How to Diagnose and Treat *Lawsonia intracellularis*

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1. Introduction

Proliferative enteropathy (PE) caused by *Lawsonia intracellularis* has emerged as a significant equine pathogen in recent years. Early diagnosis of this disease allows prompt initiation of appropriate therapy to help decrease the severity of this disease. *Lawsonia intracellularis* is an obligate intracellular, gram-negative, curve-shaped bacteria. In pigs, the organism results in lesions in the lower ileum and sometimes, the large intestine. Edema occurs in the serosal layer of the intestine, which results in the necrosis and mucosal thickening. Crypt cells expand and elongate, and the bacteria is usually seen in the apical cytoplasm of these cells. Mitotic cells are abundant, whereas inflammatory cells and goblet cells are reduced or absent. The junction between normal and abnormal tissue is clearly demarcated. Affected areas usually involve the epithelial layer but not the lamina propria or muscularis mucosae; however, these deeper layers may occasionally be affected. Immature animals around weaning age are most often affected. Affected older animals are more likely to have PE with intestinal hemorrhage. In these cases, the mucosal thickening is not as apparent. Additionally, congestion of the mucosal blood vessels occurs, and inflammatory cells are consistently present in the lamina propria. 

As in the pig, *L. intracellularis* in the horse affects the crypt cells. This causes increased mitosis and thus, ileal mucosal hyperplasia. The lack of normal crypt cells and therefore, lack of a functional brush border eventually leads to intestinal malabsorption and associated clinical findings. 

Like the pig, affected horses are most often weanlings <6–7 mo of age. The stress of weaning and other procedures that are done at several months of age (deworming, vaccinations, training, and increased population density) may contribute to the increased incidence in this age group. A decline in maternal antibodies around this age may also increase susceptibility to the organism in these young animals. Also, environmental or seasonal factors cannot be ruled out. 

The method of infection and transmission of the disease in the horse is still largely unknown, although the fecal-oral route is probable. The main source of the disease in pigs is the mixing of chronic carriers with naïve pigs. This seems less likely with the horse, because, unlike the pig and the hamster, clinical equine cases usually occur as isolated cases or a few sporadic cases on a farm as opposed to a herd outbreak. However, three herd outbreaks have been described in Canada, and...
Hagyard Equine Medical Institute had six farms with multiple confirmed cases during the past 2 yr.

2. Materials and Methods

Diagnosis

Presumptive diagnosis of *L. intracellularis* can be made based on clinical signs, hypoalbuminemia, ultrasonographic examination, and ruling out of other possible causes of enteritis and hypoproteinemia in the horse. This early diagnosis, based on the above findings, allows immediate initiation of treatment and may result in a better outcome for the animal.

Clinical signs range from mild to severe and include weight loss, rough hair coat, diarrhea, ventral edema, pot-belly appearance, and poor body condition. The most profound clinicopathologic finding is hypoproteinemia, specifically hypoalbuminemia. Other abnormalities are secondary to the albumin loss and inflammation and include hyperfibrinogenemia, pre-renal azotemia, metabolic acidosis, and electrolyte imbalances. The white cell count is variable and may be increased, normal, or decreased. Neutrophils often have toxic changes with a left shift. Increased levels of creatine kinase have also been reported. Clinically, abdominal ultrasound is useful in suggesting a diagnosis of *L. intracellularis*. The hyperplasia of the intestine often causes a grossly thickened small intestine and/or colon, which can be visualized by ultrasound as seen in Figure 1. Mural thickness >4–5 mm is consistent with intestinal thickening.

The clinical signs result from the *L. intracellularis*-induced protein-losing enteropathy. Other causes of hypoproteinemia may present with a similar clinical picture. Differential diagnoses to consider in these horses include parasitism such as encysted cyathostomes, infectious agents such as *Salmonella*, *Clostridium*, or rotavirus, inflammatory bowel disease, and gastrointestinal ulceration. Other rare causes of hypoproteinemia include glomerular disease, terminal liver disease, and severe malnutrition.

Definitive diagnosis is made using polymerase chain reaction (PCR) of a fecal sample or serology. PCR is an excellent method for determining the presence of the organism antemortem. This test is considered very specific, however, sensitivity is questionable, and false-negative results are possible. Results may be affected if treatment has been initiated before the sample is collected. Serology, using immunoperoxidase monolayer assay (IPMA), confirms the presence of antibodies to *L. intracellularis* and is a more reliable indicator of active or recent infection. Titers >1:60 are considered significant. In pigs, serology is considered a superior diagnostic modality based on higher sensitivity (90% for serology compared with 39% for PCR), but this has not been proven in the equine.

Other diagnostic methods for *L. intracellularis* have less significance in the antemortem case. Warthin-Starry silver stain of affected intestinal tissue is an excellent diagnostic tool at post-mortem examination. Unless a sample of intestine was obtained during an exploratory laparotomy, this test has limited use in the clinical case. Although rectal biopsies can be performed, the tissue obtained may not harbor the organism, even if the organism is present in the colon or small intestine. The same is true for duodenal biopsies obtained through gastric endoscopy.

The organism can be visualized through electron microscopy, but most laboratories do not have this capability; again, this would be less useful in the antemortem case. Culture of the organism from a fecal sample is difficult and not routinely performed, because the organism requires enterocyte cell cultures for replication.

Treatment

The goals of treatment are elimination of the bacteria and supportive care. Elimination of the bacteria requires an antibiotic with good intracellular penetration. The literature suggests erythromycin, either alone or in conjunction with rifampin, tetracycline, penicillin, enrofloxacin, ampicillin, or metronidazole, may be effective against *L. intracellularis*. Erythromycin should be used with caution in older horses (post-weaning), because it can actually cause or exacerbate enterocolitis. Although penicillin and ampicillin achieve intracellular levels, the gram-positive spectrum may make these drugs less effective than an antibiotic with a better gram-negative spectrum. Our recent clinical experiences suggest the use of metronidazole (10–15 mg/kg, q 8 h–q 12 h, PO) combined with either oxytetracycline (10–18 mg/kg, q 24 h, slow IV infusion) or chloramphenicol (44 mg/kg, q 6 h–q 8 h, PO). Because oxytetracycline can be nephrotoxic, kidney function should be monitored closely in ani-
mals treated with this antibiotic, especially because affected animals often present with azotemia. Also, because oxytetracycline is predominately bound to albumin, hypoalbuminemia will result in increased levels of circulating free drug, which can cause an increased potentiality for nephrotoxicity. Slow IV infusion of oxytetracycline should be used to avoid chelating calcium and causing cardiovascular complications. Care should be taken if using chloramphenicol to avoid human contact because of the risk of idiosyncratic aplastic anemia. Other antimicrobials recently being used to treat *L. intracellularis* include doxycycline (10 mg/kg, q 12 h, PO)\textsuperscript{10} and clarithromycin (7.5 mg/kg, q 12 h, PO).\textsuperscript{10}

Corticosteroid therapy has not been advocated because of the lack of an inflammatory component on histological examination of affected tissue at necropsy. Examination of post-mortem cases at the University of Kentucky Disease and Diagnostic Center suggested that only *L. intracellularis* cases with secondary complications exhibited an inflammatory response in the gastrointestinal tract.

Supportive care consists of IV fluids to correct dehydration, electrolyte abnormalities, and azotemia. Affected animals often exhibit metabolic acidosis because of the loss of bicarbonate to the intestinal tract. These animals may require either IV or oral supplemental bicarbonate. Because of fluid losses to the intestinal tract, horses are often dehydrated, which may lead to azotemia. Thus, close monitoring of the creatinine and blood urea nitrogen is required.

Colloidal support is often the most important component of treatment because of the profound loss of albumin. Plasma transfusions are often required to stabilize plasma oncotic pressure by providing albumin. Hydroxyethyl starch (10 ml/kg, q 24 h–q 48 h)\textsuperscript{10} is a synthetic colloid that also aids in maintaining colloid oncotic pressure and reducing peripheral and intestinal edema.\textsuperscript{11} It may be used alone or in conjunction with plasma transfusions as states above.

Partial or total parenteral nutrition (TPN) consisting of amino acids and dextrose, with or without lipids, may be required if the animal is weak and/or anorexic. If TPN is not available, then IV fluids with dextrose supplementation can be used.

3. Results

The medical records of 57 horses that had been diagnosed with *L. intracellularis* at Hagyard Equine Medical Institute between September 2005 and January 2007 were reviewed. Definitive diagnosis was based on the presence of clinical signs in conjunction with a serum titer to *L. intracellularis* >1:60 and/or a positive PCR.

The most significant clinical sign in horses examined at Hagyard’s was ventral edema (46 of 57 horses) followed by diarrhea (15 of 57 horses), fever (11 of 57 horses), and colic (4 of 57 horses).

The only consistent clinicopathologic abnormality was hypoalbuminemia. Of the 53 horses that had albumin levels, all had hypoalbuminemia. The majority (42 of 57 horses) had albumin levels <2.0 mg/dl (reference range = 3.4–4.1 mg/dl). White blood-cell counts and plasma-fibrinogen concentrations were not reliable indicators of *L. intracellularis* infection in these cases. Of the 55 horses that had white blood cell counts available, 25 had leukocytosis, 3 had leukopenia, and 27 had a normal total white cell count. Of the 51 horses with fibrinogen levels available, only 13 had hyperfibrinogenemia.

The majority of horses responded well to treatment, and 53 of the 57 horses studied survived. Initial antibiotic treatment of horses included oxytetracycline (41 of 57 horses), chloramphenicol (12 of 57 horses), or clarithromycin (4 of 57 horses). Duration of treatment was variable. The four horses that did not survive were treated the same as the 53 horses that did survive. One horse was euthanized based on a poor prognosis, and two horses had secondary complications from Salmonellloses and subsequently died. The fourth horse that died had been sick for 1 wk before treatment was initiated and had presented in a grievous condition.

4. Discussion

*L. intracellularis* has emerged as a significant equine pathogen in recent years. Presumptive diagnosis and subsequent early initiation of treatment can be done in horses with typical signalment, clinical signs, and clinicopathologic abnormalities. Older foals, weanlings, and yearlings with profound hypoalbuminemia and ventral edema that present in the fall or winter should be considered suspect for *L. intracellularis*. Treatment with an appropriate antibiotic such as oxytetracycline, doxycycline, chloramphenicol, erythromycin, azithromycin, clarithromycin, and/or metronidazole can be initiated while waiting for definitive diagnosis. Definitive diagnosis is based on a positive fecal PCR or a serum titer >1:60. This early diagnosis and treatment will result in faster resolution from the disease.

References and Footnotes