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Review

The role of infectious agents in the development of porcine gastric ulceration

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ABSTRACT

Ulceration of the non-glandular part of the stomach is a common disease entity of pigs worldwide, with prevalences of up to 93%. It may result in decreased daily weight gain, decreased feed intake and sudden death, thus leading to significant economic losses, as well as animal welfare issues. The aetiology is multifactorial. Diet particle size, management and infectious agents have been hypothesised to be involved. The exact mechanism behind porcine gastric ulceration is, however, not completely clear. The aim of this article is to provide an overview of the role of infectious agents in the development of porcine gastric ulceration. Results of recent studies indicate that *Helicobacter suis* infection plays an important role in gastric ulceration, probably by affecting gastric acid secretion through alteration of the number and/or function of parietal, D and G cells. In a gastric environment altered by *H. suis*, higher numbers of *Fusobacterium gastrosuis* are present and this novel pathogen has a potential role in the development of porcine gastric ulceration. Inoculation of pigs with *Lactobacillus* sp., *Bacillus* sp. or *Helicobacter pylori*-like bacteria in combination with a carbohydrate-rich diet may induce gastric lesions. It has been hypothesised that production of short chain fatty acids by some of these bacteria might be involved in the pathogenesis of porcine gastric ulceration, but the lack of taxonomic characterisation hampers the interpretation of these studies. Severe infectious diseases have also been associated with gastric lesions, probably due to interruption in feed intake and/or histamine release. Other agents, including fungi and parasites such as *Hyostrongylus rubidus* and *Ascaris suum*, have occasionally been associated with gastric lesions in pigs.

Introduction

Ulceration of the non-glandular part of the porcine stomach has been described with increasing frequency since the late 1950s as a result of pig production intensification (Queiroz et al., 1996). Now, it is a common disease entity of pigs worldwide, with prevalences of up to 93% (Thomson and Friendship, 2012; De Witte et al., 2017). Although lesions can occur at any age, pigs at slaughter age and sows around the time of parturition are most frequently affected (Thomson and Friendship, 2012; De Witte et al., 2017). In a recent study in Belgium, gastric ulcers and/or severe erosions were found in 60% of slaughtered sows (De Witte et al., 2017).

Both the prevalence and severity of lesions can vary greatly between different pig herds. The reason for this is not clear, although feeding and management strategies may sometimes be involved. The disease outcome is mainly subclinical, with only the most severe ulcers resulting in development of clinical signs of anaemia (i.e. paleness, tremor, slow gate, anorexia) or sudden death due to significant blood loss and/or perforation of the ulcers through the stomach wall, resulting in fatal peritonitis (Thomson and Friendship, 2012). Nevertheless, since even less severe lesions have been associated with a decreased weight gain of up to 75 g/day (De Bruyne et al., 2012), decreased feed intake and most likely also pain, economic losses, as well as animal welfare issues are of major importance (De Witte et al., 2017).

In contrast with other animal species, gastric ulcers of pigs are almost exclusively found in the *Pars oesophagea*, a small area around the opening of the oesophagus covered by non-glandular, stratified squamous epithelium (Fig. 1). In the normal porcine stomach, no mixing of luminal content takes place between the upper compartment (i.e. *Pars oesophagea* and cardiac gland zone) and distal compartment (i.e. fundic and pyloric gland zone). The pH of the upper compartment is 5–7 due to the presence of bicarbonate in saliva and cardiac gland secretions. In the distal compartment, the pH is low (2–3) due to hydrochloric acid (HCl) production by parietal cells. Any factor contributing to a

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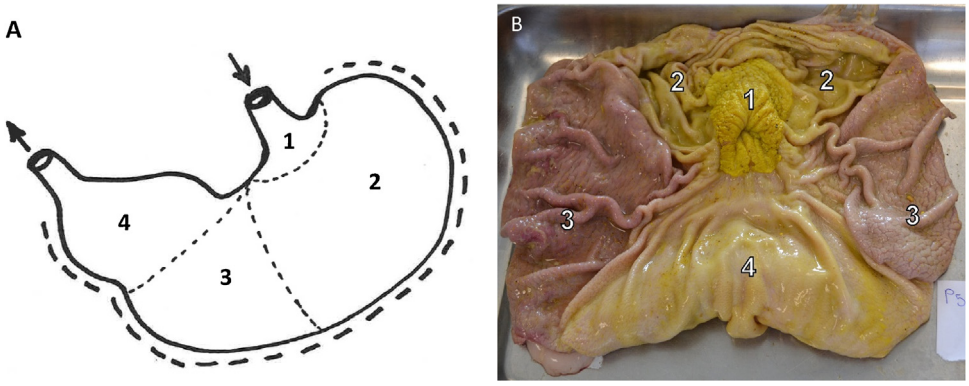

Fig. 1. Anatomy of the porcine stomach. (A) Diagram of a closed stomach. The arrows indicate the entering of the oesophagus into the stomach and the beginning of the duodenum. The greater curvature is indicated by the large dotted line. (B) When the stomach is opened along the greater curvature, the different stomach regions can be seen: 1 = *Pars oesophagea*, 2 = cardiac gland zone, 3 = fundic gland zone, 4 = pyloric gland zone.

breakdown of this pH gradient between both compartments may lead to increased contact of the *Pars oesophagea* with distally produced HCl, pepsin and bile salts. Since this non-glandular part is not protected by mucus, this chronic insult results in hyperkeratosis, erosion and, finally, ulceration (Haesebrouck et al., 2009).

The pathogenesis behind porcine gastric ulceration is not yet exactly known. The disease is clearly of multifactorial origin. In general, factors that increase the fluidity of the gastric content cause a breakdown of the pH gradient and are considered to be risk factors. Well known examples of such risk factors are small particle size of feed, pelleting of feed and interruption of feed intake (Thomson and Friendship, 2012). Apart from feeding and management strategies, other factors, such as genetic background, hormonal changes, gastric microbiota composition and infectious agents, have also been suggested to play a role in development of ulceration of the non-glandular part of the porcine stomach (Haesebrouck et al., 2009).

The aim of this article is to provide an overview of the role of infectious agents in the development of gastric ulceration in pigs. First, the possible involvement of *Helicobacter suis* will be discussed. Thereafter, other bacteria, such as *Fusobacterium gastrosuis*, *Lactobacillus* sp. and *Bacillus* sp., will be considered. Finally, the effect of *Candida* spp., respiratory infections and parasitic infestations will be discussed briefly.

Role of *Helicobacter suis* in the development of porcine gastric ulcers

In man, *H. pylori* has been associated with gastric disease, including peptic ulcers. In contrast with pigs, these peptic ulcers are mainly found in the glandular gastric mucosa and in the duodenum. Increased gastric acid secretion, as a result of *H. pylori* infection, plays an important role in the generation of these ulcers (Calam, 1999). Pigs are frequently infected with a closely related microorganism, namely *H. suis*. Although ulceration of the non-glandular region of the porcine stomach is clearly different from gastroduodenal peptic ulcers in humans, alterations in HCl production in the glandular region of the porcine stomach, induced by *H. suis*, may also play a role in the pathogenesis, as is clear from the results of recent studies (De Witte et al., 2017).

Association of Helicobacter suis *with gastric ulceration*

H. suis is a Gram-negative, spiral-shaped, motile bacterium that colonises the gastric mucosa of pigs worldwide. The agent is of zoonotic importance and it is the most prevalent non-*H. pylori* *Helicobacter* species in humans. Human infection with *H. suis* has been associated with development of gastritis, peptic ulcers and mucosa-associated lymphoid tissue (MALT) lymphoma. In a Belgian study, the prevalence of *H. suis* in suckling piglets was low (2%) and gradually increased with age to 30% in nursery pigs, 80% at slaughter age and 90% in adult pigs (Hellemans et al., 2007a). *H. suis* mainly colonises the fundic and pyloric gland zone of the stomach, inducing inflammation and a decreased daily weight gain (Haesebrouck et al., 2009; De Witte et al., 2017).

Several studies have found a positive correlation between the presence of *H. suis* in the glandular part of the stomach and the prevalence and severity of lesions in the *Pars oesophagea* (Barbosa et al., 1995; Grasso et al., 1996; Queiroz et al., 1996; Yeomans and Kolt, 1996; Cantet et al., 1999; Phillips et al., 2000; Choi et al., 2001; Roosendaal et al., 2002; Silva et al., 2002; Szeredi et al., 2005; Appino et al., 2006; Yamasaki et al., 2009), indicating that this bacterium might play a role in the development of porcine gastric ulceration. However, this association has not been found in other studies (Melnichouk et al., 1999; Accioly et al., 2000; Park et al., 2000; Mall et al., 2004; Casagrande Proietti et al., 2010). These discrepancies might be due to different sampling techniques (i.e. one vs. several gastric biopsy samples), different detection techniques for presence of *H. suis* (i.e. reverse transcriptase-PCR vs. Giemsa staining), differences in virulence between *H. suis* strains and/or presence or absence of other contributing factors, such as specific feeding and management strategies.

Since correlation does not necessarily imply a causal relationship, attempts have been made to induce gastric lesions by infecting pigs experimentally with *H. suis*. Hellemans et al. (2007b) showed a trend towards more severe lesions in 6-week-old pigs inoculated orally with mouse stomach homogenate containing *H. suis*. In contrast, Krakowka and Ellis (2006) did not find gastric lesions in 3-day-old pigs inoculated orally with mouse stomach homogenate containing '*Helicobacter heilmannii*-like organisms'. The results of these studies are, however, difficult to interpret, since no pure cultures were used to inoculate the pigs and, in the study of Krakowka and Ellis (2006), helicobacters were not identified to the species level. Other bacteria present in murine stomach homogenates may have influenced the results and *in vivo* passages of *Helicobacter* sp. isolates in mice may affect the virulence and pathogenicity of the strains (Hellemans et al., 2007b). Furthermore, the study by Krakowka and Ellis (2006) used suckling pigs, while the study by Hellemans et al. (2007b) used weaned pigs.

Pure *in vitro* isolates of *H. suis* have been available since 2008 (Baele et al., 2008), enabling more reliable *H. suis* infection trials. When 6-week-old piglets were inoculated with a pure culture of *H. suis*, hyperkeratosis and ulceration were present in the *Pars*