EDITORIAL

Clostridium perfringens and its arsenal of toxins

Christian M. Leutenegger

TOXINS produced by strains of Clostridium perfringens have a long history of research. The most studied toxin to date, the α toxin of type A C perfringens, achieved notoriety because of its role in gas gangrene in the trenches of the First World War. But it didn’t stop there; many additional toxins have been characterised since and it seems that the arsenal of toxins has reached new heights with recent discoveries.

A short communication by Mehdizadeh Gohari and others (2016), which is summarised on p 216 in this week’s Veterinary Record, highlights the identification of the novel netF-positive type A C perfringens in foals with enteritis and enterocolitis in Kentucky. The NetF toxin is one of a series of recently discovered toxins belonging to the pore-forming leukocidin/haemolysin superfamily. Additionally, NetF protein was found in the autogenous bacterin-toxoid vaccine utilising a Kentucky C perfringens type A strain that also carries genes for the α toxin (CPA), β-2 toxin (CPB2) and enterotoxin (CPE). This bacterin-toxoid vaccine was specifically developed for the local induction of lactogenic immunity in prepartum mares on Kentucky breeding farms with histories of foal diarrhoea (Timoney and others 2005).

Foal necrotising enterocolitis has long been suspected to be associated with overgrowth and toxin production by C perfringens. C perfringens is a Gram-positive anaerobe, which is ubiquitous in its environment, being found in the soil and decaying organic matter, and is also a member of the normal gut flora of many animals. The ability of the bacterium to form highly resistant endospores means that it is able to persist in the environment. Types of C perfringens are differentiated (five major types: A, B, C, D and E) based on the production of four major exotoxins: α, β, ε and ι. All strains of the bacterium possess the gene encoding the α toxin (CPA). The differential possession of other toxin-encoding genes is used to identify strains as biotypes A to E (McDonel and others 1986). In addition, isolates may have the gene known as C perfringens enterotoxin (CPE), which is produced by sporulating cells in an alkaline environment and is released on lysis of these cells. It is resistant to proteolytic enzymes and will bind and insert on the brush border membrane causing pore

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Clostridium perfringens strains produce toxins that have been heavily researched for several decades. The discovery of their association with severe haemorrhagic and necrotising enteritis in dogs and foals represents a significant development in cells, leading ultimately to cell lysis.

Likewise, acute haemorrhagic and necrotising gastroenteritis has long been a poorly understood disease of dogs, known to be often associated with C perfringens overgrowth and characterised by its dramatic peracute onset and sometimes fatal outcome (Unterer and others 2014). The pathology of fatal cases of C perfringens-associated canine haemorrhagic gastroenteritis is characterised by coagulative necrosis in the small intestine, a disease process typically associated with pore-forming toxins in C perfringens.

Mehdizadeh Gohari and others’ study associated NetE and NetF-producing strains with this disease, and has already contributed to improved diagnosis. This association was confirmed in an independent clinical study with 902 dogs which showed that 17 per cent of dogs with bloody diarrhoea harboured NetE/NetF toxigenic type A C perfringens strains compared to 7 per cent of dogs with non-bloody enteritis and 2 per cent of healthy dogs (Leutenegger and others, unpublished data).

Studies investigating CPE in the faeces of adult horses and foals with diarrhoea have produced variable results. CPE has been detected in the faeces of 7 to 33 per cent of adult horses with diarrhoea and 28 per cent of foals with diarrhoea (Wesee and others 2001). Since the α toxin is produced by all types of C perfringens, including non-pathogenic type A strains, it is not considered a primary cause of digestive lesions. Meanwhile, a newly discovered toxin called β-2 toxin produced by C perfringens type C strains was suspected to be involved in neonatal enterocolitis. In a subsequent study, β-2 toxin was found in 52 per cent of the foals with typical and atypical typhlocolitis. Interestingly, no β-2 toxigenic C perfringens was found in healthy horses or in horses hospitalised for reasons other than intestinal problems. From this we can conclude that type C strains producing β-2 toxin are responsible at least in part for foal necrotising enterocolitis (Herholz and others 1999). From a clinical viewpoint, a type C infection with a β-2 toxigenic strain in a foal younger than five days is considered a medical emergency but, despite aggressive treatment plans, many foals will succumb to the infection.

In contrast to type C β-2 toxin-bearing C perfringens strains, the role of type A toxin-producing strains in neonatal enterocolitis has been poorly understood and was not defined until the recent description of NetE and NetF by Mehdizadeh Gohari and others in 2015. The current study confirms the association between NetF in Kentucky foals and neonatal enterocolitis. Furthermore, this study also reveals that the autogenous bacterin-toxoid vaccine in use since the early 2000s, while containing the NetF component, may not induce protective levels of anti-NetF antibodies in prepartum mares. A similar association was found with the β-2 toxin component in this vaccine and led to the enrichment of the vaccine formulation with purified recombinant β-2 toxin protein. Enrichment of the bacterin with recombinant NetF, therefore, could improve antibody response and enhance lactogenic immunity to provide greater efficacy in the protection against foal necrotising enterocolitis.

Taken together, the discovery and characterisation of these novel type A C perfringens toxins and their involvement in severe haemorrhagic and necrotising enteritis in dogs and foals represent a significant advance in veterinary medicine. It opens an exciting new chapter to further our understanding of the disease process, has already triggered the introduction of new diagnostic tests, will ultimately lead to better protection of foals by improved lactogenic immunisation of prepartum mares and will hopefully lead to earlier therapy induction with better patient outcomes.

References

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