

The Moredun Foundation
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Equine Grass Sickness: A research update and look to the future



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key points

- Equine grass sickness (EGS) affects grazing equids in many countries, but is most prevalent in the UK during the spring and summer months
- It is a complex, frequently fatal disease involving damage to the nerves of the gut (as well as other anatomical sites), compromising the animal's ability to swallow and the transit of food through the gut
- The causes are still unknown but likely to be multi-factorial and there is evidence supporting the potential involvement of toxins from *Clostridium botulinum* and fungi
- Three overlapping manifestations of the disease are recognised – acute, sub-acute and chronic which are based on clinical severity
- Euthanasia is warranted for acute, sub-acute and severe chronic cases, based on welfare grounds; around 80% of diagnosed cases reported to the Equine Grass Sickness Fund (EGSF) result in death
- Around half of chronic cases survive with intensive and skilled nursing over a long time period and around 80% of those survivors return to work
- The clinical signs vary in severity depending on the disease category and are largely reflected by the severity of nerve cell loss in the gut, which is greatest in acute and sub-acute cases and less in chronic cases
- Diagnosis can be challenging and is often reliant on the presence of a pattern of clinical signs. The gold standard diagnostic approach involves microscopic study of tissues taken from the ileum by biopsy (pre- or post-mortem) and specific nerve ganglia (post-mortem) to look for changes associated with the disease
- There are certain management practices that can be implemented which can help reduce the risk of EGS
- There are currently no preventive vaccines or treatments that can cure the disease
- New technologies, used in other areas of disease research, along with an interdisciplinary approach, will be used to take a fresh look at this disease and progress research



introduction

Equine grass sickness (EGS) affects grazing horses, ponies and donkeys. It presents as a frequently fatal neurodegenerative disease involving widespread damage to neurons (nerve cells) in the nervous system of the gut (as well as other anatomical sites), severely compromising the propulsive capacity of the gut. This affects the function of the gut involved in the transit of food. Despite much research, the precise cause remains elusive and is the subject of active research, along with seeking new prevention and treatment strategies.

The disease was first described in 1909 at Barry Buddon Army camp, near Carnoustie on the east coast of Scotland, a remounting facility to supply horses to the British Army. The disease has a strong association with grazing and peak incidences (in the northern hemisphere) tend to occur in the spring and early summer, with around 60% of cases being recorded at this time. Data from recorded EGS cases sent to the EGSF over the last 10 years confirm this trend for higher disease incidence in April, May and June (see Figure 1).

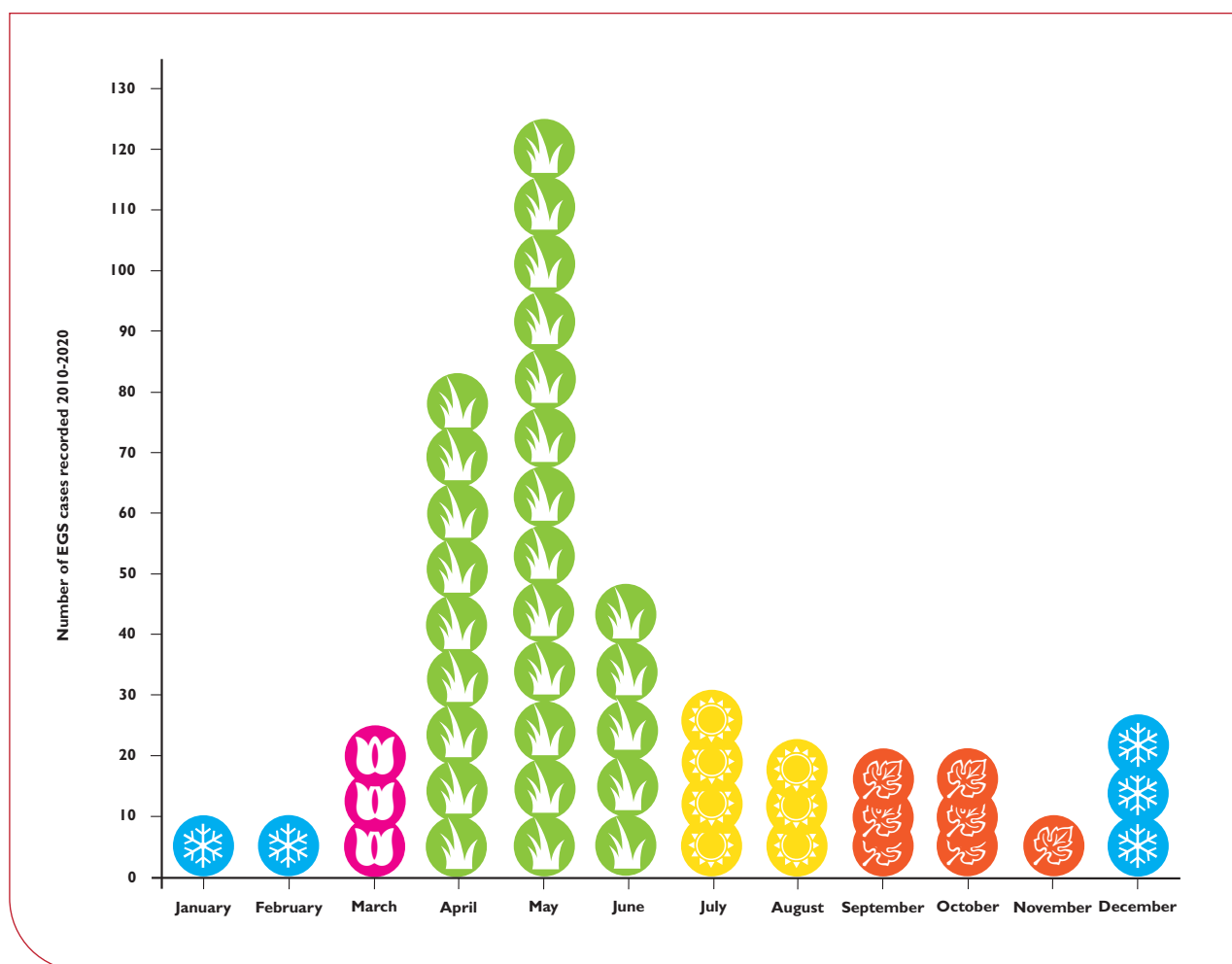


Figure 1: Number of EGS cases by month as reported to the EGSF over the last 10 years (2010-2020).



EGS survivor back to competing.

As a result of the high losses of horses due to EGS and the importance of horses as working animals on farms, there was a lot of research effort in the early years, 1920-1950, to try to find out the cause of the disease. The UK has the highest incidence of EGS compared with other countries across the world. It occurs mainly in Northern Europe, but identical diseases such as mal seco and tamboro have been recorded in several countries in South America.

Within the UK, EGS has a higher occurrence nearer the east coast compared with the west, particularly in Scotland, as shown in Figure 2. These figures should be interpreted with care as the higher number of cases in some counties may be influenced by a relatively greater horse population in that particular county. Figure 2 illustrates differences in disease occurrence relating to geography in the UK, with the highest number of cases recorded in Aberdeenshire. Therefore, it is possible that climate, soils, pasture, indigenous plants and fungi related to specific geographical regions may help provide some clues about the causative agent and associated risk factors. Climate related risk factors include cooler, drier weather and irregular ground frosts, which prevail more frequently in the eastern side of the country.

It should be noted that these data relate to owner reported cases over the past 10 years, illustrating the importance of reporting diagnosed cases to the EGSF. In reality we suspect the actual number of EGS cases to be much higher than is reflected here.

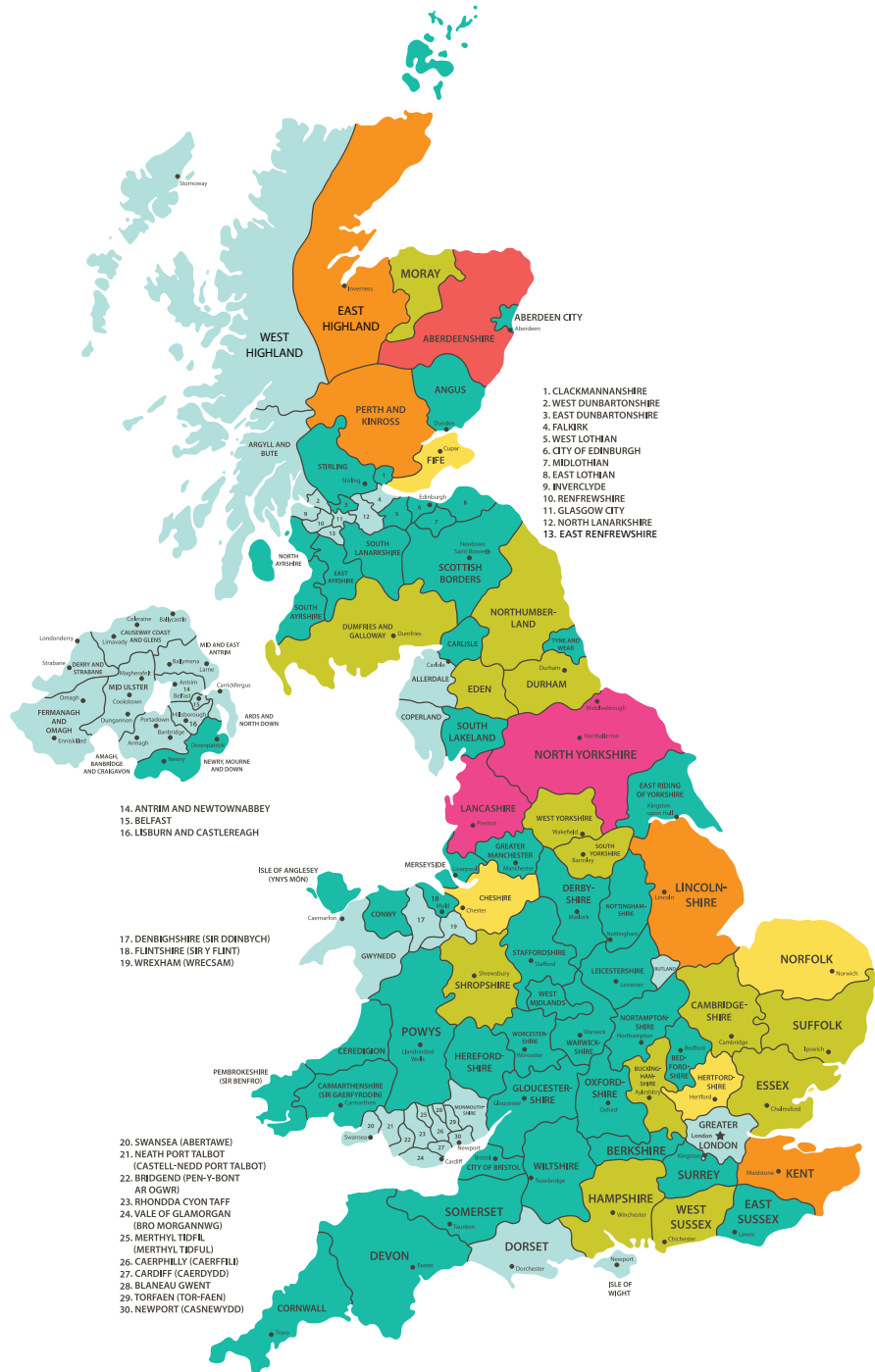


UNITED KINGDOM

SHETLAND ISLANDS



Number of equine grass sickness cases recorded, 2010-2020



GUERNSEY



Figure 2: Distribution of reported cases to the EGSF throughout the UK over the last 10 years (2010-2020). A notional line has been drawn through the middle of Highland region to illustrate that all recorded cases occurred in the east of the region



Equine grass sickness has been reported in many different horse and pony breeds, with a recent study in Scotland suggesting an increased susceptibility amongst native Scottish breeds, but there are many confounding factors which may influence this apparent association, including a higher number of native and native breed crosses within the UK. Many studies confirm that a key predisposing factor is age, with disease being more frequently seen in young adult animals (Figure 3).

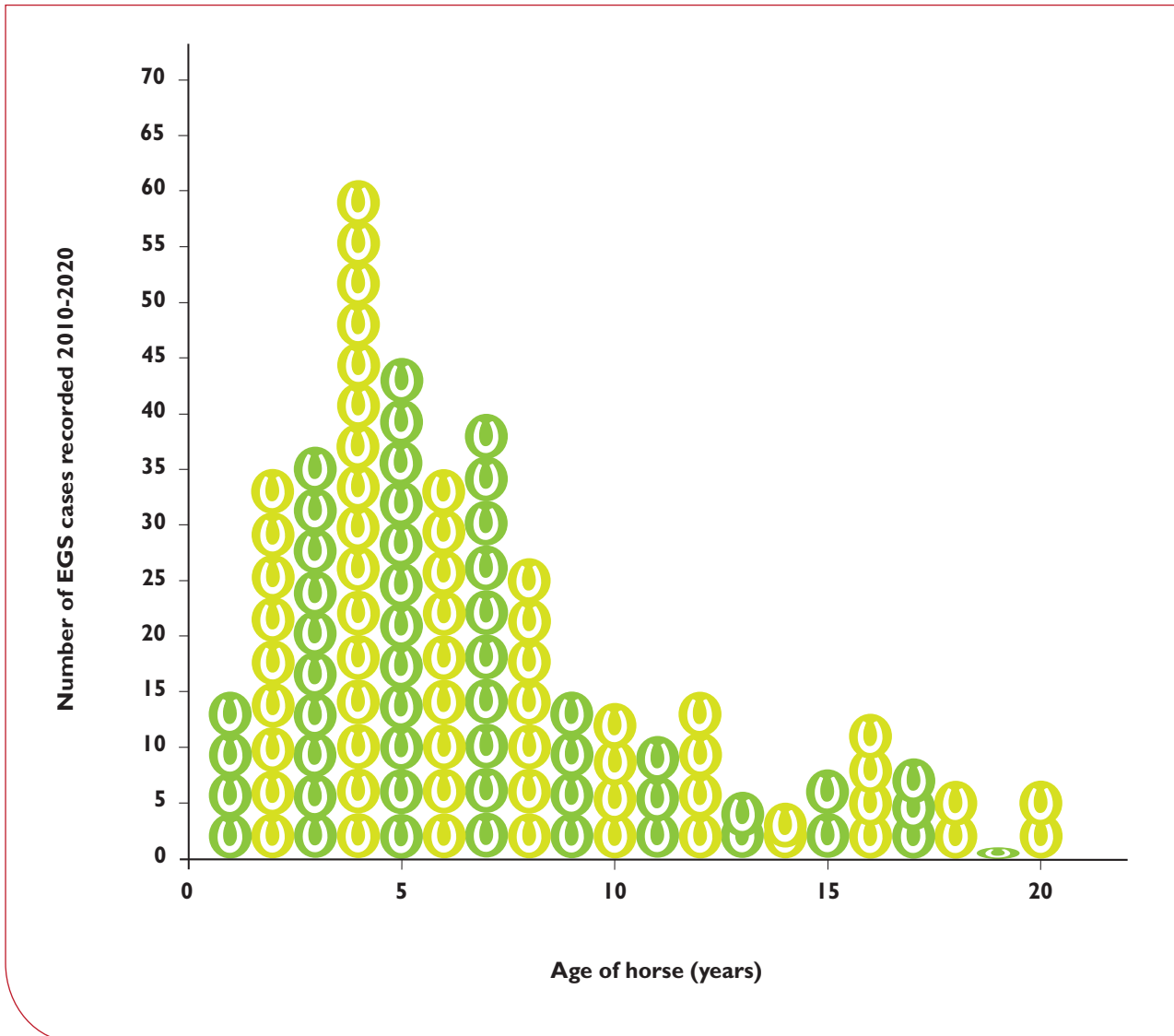


Figure 3:
UK EGS cases by age (in years) of horses as reported to the EGSF over the last 10 years (2010-2020). A further 28 cases were reported from horses aged between 20-48 years of age over the ten year period.

In this factsheet we will review current knowledge on EGS, using available information from prior and current research activities, and introduce some of the research directions currently being investigated. We will also take a look at the next steps for EGS research where new technologies and advances in investigative, interdisciplinary research may be used to shed new light on the disease.



Q1

What is EGS?

EGS is a neurodegenerative disease, characterised by a loss of function affecting both the central and the peripheral nervous systems. This causes the gastro-intestinal tract to stop functioning properly, resulting in a compromised ability to move the contents of the gut along the intestine. This can result in a build-up of fluid in the stomach and small intestine, along with dehydration and impaction of gut contents further down in the large intestine. Affected horses present with difficulty and discomfort in swallowing, may drool saliva, have an increased heart rate and patchy sweating, all of which can be related to the diverse pattern of nerve damage associated with the disease.

The disease may present as acute, sub-acute or chronic, based on the severity of clinical signs, with the acute and sub-acute forms being invariably fatal. These disease categories reflect the extent of nerve damage and there is evidence to suggest that the disease category into which each individual case falls is effectively pre-determined by the time the animal presents with clinical signs.

The loss of co-ordinated intestinal contractions, which is a key feature of acute EGS, is illustrated in a short video clip (https://youtu.be/z_fMrmSyEcs) with a commentary from Prof Bruce McGorum (RDSVS). Please be aware that this video contains images of the intestine which were recorded during an exploratory operation to confirm the diagnosis of EGS, while the horse is under general anaesthetic.

An EGS survivor.



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Q2

What are the clinical signs and outcomes of EGS?

Clinical Signs

- There are three manifestations of EGS, acute, sub-acute and chronic, with clinical signs that can overlap; in effect, these represent a scale of severity
- Euthanasia is warranted in acute, sub-acute and the most severe chronic forms of the disease, reflecting the hopeless prognosis associated with such cases
- Although chronic cases have been defined as those which survive eight or more days after the onset of disease, this duration of survival is directly related to the severity of the disease sub-type. Theoretically, some acute and sub-acute cases may survive for this length of time with ongoing intensive intervention (e.g. intravenous fluid administration, repeated gastric decompression); however, such intervention will only delay and not alter the ultimate fate of such cases and therefore has significant welfare implications
- It has been shown that with the correct nursing and care, around half of chronic cases may survive and, in the long term, many go on to lead useful working lives

In summary: Clinical signs within the three manifestations of EGS relate to the severity of the nerve damage which underlies the clinical signs seen. Nerve damage in the gut affects the animal's ability to swallow and gut peristalsis, the involuntary smooth muscle movement which moves the food along the gut, essential for digestion and excretion of waste. This nerve damage is most severe in acute cases and results in clinical signs such as difficulty swallowing, distended abdomen, absence of gut sounds and gastric reflux. In such cases, clinical signs appear very rapidly and euthanasia is indicated on welfare grounds. In sub-acute cases, weight loss may be evident as the disease takes longer to progress and in chronic cases severe weight loss may be evident as the disease progression is slower.

Comprehensive information on clinical signs associated with the different types of EGS is given at: <https://grassickness.org.uk/advice/the-clinical-presentation-of-grass-sickness/> and <https://www.worldhorsewelfare.org/advice/health/equine-grass-sickness>

Outcomes

Overall there is a mortality rate of around 80% in horses diagnosed with EGS, a figure derived from a 100% mortality rate in acute and sub-acute cases and an approximately 50% mortality rate in chronic cases. This topic is further explored in Q3 where we discuss diagnostics. An important point to note is that currently we do not have a sufficiently robust reporting system in operation for EGS cases. This will be a crucial aspect for future research and the creation of a national database (see Moredun Research Updates p19).



Q3

How would my vet diagnose EGS?



- Diagnosis of EGS can be complex and is normally achieved by clinical examination by your vet, with a particular focus on differentiating between EGS and certain forms of colic, which may have a similar clinical presentation
- The acute and sub-acute forms account for around two thirds of reported EGS cases and, after every reasonable effort to confirm the diagnosis and rule out any other diseases, such cases should be euthanased to alleviate suffering
- In both sub-acute and severe chronic cases, diagnosis may not be achieved immediately, with some cases necessitating short term supportive care until a greater level of diagnostic certainty can be achieved. Indeed definitive diagnosis is often not obtained until after a post-mortem has been carried out
- Additional diagnostic tests can be helpful in both supporting a diagnosis of EGS and/or ruling out other conditions which may have a similar clinical presentation. Such tests include laboratory analyses of blood, urine, faecal and peritoneal fluid samples, ultrasonographic examination of the abdomen, endoscopy of the oesophagus and stomach, and an eye-drop test which highlights damage to the nerves controlling eyelash position. It should however be noted that, although useful, none of these tests definitively confirms the diagnosis
- Further investigative work at specialist centres may be undertaken, such as intestinal (ileum) biopsy for histological (microscopic) examination
- Currently, microscopic examination of a biopsy from the ileum, which has the greatest neuronal loss throughout the gut, is the gold standard pre-mortem diagnostic test for EGS and involves assessing whether the nerves show features of degeneration which characterise EGS

It is important to obtain a correct diagnosis to protect any co-grazing equids, in terms of implementing management factors to reduce risk. Therefore, for non-surviving cases, it is always worthwhile carrying out a post-mortem to obtain a definitive diagnosis. Many of the management factors that can be introduced to help reduce the risk of EGS are labour intensive and expensive (see Q6) so a definitive diagnosis is very useful to the horse owner. Obtaining a definitive diagnosis post-mortem is also very important for research – see Moredun Research Updates p19 – where the creation of a national database and biobank is planned.



Q4

What is the current advice for nursing horses with chronic EGS?

The outcome for most (~80%) EGS cases is euthanasia on welfare grounds due to the hopeless prognosis for survival. However, there is a proportion (~50%) of chronic cases which, following a full clinical assessment, may be considered as suitable candidates for attempted treatment, largely in the form of nursing care. A guide to selection of chronic cases suitable for treatment is given below:

- Some ability to swallow
- Some remaining appetite
- Absence of continuous moderate to severe abdominal pain

In such cases, if treatment is considered appropriate following discussion between all parties involved (e.g. owner and veterinary surgeon) those responsible for the treatment/nursing care provision should be aware of the required level of time (and potentially financial) commitment and the real potential that their efforts may not result in a successful outcome.



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An EGS survivor.

Nursing a chronic grass sickness patient is a skilled and time consuming job. Much work has been done at the Royal (Dick) School of Veterinary Studies in Edinburgh, who have prepared very useful information to help owners do the best for their horse. Of highest importance in nursing chronic cases are:

- Welfare requirements to keep the horse stabled, warm and dry
- Optimising nutrition with a variety of feedstuffs high in protein and energy supplemented by succulents (e.g. grass, carrots) fed regularly and often
- Owner contact as frequently as possible
- Analgesic drugs (pain killers)
- Fluids including rehydration therapy
- Probiotics (although the precise value of this intervention in the treatment of EGS cases remains unknown)

Horses with grass sickness appear to love contact with their owner and it is evident that an owner who is prepared to be with the horse hour-by-hour, assessing the most palatable feed and providing company to alleviate depression, is a very valuable tool for recovery.

Please use the link below for further information on nursing horses with EGS:
www.grassickness.org.uk/wp-content/uploads/2013/10/Grass-sickness-Whw-e-booklet.pdf



Q5

What are the potential causes of EGS?

From the first reports of EGS over a hundred years ago, many potential causal agents have been proposed; however to date, the definitive cause remains unknown. Some of the potential causal candidates investigated over the years have included alsike and white clover ingestion, *Clostridium perfringens* and *Clostridium botulinum* bacterial toxins, insect vectors and fungi.



An environmental causal effect? Soil and grassland management study days inform of what is present in the field.

So what are the potential causal agents involved based on the evidence so far?

- The incidence, distribution and pattern of EGS cases and the clinical signs associated with disease are consistent with a role for ingested soil-borne neurotoxins and/or neurotoxin producing micro-organisms (e.g. bacteria or fungi). There is some evidence that serum from acute EGS cases contains a toxic component, although its precise identity remains undetermined
- The role of *C. botulinum* in EGS has been a popular theory since the early days. More recently, this theory has gained renewed interest, largely supported by the increased frequency of detection of *C. botulinum* toxin in the gut content of EGS cases and the fact that EGS cases had lower specific antibody levels to *C. botulinum* compared with other grazing horses that did not develop the disease. This suggested that an immune response to *C. botulinum* may afford some protection against EGS, which points to the potential for developing a vaccine. More about vaccines, including the recent UK nationwide trial, is discussed in Q7



- Climatic conditions associated with increased disease incidence are consistent with the potential role of fungi residing on the pasture, most likely via the production of toxins (mycotoxins). Further support for this theory has also been provided by experimental findings, including the toxic properties of *Fusarium* species when applied to equine neuronal cell cultures
- It is evident from many years of research, that this is a highly complex disease with many predisposing factors including climatic conditions, soil disturbance, pathogens related to soils and plants, the age of the horse, immune factors, nutritional components, gut microbiome and stress levels in the animal. Therefore it may require a “perfect storm” of predisposing conditions to produce clinical disease and the cause is likely to be multi-factorial
- With new techniques and advances in many areas of disease research, there is an opportunity to take a fresh look at potential causes based on the research to date and adopting an inter-disciplinary collaborative approach
- Recently, there has been some interesting work reported on heritability, looking at the relationship between parental lines and susceptibility to EGS. More work is required in this area of research and again, the technological advances that have been made in the field of genetics should allow for rapid progress



A young rider having fun with her EGS survivor.

To summarise, the precise cause of EGS remains unknown, probably due to the multifactorial and complex nature of the disease. However, with recent technological advances in the field of research (e.g. genomics, proteomics, transcriptomics, metabolomics), it is anticipated that applying a multidisciplinary approach involving such techniques, building on current knowledge, may finally unveil the elusive cause.



Q6

Which management options can I implement to reduce the risk of my horse getting EGS?

There are management options which can help to reduce the risk to the animal while at grass. Consequently, these form the basis of the currently recommended risk reduction strategies; although it should be noted that no prospective studies have been conducted to assess the value of these strategies, with the exception of the *C. botulinum* vaccine trial (see Q7). The potentially beneficial management interventions are detailed below.

1. Recommendations based on avoidance of factors associated with increased risk of disease

- Minimise exposure to pastures where previous cases have occurred
- Minimise any pasture/soil disturbance (e.g. harrowing/mechanical faeces removal/pipe-laying/construction work etc.)
- Minimise soil exposure (e.g. close grazing/poaching of fields)
- Avoid any sudden changes in diet (quantity and/or feed type)
- Avoid the "over-use" of ivermectin-based wormers particularly at high risk times of year

Note: Best practice worming advice is to test whether your horse requires a wormer before treating – consult your vet or animal health advisor for a diagnostic test (Faecal Egg Count) which will help inform if your horse needs treating.



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An EGS survivor.



Study days help owners understand disease and risk reduction strategies.

2. Recommendations based on implementation of factors associated with a reduced risk of disease

- Co-graze with ruminants
- Regular grass cutting on pastures
- Hand removal of droppings
- Supplementary forage feeding (hay or haylage)

It may not be practical to adopt all of the above strategies for all fields, for all horses and for all months of the year; consequently, they can be prioritised to certain horses, fields and seasons based on other recognised risk factors. Examples include the following which are known to be associated with increased risk:

- Young adult equids (particularly those aged 1-9 years)
- New arrivals
- Those that are overweight
- Peak season (spring and early summer)
- Cool, dry weather with irregular frosts



Q7

Are there any treatments or vaccines available to treat or prevent the disease?

1. Treatment

There are currently no treatments that can cure EGS, but there are various treatments that can be used to alleviate symptoms in an equid with chronic EGS that has been assessed as a suitable candidate for treatment – see Q4.

Research points to future treatment potential

EGS results in nerve damage to the horses' gut, so how do EGS survivors manage to maintain relatively good digestive function?

An EGSF funded study undertaken at the Royal (Dick) School of Veterinary Studies provided a very interesting insight.

Thirteen equids which survived EGS, but were euthanised for a variety of reasons between 1 and 16 years on from the original diagnosis, were compared with equids euthanised for unrelated reasons (control group). In the EGS recovered cases, the number of neurons was lower in the small intestine (especially the ileum which had very few remaining) but was normal in the large intestine. However, the pacemaker cells of the intestine, which help the neurons and intestinal muscle layers to maintain peristalsis, were not significantly depleted in the ileum.

It is possible that the continuing presence of these pacemaker cells may partially explain how peristalsis can be maintained in recovered cases, in the face of loss of neurons. If treatments could be developed to support the function of the pacemaker cells, this could be of potential clinical benefit in the future.



An EGS survivor.



2. Vaccination

There are currently no vaccines available, however, research has suggested that this may be a feasible method of disease prevention, as it has been shown that:

- Horses can produce an immune response, in the form of antibodies, against one of the suggested causal agents, *C. botulinum* type C
- Horses with low antibody levels against *C. botulinum* type C are at higher risk of developing EGS

Report from a recent vaccination field trial

From 2014 to 2018 a nationwide field trial was run to trial a vaccine using an inactivated form of the bacteria *C. botulinum* type C, which has been implicated as one of the potential causes of EGS (see Q5). Involving many experts within EGS research, and co-ordinated by the Animal Health Trust, this trial involved over 1,000 horses and ponies from 120 premises across the UK, which had previously been affected by a high incidence of EGS. The trial aimed to determine the effectiveness of the *C. botulinum* type C vaccine in preventing EGS, by comparing the incidence between groups of vaccinated and placebo-treated horses and ponies on each yard.



An EGS survivor.

What we learned from the trial

- Results showed that the vaccine used was safe, with a low frequency of local injection site reactions being reported during the trial
- Most equids vaccinated with *C. botulinum* type C had a significant immune response, in terms of raised antibodies, following the first vaccination course
- Conversely, equids in the placebo treatment group showed little change in their antibody levels to *C. botulinum* following their first placebo course
- Unfortunately, throughout the period of the trial, the incidence of EGS was considerably lower than anticipated, with just nine confirmed cases occurring amongst the enrolled horses and ponies over the entire trial period. This unfortunately meant that the study could not detect whether the vaccine was effective or not
- Consistent with previous research studies, both young animal age and low *C. botulinum* type C antibody levels were significantly associated with an increased risk of EGS
- For the first time, findings from this trial confirmed that low *C. botulinum* type C antibody levels were found in horses and ponies affected by EGS before the onset of the disease
- The results have therefore highlighted the key role of the equine immune response in the risk of developing EGS
- Further research to fully elucidate the nature of the association between *C. botulinum* type C and EGS is warranted

For a full report on the vaccine trial please visit:

<https://grasssickness.org.uk/research/results-of-a-nationwide-field-trial-for-a-vaccine-for-the-prevention-of-equine-grass-sickness/>



Equine Grass Sickness research update

Despite over 100 years of research, much about this complex and devastating disease remains a mystery. What is known is that the suspected multifactorial causes, incidence and control of the disease, point to the advantage of applying an inter-disciplinary approach with experts in many different fields working together. Alongside this, with sufficient funding, we can apply new technologies and investigative techniques allowing large scale screening of many disease parameters. There may also be value from looking at similar disease presentations occurring in other animal species to see if there are any factors that may lead to a common causal agent, such as diseases where the autonomic nervous system does not function properly, e.g. feline dysautonomia.

Outlined below are proposed projects to really attack this disease, focussing efforts on not only established lines of research, but new approaches, using novel technologies and applying inter-disciplinary thinking.

Royal (Dick) School of Veterinary Studies, University of Edinburgh

The Royal (Dick) School of Veterinary Studies has a long history of providing specialist referral veterinary care for affected equids, and performing multi-disciplinary research into EGS. The current focus of research is to determine whether EGS, and the related disease which affects cats (feline dysautonomia), are caused by fungal mycotoxins, using state of the art techniques.

Moredun

A look to the future from Moredun:

EGSF Research Fellow and Establishment of a Sample Biobank

A proposal is being developed, for consideration by the EGSF, to fund a full time early career Research Fellow, based at Moredun, to take a fresh look at the potential causes and risk factors associated with EGS adopting an inter-disciplinary collaborative approach.

The project is proposed to involve:

- Establishment of a national database through knowledge exchange with horse owners, vets and scientists to ensure that we capture all available evidence and communicate research outputs effectively to all who might benefit from them
- Establish the EGSF biobank of samples from cases and controls that can be used by the Research Fellow, and other researchers, to conduct projects looking at risk factors, associations, epidemiology, diagnostics, immune responses, novel in vitro systems, transcriptomics, microbiome, nutrition and forage, genetics, spatial and geo chemical data, botanical, soil and meteorological data
- A key element of this proposal will be to engage the expertise of a broad range of researchers with different disciplines, coming from other Research Institutes and Universities, to shed new light on the multi-factorial nature of the disease and develop new ideas on how to prevent EGS

The Moredun Foundation Equine Grass Sickness Fund

This is the only UK charity raising funds specifically for research into grass sickness. Its aim is to discover the cause and a means of prevention of the disease and improve the treatment of chronic cases. EGSF welcomes scientific grant applications, more details can be found at www.grasssickness.org.uk

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