Prevention and Control of Porcine Proliferative Enteropathy ("Ileitis")

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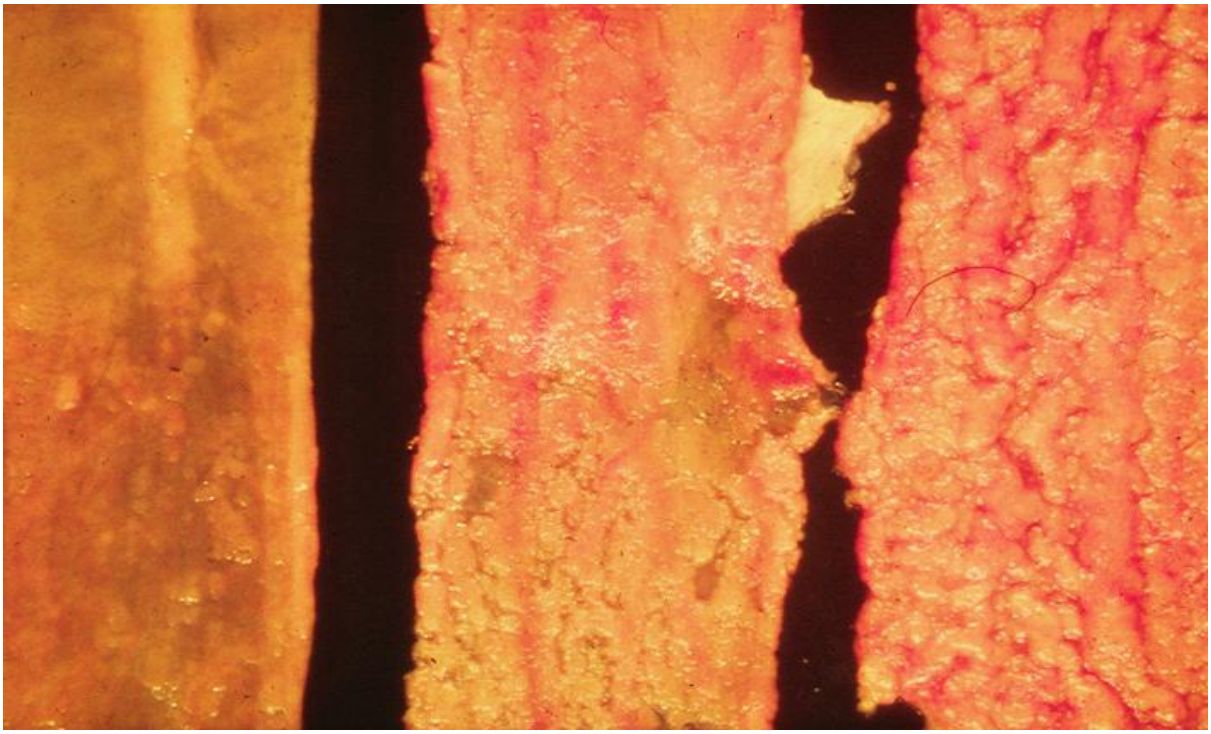
Introduction

Porcine proliferative enteropathy is an enteric disease, primarily affecting young growing pigs and associated with the end of the small intestine i.e. the ileum, hence, it is more commonly called 'ileitis'. The proliferative lesions can also extend down into the caecum and proximal colon. The disease is caused by the obligate, intracellular-living bacterium, *Lawsonia intracellularis*, named after Gordon Lawson, the Scottish researcher that discovered and first cultured the organism. The infection is transmitted by the faecal-oral route and commonly occurs in most pig farms on a worldwide basis. In the UK, 95% of pig farms are serologically positive, showing that the pigs have been exposed to the infection at some stage. With the pressure to reduce antibiotic usage in the EU this is a disease where the preventive use of antibiotics becomes a key issue, especially as an effective vaccine exists.

The disease

The organism is ingested and colonises the cytoplasm of epithelial cells lining the intestine, where it multiplies and its growth is accompanied by localised proliferation of infected immature enterocytes resulting in the thickening of the mucosa (see Photo 1). After the bacteria have multiplied they are released from the cell, where they can go on to infect neighbouring cells or are passed out in the faeces, ready to infect new hosts.

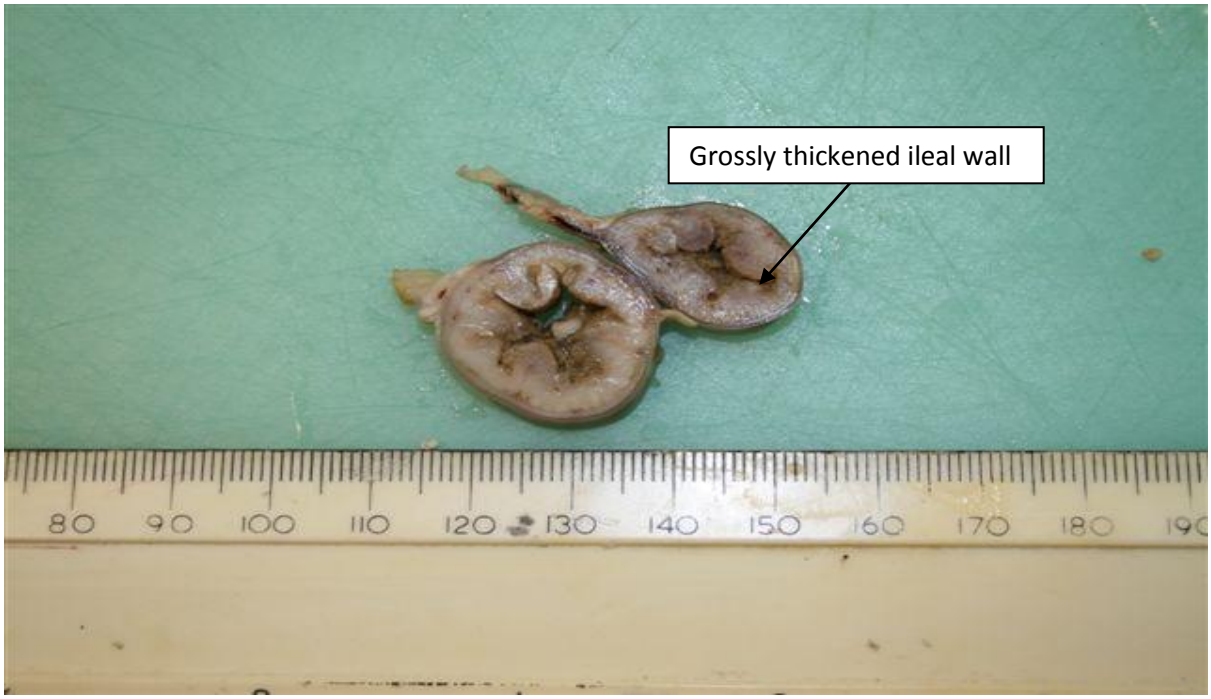
Photo 1. Development of proliferative lesions along the ileum of the pig



Degenerative and reparative changes may be superimposed on the basic enterocyte proliferation, probably, due to secondary bacterial infections. Inflammatory changes may range from superficial, fibrinous reaction to deep, coagulative necrosis, which is the lesion associated with 'necrotic

enteritis'. In some pigs, there is a substantial granulation reaction, leading to fibrous infiltration and muscular hypertrophy, which is the lesion of regional ileitis or 'hosepipe gut' (see Photo 2).

Photo 2. Thickened hosepipe gut (cross-section)



This thickening leads to poor absorption of nutrients and fluid and can result in poor growth rates, poor feed conversion efficiency (FCE) and diarrhoea and an occasional mortality. Depending on the severity of the infection and the challenge from the environment, the disease can be sub-acute, causing few clinical signs such as uneven growth and only mild diarrhoea (see Photo 3) to more severe disease such as death.

Photo 3. Mild diarrhoea associated with 'ileitis'

The acute haemorrhagic form, porcine haemorrhagic enteropathy (PHE) or 'bloody gut', is associated mainly in older pigs of greater than 4 months (finishers and young breeding stock) and is marked by severe bleeding into the lumen of the intestine but with underlying lesions of chronic ileitis. The haemorrhage occurs concurrently with the widespread degeneration and desquamation of the epithelial cells and leakage from the capillary bed (see Photo 4).

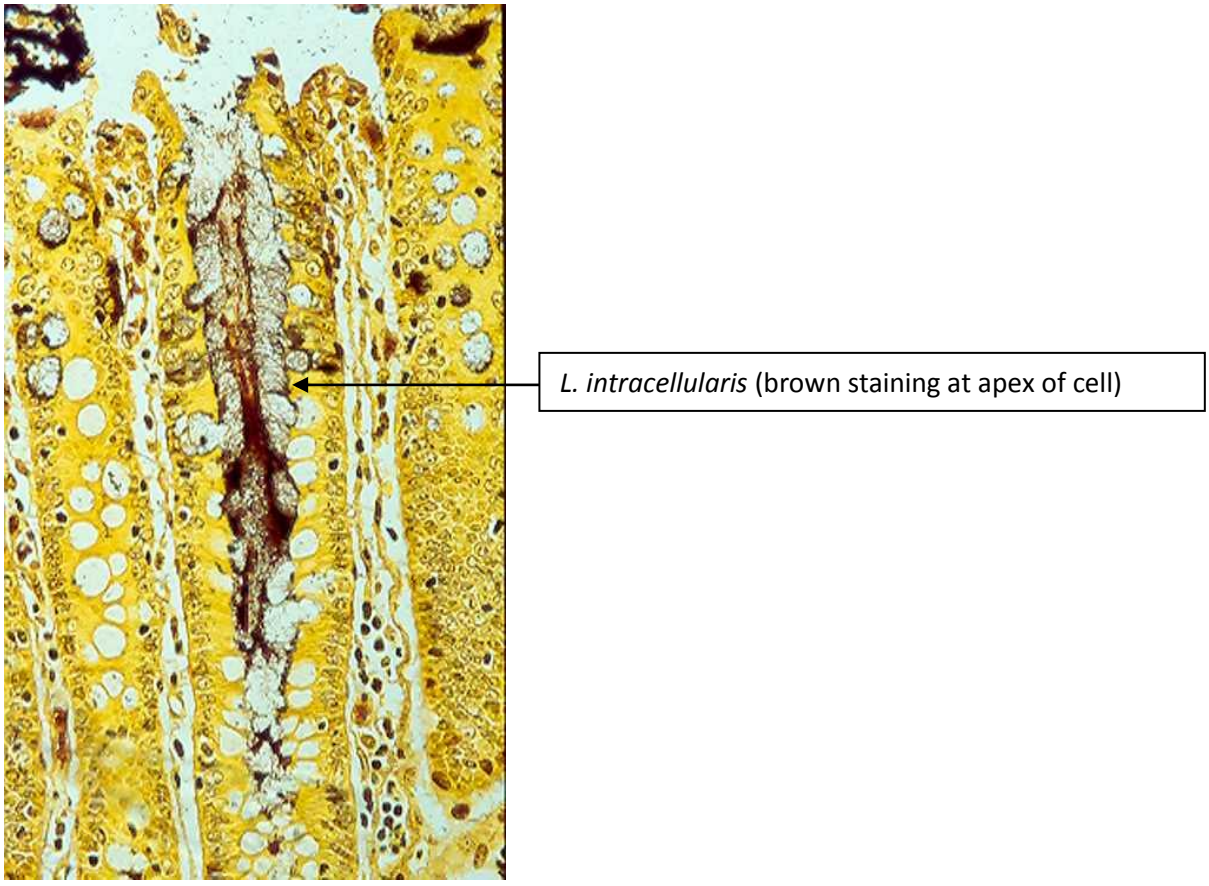
Photo 4. Porcine haemorrhagic enteropathy (Courtesy Nate Winkelman)

Clinically, the haemorrhagic form leads to the presence of pale pigs with blood being passed but more frequently, dead, blanched pigs are found in the pens which have bled out into their intestines but in the absence of ulceration.

The severity of infection appears to be related to degree of challenge. In artificial infection studies, numerous intracellular bacteria can be seen in the developing proliferative lesions in the intestine 1-3 weeks post infection, with a peak at 3 weeks after infection. In most pigs, intestinal infection, proliferative lesions and excretion of organisms persists for 4 weeks and in some cases for 10 weeks. At the peak of infection, 3 weeks after challenge, moderate or watery diarrhoea and histological lesions of proliferation are usually observed in 50-100% of pigs. Weight gain and FCE can be affected for a number of weeks until the lesions start to resolve and growth rate is reduced by 10-20% and FCE by 5-10%. Growth and FCE return to normal after recovery.

Immunity, as judged by a serological response, relates well to the development of lesions, approximately 2-3 weeks after infection and serological tests are useful on a herd basis to determine the onset of clinical disease and possibly treatment. Other diagnostics commonly used include polymerase chain reaction (PCR) testing, as well as histopathology of the lesion and observation of the bacteria in the cell using the silver Warthin-Starry stain (see Photo 5).

Photo 5. Staining of *Lawsonia intracellularis* in the crypt cells of the ileum (Courtesy Jill Thomson)



Prevention and control of ileitis

Immunity and vaccination

The development of immunity is considered an important factor in the control of the disease, both serological and cell-mediated immunity. Once immune, the pigs do not succumb to the disease again. Vaccination using a live attenuated vaccine (Enterisol – Boehringer Ingelheim) has proven effective, reducing the effects on growth and FCE. It takes 3 weeks for immunity to build up and lasts for about 17 weeks. Use in Europe, unlike the US, has been very low. Possibly, the widespread use of antibiotics after weaning or at a time when the vaccine can be given prevents many farmers using it. I have been able to use it effectively in a high-health farm at weaning by oral dosing at the same time that they get their PCV2 vaccine, with the pigs subsequently on zinc oxide only in the feed. This enabled pigs to come off routine medication for ileitis in the grower/early finisher stage.

In the US, they have adopted another procedure challenge vaccination followed by therapeutic medication with antibiotics. By challenging them at a certain time with a ground-up gut from an infected pig, it takes the guesswork out of when and how much they will be challenged naturally. Treatment is given two weeks after challenge with a variety of antimicrobials, so that the challenge stimulates natural immunity and the treatment then clears the infection. As a result you have an immune pig, which will go through finishing fully protected.

Medication and control

Again, as immunity is considered an important factor in the control of the disease, antimicrobial treatment at the time the lesions are developing (2-3 weeks after exposure/infection) along with the pig's own immunity developing (approximately 50% should be seropositive) has become an established method of long-term control, through to slaughter.

Ileitis is a self-limiting infection, where the slow development of immunity leads to the elimination of infection, the decline in the inflammatory/proliferative process and ultimately lesion resolution. Medication with therapeutic drugs hastens this process and by timely application, reduces the cell damage and inflammatory response, while maintaining the immune response, returning the pigs to normal growth and FCE more quickly. Early treatment however can delay or stop immunity developing, so that once the drug has been removed, they are open to further challenge and disease. Getting the balance right is difficult and depends on previous medication use, the contamination of the buildings that pigs are moved into (lack of cleaning between batches) and the exposure to faeces. Solid unclean floors generally increase the exposure rate in comparison to slatted floors. This uncertainty sometimes leads to prolonged use of medication or repeated pulse medication, especially in the finishers and products with a zero withdrawal period, like tylosin, are commonly used here. Serology across a finishing system can help one to determine the optimum time to medicate. In the future, this could also be important in the EU, to show that you have made a diagnosis and can justify treatment or metaphylaxis/control.

Commonly used medications

A number of antibiotic are approved in the EU for the treatment and control of ileitis (see Table 1) and these include the macrolides, tylosin and tylvalosin which are approved for use both in feed and water for the treatment of ileitis, as well as the pleuromutilin tiamulin but valnemulin only in feed. A combination of the lincosamide, lincomycin, in combination with the aminocyclitol, spectinomycin are also approved for use in water and feed. The tetracyclines, chlortetracycline and oxytetracycline, have also been used but are not necessarily specifically indicated, probably due to the age of the products. Tylosin and tiamulin have been used by injection also to treat sick pigs but are not specifically indicated.

Table 1. Medicines indicated for the treatment of ileitis in the UK

Antibiotic	Indication	Inclusion rate (ppm) - route	Dosage (mg/kg bwt)	Duration (days)
Tiamulin	Treatment	150 - feed	7.5	10-15
Tiamulin	Treatment	60 - water	8-10	3-5
Valnemulin	Treatment	75 - feed	3-4	Up to 14
Tylosin	Treatment and control	100 - feed	3-6	21
Tylosin	Prevention and control	50-100 - water	5-10	3-10
Tylvalosin	Treatment	85 - feed	4.25	10
Tylvalosin	Treatment and prevention	50 - water	5	5
Lincomycin Spectinomycin	Treatment	63 - water	10 (3.3L+6.7S)	7
Lincomycin Spectinomycin	Treatment and control	88 - feed	4.4 (2.2L+2.2S)	Up to 21

Culture of the organism is very difficult and requires the use of a suitable cell culture line, such as IEC-18 rat enterocytes or more recently McCoy cells and a micro-aerobic environment is required, probably similar to that found in the ileum and proximal colon. Only relatively few isolates have been cultured and grown in the world as a result and their intracellular Minimum Inhibitory Concentrations (iMICs) measured against a number of antibiotics (see Table 2).

Table 2. Estimated iMICs for a number of antimicrobials expressed as MIC 50, MIC 90 and range of the 20 results (10 EU and US isolates x 2 tests) (Wattanaphansak et al, 2009)

Antimicrobial	iMIC50 (µg/ml)	iMIC 90 (µg/ml)	iMIC Range (µg/ml)
Tiamulin	0.125	0.125	0.125 - 0.5
Valnemulin	0.125	0.125	0.125
Tylosin	2.0	8.0	0.25 - 32
Lincomycin	64	>128	8.0 - >128
Chlortetracycline	8.0	64	0.125 - 64

Tiamulin and a related pleuromutilin, valnemulin, showed a very high level of intracellular activity against *L. intracellularis* with iMIC 90s of 0.125µg/ml. Only one isolate in the tiamulin group showed an increased iMIC on the second passage, at 0.5µg/ml. Other antibiotics, such as tylosin seemed generally active but there was an isolate with a high iMIC whereas lincomycin demonstrated some very high iMICs with an iMIC 50 of 64µg/ml and iMIC 90 of >128µg/ml, which can probably be considered resistant. Tetracycline also demonstrated a reduced susceptibility with the iMIC 90 being recorded at 64µg/ml.

Conclusions

The incidence of *Lawsonia* infections in pigs is generally very high, worldwide. The level of disease it causes is very variable from low to quite severe in high exposure environments, where cleaning is poor and exposure to faecal contamination is high. In unmedicated herds, it may start as early as 7 weeks but generally it is seen later, probably due to medication delaying infection, until 12-14 weeks of age. In some systems like three-site production, onset may be delayed to beyond this period to 18 plus weeks and then the haemorrhagic form can be seen and can be problematic. In Europe, I think we will increasingly have to look at vaccination, when the new stricter regulations regarding antibiotic use and prevention are introduced. I cannot see the challenge vaccination/medication approach being introduced in Europe, as it is in the US but I think a reliance on antimicrobial therapy will continue to form the backbone of control, along with natural challenge and immuno-stimulation, to minimise the effects of the disease.