Porcine Proliferative Enteropathy

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Definition
Proliferative enteropathy (ileitis) is an infectious enteric disease characterized by thickening of the mucosa of the intestine due to hyperplasia of the crypt enterocytes. The disease in pigs includes several acute and chronic clinical manifestations, including proliferative hemorrhagic enteropathy and acute hemorrhagic diarrhea with sudden death of pigs close to market age, and porcine intestinal adenomatosis, a chronic mild diarrhea with reduced performance of growing pigs. Other terms used to describe this disease include necrotic enteritis, regional or terminal ileitis, garden-hose gut, and subclinical ileitis. All forms of the disease have in common the presence of proliferating crypt epithelial cells caused by an obligately intracellular bacterium, Lawsonia intracellularis. Proliferative enteropathy has been reported in various other animal species, including hamsters, horses, ferrets, foxes, rabbits, deer, some avian species, and non-human primates.

Etiology
Lawsonia intracellularis, the etiologic agent of proliferative enteropathy, is an obligately intracellular, vibroid-shaped bacterium that is found in the apical cytoplasm of infected enterocytes (Figure 1).

Figure 1: Proliferative crypt showing large numbers of curved, intracellular bacteria lining the apical cytoplasm. Warthin Starry Silver Stained section.

L. intracellularis cannot be grown on conventional, cell-free media, but can be propagated in a cell culture system using a microaerophilic atmosphere. Proliferative enteropathy has been reproduced in susceptible conventional pigs with pure cultures of L. intracellularis and with homogenates of affected intestine. Although isolates of L. intracellularis from pigs and other host species show a high degree of genetic and phylogenetic similarity, more sensitive molecular subtyping techniques suggest that the porcine isolates are distinct from those obtained from other animal species.
Epidemiology
Porcine proliferative enteropathy is worldwide in distribution and occurs in weaned pigs kept in all types of management systems. The source of infection has not been determined, though it may be endemic in certain herds. Feces from infected pigs may be the source of new infections in susceptible animals, and pig-to-pig contact is an important route of transmission. The incubation period for proliferative enteropathy is 2-3 weeks and the organism can remain viable in pig feces for 2 weeks at 5-15°C. Outbreaks have been associated with a variety of stressors, including mixing of pigs into breeding groups or transportation to new sites.

Pathogenesis
In vivo, L. intracellularis invades enterocytes and induces hyperplasia in these cells with proliferation of immature enterocytes. Crypt elongation and a reduction in the number of goblet cells are also seen; degeneration and necrosis of enterocytes and some inflammation may be present with more chronic infections. Generally, inflammation is a factor only in complicated infections and is not characteristic of the primary lesion. The mechanism by which cell proliferation is induced is unknown and may involve stimulation of an enhanced proliferative response, inhibition of maturation of the enterocytes, or interference with normal apoptotic events.

Clinical Signs
Clinical signs of the chronic form of proliferative enteropathy (porcine intestinal adenomatosis) are most commonly observed in growing pigs between 6 and 20 weeks of age. In these pigs disease is manifested by sporadic, moderate diarrhea, anorexia, wasting, and variation in growth rates. Often the signs are subclinical, with only a variation in pig performance noted. Mortality is low and most pigs recover, though there will be a reduction in average weight gain. The acute form (proliferative hemorrhagic enteropathy) occurs more commonly in young adults 4 to 12 months of age, including late finishing pigs and breeding gilts. In this form, an acute diarrhea with black, tarry, bloody feces occurs. Often, sudden death is the first sign. Mortality is high, with around half of clinically affected animals dying.

Lesions
Gross lesions of proliferative enteropathy are usually located near the ileal-cecal junction of the small intestine but can also be found in the jejunum, cecum, and proximal colon. Chronically affected pigs usually have intestines with irregular, patchy, subserosal edema. The ileal mucosa is thickened with deep folds and patches of pseudomembrane covering the mucosa (Figure 2).

As lesions progress, mucosal destruction results in necrotic debris. Hypertrophy and thickening of the muscularis mucosa may occur in surviving animals (Figure 3).
Intestines of pigs affected by the acute form of proliferative enteropathy are dilated, thickened, and turgid, with a corrugated serosal surface. Blood clots may be found in the lumen of the ileum or colon (Figure 4). Microscopically, acute and chronic forms of the disease have similar characteristics. The mucosa is composed of enlarged, branching crypts lined with immature epithelial cells. Numerous mitotic figures occurring throughout the crypt are evident, and goblet cells are decreased or absent.

![Figure 4: Gross lesions typical of the acute form of proliferative enteropathy, showing thickened, corrugated serosal surface with blood clots in the lumen of the ileum.](image)

Silver staining, specific immunostaining, or electron microscopy of affected intestinal sections reveals large numbers of intracellular *L. intracellularis* in the apical cytoplasm of the affected enterocytes. Upon recovery, the enterocytes mature, the goblet cells reappear in the crypts, and the adenomatous cells disappear from the surface.

**Diagnosis**
The difficulty of routinely culturing *L. intracellularis* has led to several alternative methods for the diagnosis of proliferative enteropathy. Confirmation of a clinical diagnosis may be obtained by demonstration of *L. intracellularis* in feces by a PCR assay using *L. intracellularis*–specific primers. However, fecal PCR analysis is not sufficiently sensitive for the diagnosis of all infections. Methods described for the serologic diagnosis of proliferative enteropathy have employed whole bacterial antigen incorporated into an indirect immunofluorescence assay or an immunoperoxidase assay. Several ELISA assays have been described incorporating differing antigen extracts. Results from serologic assays suggest that the serum antibody response to *L. intracellularis* in pigs is specific and involves IgM and IgG.

At necropsy, lesions of proliferative enteropathy must be differentiated from those of porcine circovirus type 2 infections, hemorrhagic bowel syndrome, salmonellosis, swine dysentery, and trichuriasis. Further histopathological examination of affected tissues will reveal the distinctive morphology of the proliferative lesions. Specific identification of *L. intracellularis* in the lesions is best achieved by immunohistochemical staining of fixed embedded tissues.

**Immunity**
Both humoral and cell-mediated responses are detected in the blood of affected pigs. Serum antibodies (IgG) are first detected about 2 weeks after the exposure of pigs to *L. intracellularis* and then decay to undetectable levels after recovery. Affected enterocytes contain an accumulation of intracellular IgA and intestinal lavages contain a detectable level of Lawsonia-specific IgA, suggesting that local immunity is stimulated by infection. Interferon gamma is produced by peripheral blood mononuclear cells following specific stimulation. Convalescent pigs are immune to re-infection, but the length of this immunity is unknown.

**Prevention and Control**
Both acute and chronic forms continue to be problems on high-health-status pig herds, particularly those of high-health status, and control programs must be tailored to the disease type and onset in each facility. Outbreaks may be stress-related, often following recent transportation, sorting, or commingling events. Minimum inhibitory concentrations for various antimicrobials used for the treatment or control of proliferative enteropathy have been evaluated in vitro. The macrolides (e.g., tylosin), quinoxalines (specifically carbadox) and pleuromutilins (e.g., tiamulin) were the most active, followed by the tetracyclines and lincosamides. Controlled challenge trials and field evaluations of various treatment and control measures further demonstrated that the macrolides and pleuromutilins are the most effective antibiotics. Various approaches
to medication have been used, including pulse dosing and continuous medication. The chronic form is moderated by the use of in-feed antibiotic treatment if applied prior to the peak of L. intracellularis infection. Treatment of the acute form requires the use of water-soluble and/or injectable formulations. Prevention of proliferative enteropathy is achieved by the use of an oral, modified-live vaccine (e.g., Enterisol® Ileitis), which is available worldwide. Proper vaccination has resulted in reduced clinical signs and improved growth rates. Producers should work closely with their veterinarian to properly diagnose this disease and implement an effective treatment and prevention strategy.

Further Reading
