration of acid suppression achieved under clinical conditions may be less than initially reported in previous experimental studies (Sykes 2019). Recent studies showed that EGGD favourable treatment response was only 25%, in opposition to the reported 78% of ESGD favourable treatment response at 4 mg/kg bwt per os once a day for 28–35 days (Sykes, Sykes, et al., 2014d, 2014a, 2015). Given the differences in pathophysiology between ESGD and EGGD, it is possible that a longer duration of treatment may be required for EGGD healing to occur (Sykes 2019). Therefore, it is possible to repeat gastroscopy at either 14, 21 or 28 days. If gastroscopy is not accessible, then treatment should be extended for 28 days (Sykes, Sykes, et al., 2014d, 2014a, 2015).

Also, factors such as dose and diet can affect oral bioavailability in some horses (Sykes, Underwood, Greer, et al., 2015; Sykes, Underwood, McGowan, & Mills, 2015, 2017). Therefore, the use of a single dosing recommendation which comprehends all horse types and management conditions may not be suitable and dosing recommendations that take into account the diet of the horse may be advantageous (Sykes, Underwood, et al., 2017).

In dysphagic patients, intravenous omeprazole at 1 mg/kg every 24 hours can be used, although this represents off-licence use (Hepburn, 2011).

- Efficacy

Various previous reported clinical trials (Andrews, Sifferman, et al., 1999; Doucet et al., 2003; McClure, White, et al., 2005; White et al., 2007) have found significant differences in ulcer severity between preventive treatment and sham groups, whereas others (Endo et al., 2012; Lester et al., 2005) have shown no significant differences. Also, more than 50% of the reported clinical trials to date have had a reporting attrition bias (Endo et al., 2012; Lester et al., 2005; McClure, White, et al., 2005; Sykes, Sykes, et al., 2014d).

Nevertheless, omeprazole has been shown to be efficacious in the short term in numerous previous studies (Andrews, Sifferman, et al., 1999; Doucet et al., 2003; Murray et al., 1997; Sykes, Sykes, et al., 2014a) with healing rates of 73% to 80% and improvement rates of up to 92% following 25 to 56 days of treatment. Though, recent studies (Sykes, Sykes, et al., 2014b, 2014a, 2015) have shown a lower healing rate of EGGD, in which only 25% of glandular ulcers healed with 28–35 days of omeprazole therapy at 4.0 mg/kg per os SID, compared to an ESGD healing rate of 78%. The reported EGGD healing rates suggest that specific treatment recommendations for EGGD are required and that direct extrapolation of ESGD treatment recommendations are unsuitable (Sykes & Jokisalo 2015).

Limited records are available on the relative pharmacokinetics and pharmacodynamics of different omeprazole formulations (Sykes, Underwood, McGowan, et al. 2017). However, the patent of the formulation predominately used globally - GastroGard (Merial[5]) has recently expired, and interest in different formulations has increased (Birkmann et al., 2014; Sykes & Jokisalo, 2015). A recent study compared pharmacokinetic and pharmacodynamic effects of a novel omeprazole formulation (Ulcershield: ULS) with a currently registered reference omeprazole product (OMO) and found that both formulations were pharmacodynamically equivalent, as well as a similar beneficial effect on gastric squamous mucosal ulceration (Raidal, Andrews, Nielsen, & Trope, 2017).

10.1.1.2. Esomeprazole

Esomeprazole, the S enantiomer of omeprazole, is reported more efficacious than omeprazole after oral administration in humans (Andersson, Hassan-Alin, Hasselgren, Röhss, & Weidolf, 2001; Scott, Dunn, Mallarkey, & Sharpe, 2002).

There is still limited information on the efficacy of esomeprazole in horses. One study showed that intravenous (IV) administration of esomeprazole to horses for 14 days significantly increased gastric fluid pH (Videla, Sommardahl, Elliott, Vasili, & Andrews, 2011). In a recent clinical trial, an enteric coated esomeprazole paste was found equally as effective as omeprazole paste in increasing gastric pH in horses and may be a therapeutic alternative effective as omeprazole paste in increasing gastric pH in horses (Huxford, Dart, Perkins, Bell, & Jeffcott, 2017).

The improved efficacy of esomeprazole is thought to be caused by a lower plasma clearance and larger area under the curve for plasma concentration-time when compared with omeprazole.

[5] Merial Ltd., Duluth, Georgia, USA.

The higher plasma concentrations give rise to a greater drug availability to inhibit parietal cell HCl secretion (Sykes, 2019)

10.1.1.3. Pantoprazole

Pantoprazole, another proton pump inhibitor, has been reported to significantly increase gastric fluid pH after IV (1.5 mg/kg) and intragastric administration (1.5 mg/kg, bwt) in neonatal foals (Ryan, Sanchez, Giguère, & Vickroy, 2010). Authors suggest the use of pantoprazole IV in foals with pyloric outflow obstruction, especially since IV administration of ranitidine has shown inconsistent effects on increasing gastric fluid pH (Camacho-Luna et al., 2018). However, intragastric administration of pantoprazole leads to a lower bioavailability, when compared with oral administration of omeprazole, therefore a higher dose should be used if administered orally in foals.

10.1.2. Histamine type-2 receptor antagonists

Histamine type-2 receptor antagonists, such as ranitidine and cimetidine, suppress HCl secretion by reversibly binding and competitively blocking the parietal cell H2 receptors and their efficacy is dependent on maintaining plasma concentrations of the drug (Camacho-Luna et al., 2018).

Buchanan and Andrews (2003) reported that ranitidine requires three times daily oral administration and longer treatment duration (45–60 days) compared with omeprazole (28 days) to achieve similar healing. Lester et al. (2005) later confirmed that ranitidine was less effective than omeprazole in healing ESGD in Thoroughbred racehorses. Cimetidine, however, does not seem to be effective in the treatment of EGUS and is not recommended (Sykes & Jokisalo, 2015).

10.1.3. Coating and binding agents

The use of mucosal barrier protectants may be useful given the proposed failure of mucosal defence mechanisms in the pathogenesis of EGGD (Sykes, 2019). Sucralfate, a polyaluminium hydroxide with a sulphated disaccharide structure, adheres to the mucosa and may have several positive effects (Rendle et al., 2018). Sucralfate acts as a physical barrier to acid diffusion, causes stimulation of mucus secretion, inhibition of pepsin and bile acid release, promotes re-epithelialisation by prevention of fibroblast degradation, stimulates epidermal and insulin-like growth factors and increases mucosal blood flow through increased production of prostaglandin E (PGE) (Rendle et al., 2018).

Sucralfate at 12 mg/kg PO BID combined with omeprazole (4 mg/kg PO SID) was recommended to treat glandular ulcers with a reported 80% improvement and 63% healing rates of grades ≥2 EGGD lesions in 204 sport and leisure horses (Sykes, 2019[6]). However, recently was not as effective, with reported healing rates of 22% compared with the 73% of horses receiving misoprostol alone (Varley, Bowen, Nicholls, Habershon-Butcher, & Hallowell, 2016).

Nevertheless, authors recommend sucralfate should only be used if omeprazole can be administered after 8 hours of feed deprivation, a minimum of 30 (preferably 60–90) minutes before feeding, ensuring that sucralfate is administered at least 30 minutes after omeprazole (Rendle et al., 2018).

10.1.4. Synthetic prostaglandins

The synthetic prostaglandin E2 analogue, misoprostol, has been recommended to treat EGUS (Buchanan & Andrews, 2003; Sykes, Hewetson, et al., 2015). In a more recent study, misoprostol (5 mg/kg, orally every 12 hours) was found to be superior to combined omeprazole (4 mg/kg, orally every 24 hours) and sucralfate (12 mg/kg, orally every 12 hours) therapy in horses with EGGD (Varley et al., 2016). Misoprostol may cause diarrhoea and/or colic signs, and it is not advised to be used in pregnant mares, because it might induce parturition and termination of the pregnancy (Camacho-Luna et al., 2018; Rendle et al., 2018).

10.1.5. Antimicrobial agents

As the role of bacteria in the pathogenesis of EGGD is still unclear, allied to the inexistence of evidence to support the use of antimicrobials in the horse (Sykes, Sykes, & Hallowell, 2014c), the committee declares that a routine use of antimicrobials in the treatment of EGGD is not acceptable until their efficacy is adequately recognised (Sykes, Hewetson, et al., 2015).

10.2. Pharmacological prevention

The pharmacological approach to prevention of ESGD is similar to treatment (Sykes, Hewetson, et al., 2015). Prevention should be applied according to each case, in which the greater the ability to reduce risk factors lesser will be the necessity for additional treatment. Buffered and enteric-coated omeprazole formulations are usually used at 1.0 mg/kg PO SID (McClure, White, et al., 2005; White et al., 2007). However, there are no precise rules for their use regarding dosage and duration of therapy (Sykes, Hewetson, et al., 2015).

[6] Hepburn, R.J. & Proudman, C.J. (2014) Treatment of ulceration of the gastric glandular mucosa: Retrospective evaluation of omeprazole and sucralfate combination therapy in 204 sport and leisure horses [abstract]. In: Proc. 11th International Equine Colic Research Symposium. p 108

Recently, a meta-analysis run by Mason et al. (2019) led to evidence that omeprazole prophylaxis in active training horses reduces squamous gastric ulceration by 56.6% (n=556/1000) compared with no prophylaxis.

Currently, there are no explicit instructions for the prevention of EGGD. It is still unclear of the prophylactic efficacy of omeprazole for EGGD, with reports of 23% of horses experiencing worsening of their EGGD grade in various recent studies (Sykes, Sykes, et al., 2014d, 2014a, 2015), regardless of omeprazole treatment at doses at 1–4 mg/kg PO once daily.

10.3. Environmental management of EGUS

10.3.1. Modification of exercise intensity and duration

In horses, intense exercise, racing, and race training have been shown to contribute to worsening of nonglandular gastric ulcers compared with horses kept at pasture or not in training, as discussed above (Dionne et al., 2003; Roy et al., 2005). Also, endurance exercise has been shown to play a role in the cause of EGUS in horses, with reported prevalences of 67% of horses competing in 50- and 80-mile endurance rides (Nieto et al., 2004). Also, repeated oral administration of hypertonic electrolytes commonly used in these horses has been found to increase the gastric ulcer number and severity as well as hyperaemia of the gingival mucosa and hypersialia (Holbrook et al., 2005). However, despite additional work being required to evaluate electrolyte administration under different conditions adequately, these products are recommended to be used with caution in horses and should be best given after exercise, in hydrated animals and mixed in feed to minimise their effects on the squamous mucosa (Andrews et al., 2017).

Regardless of the pathophysiological relationship, based on recent evidence provided by Sykes et al. (2019), it seems that restricting exercise to ≤4-5 days per week may reduce the risk of EGGD. Furthermore, training and exercise intensity should be reduced, when possible, until ulcers have healed (Sykes et al. 2019).

10.3.2. Pasture turnout

Stall-confinement generally has been associated with an increased risk of squamous ulcers, which therefore may not improve in stall-confined horses even when horses are fed grass hay *ad libitum* (Murray et al., 1996). Although pasture turnout may help control ESGD, the presence of certain other stress factors and whether the horse continues to be fed high NSC-containing feed may have a larger determining effect (Luthersson et al., 2009a; Malmkvist et al., 2012). However, pasture turnout is the preferred dietary method of prevention and controlling gastric ulcers.

10.4. Dietary management of EGUS

Pasture grazing, high forage (DM intake, ≥1.5% bwt) and low concentrate (≤0.5% bwt) diets, a diet low in NSC, feeding smaller more frequent meals and providing *ad libitum* forages are the primary management practices that are suggested which may reduce the risk of squamous ulceration, as discussed in detail below (Andrews et al., 2017)

10.4.1. Eliminate bolus feeding and increase forage intake

The first and principal management practice that may help decrease squamous ulcers is to feed a forage-based diet *ad libitum* or guarantee that forage is provided every few hours and before exercise (in small amounts) (Reese & Andrews, 2009).

Together with hay, horses which are stabled should be fed 3 or 4 smaller meals (without exceeding 0.5 kg/100 kg bwt every q.i.d. and containing 20% NSC or lower) per day (Nadeau et al. 2000). Smaller low NSC meals decrease intragastric fermentation, reduce the production of VFAs and improve gastric emptying rate (Nadeau et al., 2000).

Providing alfalfa hay and good quality grass hay as the forage or feeding alfalfa hay along with concentrate significantly reduced the severity of gastric squamous mucosal ulceration in young horses in training, and may may be an effective way to ameliorate or prevent gastric ulceration in horses (Lybbert, Gibbs, Cohen, Scott, & Sigler, 2007; Murray & Eichorn, 1996; Nadeau et al., 2000). Although absolute requirements have not been determined for horses, the total ration needs to be balanced to account for the alfalfa inclusion rate (Andrews et al., 2017).

A recent study (Vondran et al. 2016) investigated the effects of feeding two alfalfa preparations with different particle sizes (alfalfa chaff vs alfalfa pellets) in comparison with grass hay on the gastric mucosa. However, no significant associations between lesion scores in both groups were found, and the study failed to improve gastric mucosal lesion scores in the alfalfa fed weanling horses (Vondran, Venner, & Vervuert, 2016).

Straw as the only or main forage should be avoided as it was found to increase the risk of ESGD ≥2 by at least 4.4 times (Luthersson et al., 2009a).

The recommended levels of forage (grass and preserved forages) are preferably ≥1.5 kg DM/100 kg bwt for all horses, including those with high energy requirements (Andrews et al., 2017[7]). Lower levels may be required for those horses on a strict veterinary monitored weight loss programme (but never less than 1 kg DM/100 kg bwt) in which case appropriate measures need to be put into place to maximise the time spent chewing the restricted forage intake (Bruynsteen et al., 2014; Ellis et al., 2015). Additionally, a proper protein, vitamin and mineral

[7] Original reference: Harris, P.A., Coenen, M. and Geor RJ. 2013. Controversial areas in equine nutrition and feeding management: the editors' views. R.J. Geor PAH and MC, editor. Waltham: Elsevier Health Sciences.

balancers will be essential in order to nutritionally balance the ration particularly if concentrate feeds are not required to be fed (Andrews et al., 2017).

10.4.2. Decrease the size and increase the frequency of concentrate feeding

Another recommendation is to feed smaller grain diets. Larger grain meals result in an increased gastric retention time, which increases the fermentation by resident bacteria, resulting in higher VFA production and a greater potential for squamous injury (Harris et al., 2006; Nadeau et al., 2000). The intake of NSC, and particularly grains, should, therefore, be restricted through the use of lower NSC complementary feeds. Based on previous studies, feeding a grain-based diet <0.5 kg grain/100 kg bwt (20%NSC) should help maintain stomach VFA concentration of acetic acid below 20 mmol/l and minimise the effect on squamous ulcers (Andrews, Buchanan, et al., 2006). Feeding <2 g NSC/day or <1 g NSC/ meal has also been recommended (Luthersson et al., 2009a). This may be a difficult approach for some trainers of high intensity exercising horses to follow without a decrease in performance, hence the recurrence to the inclusion of various supplements as discussed below.

10.4.3. Oils

Additional energy could be provided through supplemental vegetable oil, which has been shown to decrease gastric acid output and increase prostaglandin E2 production at 0.3–0.5 ml/kg bwt/day (150–250 ml/day for a 500 kg horse), providing an effective and inexpensive way to increase the protective properties of the equine glandular gastric mucosa (Cargile, Burrow, Kim, Cohen, & Merritt, 2004). However, Frank, Andrews, Elliott, and Lew (2005) found that ESGD induced in horses with ulcerogenic diets (high grain ration) were not prevented by oil supplementation. Horses in that study did not have many glandular ulcers, so glandular ulcer healing rates could not be assessed. In contrast, in a recent study (Martínez, Zuluaga, & Silveira, 2016) where the objective was to resolve rather than to prevent the lesions, authors demonstrated positive therapeutic effects only in the glandular mucosa with corn oil supplementation. However, PGE2 concentration had little influence on the restitution of gastric epithelium. Therefore, additional studies should be conducted to elucidate some aspects related to the activation of antioxidant defence systems of the gastric mucosa resulting from other NSAIDs used in horses (Martínez et al., 2016)

10.4.4. Nutraceuticals, nutritional supplements and other alternatives

The use of nutraceuticals and feed supplements has increased due to their ease of use and availability (Sykes, Hewetson, et al., 2015).

Although pectin-lecithin complexes have been previously reported to increase the total mucus concentration in gastric fluid (Köller, Recknagel, Spallek, Breuer, & Schusser, 2010), other studies (Murray & Grady, 2002; Sanz, Viljoen, Saulez, Olorunju, & Andrews, 2014; Venner, Lauffs, & Deegen, 1999) failed to demonstrate a protective effect in fed/fasting models of ESGD.

Authors also have found promising results in a combination of an antacid (magnesium hydroxide), a pectin-lecithin complex and Saccharomyces cerevisiae as a prophylactic agent against both ESGD and EGGD (Sykes, Sykes, & Hallowell, 2014e).

Calcium carbonate has been shown to improve recovery of VFA-induced sodium transport in squamous mucosa in vitro Ussings chambers (Andrews, Buchanan, et al., 2006), which suggest that calcium carbonate preparations may have some efficacy in maintaining mucosal integrity, but because of the short duration effect on gastric fluid pH, more frequent feedings may be necessary to help prevent squamous ulcers. Woodward et al (2014) evaluated the efficacy of two commercially available feed supplements, containing calcium bicarbonate, sodium bicarbonate, lecithin and pectin (Egusin 250® (E-250) and Egusin SLH® (E-SLH), Centaur Animal Health[8]), showed an improvement in the severity of gastric ulcers after a period of 35 days of treatment.

Similarly, a feed supplement containing salts of organic acids in combination with B-vitamins may be beneficial in the management of ESGD, and a preparation containing sea buckthorn berries was shown to have protective properties against the development of EGGD (Huff et al., 2012).

Kerbyson et al. (2016) developed a clinical trial which demonstrated that a nutraceutical supplement (Succeed®, Freedom Health LLC[9]) that provides several ingredients targeted to support gastrointestinal health is noninferior to omeprazole in terms of its ability to improve squamous ulceration in the horse when provided in the diet. When used at a dosage of 27g PO SID for at least 90 days, was found to be noninferior to 4 mg/kg omeprazole administered SID at the end of 90 days, using the complete resolution of ulceration as the measure of success. The healing rate on omeprazole compared with Succeed was higher at days 30 and 60. Then at day 90, there was no difference between the two treatments reporting 52.6% of horses on omeprazole and 52.9% of horses on Succeed.

[8] Centaur Animal Health, 1351-F W. Highway 56 Olathe, KS 66061, USA.

[9] Freedom Health LLC, 65 Aurora Industrial Pkwy, Aurora, OH 44202, USA.

In a preliminary study (Craveiro, 2017), *Trigonella foenum-graecum L*. seed aqueous extract fed to horses was shown to be efficient in the treatment of EGGD (P = 0,018) in comparison to untreated control horses and found positive results in increasing gastric pH value. Still, positive treatment response of the ESGD lacked.

Another recent report (Bush, van den Boom, & Franklin, 2018) focused on the potential of aloe vera as an alternative treatment, however, in the horse treatment response with aloe vera (17.6 mg/kg bwt BID for 28 days) was inferior to treatment with omeprazole buffered paste at 4 mg/ kg bwt SID.

Nonetheless, there is still little evidence to support the use of the unlicensed products for the treatment of EGGD, such as ranitidine, aloe vera, pectin/lecithin complexes, polysaccharides, kaolin, bismuth subsalicylate, sea buckthorn, acupuncture and homoeopathy (Rendle et al., 2018). While some of these products/procedures may contribute for prevention purposes, the beneficial effects in treatment are dubious, and as interactions with other treatments are unknown, it is in the author's opinion that their use should be limited and entails further investigation (Rendle et al., 2018).

III. Retrospective study

This study took place at the Equine Unit of the Teaching Hospital, FMV-ULisboa. The cases described below were evaluated between June 2010 and May 2015, during which time the author took her internship.

1. Objectives

- To determine the presence of EGUS in the horses referred for gastroenterology evaluation and measurement of gastric pH value;
- To classify the gastric ulcer lesions observed according to the gastric ulcer scoring system established by MacAllister et al. (1997);
- To identify the possible risk factors associated with the appearance of gastric lesions;
- To evaluate the response to treatment with omeprazole of patients diagnosed with EGUS;
- To determine associations between the severity of gastric ulceration and clinical symptoms; and between both level of implementation of recommended management changes and endoscopic screening interval, and the treatment outcome.

2. Material and Methods

2.1. Sample selection

The initial inclusion criteria were that the horse had to be referred for EGUS suspicion, either from demonstrating vague clinical signs potentially attributable to gastrointestinal discomfort (behavioural, appetite and/or performance changes) or from displaying apparent clinical signs of abdominal pain.

Furthermore, eligible horses had to meet two other inclusion criteria namely, to have grade 1 or greater gastric ulceration according to the McAllister et al. (1997) and to have had undergone at least two gastroscopic examinations, before and after treatment with omeprazole.

The horses that underwent only one gastroscopic examination were excluded from the study group but were included to document the prevalence of gastric ulcer referrals. The remaining horses, our study population, underwent at least two examinations.

Treatment with acid suppressive therapy was recommended for this selected group, as well as environmental and dietary changes.

2.2. Epidemiological questionnaire

A questionnaire was filled in for all gastroscopies, before and after treatment with omeprazole. The purpose was to either evaluate the presence of any nonspecific signs of gastric ulcers, elaborate a complete clinical history or to evaluate any possible changes of clinical signs or behaviour following the treatment period. The questionnaire is available in Annexe 2.

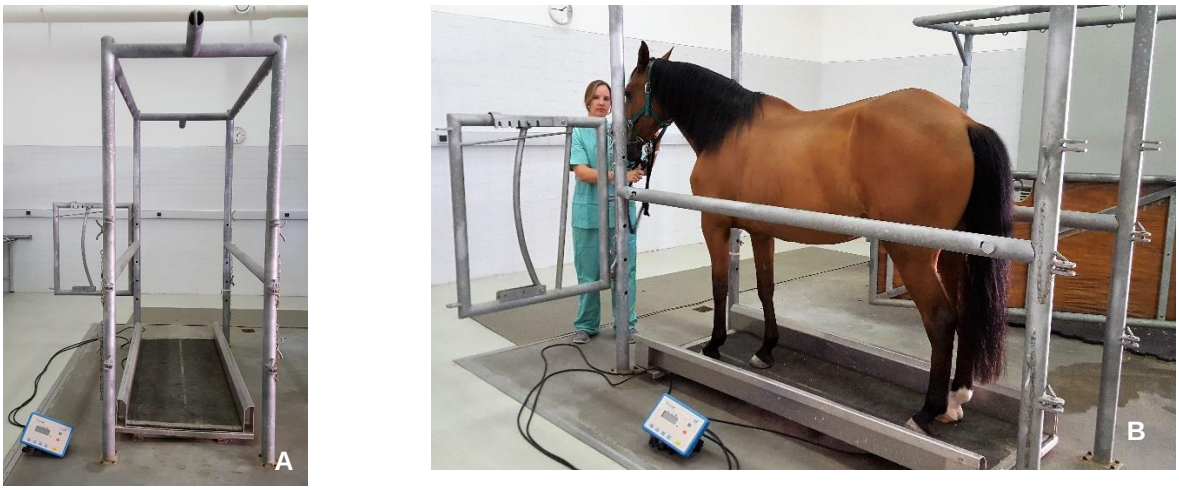
2.3. Physical examination

Before the gastroscopic exam, each horse underwent a physical examination, which included measuring the horse's weight, assessment of dehydration level by inspection of the mucous membranes (oral and ocular), capillary refill time, and skin pinch test on the neck, measurement of rectal temperature, evaluation of heart rate and respiratory rate, auscultation of the abdomen on both sides (colon and cecum motility), and finally inspection of the teeth, mane, coat, and hooves (Table 1).

Table 1 - Parameters included in the physical examination, reference range and grading system (Rose & Hodgson, 2000).

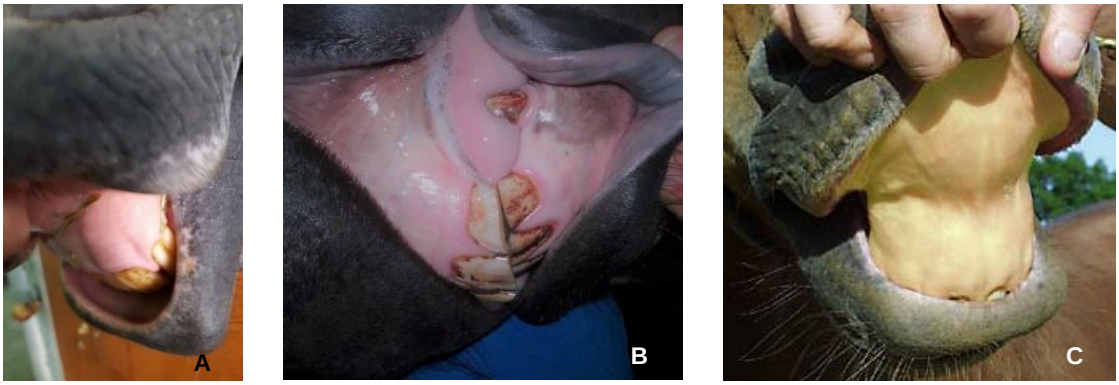
Physical examination checklist	Reference range and grading system
Body Weight (Figure 4)	Kg
Colouration of mucous membranes	0 – pink (normal)
(Figure 5)	1 - hyperaemic
	2 - icteric
Capillary refill time	0 - < 2 seconds (normal)
	1 - > 2 seconds (increased)
Skin pinch test (neck)	0 – Flattens in <2 seconds (normal)
	1 – Slightly elevated for 2-4 seconds (moderately dehydrated)
	2 – Remains raised >4 seconds (severely dehydrated)
Rectal temperature	36,5-39ºC (normal)
Heart rate	28-40 bpm (normal)
Respiratory rate	8-16 mpm (normal)
Auscultation of abdominal sounds	
Ileocecal valve sounds (right paralumbar fossa)	Every 30 seconds-1 minute
Colon motility	Every 1-2 minutes
Dental care	0 – up to date
	1 – in need (sharp edges)
Mane and coat	0 – Shiny
	1 - Dull
Hooves' quality (Figure 6)	0 - Normal and hydrated
	1 - Dry

Figure 4 - Illustrative image of weighing (Original photographs).



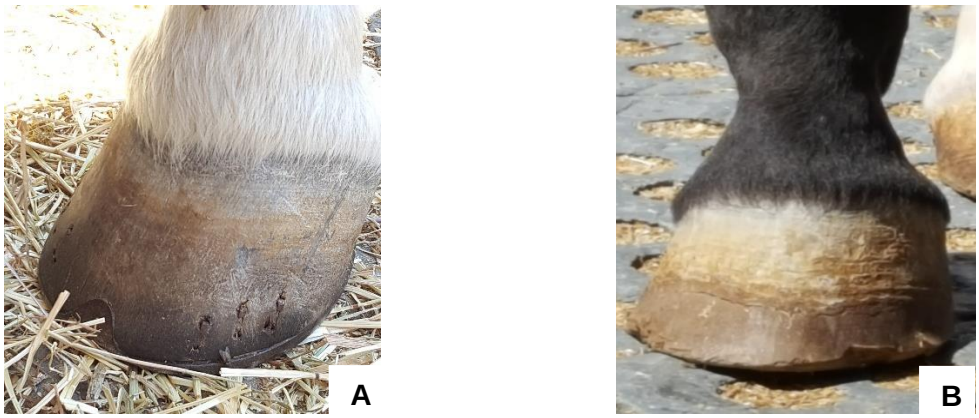
Legend: A - Weighing-machine; B - Weighing of the horse.

Figure 5 - Oral mucosa classification (Original photographs).



Legend: A - Normal pink color; B - Hyperaemic coloration; C - Icteric coloration.

Figure 6 - Classification of the hooves' quality (Original photographs).



Legend: A - Normal and hydrated hoof; B - Dry and cracked hoof.

2.4. Gastroscopy examination

To examine the stomach for ulceration lesions, gastroscopy was performed on all horses. The horses endured a fasting period before examination. Feed was withheld for 12 hours (using a muzzle), and water for 2 hours.

The horses were sedated with 0,1ml/100kg bwt of detomidine at 100mg/ml (Domosedan®, Esteve[10]) i.v. and 1,5ml/100kg bwt of butorphanol at 100mg/ml (Dolorex®, MSD Animal Health[11]) i.v. (Figure 7).

The endoscopy was performed using a Storz® (Karl Storz[12]) equine video-gastroscope (Figure 8), with a working length of 325 cm and with an outer diameter of 13 mm.

The endoscope entered the horse's nares, and once at the glottis, water was squirted through the endoscope air-water channel onto the rima glottis to induce a swallowing reaction and facilitate the progression of the endoscope into the oesophagus. Forcing the endoscope into the oesophagus may accidentally retroflex and then advance towards the mouth. The oesophagus was carefully examined while the endoscope advanced slowly, by insufflating air with the insufflation/irrigation valve.

To observe the stomach thoroughly, it was distended by insufflating air through the suction and irrigation system (Duomat®, Karl Storz[13]) until the non-glandular and glandular regions of the gastric surface could be observed. Whenever necessary, the gastric contents were removed by rinsing the stomach's surface with tap water flushed through the biopsy channel, using a 100 ml syringe. In cases where there was excessive fluid within the stomach, it was aspirated, using the Duomat® pump system, referred above.

During the examination, different structures were observed, namely the non-glandular and glandular surface, the *margo plicatus*, and the antrum and pylorus, excluding the portion that is covered by liquid gastric content, which is not completely eliminated by fasting and/or pump aspiration. In most cases, it was possible to advance the endoscope to see the major duodenal papilla. Once the procedure was completed, the air was removed from the stomach before withdrawing the endoscope. The oesophagus was better evaluated while the endoscope was being removed.

Gastroscopic ulcer grading was carried out in real time. Besides, images of the oesophagus, fundus, *margo plicatus*, greater curvature and lesser curvature were saved from all horses for future analysis.

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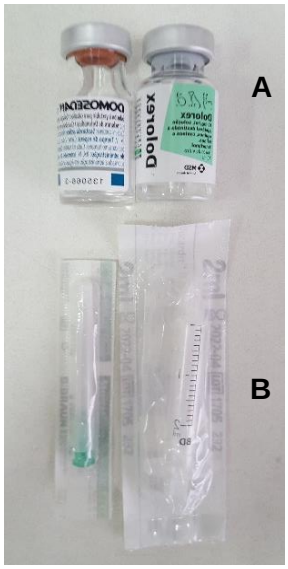
[10] Esteve veterinaria Laboratorios Dr. Esteve S.A., Av. Mare de Déu de Montserrat 221 08041 Barcelona (España).

[11] MSD Animal Health Lda., Edifício Vasco da Gama, nº 19, Quinta da Fonte, Porto Salvo 2770-192 Paço de Arcos.

[12] Karl Storz GmbH&Co. KG, Postfach 230, D-78503 Tuttlingen, Germany.

[13] Karl Storz GmbH&Co. KG, Postfach 230, D-78503 Tuttlingen, Germany.

Figure 7 - Sedation protocol (Original photographs).



Legend: A - Detomidine (Domosedan®) and butorfanol (Dolorex®); B – 21-gauge needle and 2 ml syringe.

Figure 8 - Image of the Storz® equine-gastroscope used for this study (Original photographs).

Figure 9 - Gastroscopy procedure (Original photographs).

Figure 10 - Illustrative image of the horse immobilised for the gastroscopy procedure (Original photographs).

2.5. Gastric ulcer lesions scoring system

The gastric mucosa was examined, and the gastric ulcer lesions observed were scored according to the gastric ulcer scoring system established by MacAllister et al. (1997). This being a retrospective study, the classification of gastric ulcers according to MacAllister was maintained, in order to equally classify the endoscopies carried out before and after the EGUS consensus classification. The grading system scores both types of mucosa together, according to the number of lesions and severity (Table 2). In this study, hyperkeratosis in the nonglandular part of the stomach was not registered as ulcers, since the MacAllister scoring system does not include hyperkeratosis as a lesion. In other studies and scoring systems (Andrews et al., 2002; Andrews & Nadeau, 1999), hyperkeratosis is included in grade 1 of EGUS.

The type of mucosa affected was noted, and the approximate locations of the lesions were identified using a schematic representation (oesophagus, glandular mucosa, non-glandular mucosa, *margo plicatus*, pylorus), in order to compare with follow-up exams. The gastroscopy report form is available in Annexe 3 for further observation.

Table 2 – Number/Severity scoring system for grading of EGUS lesions in horses (Adapted by MacAllister et al. (1997)).

Score	Number	Severity
0	No lesions	No lesions
1	1 to 2 lesions	Appears superficial (only mucosa missing)
2	3 to 5 lesions	Deeper structures involved (greater depth than 1)
3	6 to 10 lesions	Multiples lesions and variable severity (1,2 and/or 4)
4	> 10 lesions or diffuse (or very large) lesions	Same as 2 and has active appearance (active=hyperaemic and/or darkened lesion crater)
5	n/a	Same as 4 plus active haemorrhage or adherent blood clot

Legend: n/a = Not applicable.

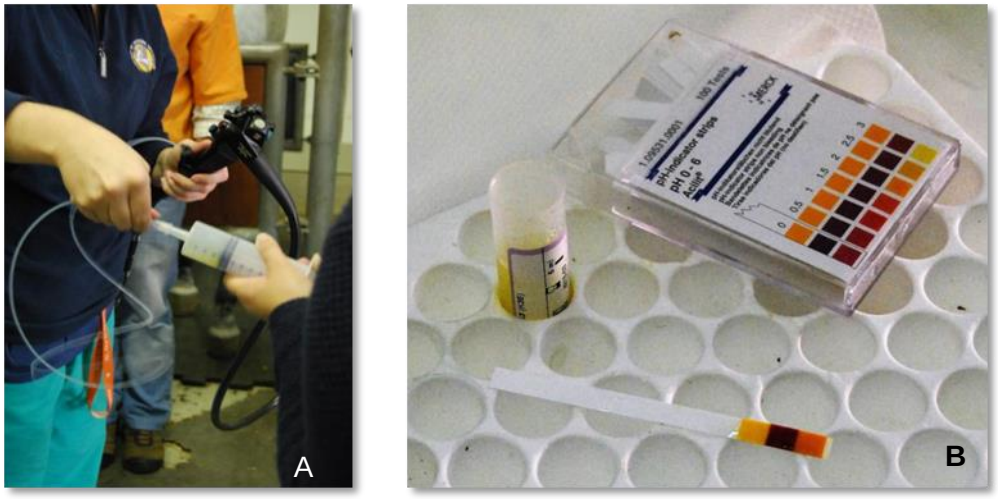
Figure 11 - Exemplification of characteristic lesions of each severity score according to the adapted scoring system of MacAllister et al. (1997) (Original photographs).

Legend: A – Grade 0; B- grade 1; C- grade 2; D – grade 3; E- grade 4; F – grade 5.

2.6. Measurement of gastric pH value

Measurement of gastric pH required the collection of gastric fluid (Figure 12). Before insufflating the stomach, a tube was placed through the endoscope's biopsy channel, using a three-way stopcock and a 100ml syringe (B Braun[14]). The gastric pH level was measured using colorimetric pH indicator strips ranging between 0 and 6 (Acilit®, Merck[15]).

Figure 12 - Collection of gastric fluid and measurement of gastric pH value (original photographs).



Legend: A –100ml syringe and gastric fluid harvesting probe; B - colourimetric pH indicator strips (Acilit®).

2.7. Questionnaire on treatment follow up

After the recommendation of treatment, as well as environmental and dietary changes, a questionnaire was performed to confirm which treatment each horse endured, for how long, and which changes were established (available in Annexe 4).

2.8. Statistical analysis

Results were recorded in a Microsoft Excel 2016® spread sheet and statistically analysed using SPSS statistical software program, version 22.0 (SPSS Statistics Base 22.0).

To characterize the sample and results, descriptive statistic was preformed and analysed. Parametric T tests for paired samples were performed regarding all the quantitative variables to assess differences between means at the two moments. Normality distributions and homogeneity of variances were ensured through Shapiro-Wilk and Levene tests, respectively.

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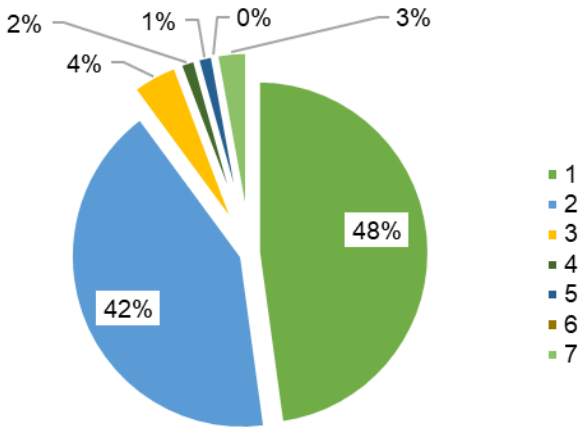
To compare paired results in a dicotomical nominal scale (yes/no) McNemar's nonparametric test was used. To compare dependent variables in an ordinal scale (ulcer lesion scores) between two groups the non-parametric Mann–Whitney U test was performed, while for comparisons between three or more sets of values a non-parametric Kruskal-Wallis test was used. Wilcoxon paired tests were used regarding the ordinal qualitative variables (ulcer scores) to compare ulcer scores on two distinct moments as to assess treatment outcome. Chi-squared tests ($\chi 2$) were used to evaluate the relation between two categorical/qualitative variables. Chi-square independent test was used to evaluate associations between the lesion score evolution (no change, decrease, increase) and the endoscopic screening interval. When the conditions of application of the chi-square were not verified, the Monte Carlo simulation was used, and trends were identified for adjusted residuals ≥2. Chi-square homogeneity test was used to determine whether the distribution of proportions in numeric score evolution and in Severity score evolution are homogeneous according to the different levels of implementation of the corrective measures. Significance was determined when p-value <0.05.

3. Results

3.1. Sample selection

The initial group referred for EGUS suspicion totalled sixty-nine horses (n=69), aged 2-22 years, of different genders (mares, geldings and stallions), all of which presented a certain degree of gastric lesion (grade ≥1). The horses that underwent only one gastroscopic examination were excluded from the study group but were included to document the prevalence of gastric ulcer referrals (n=33/69, 48%). The remaining horses, our study population (n=36/69, 52%), underwent at least two examinations. Figure 13 shows the number of examinations per horse.

Figure 13 - Number of gastroscopies performed on each horse (n=69).



Treatment with acid suppressive therapy was recommended for this selected group (n=36/69), as well as environmental and dietary changes. The final sample population were the horses treated with an enteric coated omeprazole paste formulation (n=22/36), 4mg/kg bwt, SID, *per os*, for 28 days, followed by 2mg/kg bwt, SID, *per os*, for another 28 days. Horses who were treated with other pharmacologic agents (GNF) (n=1/36), as well as those who exclusively underwent environmental and dietary changes (n=2/36), and others because of incomplete history information (n=11/36) were excluded from our sample population.

3.2. Epidemiological questionnaire

3.2.1. Sample characterization

First examination horses were aged between 2 and 22 years, and the average age was 9,86 (SD=4,246).

Detailed characterization of the sample population according to the age, gender, equestrian discipline, training regime, temperament and number of riders and grooms is presented in Table 3. The horses were arranged in four age categories. Overall 59,10% (13/22) were aged between 6 and 10 years and the majority were male 86,4% (19/22). The main equestrian disciplines are referred, being the most frequent show-jumping, representing 45,5% (10/22), while the training regime most described was a high intensity training regime in 68,9% of cases (15/22). Regarding the horse's temperament, 72,7% (16/22) where described as being calm and docile, and the remaining 27,3% (6/22) as being aggressive and/or nervous. The majority were ridden by one rider (59,10%, 13/22) and were handled by one groom (63,6%, 14/22).

Table 3 - Distribution regarding sample characterization according to age, gender, equestrian discipline, training regime, temperament, also number of riders and grooms (n=22).

Sample characterization		Absolute Frequency	Relative Frequency (%)	Cumulative Frequency (%)
Age	Less than 5 years	1	4,5	4,5
	6-10 years	13	59,1	63,6
	11-15 years	6	27,3	90,9
	More than 16 years	2	9,1	100,0
Gender	Stallion	9	40,9	40,9
	Gelding	10	45,5	86,4
	Mare	3	13,6	100,0
Discipline	Hacking	3	13,6	13,6
	Show-jumping	10	45,5	59,1
	Dressage	5	22,7	81,8
	Endurance	3	13,6	95,4
	Bullfighting	1	4,5	100
Training regime	Absent	2	9,1	9,1
	Low intensity (≤ 3x a week)	5	22,7	31,8
	High intensity (4-6x a week)	15	68,2	100,0
Temperament	Docile/calm	16	72,7	72,7
	Nervous/aggressive	6	27,3	100,0
Number of riders	One	13	59,1	59,1
	More than one	9	40,9	100,0
Number of grooms	One	14	63,6	63,6
	More than one	8	36,4	100,0

3.2.2. Clinical complaints

On the first examination, 59,1% (n=13/22) of horses were referred for gastroenterologic examination for having displayed colic episodes in the last year, while at the follow-up examination, this complaint decreased by 9,1% (n=2/22). The colic episodes were described according to the duration and pain scale, and the distribution of such results are present in Table 4.

Table 4 - Distribution of presence of colic in the last year and characterisation of the colic episodes.

		First exam	Second exam
Presence of colic in the last year (n=22)			
	No	9 (40,9)	11 (50,0)
	Yes	13 (59,1)	11 (50,0)
Duration of colic episode			
	Half a day	10 (76,9)	9 (81,8)
	1 day	3 (23,1)	2 (18,2)
Pain scale			
	Very mild	1 (7,7)	0 (0)
	Mild	1 (7,7)	3 (27,3)
	Moderate	8 (61,5)	5 (45,5)
	Severe	1 (7,7)	3 (27,3)
	Very severe	2 (15,4)	0 (0)

Legend: Values are expressed as the number (percentage).

Table 5 shows the descriptive statistics regarding the number of colic episodes accounted, before and after treatment.

On the first examination, the group who displayed colic in the last year experienced between one and six episodes (minimum, maximum), 38,5% (n=5/13) having experienced one colic episode. At the second examination, the number of colic episodes described in the last year decreased in the cases which reported between one and three episodes, while 18,2% (n=2/11) were stated to have had ten episodes, representing an increase compared to the first questionnaire.

Table 5 - Minimum, maximum, mean, median and standard deviation regarding the number of colic episodes accounted in the last year, determined for both moments.

	Number of colic episodes	
	First exam (n=13)	Second exam (n=11)
Mean	2,62	3,91
Median	3	3
SD	1,66	3,239
Minimum	1	1
Maximum	6	10

Table 6 - Distribution of number of colic episodes accounted in the last year at both examination moments (n=13).

Number of colic episodes in the last year	First exam	Second exam	Observations
0	0 (0)	2 (15,4)	
1	5 (38,5)	3 (23,1)	1 total remission 1 increased (4 episodes)
2	1 (7,7)	1 (7,7)	1 =
3	4 (30,8)	2 (15,4)	1 total remission; 2 increased (4; 10 episodes); 1 =
4	1 (7,7)	3 (23,1)	1 =
5	1 (7,7)	0 (0)	1 decreased (3 episodes)
6	1 (7,7)	0 (0)	1 increased (10 episodes)
10	0 (0)	2 (15,4)	

Legend: Values are expressed as the number (percentage); (=) accounted the same number of episodes.

No differences were significant when comparing the information gathered in both questionnaires regarding the colic episodes ($p>0.05$).

Concerning the presence of behavioural and physical changes referred by the horse's owners, riders or grooms, Table 7 indicates the distribution of such changes in both moments.

Although differences in several variables were described between the two examinations, there were only statistically significant differences in weight loss (Mc Nemar; p=0,008) and occasional signs of mild colic (Mc Nemar; p=0,031).

Table 7 - Comparison between results of the epidemiological questionnaires (n=22).

Clinical complaint	First exam	Second exam	Observations
Nervous temperament	6 (27,3)	6 (27,3)	=
Signs of mild colic once in a while	7 (31,8)	1 (4,5)	6 improved
Plays with water	3 (13,6)	6 (27,3)	3 more recorded
Lays snout in drinking bowl	1 (4,5)	1 (4,5)	=
Crib-biting	3 (13,6)	2 (9,1)	1 improved
Grinds teeth when stabled	0 (0)	0 (0)	NTA
Grinds teeth during training	3 (13,6)	6 (27,3)	3 more recorded
Takes time to eat	5 (22,7)	2 (9,1)	3 improved
Eats partially once feed is given	2 (9,1)	3 (13,6)	1 more recorded
Turns rear when entering stall	4 (18,2)	3 (13,6)	1 improved
Stays still	7 (31,8)	6 (27,3)	1 improved
Approaches person	15 (68,2)	16 (72,7)	1 improved
Sad	5 (22,7)	1 (4,5)	4 improved
Lack of energy during training	10 (45,5)	5 (22,7)	5 improved
Lacks concentration during training	7 (31,8)	7 (31,8)	=
Unlearning	0 (0)	0 (0)	NTA
Weight loss	12 (54,5)	4 (18,2)	8 improved
Signs of abdominal discomfort	8 (36,4)	6 (27,3)	2 improved
Dull coat	6 (27,3)	3 (13,6)	3 improved

Legend: Values are expressed as the number (percentage). (=) clinical complaint reported in the same number of horses.

3.3. Physical examination

The measured temperatures were within the reference values and were between 37,5ºC and 38,5ºC. The descriptive statistics and distributions regarding first and second physical examination results relative to body weight, respiratory and heart rate are present in Table 8.

At follow-up examination, the average weight increased by 10 kg to 495,23 kg (SD=62,27) associated with an increase of the maximum weight to 600kg, and of the median to 479,50 kg. In general, after treatment, 50% (11/22) of cases increased their body weight, while 9,1% (2/22) decreased, and 40,9% (9/22) maintained their weight.

Table 8 - Descriptive statistics regarding weight, respiratory and heart rates (n=22).

	Body weight (Kg)		Respiratory rate (N=8-16 mpm)		Heart rate (N=28-40 bpm)	
	First exam	Second exam	First exam	Second exam	First exam	Second exam
Mean	485,27	495,23	13,68	15,86	36,45	36,95
Median	460,50	479,50	12	16	36	36
SD	64,76	62,27	5,64	6,36	9,56	6,49
Minimum	387	386	8	8	24	24
Maximum	590	600	24	34	54	49

Most of the study group, namely 72,7% (n=16/22) of the horses, at first examination registered respiratory rates in the normal reference range (8-16 mpm), whereas only 27,30% (n=6/22) had abnormal increased respiratory rates. At second examination, there was a general increase in the respiratory rates, reaching a maximum of 34 bpm and 45,5% (10/22) presented abnormally increased respiratory rates.

Concerning the heart rate, they were slightly lower at the second examination, where the maximum value was 49 bpm, although neither the average (36,95 bpm (SD=6,49)) nor the median (36 bpm) change significantly. Also, from the group of horses that presented increased heart rate initially only one presented a lower heart rate reaching the normal reference range in the second examination, and the remaining 22,7% (5/22) of the cases showed increased heart rates.

The distribution of the remaining physical examination data from both moments is presented in Table 9.

Concerning the other physical examination findings in both examinations, it is worth mentioning that the weight (Paired T test: $t_{(21)} = -2,784$; p=0,011) showed significant differences ($p<0.05$). No other significant differences were found.

Table 9 - Distribution of qualitative analysis for physical examination findings in both examinations (n=22).

Physical examination findings	Classification	First exam	Second exam
CRT	< 2 seconds	20 (90,9)	22 (100)
	> 2 seconds	2 (9,1)	0 (0)
Mucous membranes	Pink	13 (59,1)	16 (72,7)
	Hyperaemic	4 (18,2)	4 (18,2)
	Icteric	5 (22,7)	2 (9,1)
Skin pinch test	Flattens in < 2”	13 (59,1)	15 (68,2)
	Slightly elevated for 2”-4”	8 (36,4)	7 (31,8)
	Remains raised for > 4”	1 (4,5)	0 (0)
Cecum motility	Normal (30''-1')	14 (63,6)	19 (86,4)
	Decreased	8 (36,4)	3 (13,6)
Colon Motility	Normal (1-2 min.)	15 (68,2)	16 (72,7)
	Decreased	7 (31,8)	6 (27,3)
Dental care	Up to date	17 (77,3)	16 (72,7)
	In need (sharp edges)	5 (22,7)	6 (27,3)
Mane and Coat	Shiny	12 (54,5)	11 (50)
	Dull	10 (45,5)	11 (50)
Hooves	Normal and hydrated	16 (72,7)	18 (81,8)
	Dry	6 (27,2)	4 (18,2)

Legend: Values are expressed as the number (percentage).

3.4. Gastroscopy examination

An in-depth examination of the non-glandular mucosa was possible in all horses. In the majority, a thorough examination of the glandular region was also possible, except for a small area where residual fluid was merging at the ventral part of the fundus.

Of the 22 horses examined, 100% presented a certain degree of gastric lesion, from hyperaemia and ulceration of the mucosa observed. The first gastroscopy showed that 9,1% (2/22) had only lesions in the glandular part of the stomach; 31,8% (7/22) only in the nonglandular part and 59,10% (13/22) in both parts of the stomach.

After the treatment period with omeprazole, the control gastroscopy was performed, and it was found that several of the horses had some degree of healing (involution) of the lesions initially observed, with two cases of total remission. The distribution regarding the lesion location is shown in Table 10.

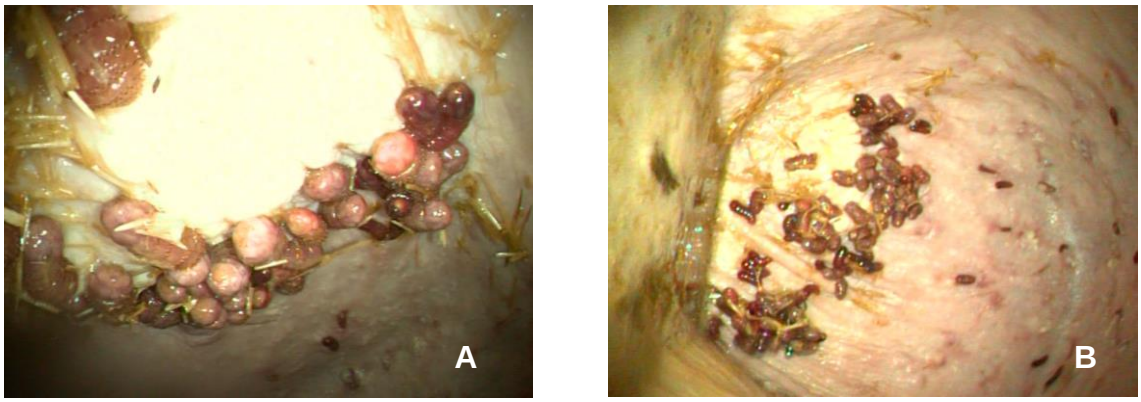
Gastric parasites were found in one horse at both examinations (Figure 14).

Table 10 - Distribution regarding lesion location (n=22).

Lesion location	First exam	Second exam
Oesophagus	0 (0,0)	2 (9,1)
Non-glandular squamous mucosa	20 (90,9)	17 (77,3)
Margo plicatus	7 (31,8)	4 (18,2)
Glandular mucosa	15 (68,2)	14 (63,6)
Pylorus	8 (36,4)	9 (40,9)

Legend: Values are expressed as the number (percentage).

Figure 14 - Image of the gastric mucosa of a parasitised horse (original photographs).



Legend: A and B - Parasites of the genus *Gastrophilus* in the glandular and non-glandular squamous mucosa.

The distribution regarding the lesion scores registered in both examinations is displayed in Table 11. Among the study group, the most prevalent lesion number score was grade 4, 59,1% (13/22) of horses on the first examination and 36,4% (8/22) on the second examination. In terms of the lesion severity score, the most prevalent were grades 3, 4 and 5, each being present in 22,7% (5/22) of horses on first examination and all showing a decrease on the second examination.

Table 11 - Distribution regarding gastric lesion scores at both gastroscopic examinations (n=22).

Score	Number		Severity	
	First exam	Second exam	First exam	Second exam
0	0 (0,0)	2 (9,1)	0 (0,0)	2 (9,1)
1	1 (4,5)	2 (9,1)	3 (13,6)	4 (18,2)
2	4 (18,2)	5 (22,7)	4 (18,2)	6 (27,3)
3	4 (18,2)	5 (22,7)	5 (22,7)	2 (9,1)
4	13 (59,1)	8 (36,4)	5 (22,7)	4 (18,2)
5	n/a	n/a	5 (22,7)	4 (18,2)

Legend: Values are expressed as the number (percentage); n/a= Not applicable.

Below are two tables (Tables 12 and 13) that summarize the results attained in the gastroscopy of both protocol phases, and the rightmost column indicates the evolution of the horses after therapy with enteric coated omeprazole paste, at the treatment dose of 4mg/kg PV PO for 28 days, followed by maintenance dose 2 mg/kg PV for 28 days.

Table 12 - Number of horses per numeric score in each gastroscopy (n=22).

Number score	First exam	Second exam	Observations
0	0	2	NTA
1	1	2	1→ grade 3
2	4	5	2 → no evolution
			1 →grade 3
			1→grade 4
3	4	5	1→grade 2
			1→grade 1
			1→ total remission
4	13	8	3→grade 3
			2→grade 2
			1→grade 1
			1→ total remission

Table 13 - Number of horses per severity score in each gastroscopy (n=22).

Severity score	First exam	Second exam	Observations
0	0	2	NTA
1	3	4	1→ no evolution
			1→grade 3
			1→ total remission
2	4	6	2→ no evolution
			1→ grade 1
			1→ grade 4
3	5	2	1→ no evolution
			1→ grade 1
			2→ grade 2
			1→ grade 4
4	5	4	1→ no evolution
			1→ grade 1
			2→ grade 2
			1→ grade 5
5	5	4	3→ no evolution
			1→ grade 4
			1→ total remission

While 36,36% (8/22) of the cases maintained the initial ulcer scores, it should be referred that 45,45% (10/22) decreased, and the remaining 18.18% (4/22) increased.

Although there were confirmed changes in the scores after treatment, Table 14 shows that there were no significant differences of the lesion number score (Wilcoxon=-1,751; p=0,080), and the lesion severity score (Wilcoxon=-1,568; p=0,117), therefore no significant treatment effect.

3.4.1. Measurement of gastric pH value

The pH values recorded were between 1.5 and 6 (Table 15). It should be referred that the cases with no record of gastric pH, one at first examination and five at the second examination, were due to the presence of ingesta.

Comparing the pH values recorded in both exams, there were 31.83% (7/22) of cases with pH increase, with 27.27% (6/22) showing pH values above 4, and only 4.55% (1/22) maintained a

value below 4, while 18.18% (4/22) of cases registered a decrease in pH maintaining values below 4, and finally 27.27% (6/22) of cases had no changes in pH values remaining above 4. No significant differences were found in pH values between both examinations (p>0.05).

Table 14 - Testing of changes in the number and the severity of lesions before and after treatment.

		N	Mean Rank	Sum of Ranks	Wilcoxon	*p*
Lesion Number Score - 2nd exam vs 1st exam	Negative Ranks	10[a]	8,00	80,00	-1,751	0,080
	Positive Ranks	4[b]	6,25	25,00		
	Ties	8[c]				
	Total	22				
Lesion Severity Score - 2nd exam vs 1st exam	Negative Ranks	10[d]	7,70	77,00	-1,568	0,117
	Positive Ranks	4[e]	7,00	28,00		
	Ties	8[f]				
	Total	22				

Legend: a - Lesion Number Score at 2nd exam < Lesion Number Score at 1st exam; b - Lesion Number Score at 2nd exam > Lesion Number Score at 1st exam; c - Lesion Number Score at 2nd exam = Lesion Number Score at 1st exam; d - Lesion Severity Score (2nd exam) < Lesion Severity Score (1st exam); e - Lesion Severity Score (2nd exam) > Lesion Severity Score (1st exam); f - Lesion Severity Score (2nd exam) = Lesion Severity Score (1st exam).

Table 15 - Descriptive statistics regarding the gastric pH value (n=22).

Descriptive statistics		First exam	Second exam
n	Valid	21	17
	Missing	1	5
Mean		3,98	4,77
Median		5	5,5
SD		2,01	1,37
Minimum		1,5	2
Maximum		6	6

3.5. Identification of associations between independent variables and ulcer scores.

The presence of colic in the last year (*p*=0,029) was significantly associated with lesion number scores (Table 16). The horses that presented colic in the last year displayed a higher mean rank lesion number score (MR=13.73) in comparison with the horses that did not present colic (MR=8.28) whereas the coat condition (*p*=0,038) was significantly associated with lesion severity. The horses with shinny coats have a higher mean rank lesion number score (MR=13.22) in comparison with the horses with dull coats (MR=6,92).

There were no significant associations (*p*>0.05) observed between the remaining clinical signs and ulcer scores, nor between any of the risk factors evaluated and the ulcer scores. Furthermore, there was no significant association between the location of lesions or pH value and ulcer scores.

Table 16 – Comparison of lesion number score and lesion severity score with independent variables (P-values resulting from non-parametric tests of Mann-Whitney and Kruskal-Wallis).

	DV (first exam)	
IV (first exam)	Lesion Number Score	Lesion Severity Score
	p	p
Gender [a]	0,187	0,420
Age[a]	0,179	0,147
Temperament[b]	0,453	0,598
Training regime[a]	0,465	0,728
Discipline[a]	0,139	0,407
Number of Riders[b]	0,521	0,246
Number of Grooms[b]	0,616	0,163
Colic in the last year[b]	0,029*	0,172
Mean Rank	*No=8.28 Yes=13.73*	
Pain scale[a]	0,244	0,444
Signs of mild colic once in a while[b]	0,067	0,388
Plays with water [b]	0,144	0,130
Lays snout in drinking bowl[b]	0,476	0,171
Crib bitting[b]	0,589	0,282
Grinds teeth when stabled	c	c

Legend: IV – Independent variables; DV – Dependent variables; c - Test wasn't performed due to existing only one condition in Independent variable; (*) Significative for α=0,05; ([a]) Kruskal-Wallis Test; ([b]) Mann-Whitney Test.

Table 16 – (Continuation)

Grinds teeth during trainingb	0,144	0,494
Takes time to eatb	0,825	0,631
Eats everything once feed is given[b]	0,423	0,537
Eats partially once feed is given[b]	0,245	0,771
Turns rear when entering stall[b]	0,083	0,207
Stays still[b]	0,873	0,313
Approaches person[b]	0,873	0,313
Sad[b]	0,894	0,779
Lack of energy during training[b]	0,794	0,225
Lacks concentration during training[b]	0,130	0,885
Unlearning[b]	c	c
Weight loss[b]	0,233	0,281
Signs of abdominal discomfort[b]	0,143	0,163
Dull coat [b]	0,588	0,038
Mean Rank		*No=13,22; Yes=6,92*
Respiratory Rate[b]	0,279	0,940
Heart Rate[a]	0,279	0,407
CRT[b]	0,949	0,815
Mucous membranes[a]	0,957	0,906
Skin pinch test[a]	0,719	0,653
Cecum motility[b]	0,396	0,464
Colon motility[b]	0,605	0,614
Dental care[b]	0,894	0,447
Mane and Coat[b]	0,823	0,788
Hooves[a]	0,490	0,521
Gastric parasites (gastrophilus)[b]	0,423	0,573
Non-glandular squamous mucosa [b]	0,701	0,779
Glandular mucosa [b]	0,078	0,407
Margo plicatus [b]	0,891	0,891
Pylorus [b]	0,110	0,095
pH [b]	0,654	1,000

Legend: IV – Independent variables; DV – Dependent variables; c - Test wasn't performed due to existing only one condition in Independent variable; (*) Significative for α=0,05; ([a]) Kruskal-Wallis Test; ([b]) Mann-Whitney Test.

3.6. Effect of screening interval on treatment outcome

The second examination occurred between 63 and 208 days (Table 17). In most situations (86.4%), the second examinations occurred between one and four months after the first examination, as shown in Table 18. Distributions regarding EGUS score changes and endoscopic screening interval are displayed in Table 19.

Table 17 - Descriptive statistics regarding the number of days between examinations.

Descriptive statistics	
Mean	98,45
Median	89,00
SD	35,68
Minimum	63
Maximum	208

Table 18 - Distribution regarding endoscopic screening interval.

Endoscopic screening interval	Number of horses
1-4 months	19 (86,4%)
4-6 months	2 (9,1%)
6 months - 1 year	1 (4,5%)
Total	22 (100%)

Table 19 - Distributions regarding score evolutions and endoscopic screening interval.

EGUS score evolution after treatment		Endoscopic screening interval			
		1-4 months	4-6 months	6 months-1 year	Total
Numeric score evolution	No change	8 (36,36)	0 (0)	0 (0)	8 (36,36)
	Decreased	9 (40,91)	0 (0)	1 (4,55)	10 (45,45)
	Increased	2 (9,09)	2 (9,09)	0 (0)	4 (18,18)
	Total	19 (86,36)	2 (9,09)	1 (4,55	22 (100)
Severity score evolution	No change	7 (31,82)	1 (4,55)	0 (0)	8 (36,36)
	Decreased	9 (40,91)	0 (0)	1 (4,55)	10 (45,45)
	Increased	3 (13,64)	1 (4,55)	0 (0)	4 (18,18)
	Total	19 (86,36)	2 (9,09)	1 (4,55)	22 (100)

Legend: Values are expressed as the number (percentage).

There was a significant association between the endoscopic screening interval and the numeric score evolution ($\chi^2(4) = 11{,}000$; $p=0{,}024$) as displayed in Table 20. Adjusted residual values indicate a tendency for the endoscopic screening interval between 4-6 months to present an increase in numeric scores (resAjust=3,1).

Table 20 - Chi- square tests to determine association between endoscopic interval and score evolution (n=22).

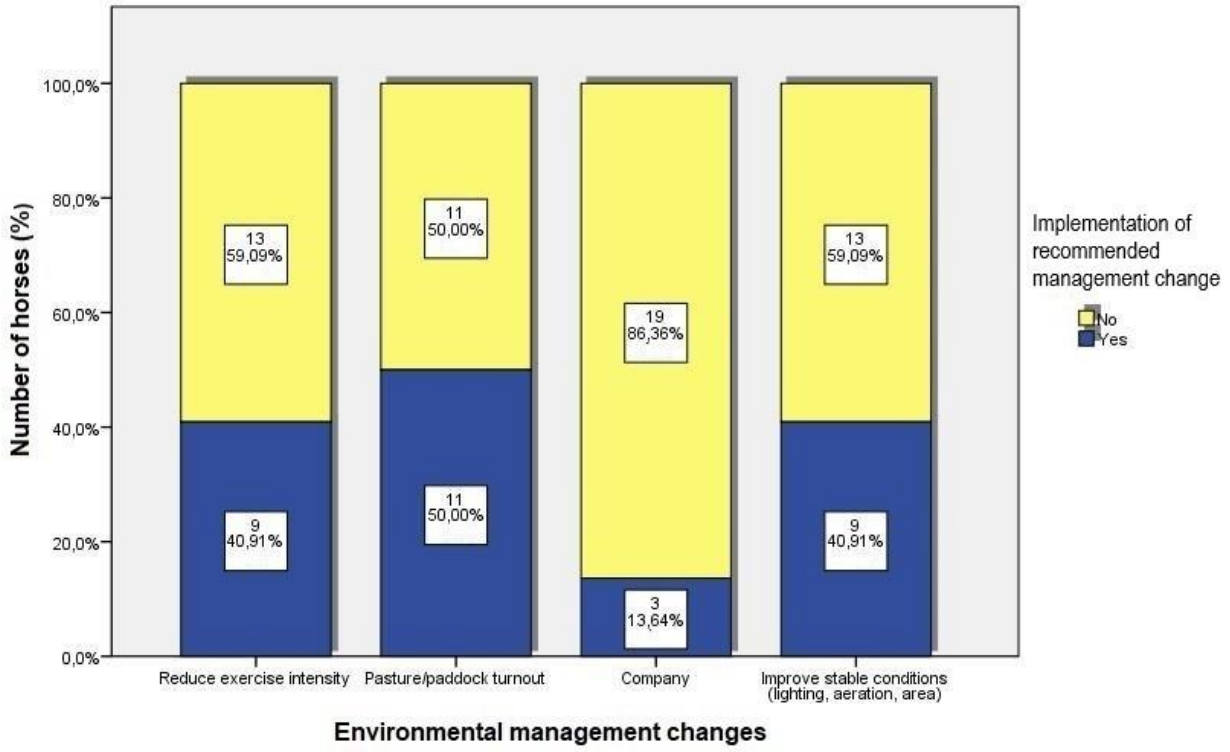
	χ^2	df	Monte Carlo Sig. (2-sided) *p*
Endoscopic screening interval x Numeric score evolution	11,000 [a]	4	0,024
Endoscopic screening interval x Severity score evolution	3,401[a]	4	0,643

a- The Monte Carlo variant was used due to non-satisfaction of the chi-square application conditions.

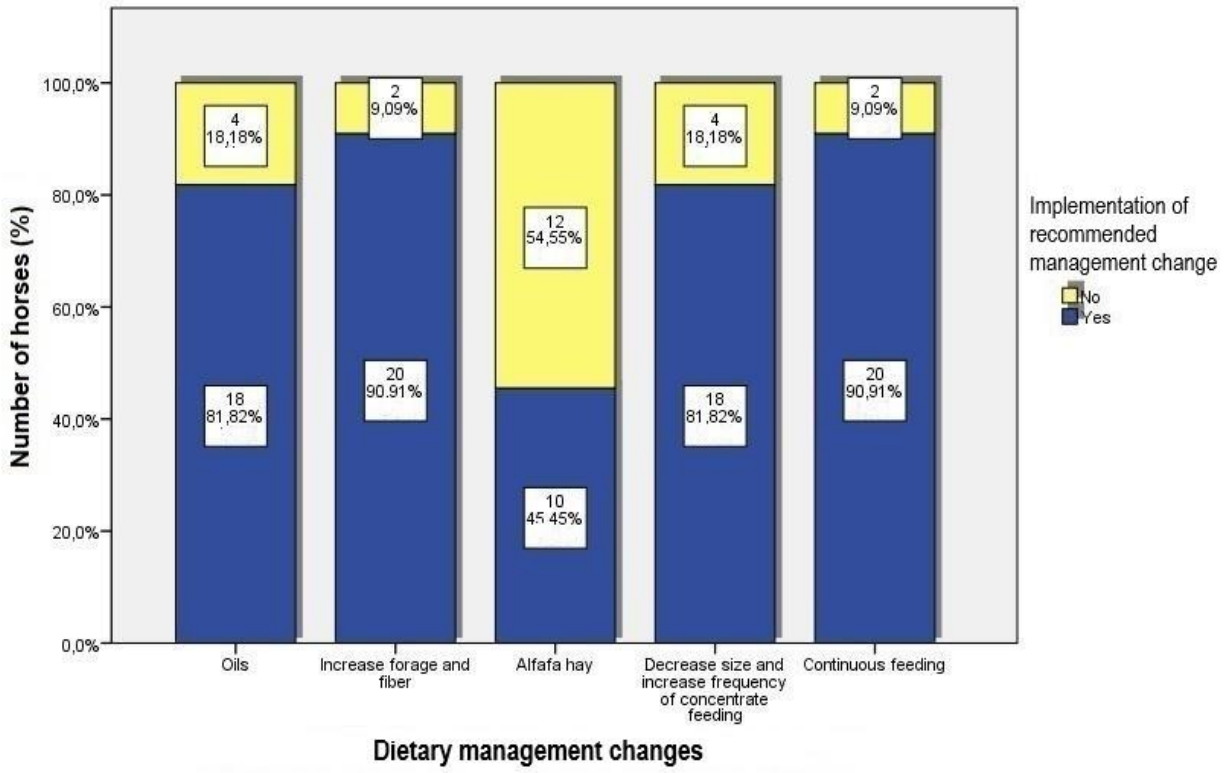
3.7. Influence of implementation of recommended management changes over the treatment outcome

According to the results gathered from the final questionnaire on treatment follow-up, Graphs 1 and 2 reveal the distributions concerning the environmental and dietary changes that were implemented. The management changes worth mentioning are mainly dietary changes due to the high accession in the study group. The most accepted dietary changes were the addition of oils, decreased the size and increased the frequency of concentrate feeding in 81,8% (18/22) of cases and the increase of forage and fibre together with the implementation of continuous feeding in 90,91% (20/22) of cases.

Graphic 1 - Distribution regarding the level of implementation of environmental management changes (n=22).

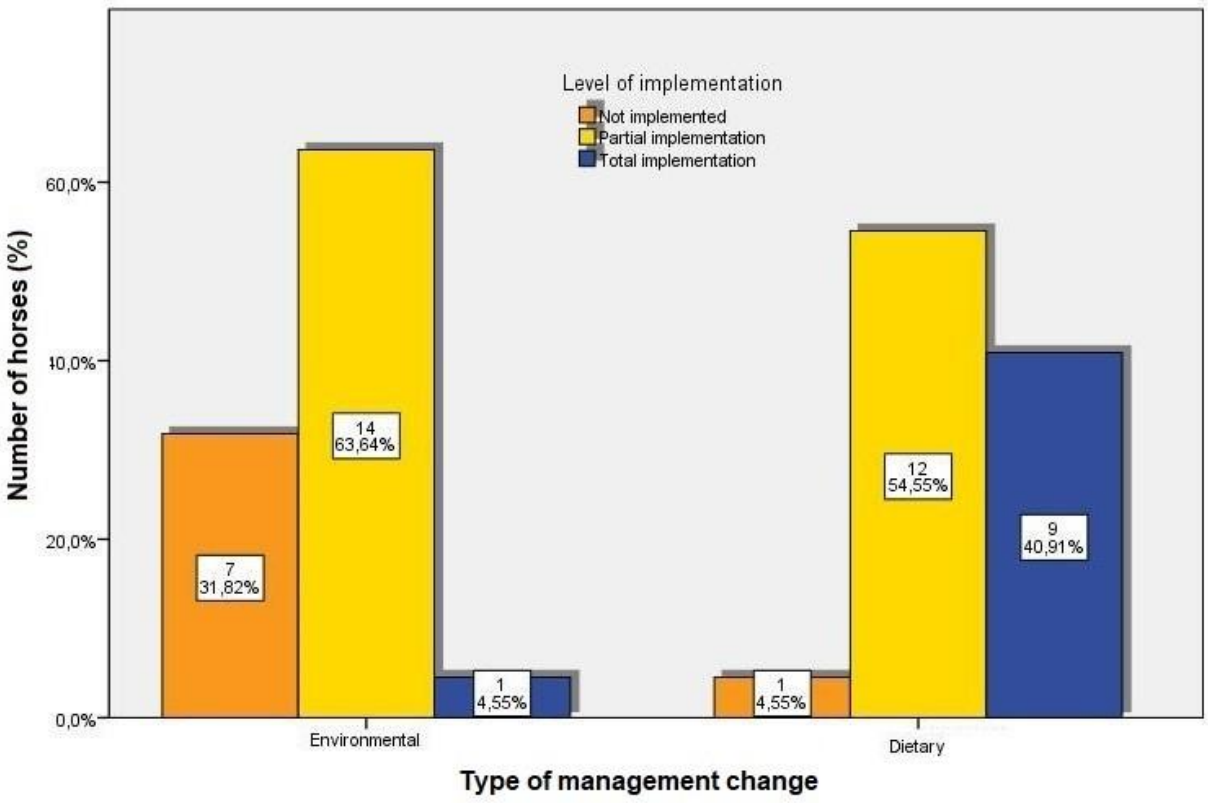


Graphic 2 - Distribution regarding the level of implementation of dietary management changes (n=22).



Overall, the management changes were in most cases only partially implemented, as shown in Graphic 3.

Graphic 3 - Level of implementation of recommended management changes established (n=22).



To assess a possible influence of management changes over score evolution, the distributions of the levels of implementation of the recommended management changes according to score evolution are displayed in Table 21.

It was determined that in any type of implementation (not implemented, partial or total implementation) (Table 22), there were no significant differences in numeric score evolution and severity score evolution ($p>0,05$).

Table 21 – Distributions of the levels of implementation of the recommended management changes according to score evolution.

Level of implementation		Numeric score evolution			Total	Severity score evolution			Total
		NC	DC	INC		NC	DC	INC	
Environmental Changes	Nothing	4 (57,1)	1 (14,3)	2 (28,6)	7 (100)	3 (42,9)	2 (28,6)	2 (28,6)	7 (100)
	Partial	3 (21,4)	9 (64,3)	2 (14,3)	14 (100)	4 (28,6)	8 (57,1)	2 (14,3)	14 100,0
	Total implementation	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)
Total		8 (36,4)	10 (45,5)	4 (18,2)	22 (100)	8 36,4	10 45,5	4 18,2	22 100
Dietary Changes	Nothing	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)
	Partial	4 (33,3)	5 (41,7)	3 (25,0)	12 (100)	3 (25,0)	7 (58,3)	2 (16,7)	12 (100)
	Total implementation	4 (44,4)	4 (44,4)	1 (11,1)	9 (100)	5 (55,6)	2 (22,2)	2 (22,2)	9 (100)
Total		8 (36,4)	10 (45,5)	4 (18,2)	22 (100)	8 (36,4)	10 (45,5)	4 (18,2)	22 (100)

Legend: NC – No score change; DC – Decrease in score; INC – Increase in score. Values are expressed as the number (percentage).

Table 22 - Chi-square tests to determine association between level of implementation of recommended changes and score evolution.

Independent variables		Dependent variables	χ^2	*p*
Implementation of environmental changes	by	Numeric score evolution	6,561[a]	0,150
	by	Severity score evolution	3,457[a]	0,576
Implementation of dietary changes	by	Numeric score evolution	1,986[a]	0,829
	by	Severity score evolution	4,140[a]	0,463

Legend: ([a]) - The Monte Carlo variant was used due to non-satisfaction of the chi-square application conditions.

4. Discussion

In the present study, it was determined that all referred sixty-nine animals had gastroscopic evidence of gastric ulceration.

Overall, we found a high presence (100%) of gastric ulcers in the horses examined. The group of horses examined, as with previous studies, was not randomly sampled and may only approximate the true prevalence of the disease in the population.

The incidence found in the present study was higher than that found in previous studies (Niedźwiedź et al., 2013; Aranzales et al., 2014; Ward et al., 2015) where a prevalence of 50% was reported in sport and leisure horses in the UK, Poland and Brazil or racehorses in Denmark and USA (Cate et al., 2012; Luthersson et al., 2009b). On the other hand, it matches the prevailing prevalence in racehorses (80-100%) reported in various locations around the world (Begg & O'sullivan, 2003; Bell, Kingston, Mogg, et al., 2007; Roy et al., 2005; Sykes, Sykes, et al., 2014b). This finding is not surprising, and the high occurrence may be explained by the inclusion criteria, as the horses in the present study were selected by presenting some clinical signs presumably attributed to EGUS. Also, as described previously, the number of selected cases was abridged by the failure to collect complete information from all the owners/caretakers of horses that met the inclusion criteria, and this could have led to attrition bias. We will discuss here the prevalence's relative to the sample population (n=22).

Some authors have been associating overall prevalence of ulceration with different sex groups, age and breed (Bell et al. 2007; Luthersson et al. 2009b; Orsini et al. 2009). We found gastric ulceration to be most prevalent in castrated males and ages between 6 and 10, whereas it was lower in females and stallions, which is in agreement with Rabuffo et al. (2002). Despite these findings, these risk factors were not found significant for the presence of EGUS nor for number and severity of ulcers as found by Cate et al. (2012) and Martinez and Silveira (2013).

The high prevalence of gastric ulcers is well known in racehorses, and high-intensity training has been associated with an increased risk and severity of disease (Orsini et al., 2009; Ward et al., 2015). In the present study, we found a higher prevalence in show-jumping horses (45,5%) versus other disciplines and in high-intensity training regime (68,2%), which is consistent with previous studies (Dionne et al., 2003; Luthersson et al., 2009b; Sykes et al., 2019).

Another possible risk factor that has been appointed to gastric ulceration in horses is the horse's temperament as discussed by McClure and Glickman (1999), but in our study, only 27,3% of animals were described as aggressive and/or nervous. This factor is very hard to evaluate, as riders/caretakers might have a subjective opinion of the horse's attitude. Many studies have been conducted in the past to try to evaluate the human-animal relationship by judging behavioural characters using subjective scores (Cats: Turner et al. (1986), dogs: Goddard and

Beilharz (1983)). Then a simple test was developed to evaluate and score these interactions based on observations (Hausberger & Muller, 2002) and significant differences were identified between horses according to the caretaker. Mönki et al. (2016) succeeded in associating gastric lesions with a human-horse relationship factor, where the trainer and increased number of caretakers and riders were defined as possible risk factors for EGGD. Unfortunately, we were unable to achieve the same results.

Similar to a previous study conducted at Lisbon Veterinary School Teaching Hospital (Simões, 2011), the gastric mucosa was divided into five regions (oesophagus mucosa, squamous non-glandular mucosa, *margo plicatus*, glandular mucosa and pylorus) in order to organise the lesions found in areas with similar aggression exposure. Consequently, the *margo plicatus* due to its capillary network and susceptibility to ischemic lesions was considered an independent region of the non-glandular mucosa (Staszyk et al., 2001). Then, the pylorus was considered an independent portion of the body of the glandular mucosa, because although possessing similar physiological characteristics, they have histological differences, such as the presence of mucin submucosal glands (Murray, Nout, et al., 2001b). Lastly, the oesophagus was examined upon withdrawing the endoscope as even though uncommon due to the nature of the cardia sphincter gastroesophageal reflux may occur (Andrews & Nadeau, 1999).

The fasting period and procedures applied before endoscopy was generally enough to allow the non-glandular squamous mucosa to be assessed completely in all horses. Still, as the presence of residual feed material in a few areas of the glandular mucosa can complicate the evaluation of possible lesions in that area in a few cases, it is not certain that the smaller lesions were analysed (Andrews et al., 2002).

The results gathered from both gastroscopic examinations in the present study are in agreement with the results obtained by others on the prevalence of ESGD and EGGD (Begg & O'sullivan, 2003; Sykes & Jokisalo, 2015, 2015). Nearly all horses in this study (90,9% in the 1st exam and 77,3% in the 2nd exam) presented lesions in the squamous non-glandular portion of the stomach, along the greater and lesser curvature near the *margo plicatus* which is in agreement with Tamzali et al. (2011). The lower presence of lesions in the glandular mucosa (68,20% in the 1st exam and 63,6% in the 2nd exam) is consistent with previous reports of 70.6% of EGGD in domesticated horses (Ward et al. 2015), while the lesions in the pylorus region (36,4% at 1st exam and 40,9% at 2nd exam) are somewhat similar to a previous report of 47% (Begg & O'sullivan, 2003), but less than the 58% found in another report (Murray, Nout, et al., 2001b).

The relatively high incidence and severity of lesions in the glandular mucosa and pylorus area confirms the importance of a thorough assessment of all areas of gastric mucosa and justifies the recent emerging interest in EGGD (Luthersson et al., 2009b; Mönki et al., 2016; Sykes,

Sykes, et al., 2014b, 2014a, 2015), while gastroscopy continues to be the only method currently available to obtain a definitive diagnosis of gastric ulcers (Camacho-Luna et al., 2018).

As suspected, the oesophagus was the least affected region as only two horses presented lesions in the oesophagus mucosa in the second examination.

As found in previous studies (Begg & O'sullivan, 2003; Murray, Nout, et al., 2001b), there was no association between the presence of lesions at one site and the other, and there was a low correlation between lesion score and location, with the pyloric ulcer score being the lowest.

By analysing the epidemiological questionnaires, the clinical symptoms described were found vague and diverse, and for this reason insufficient for a definite diagnosis, but sufficient to consider EGUS as a differential diagnosis according to various authors (Hepburn, 2011; Murray et al., 1989; Sykes & Jokisalo, 2014; Wickens et al., 2013).

The results of the epidemiological questionnaire demonstrated that the main factors were history of colic (presence of colic in the last year and/or recurrent signs of colic), signs of abdominal discomfort (oral stereotypes, bruxism, cribbing), behaviour changes (nervous/aggressive temperament and attitude, indifferent or sad posture), poor performance (lack of concentration and energy), and poor body condition (weight loss and dull coat).

As found in previous studies (Dukti et al., 2010; Mönki et al., 2016) colic was one of the main clinical complaints, where 59,10% of horses presented with colic episodes in the last year and was significantly associated to ulcer scores. This finding is in line with previous studies (Hepburn, 2011; Murray et al., 1989) which stated that EGUS can occur in horses that present concomitant disease, where delayed gastric emptying increases the residual gastric fluid volume which results in a dorsal movement of acid, associated to pyloric disease and colic. On the contrary, Rabuffo et al. (2009) found that hospitalised colic patients are at higher risk to developing gastric ulceration due to management and environmental factors, but no association between developing EGUS and the complaint of colic.

The horse's mane and coat condition was the only other symptom significantly associated with ulcer scores. Curiously this was a surprising finding, as the author expected an association between the presence of a dull coat and an increase in ulcer severity but found a higher severity instead in horses with healthy shiny coats. This result confirms that gastric lesions can be prevalent in apparently asymptomatic horses (Cate et al., 2012; Fernandes et al., 2003; Niedźwiedź, Kubiak, et al., 2013). Nevertheless, poor body condition in horses in training has been associated with unresponsive posture and demeanour, consistent with illness, exhaustion, chronic pain, or depression-like states (Burn, Dennison, & Whay, 2010), even though assessment of behavioural changes such as temperament or posture can be difficult to interpret.

The correlations found in our study align with the proven previously published associations between ulcers and clinical symptoms (Belli, Silva, & Fernandes, 2005), namely the fact that the higher the ulcer degree, the greater the association between ulcers and clinical symptoms. Moreover, that ulcers lower than grade 2 are not likely to be associated with clinical findings or performance changes (Luthersson et al., 2009a; Sykes & Jokisalo, 2015).

After treatment with omeprazole, there was a general improvement of symptoms and clinical complaints, especially related to colic, body condition (body weight and coat condition) and behavioural changes (Table 7). However, three new cases of bruxism during training were appointed. Another horse played with water, and yet another took longer to eat. Signs of abdominal discomfort such as playing with water, bruxism and/or cribbing are associated with EGUS (Murray et al., 1989), but can be frequently interpreted as bad habits by owners/caretakers, and if present during training can indicate problems with the horses bit or due to tooth wear, possible sharp edges on both the labial side of the upper cheek teeth and the lingual side of the lower cheek teeth or any dental abnormalities (Simões, 2011).

Important to refer that there was a total abolition of colic symptoms in two cases, while three other cases did not register new episodes. Nevertheless, four cases increased the number of colic episodes (Table 6).

Although not statistically significant, the general improvements registered after treatment with omeprazole show evidence that these unspecific and various symptoms might be associated with the presence of EGUS.

During the physical examination, the prime change appointed was also a dull mane and coat. However, after treatment with omeprazole, none of the horses improved the mane and coat condition, and oddly one horse seemed worse. Although surprising, many diverse factors can be responsible for this fact, such as concomitant disease (e.g. endocrinal disease), nutritional factors (e.g. malnutrition), parasitism, age or even season of the year (the cold and wet season before shedding) (Scott & Miller, 2011).

At first examination, six horses presented increased heart rate (>40bpm) as well as the respiratory rate, which can be explained by nervousness from being immobilised and in a strange environment. After treatment with omeprazole, five horses still presented increased heart rate, whereas the respiratory rate was increased in ten horses at the second examination, which could be related to the fact that they maintained a nervous temper.

Reflecting the horse's circulatory status, hyperaemic and icteric colouration of the mucous membranes along with increased CRT were also a frequent detection in the study group.

After treatment, only three horses with icteric mucous membranes changed to a normal moist and pink appearance. The horses with increased CRT returned to normal. Hyperaemic

membranes accompanied by normal or increased CRT are usually related to a septic or endotoxic condition associated with proximal enteritis, enterocolitis, prolonged strangulation obstructions, non-strangulating infarction or peritonitis. On the other hand, icteric mucous membranes are characteristic of patients with an obstructive biliary disease or associated with prolonged periods of decreased food intake or even anorexia (Moore, 2006).

Decreased intestinal motility (cecum and colon motility) was another common clinical finding which improved after treatment with omeprazole. The absence or decrease of frequency and intensity of sounds at auscultation can be associated with different causes such as stress, alimentary factors (the type of feed, decreased intake, fasting), but also hypoperfusion during colic (Moore, 2006), however it was likely to be due to the fasting endured.

Mouth examination in both periods detected the same number of horses needed dental care, as they presented uneven tooth wear and sharp edges on both the labial side of the upper cheek teeth and the lingual side of the lower cheek teeth. Just as any of the other clinical findings, the teeth could explain the weight loss (malnutrition), oral stereotypes (bruxism), poor performance, and aggressive posture when approached.

Overall there was a general improvement of the horse's physical condition. However, the increase in body weight was the only significantly relevant changes confirmed after treatment with omeprazole, which demonstrates a positive association with the presence of EGUS.

The lack of standardisation and vast diversity of scoring systems published prevents a better assessment and a correct comparison between clinical cases (Luthersson et al., 2009b). Despite the recent recommendations in the Consensus Statement (Sykes, Hewetsen et al. 2015), we opted for an adaptation of the classification system of MacAllister et al. (1997), as it was the classification method used by the Teaching Hospital since the beginning. In spite of being emphasized by Sykes and Jokisalo (2014) that ESGD and EGGD should be considered as separate concepts, the classification of both types of mucosa was done together, according to the number of lesions and severity, since detailed image records of the gastroscopy of each horse was routinely stored, with no advantage in assigning a degree of classification by type of mucosa.

The equine stomach presents a pH stratification, being the most alkaline pH near the oesophagus and acid at the pylorus level (Andrews & Nadeau, 1999; Merritt et al. 2003). Authors have found that low pH values (< 4) may contribute to the development of lesions in the nonglandular mucosa, as this region is inept of defence mechanisms towards acid injury (Nadeau et al., 2003).

In the evaluated horses, it was not possible to relate the pH value of the gastric fluid with the degree of ulceration. We found animals with high levels of ulceration, with both high (pH = 4)

and low pH values (pH = 1.5), and horses with the same degree of ulceration had distinct pH values. Also, after therapy with omeprazole, in some horses, the pH values increased while in others, it decreased. Nevertheless, one cannot fail to mention that although the harvest was made at the level of the *margo plicatus*, several samples of gastric fluid (40,90% at first exam and 31.82% at control exam) had pH values lower than 4 which is considered ulcerogenic. Low pH values may partly be a consequence of fasting for gastroscopy preparation since horses are continuous producers of hydrochloric acid (Murray, 1994).

Despite the lack of overall significant effect of treatment on gastric pH (p=0,210), it should be referred that the mean pH of the gastric fluid samples was higher in the horses after treatment (4.77; SD 1.37) than at first examination (3.98; SD 2.01) which indicates that omeprazole paste was effective in increasing gastric pH in horses. These results complement the results from previous studies which investigated the therapeutic application of omeprazole in horses (Andrews, 2015; Andrews, Frank, et al., 2006; Andrews & Nadeau, 1999; Huxford et al., 2017; Merritt et al., 2003; Sykes, Underwood, et al., 2017; Videla et al., 2011)

Many animals presented a high numeric score (n=13/22) and high ulceration severity (n=5/22) on the first gastroscopy. After treatment with omeprazole, regardless of the high grades attributed to each horse according to the above mentioned scoring system, it is essential to point out that several animals (45.5 %, 10/22) presented lesions with a healing aspect and a less severe injury compared to first gastroscopies performed, with two cases of total remission (9.1%). However, injuries of a more aggressive nature remained unsolved (36.36%, 8/22), while others still suffered an increase in lesion number and severity (18.18%, 4/22).

In order to assess the efficacy of the treatment, the endoscopic evaluations should have been performed following medical treatment. However, the re-evaluation examinations were performed at different periods. Most horses (86.4%) were re-evaluated between one and four months when the treatment lasted two months. Therefore, some horses exceeded the treatment period. Furthermore, there was a tendency for the endoscopic screening interval between 4-6 months to present an increase in the number of gastric ulcers. These results suggest that the high discrepancy in screening intervals in the study group may be associated with a lower treatment response and/or a possible recurrence of the gastric ulceration. Authors in previous studies have reported different levels of treatment response to the standard recommended a treatment duration of 2x28 days, suggesting that given the pathophysiology differences between ESGD and EGGD, some cases may require different treatment durations (Sykes et al. 2014; Sykes et al. 2014a; Sykes et al. 2015). Thus, the importance of repeating gastroscopy at either 28 or 56 days.

Alongside the pharmacological therapy, in order to lessen ulcer severity and avoid recurrence of the lesions, long-term environmental and dietary management changes were recommended (Andrews et al. 1999; Andrews et al. 2017). The remission of the gastric lesions should be expected to be all the more exuberant, the greater the number of risk factors corrected (Videla & Andrews, 2009).

Overall, the management changes were partially implemented in most cases, where environmental changes where consented partially in 63.64% (14/22) and dietary changes in 54-55% (12/22) of cases. Still, there were cases of total implementation, 40.91% (9/22) referring to dietary changes and solely 4.55% (1/22) to environmental changes. However, the changes that were reported to have the highest accession in the study group were the dietary changes, such as addition of oils, a decreased in size while increasing the frequency of grain in 81,8% (18/22), also an increase of forage and fibre by access to continuous feeding in 90,91% (20/22) of cases. Effective acid control is accomplished by dietary management strategies (Andrews et al. 1999b; McClure et al. 2005), such as increasing forage intake, eliminating bolus feeding, decreasing the size and increasing the frequency of concentrate feeding.

The level of owner compliance reported in this study may be due to the fact that the horse's diet can be managed and readily modifiable (Luthersson et al., 2009a). Whereas environmental changes, such as access to pasture/paddock or adding company in many cases is not feasible as many horses are kept in suburban and urban areas (Houpt, 1987). Also, reducing the level of exercise in high-level competition horses can prove difficult.

Although the implementation of the aforementioned changes has been reported to help control gastric ulceration, in this study, there were no significant differences in either numeric or severity score evolution identified for any possible type of implementation. Nonetheless, analysing the score evolutions according to the different level of implementations, the author verified that 45.5% (10/22) of the horses that demonstrated a decrease in numerical and severity score were mostly those who had implemented the management changes in some way. From the horses which demonstrated decreased numeric score, nine horses had environmental and dietary changes implemented in some way. Whereas from the horses with decreased severity scores, eight horses had environmental changes implemented partially, while nine horses had dietary changes implemented. These results suggest that associating long-term management changes may help control and decrease the chance of recurrence of gastric ulcerations.

At control gastroscopy, two cases of total remission were observed, indicating a positive response to the omeprazole paste, in the treatment dose of 4mg/kg bwt PO for 28 days, followed by the maintenance dose of 2 mg/kg bwt for 28 days (Direção Geral de Alimentação e Veterinária 2018).

From the four horses that presented an increased number of lesions at control exam, only two showed an increase in severity. The horse that changed from a severity grade 2 to a grade 4 is a 9-year-old show-jumping stallion with a high-level exercise regime. The high-level of exercise, a well-reported risk factor for EGUS (Pedersen, 2017), may be the possible cause of inferior treatment response in this case. The level of exercise was not reduced even after recommendation and only a few of the dietary changes were implemented (addition of oil, low doses and increase of meal frequency). As discussed above, there is evidence that reducing exercise decreases the risk of ESGD. However, without changes in management, squamous ulcers may quickly return if horses are maintained in training (Andrews, Sifferman, et al., 1999). Also, the re-evaluation of this horse was performed 4 months post-treatment, which might have heightened the opportunity for recurrence (Sykes, Sykes, et al., 2014d, 2014a, 2015).

The horse that changed from a severity grade 1 to a grade 3 is a 22-year-old gelding leisure horse who was evaluated after an episode of colic and had been given by mistake an excess dose (15,5mg/kg bwt SID) of a top-dress formulation of Suxibuzone (Danilon®, Ecuphar[16]). Danilon® is a NSAID which comes in sachets of a yellow, odourless granules to add to the horses feed with a recommended label dose at 6,25 mg/kg bwt (equivalent to 2 sachets of 10g/480kg bwt) BID, for the first two days, and a half the dose (3,1 mg/kg bwt BID) the following 3 days. If necessary, this maintenance dose can be given SID or every other day until a positive clinical response is achieved (Direção Geral de Alimentação e Veterinária 2019). Previous research suggests the NSAIDs as primary agents in the development of EGGD if used in excessive doses or prolonged treatments (MacAllister et al., 1993; Martínez Aranzales et al., 2015). Although, authors have suggested that NSAIDs given at recommended doses are unlikely to cause EGUS (Andrews et al., 2009; Nieto et al., 2012). There is conflicting evidence regarding the influence of NSAIDs on the development of EGUS (Sykes, Hewetsen et al., 2015). Nevertheless, in the authors opinion, the age should be taken into consideration, as increased risk is associated with elderly horses (Direção Geral de Alimentação e Veterinária 2019). Additionally, it was referred that even after treatment with omeprazole along with dietary (oil's, hay *add libitum* and feeding practices) and management changes (access to paddock), the horse in question did not gain weight neither did the coat's condition improve. However, this can be explained again by the horses' age, chronic pain given the severity of the gastric lesions (Burn et al., 2010; Scott & Miller, 2011) and the abnormal dental wear characteristic of elderly horses (Andrews et al., 2017) and the non-correction of this situation even after recommendation. Even though increased lesion scores were observed in the second

[16] Ecuphar NV, R. Sintra Business Park, 2710-089 Sintra, Portugal.

examination, the lesions in the glandular mucosa identified in the first examination healed in contrast with the one in the squamous mucosa, which suggests a positive response to the omeprazole therapy associated with the recommended long-term changes.

The remaining two horses that maintained the severity scores, both presented severity score > 2. One was a nervous tempered, 12-year-old mare used in high-level show-jumping, which in the first examination referred poor performance for over a year, had been diagnosed with ESGD three months prior and had previously been treated with GastroGard® and ranitidine. However, even after another round of treatment with the recommended label dose of omeprazole, in the second examination, this horse maintained the grade 2 severity lesions, along with lesions identified in the glandular region. In the author's opinion, the low treatment response can be justified by the low compliance to the recommended long-term environmental management changes, as the level of exercise was not reduced, nor did the horse have access to paddock. Regarding dietary management, the only change that was not assumed was the addition of oil to the diet, a reported effective option to increase the protection properties of the glandular mucosa, as discussed above (Cargile et al., 2004). Also, it should be referred that the follow-up examination was performed after six months, instead of the recommended interval, which might explain the possible recurrence and worsening of the gastric lesions.

The other horse that maintained a severity score grade 3 was a 7-year-old stallion used in Dressage, with a reported difficulty in the gallop gait over the course of the year as the only complaint. Despite the treatment with omeprazole at label dosage and recommended duration, associated with nearly a total implementation of the long-term management changes, there was still a low treatment response. These results may suggest the need for increased treatment duration, as there were lesions identified in both glandular and squamous mucosa.

The remaining eight horses presented involution of the lesions. Even in those that continued to present high degrees of ulceration, the lesions appeared to be healing. This demonstrates the importance of keeping records of the observed lesions so that there can be a comparison between the appearance of the mucosa before and after therapy. The use of a system of classification of the lesions found in the stomach is a useful and simple way to assess the number and severity of these lesions, thus obtaining a general overview of the state of the gastric mucosa of the horse. However, classification systems are not sufficient to assess the evolution of the lesions initially observed, so it is necessary to maintain records of the appearance and location of the main lesions, notably through film and photographs, as shown by the results obtained in this study.

Parasites do not seem to have played an important role in the aetiology of these twenty-two cases of EGUS. However, organisms from the genus *Gastrophilus* were identified in only one

horse during both examinations. This horse was a nervous tempered, 2-year-old filly, trained for endurance with a high-level exercise regime. Therefore, in the author's opinion, various risk factors such as exercise, age and temperament may have played a role in the development of gastric ulcers in this case, other than parasites.

5. Conclusion

The results of the present study showed a prevalence of 100% of gastric ulceration in the target population, confirming the presence of some degree of EGUS in the initial group composed of sixty-nine animals. However, as these animals were not randomly chosen, it should be assumed as only an estimate of the real prevalence of the disease in the population. Also, due to incomplete clinical history information or lack of follow-up examination, the final sample population was reduced to 22 horses, which might have led to attrition bias.

The high numerical and severity scores of the ulcer lesions observed in several of the horses, according to an adaptation of the classification system by MacAllister et al. (1997), demonstrated a certain character of aggressiveness, with seventeen horses holding a numerical grade > 3 and ten horses holding severity grades > 4. Considering the aggressive nature of the lesions, the symptomatology presented in our sample population was in general as exuberant as would be expected, although very unspecific. The most frequent clinical signs reported were history of colic (presence of colic in the last year and/or recurrent signs of colic), signs of abdominal discomfort (oral stereotypes, bruxism, cribbing), behaviour changes (nervous/aggressive temperament and attitude, indifferent or sad posture), poor performance (lack of concentration and energy), and poor body condition (weight loss and dull coat). Moreover, the higher the ulcer degree, the greater the association between ulcers and noticeable clinical symptoms (colic and coat condition). However, higher severity scores were found in horses with healthy shiny coats, which corroborates the fact that EGUS often exists in apparently asymptomatic horses.

Although gastric ulceration lesions were found most frequently in castrated males, horses aged between 6 and 10, and show-jumping horses, none of the presumable risk factors was found significantly associated with the number or severity of gastric lesions.

Therefore, in order to obtain a definite diagnosis of gastric ulceration, the only currently available method is an endoscopic examination of the gastric mucosa, since parameters such as age, gender, performance, behaviour, eating habits provide only weak clues as to which horses might be affected.

Gastric lesions were found more prevalent in the squamous non-glandular mucosa than in the glandular mucosa (including pylorus), which is in agreement with previous prevalence studies of ESGD and EGGD. Still, the high incidence and severity of lesions found in the glandular mucosa

and the pylorus area should prove the importance of a detailed and systematic assessment of gastric mucosa and gives reason to the emerging attention to EGGD.

It was not possible to correlate the measured pH values with gastric ulceration, although the low pH values cannot be ruled out as a consequence of fasting before gastroscopy. However, several horses withstood pH < 4, which is considered ulcerogenic.

The results obtained in this group of horses met the already tested efficacy of omeprazole in the treatment of gastric ulcer, with observed cases of complete remission. Most horses presented lesions with a healing aspect, as even the ones without complete remission tended to be less severe.

The positive healing response of the lesions, along with a confirmed increase in mean pH, was accompanied by a general improvement of physical condition, symptoms and clinical complaints, which also demonstrates a positive treatment response with omeprazole paste. Still, there were identified cases of lesion aggravation/recurrence possibly due to a discrepancy in screening intervals, along with the role of individual dose responsiveness, indicating the importance of follow-up examinations in the recommended intervals.

The recommended long-term environmental and dietary management changes were found to have an important role in the success of the treatment. The therapy was more effective, the greater the number of risk factors corrected, namely the implementation of long-term management changes.

Although not significantly associated with the level of gastric ulceration, risk factors such as age, exercise and administration of NSAIDs may have determined a lower treatment response in certain animals.

As with any questionnaire-based analysis, recollection bias may have been present. Owners may fail to reveal medications administered or may not accurately recall management practices. Also, clients sensitive to their horse's gastrointestinal health may have more accurate recall as they may pay more attention to their horse's management than someone not concerned about gastric disease in their horse. In conclusion, the level of co-operation and compliance of the owners/riders is essential for the therapy to succeed.

IV. Further studies

Due to the negative impact of EGUS on the equine industry, further studies are required to determine the aetiology of the syndrome and to find ways to reduce, if possible, the frequency of gastric ulcers.

Also, more attention should be given to individual assessment of gastric mucosa to improve the quality of EGUS prevalence studies. A correlation between anatomical location and lesion scores, and the anatomical distribution by age, by gender and type of work, would provide very relevant information. The apparent differences in the prevalence of lesions in the different regions of the stomach should be further investigated and, where sufficient cases are available, risk factors for each location should be investigated.

This study was performed with a quite diverse population and several variables. So, it would be interesting to reduce the variables by increasing inclusion criteria and to extend the study to a larger sample population, in order to study specific risk factors for EGUS, such as level of exercise and age.

Most prevalence studies focus on Thoroughbred or Standardbred racehorses worldwide. However, despite the growing demand for Lusitano breeds abroad, little research has been done regarding the prevalence of gastric ulceration in the Lusitano Purebred horse, to the author's knowledge. Further prevalence studies are also required regarding horses used in other demanding equestrian sports, such as Horseball and Working Equitation.

Recent research on the use of alternative proton pump inhibitor therapy has been reported, such as esomeprazole (both oral and i.v.) and a novel, long-acting, injectable formulation of omeprazole, but this still requires further evidence, and further investigation of it’s use in cases where oral omeprazole therapy is ineffective or inappropriate.

Furthermore, additional clinical trials are essential to discovering alternative, effective, and low-cost therapies for gastric lesions in the horse in order to allow higher owner compliance.

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VI. Annexes

Annexe 1a. Submitted and accepted abstract for poster presentation for the IV Jornadas do GTIE (11th November 2015)

Uso da gastroscopia na Avaliação da Evolução do Tratamento de Síndrome de Úlcera Gástrica Equina (SUGE)

FILIPA GRAÇA PAIT CORTEZ[17], JOANA DE SOUSA AZEVEDO SIMÕES[24], JOSÉ PAULO SALES LUÍS[24], PAULA ALEXANDRA BOTELHO GARCIA DE ANDRADE PIMENTA TILLEY. [24]

A SUGE constitui um grave problema do ponto de vista económico e clínico pela sintomatologia inespecífica e efeitos negativos no desempenho desportivo[1]. Os princípios ativos mais utilizados são eficazes, mas dispendiosos e com elevada taxa de recorrência[1]. É essencial tomar simultaneamente medidas preventivas, como redução da estabulação, forragem *ad libitum*, redução de exercício/*stress*[1].
Foi objetivo deste trabalho avaliar por gastroscopia a evolução do tratamento e identificar os fatores de risco da SUGE.
Foram avaliados 68 cavalos com suspeita de SUGE através de exame clínico, pesagem, gastroscopia, medição do pH gástrico e inquérito epidemiológico. Os cavalos que apresentaram graus de ulceração ≥ 2 (MacAllister) foram medicados com Omeprazole PO (GastroGard™, Merial). Cavalos com grau de ulceração inferior a 2 (MacAllister) foram medicados com GNF (TRM) e sucralfato genérico. A todos os cavalos foram recomendadas medidas preventivas como alterações no maneio alimentar e redução do *stress*. Apenas 35 cavalos foram reavaliados 2-6 meses após o tratamento.
Confirmou-se a ocorrência de SUGE no grupo estudado, sendo identificada sintomatologia com relevância clínica e relativa ao desempenho desportivo. Após terapêutica com GastroGard™ observou-se franca melhoria das lesões e dos sinais clínicos, tendo-se verificado remissão total das lesões em 2 cavalos. A terapêutica com GNF (TRM) mostrou ter alguma eficácia, tendo sido observada ligeira melhoria das lesões e sinais clínicos.
Reforçou-se a relevância de se realizar história pregressa e exame fisico detalhados para ponderar realizar a gastroscopia, sendo este o único meio de diagnóstico *in vivo* de SUGE. Verificou-se que fatores de risco como alimentação, maneio, exercício e *stress* têm grande influência na ocorrência e evolução da SUGE, sendo fulcral a sua identificação e correção atempada. A terapêutica foi tanto mais eficaz, quanto maior o número de fatores de risco corrigidos. Concluiu-se ainda a importância da cooperação dos proprietários/cavaleiros para que a terapêutica tenha sucesso.

Bibliografia: Nadeau, JA, Andrews, FM. 2009. Science: Overviews - Equine gastric ulcer syndrome: The continuing conundrum. *Equine Veterinary Journal*, 41, 611-615.

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Annexe 1b. Poster presented at the IV Jornadas do GTIE (11th November 2015)

TRATAMENTO DE SÍNDROME DE ÚLCERA GÁSTRICA EQUINA (SUGE)

CORTEZ, F.[1]; SIMÕES, J.[1]; LUIS, J.[1], TILLEY, P.[1].

1. Departamento de Clínica, Faculdade de Medicina Veterinária, Portugal

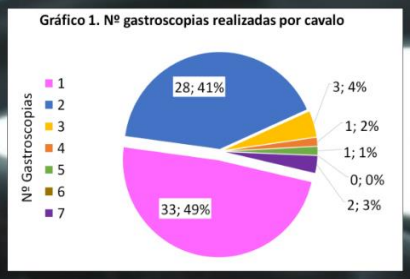
INTRODUÇÃO E OBJECTIVOS:

A SUGE constitui um grave problema do ponto de vista económico e clínico pela sintomatologia inespecífica e efeitos negativos no desempenho desportivo. Os princípios ativos mais utilizados são eficazes mas dispendiosos e com elevada taxa de recorrência. É essencial tomar simultaneamente medidas preventivas, como redução da estabulação, forragem *ad libitum*, redução de exercício/ stresse (NADEAU, et al. 2009).

Foi objetivo deste trabalho avaliar por gastroscopia a evolução do tratamento e identificar os fatores de risco da SUGE.

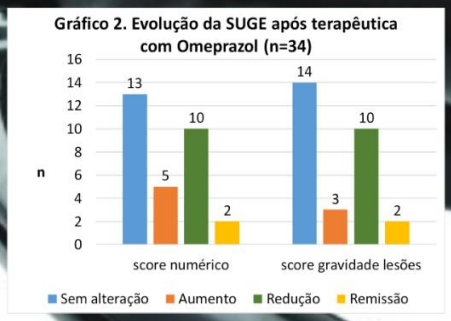
MATERIAL E MÉTODOS:

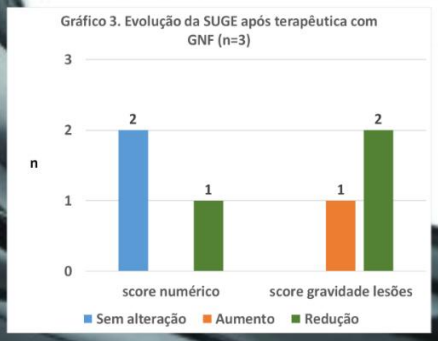
Foram avaliados 68 cavalos com suspeita de SUGE através de exame clínico, pesagem, gastroscopia (figuras 1 e 2), medição do pH gástrico (figura 3) e inquérito epidemiológico. Os cavalos que apresentaram graus de ulceração ≥ 2 (McAllister) (figura 4) foram medicados com omeprazol PO (GastroGard™, Merial)(n=61). Cavalos com grau de ulceração inferior a 2 (McAllister) (figura 4) foram medicados com GNF (TRM) (n=3). A todos os cavalos foram recomendadas medidas preventivas como alterações no maneio alimentar e redução do stress. Apenas 35 cavalos foram reavaliados 2-6 meses após o tratamento .



RESULTADOS:

Confirmou-se a ocorrência de SUGE no grupo estudado (n=68), sendo identificada sintomatologia com relevância clínica e relativa ao desempenho desportivo. Após terapêutica com GastroGard™ observou-se franca melhoria das lesões e dos sinais clínicos, tendo-se verificado remissão total das lesões em 2 cavalos (gráfico 2). A terapêutica com GNF (TRM) mostrou ter alguma eficácia, tendo sido observada ligeira melhoria das lesões e sinais clínicos (gráfico 3).





DISCUSSÃO E CONCLUSÃO:

Reforçou-se a relevância de se realizar história pregressa e exame físico detalhados para ponderar realizar a gastroscopia, sendo este o único meio de diagnóstico in vivo de SUGE. Verificou-se que fatores de risco como alimentação, maneio, exercício e stresse têm grande influência na ocorrência e evolução da SUGE, sendo fulcral a sua identificação e correção atempada. A terapêutica foi tanto mais eficaz, quanto maior o número de fatores de risco corrigidos. Concluiu-se ainda a importância da cooperação dos proprietários/cavaleiros para que a terapêutica tenha sucesso.

Figura 1. Realização de gastroscopia no Hospital Escolar, FMV-UL (fotografia original).

Figura 2. Realização de gastroscopia no Hospital Escolar, FMV-UL (fotografia original).

Figura 3. Medição de pH gástrico (fotografia original).

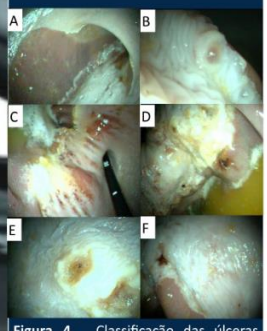


Figura 4. Classificação das úlceras gástricas (McAllister) - A (Grau 0 sem lesões), B (Grau 1) , C (Grau 2), D (Grau 3), E (Grau 4), F (Grau 5) (fotografias originais).

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Annexe 2. Epidemiological questionnaire

Questionnaire on the horse's behaviour

Number**:** Date:

1- Horses Name: _____ Date of birth: _____
2- Rider's name/Groom's name: _____
3- Temperament: Docile☐ Aggressive☐ Calm☐ Nervous☐
4- Colic in the last year: Yes ☐ No ☐
   a. Duration: ½ day☐ 1 day ☐ 2 days☐ 3 days☐ >3days ☐
   b. Pain scale: Very mild ☐ Mild ☐ Moderate☐ Severe☐
      Very severe ☐ Violent ☐
   c. Medication? Yes☐ No☐
5- Presents signs of mild colic once in a while? Yes☐ No☐
(Colic that manifest by signs of mild discomfort, appears lying down frequently, doesn't eat full meal, but eventually recovers with diet, walking, or one minimal dose of Vetalgin.)
6- Plays with water in drinking bowl? Yes☐ No☐
   Lays snout in drinking bowl? Yes☐ No☐
   Swallows air ("Crib-biting")? Yes ☐ No☐
7- Grinds teeth when stabled? Yes☐ No☐
   Grinds teeth during training? Yes ☐ No☐
8- Takes a long time to eat? Yes ☐ No☐
   Eats everything once food is given? Yes☐ No☐
   Eats partially once is given, and leaves a portion to eat throughout a period of time? Yes ☐ No ☐
9- Horse turns rear when entering the stall? Yes☐ No☐
   When someone opens the door to the stall the horse stays still?☐ Approaches the person? ☐
10- Horse is sad? Yes☐ No☐
   Horse is lacking energy during training? Yes ☐ No☐
11- Horse lacks concentration during training? Yes ☐ No☐
   Horse is unlearning? Yes☐ No☐
12- Do you think the horse has lost weight? Yes☐ No☐
   Do you think the horse shows signs of abdominal discomfort? Yes☐o ☐
   Do you think the horse's coat has turned dull? Yes ☐lo ☐

Notes: _____

_____

_____

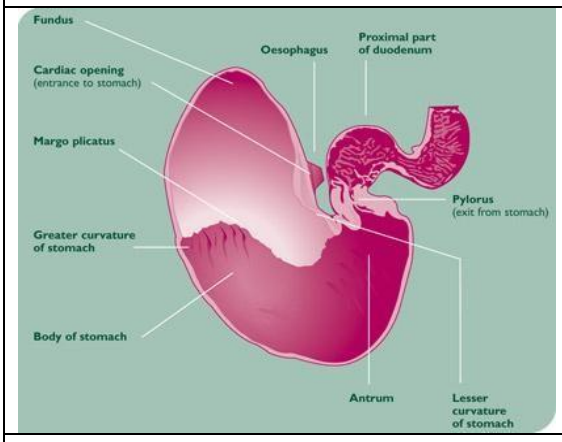
Annexe 3. Gastroscopy report form

GASTROSCOPY…….. nº_____/_____

DATE	Horse's Name	Weight

GASTROSCOPY – LESION NUMBER SCORE		
0	No lesions	
1	1-2 localized lesions	
2	3-5 localized lesions	
3	6-10 lesions	
4	> 10 lesions or diffuse (or very large lesions)	

GASTROSCOPY – LOCATION	
Glandular	
Non-glandular	
Both	



GASTROSCOPY – LESION SEVERETY SCORE		
0	No lesions	
1	Appears superficial (only mucosa missing)	
2	Deeper structures involved (greater depth than nº1)	
3	Multiples lesions and variable severity (1,2 and/or 4)	
4	Same as 2 and has active appearance (active=hyperaemic and/or darkened lesion crater)	
5	Same as 4 plus active hemorrhage or adherent blood clot	

BIOPSY HARVESTING Number of fragments_____ Urease test_____
GASTRIC FLUID COLLECTION pH _____
ENDOSCOPY REPORT
FUTURE THERAPEUTIC INDICATIONS

Veterinary Physician _____

Annexe 4. Questionnaire on treatment follow up

Treatment Follow up

Horse: _____ **Owner:** _____
Gender: _____ **Rider (s):** _____
Discipline: _____ **Groom (s):** _____
Training regime: _____
Frequent medication: _____

Measures implemented after recommendation

I. Pharmacologic therapy

Pharmacologic agent	**Yes**	**No**	**Notes**
Omeprazole			
Cimetidin			
Ranitidin			
Sucralfate			
Other(s)			

II. Environmental Management

Environmental Factors	**Yes**	**No**	**Notes**
Reduce exercise intensity			
Pasture/paddock turnout			
Company			
Improve stable conditions (lighting, aeration, area)			
Others			

III. Dietary Management

Diet changes	Yes	No	Notes
Add Oils (corn, olive)			
Increase forage and fibre			
Add Alfalfa hay			
Continuous feeding			
Decrease size and increase frequency of concentrate feeding			
Calcium carbonate supplements			
Concentrated electrolyte paste or solutions			
Salt			
Vitamins			
Others			

Notes: _____

_____

_____