# *Lawsonia Intracellularis* pathogenesis

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As an obligate intracellular bacterium, *Lawsonia intracellularis* has specific infection and spreading mechanisms in the host. The infection takes place through the oral route, and naïve pigs from different age groups are susceptible. However, infection is usually seen in the late nursery period and in the growing-finishing phases. Sporadically, young adults (replacement animals) develop an acute haemorrhagic form of the disease. There is no definitive explanation as to why some animals develop this acute form of the disease.

The infective dose is around 103 microorganisms (Collins et al., 2001), and the intestinal microbiota is essential for the development of the disease, as gnotobiotic pigs do not become infected when inoculated with a pure culture of *L. intracellularis* (McOrist et al., 1993). Studies using a dual infection with PCV2 or Salmonella sp. (Opriessnig et al., 2011; Borewicz et al., 2015) associated with *L. intracellularis* in commercial pigs have been conducted, but no evident synergic effect was demonstrated.

Ileitis can be reproduced in pigs by using pure cultures of *L. intracellularis* or diseased mucosa of infected pigs as the inoculum (Guedes & Gebhart, 2003ab). The bacteria can be detected in the faeces of infected pigs two to three days after the inoculation. The majority of the experimentally inoculated pigs shed the bacteria from day 7 to 21 post-inoculation, and this coincides with the peak of the infection. Some animals can still be shedding *L. intracellularis* up to 10 to 12 weeks after the inoculation (Smith & McOrist, 1997; Guedes et al., 2002ab).

## VIRULENCE FACTORS

The virulence factors of *L. intracellularis* are not yet known.

> Its main pathogenic mechanism is the infection of and induction of hyperplasia in enterocytes (Lawson & Gebhart, 2000).

Inflammation is not a major feature associated with the infection, even though inflammation and superficial necrosis are often seen, mainly due to secondary bacterial infections. The attachment and entry into the epithelial cells of the intestines were believed to occur only in immature enterocytes of the crypts of the small intestine. However, Boutrup et al. (2010ab) have shown that enterocytes from the apex of the villi also become infected in the early stages of the infection.

Specific adhesins or receptors for *L. intracellularis* have not been characterized yet. However, the attachment and entry into the epithelial cells seem to require a specific bacterium-host cell interaction (McOrist et al., 1997). The process of invasion does not depend on the viability of *L. intracellularis*, as formalin-fixed organisms could still be internalized by eukaryotic cells (Lawson et al., 1995). But it is possible that the single unipolar flagellum present in *L. intracellularis* (Lawson & Gebhart, 2000) is involved in the intestinal colonization (Smith & Lawson, 2001). The mechanism of escape from the membrane-bound vacuole into the cytoplasm and the avoidance of the damaging effects of the phagolysosomal fusion is also observed in several other ***species*** of intracellular bacteria, *such as: Shigella, Listeria, Rickettsia spp. and Clostridium piliforme.*

 

## ENTEROCYTE PROLIFERATION

The mechanism of induction of cell proliferation, an important feature of ileitis, has not been explained yet. The temporary reduction of apoptosis induced by the *L. intracellularis* infection was suggested as a possible mechanism involved in the proliferation of the enterocytes. However, two different studies published recently (Guedes et al., 2017; Huan et al., 2017) have shown that the crypts infected with *L. intracellularis* have, actually, more apoptotic events than the non-infected ones, this showing that the reduction of apoptosis is not a likely explanation for enterocyte proliferation.

> So far, the mechanism of induction of enterocyte proliferation caused by *L. intracellularis* remains unsolved.

Enterocytes seem to be the only cell type infected by *L. intracellularis*. Bacteria antigen has been found in the tonsils, lamina propria of the intestines, mesenteric lymph nodes and liver. However, the presence of the bacteria in the tonsil crypts are likely due to environmental contamination and not infection, while in the other tissues and organs it is assumed to consist in digested bacteria contained in macrophages. In contrast, Boutrup et al. (2010b), using fluorescent in situ hybridization, have demonstrated the presence of viable *L. intracellularis* in the cytoplasm of mononuclear cells in the lamina propria of the small intestine. They hypothesized that the bacteria could survive in macrophages, which could help in the spreading of the infection not only through the apical portion of the enterocytes but also via the basolateral surface. *L. intracellularis* seems to initiate the infection in the small intestine, mainly in the jejunum and ileum, and then moves towards the large intestine, where the infection and lesions can be seen from the caecum to the rectum (Guedes et al., 2017).

> As a result, despite of being commonly called “ileitis”, the infection and lesions can be found in both the small and large intestines.

Diarrhoea and the reduction of growth, that are common features of different forms of presentation of ileitis, were explained by the hyperplasia of immature enterocytes and the subsequent villous atrophy, that are characteristic histologic findings of the disease.

> However, Vannucci et al. (2010) have shown that even infected intestines with no clear villous atrophy showed a reduced absorption of glucose, potassium and chloride.

As a result, the malabsorption observed in ileitis is not only due to villous atrophy but also to the possible molecular and protein membrane alterations induced in infected hyperplastic enterocytes. In conclusion, the pathogenesis of *L. intracellularis* involves intricate and complex mechanisms to avoid the acid digestion in the stomach; to evade the enterocytes’ lysosomal digestion mechanism; to induce the proliferation of enterocytes, blocking their differentiation during maturation, and, consequently, resulting in modifications in the expression of outer membrane proteins, malabsorption and the reduction of growth.