Ileitis - one Pathogen, several Diseases

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Introduction

The main forms of proliferative enteropathy or Ileitis seen in pig farming situations around the world are the chronic, subclinical and acute forms. Although these have different clinical signs, they are all caused by the same bacterium, *Lawsonia intracellularis*. It has not been possible to eradicate Ileitis with modern management tools such as medicated early weaning; therefore this disease has been a major driver for continued use of oral antibiotics in modern pig farms. However, the final development and launch of the world’s first useful vaccine for Ileitis has seen the dawn of a new era in Ileitis control.

Chronic and subclinical proliferative enteropathy

On a typical pig farm affected with Ileitis, the chronic and subclinical cases of proliferative enteropathy (Ileitis) generally include: i) diarrhoea and ii) reduced weight gains, or “variation” in the grower pigs. In more severe chronic situations there is a notable number of runted pigs. Young pigs exposed to a low or moderate level of infection are much more likely to develop this chronic or subclinical form of the disease, so it usually occurs in nursery or grower or finisher pigs, aged somewhere between 6 and 20 weeks old. It is sometimes known as PIA or porcine intestinal adenomatosis.

The diarrhoea seen is generally moderate, with loose pasty stools of normal colour. In many cases, the degree of loose faeces seen is a sloppy, poorly formed stool, resembling cow faeces. In more severe cases, the faeces may become more liquid watery texture. In the subclinical form, these cases of diarrhoea are less frequent and less obvious to the eye.

It is therefore important in suspect groups of pigs with Ileitis, to develop a good strategy for diagnosis. Faeces can be analysed for evidence of *Lawsonia intracellularis* DNA by the PCR method. Also, serum from pigs can be analyzed for specific antibodies in many laboratories. Some farms develop a profiling system, with serum being tested at regular intervals, say at 8, 10, 13, 16 and 20 weeks old pigs.

The spread of Ileitis on farms

Overall epidemiological features of Ileitis include the facts that *Lawsonia intracellularis* can remain viable in faeces at 5°C to 15°C for 2 weeks, the infectious dose is relatively low and faecal excretion may be high in infected “spreader” pigs, and that sanitation methods are incompletely understood. Only quaternary ammonium compounds and iodine-based compounds, of 6 disinfectants tested in one study, showed complete bactericidal activity.

The chronic and subclinical forms are especially common on traditional, single-site, farrow-to-finish farms with all the farm buildings on one property. These are the most common types of farms in Europe and Asia. This form is common because there is a simple flow of pigs and infected faeces around the farm, passing the disease from one pig to the next (Chouet et al., 2003). Outdoor farms suffer as commonly as indoor facilities. There
appears to be little real influence of other vectors such as birds or rodents in *Lawsonia intracellularis* infections.

The acute haemorrhagic form of Ileitis is a much more dramatic and severe type of disease. Cases are usually seen in the finishing or fattening period, or in young adult pigs in breeding groups (Stege et al., 2000). So the affected pigs are usually 3 to 12 months old. It is common to see a number of cases together, usually soon after some specific event in the group of pigs. Exposures are such as moving them to a new building, moving them to a new pen, introduction of new breeding animals to the group, isolating the animals in testing or gestation barns, transporting the group on trucks etc. It seems to be particularly common in The Netherlands, Belgium, Canada and the United States of America (McOrist et al., 2003). It is sometimes known as PHE or proliferative haemorrhagic enteropathy.

This acute form is more likely to develop in “older” pigs that have not been previously exposed to the disease – naïve pigs exposed to a relatively high oral challenge dose of bacteria. One way that pigs can remain naïve until they are older is if they receive antibiotic medication programs that reduce early exposure to *Lawsonia intracellularis*. The increase in age separation among pigs in modern pig farms can have marked benefits for reduction of pneumonias, but seems to affect the immunity of pigs to proliferative enteropathy and can also lead to more acute cases.

In modern “high health” farms, the breeding herd is very clean and may be well separated from the growing pigs. In many of these farms it has been found that the breeding pigs are in fact negative for proliferative enteropathy. This is in contrast to single site farms, where up to 30% of the breeding herd may be positive. An important result is that the time when the offspring (piglets) of these clean breeding animals first become exposed to *Lawsonia intracellularis* is delayed until later in the finishing period, making them much more susceptible to the acute form of disease. Early cases of the acute disease should be isolated and treated with effective injectable and oral antibiotics such as Tiamulin or Tylan. Medication of sows to limit infection is not likely to have a major impact.

Exactly where this later infection comes from in the finishers is not 100% clear, but it is probably from infected faeces remaining in some part of the farm itself, such as the slurry pit, recycled water from drainage pits, faeces material on boots, clothing, pens or insects. This would explain the consistent nature of this later infection on these farms.

**Pathogenesis and immunity**

In typical oral challenge exposure studies of postweaned pigs (4 weeks-old) with a standard inoculum of $10^8$ *Lawsonia intracellularis* bacteria, numerous intracellular *Lawsonia intracellularis* bacteria can be visualized in the developing proliferative intestine and faeces 1 to 3 weeks following inoculation with a peak of infection and lesions 3 weeks after challenge. In most of these pigs, intestinal infection, proliferative lesions and excretion persists for approximately 4 weeks, but in some 5 to 10% of exposed pigs, excretion may persist for at least 10 weeks.

*Lawsonia Intracellularis* isolates associated with one type of Ileitis (acute or chronic) appear capable of initiating the range of
pathological sequelae, indicating the “single strain” nature of *Lawsonia intracellularis*. Pigs of a wide age range are susceptible to oral challenge: pathogenic infections have developed following oral challenge of neonatal piglets aged 7 or 14 days and in pigs at least 18 weeks-old.

Ileitis develops initially as a progressive proliferation of immature epithelial cells populated by numerous intracellular bacteria. In most cases, no significant inflammatory reaction occurs and the organisms remain in the epithelium at this stage. In severe cases, *Lawsonia intracellularis* can also be observed in the mesenteric lymph node and tonsils, but these appear to be secondary sites. In vivo and in vitro studies have elucidated some of the early events in bacteria-cell interaction. Bacteria associate with the cell membrane and then quickly enter the enterocyte via an entry vacuole. Specific adhesins or receptors have not been identified, but *Lawsonia intracellularis* may possess a type III secretion system. The entry vacuole rapidly breaks down (within 3 hours) and the bacteria flourish and multiply free (not membrane-bound) within the cytoplasm. The entry of bacteria into cells is dependent on cell, but not necessarily bacterial, viability, that is, a type of induced phagocytosis. The mechanism whereby the bacteria cause infected cells to fail to mature, but continue to undergo mitosis and form hyperplastic crypts is not yet understood fully. It may reflect an inhibition of the normal crypt cell differentiation process, as regulated locally at the crypt neck. *Lawsonia intracellularis*-infected intestinal crypts can become enormously elongated and often branched. Loss of body protein and amino acids into the intestinal lumen and the reduced nutrient absorption by the intestinal mucosa lacking mature enterocytes are the likely causes of the reduction in weight gain and feed conversion efficiency seen in pigs affected with chronic uncomplicated lesions.

Early lesions contain very few infiltrating inflammatory cells, probably not above the normal for pig intestines. Affected epithelial cells contain a large accumulation of intracellular IgA and intestinal lavages contain a high level of *Lawsonia*-specific IgA indicating local mucosa responses are important. Macrophage ingestion of *Lawsonia intracellularis* in developing lesions probably leads to a typical Th1 type immune cell response in the lamina propria. Both cell-mediated and humoral responses occur in the blood of affected pigs. These are first detectable 2 weeks after exposure and can persist for some 3 months in acutely infected pigs (Guedes and Gebhart, 2003). It is therefore likely that animals exposed to *Lawsonia intracellularis* show a specific immune response.

Acute haemorrhagic Ileitis (PHE) is marked by severe bleeding into the lumen of the intestine, but with underlying lesions of chronic disease. The haemorrhage occurs concurrently with the widespread degeneration and desquamation of many epithelial cells and leakage from the capillary bed. PHE has been reproduced in older naïve pigs, challenged once with a high dose of *Lawsonia Intracellularis*, indicating a host rather than bacterial effect. The pathogenesis of this lesion has not yet been determined fully, but may involve an alteration of cytokine pathways, such as vasoactive TNF $\alpha$ expression, during infection.

Ileitis vaccine development

Once the causative agent of Ileitis, *Lawsonia intracellularis* was first cultured in 1993, a start was then possible on developing a vaccine strategy. This was to take over 7 years of considerable research and development effort. For intracellular bacterial pathogens and for post-weaning enteric infections like *Lawsonia intracellularis*, live attenuated bacteria delivered orally offer the most “natural” immunity and are widely considered the best form of vaccine approach (Kroll et al., 2004). An attenuated live vaccine formulation of *Lawsonia intracellularis* was therefore developed (Enterisol® Ileitis, Boehringer Ingelheim). Because it is a live bacterial form that is administered orally to pigs, it is best administered in the middle of a 7-day antibiotic-free period. That way, any antibiotics that had previously been in the pig would be eliminated and would not kill any vaccine bacteria prior to its uptake. Many farms find that an antibiotic-free period can be readily developed 1 to 4 weeks after weaning to allow the live
vaccine use. The vaccine may be applied by adding it into the drinking water via a “Dosatron” type proportioner, or by using a simple drinking trough for each pen.

A large study of on-farm immunizations of over 100,000 pigs against proliferative enteropathy caused by *Lawsonia intracellularis* has been completed in North America. These studies monitored non-medicated (or part-medicated) finisher-stage vaccinates to non-vaccinated controls, which received full “standard” antibiotic programs for Ileitis during the finishing stage. The results indicate that the vaccine was indeed efficacious, with a significant reduction in lesions and reduction in the intestine colonisation of *Lawsonia intracellularis*. An interesting and consistent finding was that there was a significantly improved growth rate and reduced mortality in vaccinates compared to medicated control pigs. Along with this vaccine-enhanced growth effect due to control of the growth-retarding subclinical disease, vaccination allowed a 50-100% reduction in antibiotics in the finisher period, allowing major cost savings. There are also clear-cut cost and welfare savings in the prevention of any occurrence of acute Ileitis in groups of gilts and other breeders by this simple vaccination method.

The overall average improvement in the daily weight gain of vaccinates in these studies was 6%, the average reduction in culls was 23%, but no significant improvement was evident in studies of feed efficiency. The reduction in culls and improved weight gains lead directly to an improvement in the overall weight grouping of finisher vaccinates at the time of marketing. It is possible that successful vaccines for endemic intestinal diseases may provide innately more positive growth and feed utilisation impact than those for diseases in other body systems. A further clear benefit of the Ileitis vaccine is the possible reduction in transmissible antibiotic resistance factors being present on pig farms, due to the possible reduction of antibiotic usage.

Additional advantages of vaccination via the water system are the elimination of animal and human stresses, time, costs and effort (including possible difficulties with full compliance and actual administrator injuries) with individual vaccinations, compared to mass vaccination methods such as oral vaccination. Further advantages include the elimination of the possible transmission of blood-borne infections such as PRRS virus via multi-use needles and the reduction of injection site reactions and needles retained in carcasses. Oral mass vaccination methods have been widely used on poultry farms for many years and they will probably become more widely used on pig farms.

The success of the *Lawsonia intracellularis* vaccine may be partly due to actual exposure of this agent to the immune system via intestinal mucosal macrophages, with specific humoral and mucosal responses following oral infection (Guedes and Gebhart, 2003). Protective immunity to infection by other intracellular bacterial pathogens (such as *Brucella* sp. and *Chlamydia* sp.) has only been demonstrated following delivery of whole live attenuated bacteria. In contrast, use of recombinant bacterial or killed vaccine approaches for these types of infections has not yet led to protective immunity being noted.

References


Guedes, RMC; Gebhart, CJ. (2003). Onset and duration of fecal shedding, cell-mediated and humoral immune responses in pigs after challenge with a pathogenic isolate or attenuated vaccine strain of Lawsonia intracellularis. Veterinary Microbiology 99, 135-145.


