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Overview: *Lowsonia Intracellularis* in Pig and Horse

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Authors' contributions

This work was carried out in collaboration between both authors. Authors MARP and GISP designed the study, wrote the protocol and wrote the first draft of the manuscript, managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Lowsonia intracellularis is a Gram negative, obligate intra cellular, motile, anaerobic organism which resides in apical cytoplasm of enterocytes. It is one of the economically important pathogens in current pork industry in the world. *Lowsonia intracellularis* is an important pathogen in equine, also been reported in rodents, dogs, cats, foxes, sheep, deer, hamsters, rabbits, opossums, skunks, mice, coyote deer, ferrets, ostriches, and non-human primates.

Feco-oral rout of transmission occurs common *Lowsonia intracellularis* in livestock, companion animals and wild animals under natural conditions. Shedding of the organism is commenced on 7 days of post inoculation and excretion was observed until 12 weeks in infected animals. The clinical infection is called as porcine proliferative enteropathy (PPE) or |equine proliferative enteropathy (EPE) in pigs and horses respectively. The disease is characterized by thickening of mucosae in distal small intestine and proximal part of large intestine. Hyperplasia in enterocytes were the commonest histopathological finding in infected animals. Determination of *Lowsonia intracellularis* in feaces by qPCR and serological diagnosis are practised common in swine industry. Hypoproteinemia and hypoalbuminemia were significant finding in clinical pathology around 4 weeks before the onset of clinical infection. Gross pathology, histopathology, and immunohistochemistry are used widely in confirmatory diagnosis after the post-mortem examination.

Antimicrobial therapy and vaccination are two main methodology to control the infections in pigs and

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foals. Live attenuated and killed whole cell vaccine are widely used against *Lowsonia intracellularis* in pigs. Both cell mediated and humoral immune responses are required to eliminate the organism from body of animals. Minimizing stress factors, good bio security, continue screening of herd in endemic zones, early recognition of the disease are the important strategies in minimizing the clinical emergence of *Lowsonia intracellularis.* Screening, identification and culling of infected animals are recommended as part of the programme on minimizing unnecessary health burden in the industry.

Keywords: Lowsonia intracellularis; anaerobic organism; Hypoproteinemia.

1. INTRODUCTION

Porcine proliferative enteropathy (PPE) is caused by *Lowsonia intracellularis* is considered as one of the most important infectious disease in modern pork production based on economic significance [1,2,3]. Reduction of daily weight gain is one of the common clinical sings in the pig industry with diarrhoeic infections [4,3]. *Lowsonia intracellularis* is Gram negative bacterium and reported clinical infection in number of worm blooded animals [5]. It is an obligate intra cellular, motile, anaerobic, curved organism which resides in apical cytoplasm of infected enterocytes [6,2]. In extra cellular environment away from natural host, the bacterium was shown a darting type of movement with a presence of single flagella. It is common disease in pigs and clinical infection is mostly found in growing pigs with large economical impact to the industry [7]. Reduced weight gain, mortality and high feed conversion ratio have been contributed as factors which causes economic losses in pig farming [5]. *Lowsonia intracellularis* is one of the common causes of diarrhoea in pigs [8]. Other bacterial agents also are caused a similar kind of diarrhoea in pigs such as *Escherichia coli*, *Brachyspira pilosicoli, Brachyspira hyodysenteriae,* Salmonella spp [8]. Correlation of Salmonella and *Lowsonia Intracellularis* has been shown diarrhoea in pigs [9,3]. Similarly, diarrhea with equine proliferative enteropathy has been found in foals [10,9,2] .

2. EPIDEMIOLOGY

Lowsonia intracellularis, was first reported in 1931, is primary agent for porcine proliferative enteropathy (PPE) in pigs [5] . The disease has been reported worldwide, commonly found where pig farming are found common including USA, Canada, Europe, South Africa, Australia, Brazil and Japan [5]. In equine practice, bacterium causes equine proliferative enteropathy, specially among post weaning foals and occasionally in adults [6] . In addition, the clinical infections have been reported in cats, chicken, wild rodents [11]. Furthermore, *Lowsonia intracellularis* has been also reported in dogs, foxes, sheep, deer, hamsters, rabbits, opossums, skunks, mice, coyote deer, ferrets, ostriches, and non-human primates [5,6]. Feco-oral rout was identified as way of transmission of *Lowsonia intracellularis* in livestock, companion animals and wild animals under natural conditions [5]. Furthermore, it has been thought that role of wildlife is critically important on spreading *Lowsonia intracellularis* in livestock and equine since *Lowsonia intracellularis* has been isolated and identified in fecal samples of wild rodents and wild cats in South Korea [11].

Herd prevalence was 57% in China specially intensive pig production system in the country were shown high prevalence than extensive herds [12]. Herd prevalence of |*Lowsonia intracellularis* in pigs is varied from 6.7% to 93.7% in country to country while number of animals who serologically positive per herd were varied as 0.7- 43.2% [7]. In Europe, high herd prevalence were observed in Denmark, Germany, Spain, France, The Netherlands, Ireland and UK based on qPCR [7] . Growing pigs and finishing pigs were shown significantly high herd prevalence except in Denmark where herd prevalence were high among nursery pigs [7]. In contrast, high herd prevalence were reported in finishing pigs with serological testing such as ELISA in same collection of countries [7]. Similarly, Therefore, test methodology and type of animal category may play a vital role on detection of disease prevalence in *Lowsonia intracellularis* infection in pigs. In addition, high serological herd prevalence of *Lowsonia intracellularis* was reported in equine within the rage of 11-100% in USA [11]. Importantly, presence of the organism in fecal samples are not indicated or expressed as a clinical infection in pigs. The organism is survived without a clinical infection or subclinical infection, either acute or chronic infections in pigs [7,5]. Importantly, the organisms are survived in the environment and in wild animals who inhabitant

in farm premises [5] . As an example, cottontail rabbits who found in hay barn in California with horses were observed positive for *Lowsonia intracellularis* (feces 7.5% and serum 27%) [6]. Rabbits were moved freely with foals and foal had been acquired the infection through ingestion of contaminated food [6]. The infective dose of *Lowsonia intracellularis* has been calculated as 10^5 colony forming units in pigs and the quantity has not been calculated in foals. Mice and rats have been recognized as an important source of infection in livestock being reservoir of *Lowsonia intracellularis*[6]. High reproductive rates, high level of susceptibility and identified close contact with livestock has been identified as positive points to be survived in rodents [6]). Importantly, the organisms are transmitted through faeces, reinfection therefore can be occurred through fecal contamination [6].

Some clinical isolates of *Lowsonia intracellularis* were shown species specificity on selected natural hosts [5]. The species-specific isolates were shown strong serological immune response, observed shedding of the organism for longer period than species nonspecific isolates of *Lowsonia intracellularis* [6]. Therefore, it has been discussed in the literature as host adapted organism since organism is survived more than one natural host in the environment [6]. However, natural host adaptation mechanism in *Lowsonia intracellularis* need to be investigated extensively to achieve better conclusion [6]. Rabbits were shown more susceptible for equine derived isolates while hamsters were for porcine derived isolate [6]. In summary, that can be concluded as porcine isolates are not pathogenic against rabbits and isolates from equine are not pathogenic against hamsters [5] .

Predisposing factor leading to a clinical infection caused by *Lowsonia intracellularis* in pigs has been identified as large group size, weaning stress, transportation, diet change and mixing of feed while stress of weaning, overcrowding, decline in *Lowsonia intracellularis*-specific colostrum antibodies, endoparasitism and introduction of new animals in foals [7,5,6]. *Lowsonia intracellularis* is excreted through faeces of infected animals for 12 weeks while faecal shedding is varied 17-27 days [5]. The bacterium can be survived at outside environment for 1-2 weeks at 5 to 15^0C [5] .

Size of the genome of 1.46 Mbp [5]. In contrast, high diversity of sequences was observed in isolates found in same species of natural host [11,5,6] .

2.1 Pathogenesis of *Lowsonia intracellularis* Infection in Pigs, Foals and Wild Animals

Pathogenesis of *Lowsonia intracellularis* is not well understood in animal [13]. Once the organism is entered into the gastrointestinal tract though oral ingestion, the bacterium is survived in the stomach with its enzymatic and protein mechanism [13]. The organism penetration mucous layer through single flagellum and reached to epithelial layer of the intestine. The bacterium multiply by binary fission when it enters to epithelial cell by endocytosis [13]. When epithelial cells are ruptured by exfoliation, *Lowsonia intracellularis* comes out and infect another set of epithelial cells in the intestine [13]. Host cells mitosis is also used in propagation of bacterium and macrophages also shown a role on dissemination of *Lowsonia intracellularis* in intestine [13]. The survival of the organism in polyphagosome were shown in Lowsonia intracellularis while it has been reported in other bacteria species such as *Rhodococcus equi* and *Coxiella burnetti*. It is believed that organism has high affinity on cell with high mitogenic potential such as intestinal crypt cells, both immature and undifferentiated cells are affected by bacterium [13].

Hyperplasia of enterocytes were common histopathological finding in *Lowsonia intracellularis* infection both in pigs and foals [5,6]. Under experimental condition, establishment of intestinal infection occurred within 3-5 days post inoculation and gross pathological changes appeared in 11-15 days of post infections in pigs [5]. The pathological changes were remained persisted for additional 14 days in intestine of pigs [5]. Diarrhoea were shown 7 days post infection and remained for 21 days in pigs [5]. In histopathological finding suggested that bacterium was shown in small intestine and large intestine until 28 post infection [5]. In addition, excretion of the organism was commenced 7 days post infection till 12 weeks [5]. Therefore, possibility of rapid horizontal transmission of the disease in high in an infected herd. Molecular pathogenesis of *Lowsonia intracellularis* has not been understood thoroughly while individual steps on pathogenesis such as adherence to the host cells, propagation of the organism , mortification

of host cells, spread of bacterium to adjacent cells are not known [5].

2.2 Clinical Disease In Pigs

The clinical condition is called as porcine proliferative enteropathy (PPE) or "ileitis" and characterized by thickening of mucosae of distal small intestine and large intestine [5]. Two main form of diseases were reported in pigs by *Lowsonia intracellularis*. The chronic form is called as proliferative enteropathy and commonly found in less than 4 months of age of pigs [5]. Inversely, acute form of haemorrhagic enteritis is noticed in more than 4 months of age [5]. Sudden death and diarrhoea were common in acute infection in mature pigs [5]. Acute diarrhoea was a characteristic of the disease with black tarry faeces, the condition can be progressed to watery diarrhoea with frank blood clots [5]. Dark and tarry coloured diarrhoea is often complained in pig farming, Europe and North America with *Lowsonia intracellularis* [14]. Sub clinical infection were the most common clinical picture pig industry with variation of sizes [5]. Weight gain can be used as early diagnostic tool of subclinical infection in pigs and continue monitoring weight is strongly recommended in endemic pig herd for *Lowsonia intracellularis* [5]. PPE is mostly associated with other diseases and coinfection with viral and bacterial agent are quite common such as porcine Circo virus type 2, *Mycoplasma hyopneumoniae* respectively [14] . Importantly, The organism can be found in macrophages in lamina propria even when organism has been cleared off in epithelial cells in the intestine [5].

2.3 Clinical Disease in Foals

This is a seasonal disease in North America among 4-7 months old weaning foals, usually the disease is reported in Fall from August to January [6] . The disease is occurred in young foals occasionally. Lethargy, fever, anorexia, peripheral oedema, weight loss, colic and diarrhoea had been observed as common clinical sings [15,16,6,17]. Clinical pathological finding such as hypoproteinemia and hypoalbuminemia are an important tool to diagnose clinical infection in equine proliferative enteropathy (EPE) [6].

Lowsonia intracellularis causes thickening of enterocytes in small intestine and large intestine [5,6]. Thickening is also called as "hose line thickening" while lesion were common in 60 cm proximal to the ileocecal valve and first one third of proximal colon [5]. Although thickening of mucosae was considered as a common finding while differentiation and identification of the causative agent is quite challenging only through gross pathology [5,6]. Ileum mucosa are thickening with deep folds. Irregular patchy sub serosal oedema was shown in intestine [6] .

In histopathology, the lesions were found common in ileum and ileocecal junction of intestine [5]. Adenomatous proliferation was observed among epithelial cells in crypt of intestine, cytoplasm of enterocytes was shown curved and intra cellular bacteria are found in apical surface of enterocytes in EPE [6]. Hyperplasia of crypt glands with increased mitotic figures and reduced goblet cells were shown common in examined histopathological slides [6].

3. DIAGNOSIS AND LABORATORY CONFIRMATION

The clinical diagnosis is followed by laboratory confirmation is routine practised in veterinary medicine which is almost same in detection of clinical infection of *Lowsonia intracellularis*. Isolation and identification of *Lowsonia intracellularis* in fecal samples by qPCR and serological diagnosis such as ELISA, are found common in diagnosis of *Lowsonia intracellularis* infections in pigs [5]. Gross pathology, histopathology, and immunohistochemistry are used widely in confirmatory diagnosis of *Lowsonia intracellularis* in post-mortem examination of pigs [5] . Number of serological assays has been developed and optimized as indirect fluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA), immunoperoxidase monolayer assay and this test has been validated for pigs [5] .

In equine practice, additional diagnostic tests are used common as confirmatory tests such as abdominal ultrasonography and clinical pathology [6]. Isolation and identification of *Lowsonia intracellularis* in infected fecal sample by qPCR was considered as highly sensitive tool in swine and equine [5,6]. Immunohisto-chemistry with antibodies against *Lowsonia intracellularis* was considered as gold standard of histopathology in diagnosis of equine proliferative enteropathy.

Lowsonia intracellularis is acid fast organism and this technique is used common in histopathology

[6]. Combination of molecular and serological techniques have been shown success in identification of causative agent as *Lowsonia intracellularis* [5,6] . Furthermore, application of two or more tests to identify the organism would increase specificity of diagnosis.

3.1 Treatment on *Lowsonia intracellularis*

Antimicrobials are used common against *Lowsonia intracellularis* infection caused by in pigs. Penicillin, erythromycin, difloxacin, virginiamycin, chlorofluorocarbon, tiamutine, tilmicosin were categorized and identified as antimicrobial with the highest susceptibility against *Lowsonia intracellularis* [5]. In addition, tiamutin, tylosin, tetracycline, lincomycin and quinoxaline had been used for prophylaxis purpose for long time in swine farming [5]. However, prophylaxis application of antimicrobials are no more practised and such practices are discouraged strongly due to emergence of antimicrobial resistance in livestock around the world.

Antimicrobial therapy is recommended on treating EPE with more than 93% prognosis [6]. The prognosis depends upon stage of diagnosis, and ongoing polymicrobial infections observed. Chronic infection and complicated clinical cases in foals were shown poor clinical success [6]. Although there is a possibility to use limited antimicrobials, the selection of right antimicrobial is a veterinarian decision which based on number of factors such as severity of infection, dehydration, withdrawal period, government regulations, effect to other systems and other polymicrobial complication [6]. A class of macrolide can be used alone or combination with rifampin, chloramphenicol, oxytetracycline, doxycycline or minocycline in horses [6]. Minimum disturbance into gastrointestinal microflora and renal toxicity is considered in equine practiced [6] .

3.2 Vaccination against *Lowsonia intracellularis*

Both live attenuated and killed vaccine are commercially available to prevent *Lowsonia intracellularis* in pigs [5,18] . Both cell mediated and humoral immune responses are shown to be effective at post vaccination either by live attenuated or killed vaccine [5]. Vaccination with live attenuated vaccine is practised with success in European Union as an oral vaccine and fatteners are vaccinated at 3 weeks of age [14] . Application of live vaccine (Enterosol ileitis^{R}) were achieved high meat yield with significantly high live weight and daily weight gain in Finland [18]. The advantages of live vaccine were pointed out as possibility of oral administration with drinking water/ drench/ liquid feed base, which is cost effective methods of vaccination and additional labour resources are not required. No proven interference with maternal antibodies against *Lowsonia intracellularis* is the second advantage of live attenuated vaccine [5]. Similarly, induced immune response by vaccine strain were shown difference from induced immunity by pathogenic strain of *Lowsonia intracellularis* from clinical infections [5]. This is a common phenomenon in life science and always high immune response are observed in an infection than vaccination. Although no inter-reference were reported live attenuated vaccine, effect of killed vaccines on maternal antibodies has not been thoroughly investigated in *Lowsonia intracellularis*. Mean while, oral and intra peritoneal rout of vaccination were shown better IgA response than intramuscular route no different immune responses were observed in IgG [5]. Incompatibility with commonly used other vaccines given at same age such as Circo viral infection and *Mycoplasma hyopneumoniea* is considered as negative factor on application of live attenuated vaccine in pigs [5]. Lack of compatibility to the concurrent antimicrobial therapy is also been considered as negative effect of live attenuated vaccine against Lowsonia *intracellularis* in pigs [14]. However, killed vaccine were shown satisfactory compatibility with other commonly used vaccines at same age in swine industry (Ex: Porcilis Lowsonia) [5]. The killed vaccine consists of freeze-dried antigen fraction and solvent fraction containing an adjuvant [5]. A single dose of intramuscular administration was sufficient to develop an adequate protection against *Lowsonia intracellularis* in pigs [14]. According to the Jacobs et al. [14], protection efficacy was high in inactivated vaccine comparing to live attenuated vaccine in pigs. In theory, live attenuated vaccine induces an innate immune response which is vital and prevent mucosal infection against microbes such as *Lowsonia intracellularis*. However, recent finding by Jacobs et al. [14] has shown that both live and killed vaccine of *Lowsonia intracellularis* were shown 16 weeks of protection efficacy of post vaccination [14]. The killed vaccine was observed with low clinical scores, improved weight gain, reduced shedding of the organism and reduction of damaged to ilieum by *Lowsonia intracellularis* in pigs [14].

3.3 Prevention of *Lowsonia intracellularis* in Pig Farming

Minimizing stress factors in management has been recognized as main methodology of reducing clinical infections mainly in swine and equine practices [14]. In addition, good biosecurity, continue screening of herd in endemic zones, early recognition of the disease is considered as important strategies in minimizing *Lowsonia intracellularis* infection in pigs [14]. Under the biosecurity measurement, rodents' control, pest control and proper disposing of fecal material is highly recommended to minimize feco-oral transmission [14]. In foals, continue monitoring of clinical pathology is vital since clinical pathological changes such as hypoproteinemia and hypoalbuminemia are shown significant around 4 weeks before the onset of clinical infection [14]. Disinfectant such as Quaternary ammonium compounds, aldehydes, oxidizing agents, biguanides, phenol, iodine, chlorine, potassium peroximonosulfate, phosphate compounds, sulfate compounds inactivate *Lowsonia intracellularis* [5]. However, minimum contamination time at least 10-30 minutes is required for high accuracy. Water hardness and presence of organic material may interfere inactivation process of disinfectants [5].

The feed grade antimicrobial has been banned in most of the countries including in Sri Lanka. Several commercial vaccines are found to minimize clinical losses in livestock industry [14]. In addition, vaccination is practiced in endemic equine farms with various degree of success. Rectal administration of live vaccine was shown better results in foals, specially in endemic region of *Lowsonia intracellularis* . Application of feed additive such as probiotic and prebiotic have been practiced in feed farming with good proven result for *Lowsonia intracellularis* infection in pigs [5]. However, understanding gut microbiome of pigs and extensive study on diversity of microbiome may have beneficial effect on control most of enteric disease cased by microbes [19].

Lowsonia intracellularis has not been reported in pig or horse, Sri Lanka and clinical disease has not been suspected both these animal species in the country. Comparatively low number of pig farms, low density, availability of few numbers of horses can be considered as positive factors on not detecting the organism in the country. In addition, lack of standard screening programme targeting on possible pathogen such as *Lowsonia Intracellularis* needs to be implemented.

4. CONCLUSION

Lowsonia intracellularis is an important pathogen in swine and equine although the organism has been isolated and identified in wide host range. Being intestinal inhabitants, feco oral route is the main methods of transmission in pigs and horses. *Lowsonia intracellularis* is emerging pathogen in swine and equine while very few studies have done in developing world. Antimicrobial therapy and vaccination have been recognized as the method of controlling the disease in animals. Minimizing stress factors, good biosecurity, continue screening of herd in endemic zones, early recognition of the disease are the important strategies in minimizing the clinical emergence of *Lowsonia intracellularis*

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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