Diversification of clostridial conditions in cattle and sheep

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The past 20 years has seen a big increase in the amount of research conducted into clostridial disease. While a large proportion of this has been centred on *Clostridium difficile* and *Clostridium perfringens* infections in humans, important advances have been made when it comes to clostridial disease in animals.

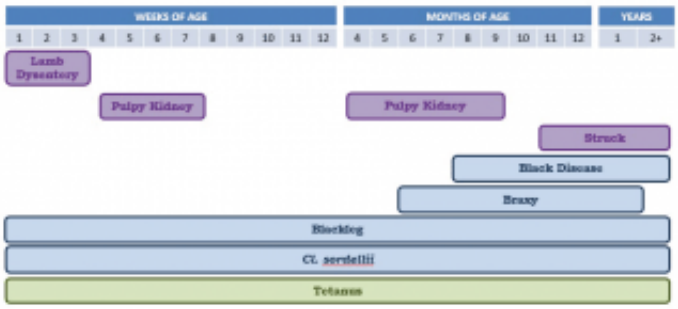

Figure 1. Age distribution of the more common clostridial diseases affecting sheep: entertoxaemias (purple), histotoxic clostridia (blue) and neurotrophic clostridia (green).

However, despite widening our knowledge of clostridia and the availability of effective vaccines, clostridial disease still results in a large number of sheep and cattle deaths each year.

Organisms

The pathogenic *Clostridium* species are large, Gram-positive, rod-shaped, spore-bearing bacteria. They are predominantly saprophytes and can be found growing in water, soil and decomposing animal and plant matter. Others, such as *C perfringens*, are normal inhabitants of the intestinal tract and are important in postmortem carcase decomposition as they rapidly multiply and invade the blood and tissue after death.

The pathogenic clostridia can be divided into three categories based on the action of the toxins they produce: the enterotoxaemias, neurotrophic clostridia and histotoxic clostridia. Animals are not always at risk from all different types throughout their lives, but, instead, risk can vary with age, particularly in sheep (**Figure 1**). The outcome of all diseases is usually fatal and, due to their sudden onset and severe nature, often cause death before any clinical signs are seen. Even when diagnosed early, treatment is very rarely successful.

Enterotoxaemias

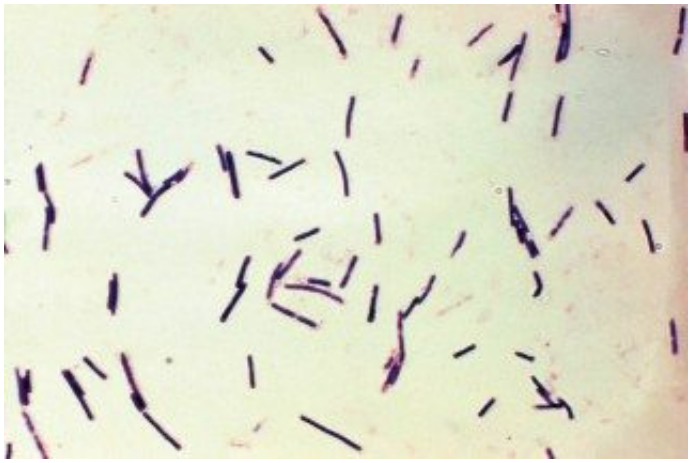

Figure 2. *Clostridium perfringens* is a ubiquitous bacteria whose toxins cause the enterotoxaemia clostridial diseases.

Enterotoxaemia occurs when toxins produced in the intestine by *C perfringens* are absorbed into the circulation (Songer, 1996). First described in 1892 by William Henry Welch, it is a Gram-positive anaerobic, oxygen-tolerant, rod-shaped bacterium (Lucey and Hutchins, 2004) and is one of the most widespread bacteria in the world, with a ubiquitous environmental presence in soil, decaying matter and faecal-contaminated material (**Figure 2**). However, it is also part of the normal intestinal flora in healthy animals. The bacterium can form highly resistant endospores, enabling it to persist in the environment.

Five major types of *C perfringens* exist, which are differentiated based on their toxinotype – the combination of toxins they produce. All strains produce a toxin, with classification of the different subtypes A, B, C, D and E based on the possession of other toxin-encoding genes for ?, ? and ? toxins (Leutenegger, 2016). Types A and D affect cattle and types B, C and D affect sheep.

C perfringens type A

C perfringens type A is the most studied species to date – predominantly due to its role in gas gangrene in the trenches of the First World War. It is the most dominant toxinotype causing enterotoxaemia in cattle. It is a non-contagious, sporadic disease and is commonly associated with stressful conditions around 24 hours to 36 hours prior to death. These may include an abrupt change in diet, transportation or even physiological events, such as calving or oestrus (Lebrun et al, 2010).

Typically, enterotoxaemia results in sudden death due to multiple organ failure, although, in a very small number of cases, signs of abdominal pain or neurological signs may be present prior to death. While in Europe no associated haemorrhagic diarrhoea exists, this appears to be a feature

of the disease in the United States, where it is referred to as haemorrhagic bowel syndrome (Ceci et al, 2006).

On postmortem, the presence of acute haemorrhagic jejuno-ileitis with haemorrhagic intestinal contents is highly specific, although not restricted to, clostridial enterotoxaemia. It should be noted the length of affected intestine may extend from just 10cm to the entire length of the small intestine and, in some cases, lesions may involve more than one intestinal segment (Worrall et al, 1987; Lebrun et al, 2010). Diagnosis can be supported through detection of large numbers of Gram-positive bacilli on Gram-stained smears of the intestinal contents. Toxin detection can be carried out commercially on the intestinal contents, faeces or serum; however, due to the rapid degradation of the toxins in the intestine, false-negative results can occur.

C perfringens type B

C perfringens type B is the cause of lamb dysentery characterised by haemorrhagic enteritis in stronger animals up to three weeks of age, with high milk intakes predisposing to the condition. Infection occurs due to ingestion of the bacteria through soil or faecal contamination of udders. Outbreaks can occur in unhygienic conditions and losses can be severe, with 20 per cent to 30 per cent mortality. Although, in most cases, lambs are found dead, if symptoms are seen, they include signs of abdominal pain, blood-stained faeces and, in rare cases, CNS signs due to focal encephalomalacia (Lewis, 2007).

C perfringens type C

C perfringens type C is the rarest of the enterotoxaemias and causes struck – a condition in sheep at pasture – typically in the spring. Associated with sporadic deaths, it causes sudden onset abdominal pain and haemorrhagic enteritis, which is rapidly followed by death. It has been suggested a relationship exists between the ingestion of liver fluke metacercariae and the disease (Lewis, 2007). As with the other enterotoxaemias, it tends to affect animals in the best condition.

C perfringens type D

C perfringens type D produces the potent ? toxin, which alters the permeability of the intestinal mucosa, enhancing toxin absorption into the blood stream and resulting in widespread vascular damage, which further increases vascular permeability (Lewis, 2007). While it has been reported in cattle, it is more common in lambs between the ages of 4 weeks and 10 weeks, and growing lambs of 6 months of age and older, resulting in pulpy kidney disease. Adults can also be sporadically affected – particularly rams on a rising plane of nutrition prior to tupping.

As with most clostridial diseases, the first sign is often sudden death, although diarrhoea and CNS signs are present in a very small proportion of animals that survive for a short period of time.

Diagnosis can be supported through detection of the ? toxin in the intestinal contents; however, this is neither sensitive nor specific enough for a definitive diagnosis. False-negatives can occur through sample degradation and false positives can occur since some healthy sheep have been found to have ? toxin in their intestinal contents (Bullen, 1952). A study by Jones et al (2015) found specificity of intestinal ? toxin in the diagnosis of cattle disease was 80.4 per cent and that a definitive diagnosis can only be made through histological examination of the brain.

Neurotrophic clostridia

Tetanus

Figure 3. Rumen contents of a cow that died of botulism after eating contaminated feed. The arrow is pointing to chicken bones. Image: Bae et al (2013).

The potent neurotoxins produced by *Clostridium tetani* result in tetanus, which occurs sporadically in cattle and sheep of all ages. *C tetani* is a slender, Gram-positive, anaerobic rod-shaped bacteria found in soil and also normal intestinal flora. When exposed to oxygen, it forms a protective capsule, allowing it to survive in soil as a spore form for months to years. Infection occurs through contamination of wounds or traumatised tissues allowing the spores to germinate and multiply, resulting in the production of a tetanospasmin toxin, which is subsequently taken up by nerve endings. The incubation period is typically 3 days to 10 days, but has been reported to be up to several weeks.

Clinical signs include stiffness and reluctance to move, progressing to bloat (more obvious in cattle), trismus (lockjaw), a raised tailhead and prolapse of the third eyelid. In the final stages of disease, the animal becomes recumbent, before developing tetanic spasms. Death usually occurs within 3 days to 4 days after the onset of signs, although the majority of animals will be euthanised

prior to this on welfare grounds.

Botulism

In contrast to *C tetani*, the toxins released by *Clostridium botulinum* spores cause spastic paralysis. Found in decaying vegetable matter and carcases, seven types of botulinum toxin exist (A to G), but types C and D are responsible for the majority of cases, with as little as 10?g being sufficient to kill a cow (Rings, 2004). When outbreaks occur, it can result in high morbidity rates and these cases will typically be due to feedstuff or water supply contamination (**Figure 3**). The most common risk to ruminants is access to broiler litter, which has the potential to contain decaying carcases.

Clinical signs occur within 1 day to 17 days of infection, with disease progression suspected to occur at a dose-related rate.

In cattle, intoxication results in a progressive, symmetrical, flaccid, cranial and peripheral nerve paralysis, which starts in the hindlimbs and progresses cranially (Hogg et al, 2008). Recumbency follows and loss of muscle tone, which may include the tongue muscles, allows it to protrude from the mouth. Paralysis of the diaphragm muscles results in respiratory arrest and death; however, affected animals are often euthanised long before this stage.

Signs in sheep are similar, but the masticatory muscles are less commonly affected and they tend to develop a characteristic arched back.

Histotoxic clostridia

Histotoxic clostridia produce exotoxins, which cause localised tissue necrosis and systemic toxaemia.

Blackleg

Blackleg (gangrenous myositis) is the most common clostridial disease of cattle, but less common in sheep. Young grazing cattle during the summer are most commonly affected, although reports are made of disease in housed cattle of all ages throughout the year. Disease is due to ingestion and activation of *Clostridium chauvoei* spores. Most affected animals are found dead, but if signs are observed, they include depression and lameness.

When treated at a very early stage, high doses of penicillin can be effective. Following death, the carcase bloats rapidly and the affected muscles are crepitant, palpably spongy and, when incised, they appear blackened, dry and have a rancid odour. Fluorescent antibody testing can be used to confirm a suspected diagnosis.

Malignant oedema

Sometimes referred to as false blackleg, malignant oedema is caused by combinations of clostridial organisms. In cattle and sheep, *Clostridium septicum* is most frequently involved. *Clostridium novyi* type A is a common cause of big head in rams, where lesions are restricted to the head and are usually a result of fighting (Lewis, 2007).

Clinical signs appear soon after soil contamination of a wound – for example, shearing wound – allowing clostridial spores to germinate. Affected muscles may appear dark red and there will be extensive oedema of surrounding tissues with crepitus due to emphysema. Animals have a marked pyrexia and will be dull and toxic, with death following within 1 day to 2 days.

Unlike other clostridial diseases, early aggressive antibiotic treatment has been reported to be successful in sheep (Lewis, 2007).

Braxy

Also due to *C septicum*, braxy affects sheep most commonly in autumn and winter. Typically, the spring lambs, or sometimes shearlings, are affected and toxaemia occurs after ingestion of frozen forage initiates an abomasitis allowing colonisation by *C septicum* and toxin release. Progression of disease is rapid and, even if cases are identified, treatment is unrewarding.

Black disease

Figure 4. Black disease is typically associated with migration of immature liver fluke through the liver and, thus, cattle are often found dead. Image: National Animal Disease Information Service.

Also known as infectious hepatitis, black disease is caused by *C novyi* type B and is confined to wetter areas of the UK. Normally found in the liver, the environment created by migrating immature liver fluke larvae allows the bacteria to proliferate and produce large quantities of lethal toxins.

Thus, late summer/early autumn are the typical risk periods.

Clinical signs are rarely observed and animals are commonly found dead (**Figure 4**).

Bacillary haemoglobinuria

Caused by *Clostridium haemolyticum*, bacillary haemoglobinuria is predominantly a disease of cattle, but is occasionally seen in sheep, with summer and autumn being the greatest risk periods. The organism is found in the liver of normal animals and in faecal-contaminated soil. Affected animals have dark red urine and fresh blood in their faeces, an arched back and are reluctant to move. Recumbency follows with respiratory distress and death within 24 hours.

Postmortem signs include jaundice and a mahogany-coloured liver, which will have at least one area of focal necrosis. It can be differentiated from black disease via toxin-antitoxin tests.

Clostridium sordellii

While more traditionally associated with wound infections leading to gas gangrene, *Clostridium sordellii* has increasingly become associated with acute abomasitis in young lambs of 4 weeks to 10 weeks of age, sudden death of finishing lambs and fatal metritis in ewes (Lewis and Naylor, 1998; Clark, 2003). It has also been identified in cases of bovine abomasitis.

Unlike other clostridia, *C sordellii* is not a normal inhabitant of the gut flora, but is found widely in the environment. The reason why it rapidly multiplies in the abomasum remains unclear. However, it has been suggested it could be due to a sudden change in diet, particularly related to carbohydrates (Lewis, 2007).

Control strategies

The fact clostridia are almost ubiquitous in the environment means they are a constant threat. While some measures can be taken to reduce the risk of specific clostridial diseases – for example, fluke control to prevent black disease – it is virtually impossible to eliminate risk.

When outbreaks or sporadic cases of suspected clostridial disease occur, frustratingly, the only presenting sign can be sudden death. The priority is to determine the suspected source or risk factor for the outbreak and then eliminate this risk if it still exists – for example, contaminated feed in the case of botulism.

In the case of enterotoxaemias, vaccination in the face of an outbreak has proved effective. Another strategy is to prophylactically treat all at-risk animals with long-acting penicillin to prevent further losses. This is not a guarantee, though, and not without risk due to the stress of handling during treatment, which could accelerate disease in already infected animals.

Vaccines also provide an extremely cost-effective method of future control, but the vaccine used must be chosen carefully to ensure protection is acquired against the required bacteria and its toxins.

Therefore, where possible, a definitive diagnosis should be obtained, since not all vaccines protect against the same clostridia species or their toxins. For example, suspected cases of blackleg could be malignant oedema and vaccination against C chauvoei only would be ineffective.

Table 1. Clostridial vaccines licensed in cattle and sheep

Disease	Cattle and sheep			Sheep only			Cattle only
	Blackleg vaccine	Bravoxin 10 and Covexin 10	Covexin 8	Heptavac P Plus*	Lambivac	Ovivac P Plus*	Tribovax T
Clostridium perfringens type A		×					
Clostridium perfringens type B		×	×	×	×		×
Clostridium perfringens type C		×	×	×	×		
Clostridium perfringens type D		×	×	×	×	×	
Clostridium tetani		×	×	×	×	×	×
Clostridium chauvoei	×	×	×	×		×	×
Clostridium septicum		×	×	×		×	×
Clostridium novyi type A							
Clostridium novyi type B		×	×	×			
Clostridium haemolyticum		×	×				×
Clostridium sordellii		×					

*Also protects against *Mannheimia haemolytica* and *Pasteurella trehalosi*.

Table 1. Clostridial vaccines licensed in cattle and sheep.

Several commercial clostridial vaccines are licensed for use in cattle and sheep, providing protection against a range of the clostridial species – depending on the target species and individual vaccine (**Table 1**).

Since immunity wanes over the course of a year – sometimes less for individual strains – annual boosters are required. The only species with no general licence is C botulinum, although this can be obtained under special treatment authorisation from the VMD.

While young animals can be vaccinated from an early age, they do not receive adequate protection for 1 month to 2 months following vaccination, leaving them at risk of infection – especially in the case of lamb dysentery. Therefore, vaccination of the pregnant dam is required to provide passive transfer of immunity to the offspring via colostrum.

Summary

A wide range of clostridial diseases exist – all of which can result in severe losses when outbreaks occur.

Due to sudden death being the most common clinical sign and the fact treatment of animals found in the early stages of disease is often unrewarding, they can be the cause of great distress to the farmer.

Because of their ubiquitous nature and the challenges in minimising risk, vaccination of animals on farms with a history of clostridial disease provides cost-effective protection from potentially devastating losses.

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