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L. intracellularis Research Review

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Researchers around the world are always working to better understand a bevy of horse health problems. And while moving forward is the ultimate goal, sometimes it pays to look back at what previous research has revealed.

During his recent PhD defense seminar at the University of Kentucky, Allen Page, DVM, presented a review of *Lawsonia intracellularis*, described his research on the bacterium, described its seroprevalence in a horse population, and characterized factors that could contribute to equine proliferative enteropathy (EPE) infection development.

Background

L. intracellularis is an obligate intracellular bacterium that causes proliferative enteropathies (a spreading disease of the intestines) in a variety of species—including horses. In horses, EPE typically affects weanlings aged 4 to 7 months.

Page said EPE's etiology remains largely unknown; however, researchers believe it has a fecal-oral route of transmission and that bacteria shedding halts within four to five days of treatment commencing. Additionally, he said, veterinarians often see signs of seroconversion (production of detectable antibodies) and exposure to bacteria in the fall before seroconversion trails off during the winter months.

L. intracellularis infections cause diarrhea, depression, fever, inappetence (anorexia), weight loss, edema (fluid swelling) on the abdomen or lower limbs, a poor hair coat, and intermittent colic due to thickening of mucosal lining in the small and large intestine. Additionally, Page noted, the disease causes significant economic concern in the Thoroughbred industry: Smaller foals, due to reduced daily weight gain and weight loss, tend to bring lower prices at auction.

Page said veterinarians can use several tests to diagnose EPE, including:

- An immunoperoxidase monolayer assay (IPMA, commonly used to test swine for EPE);
- An enzyme-linked immunosorbent assay (ELISA);
- Fecal polymerase chain reaction (commonly known as PCR), which Page said has a high specificity, but variable sensitivity;
- Total protein and albumin concentrations;
- Abdominal ultrasound; and
- Post-mortem exam, which remains the gold standard, Page said.

Fortunately, many horses with EPE recover with treatment. Current treatment options include antimicrobial medication administration, supportive care, intravenous fluid and colloid administration, and plasma transfusions.

Page said researchers are still working to understand exactly why *L. intracellularis* causes problems far more frequently in weanlings than other age groups. Some theories include:

- A decline in maternal antibodies resulting from weaning;
- Post-weaning management changes;
- Internal parasite infections; and
- Poor or immature infection response.

Additionally, researchers are still working to understand several other things about *L. intracellularis* and EPE:

- What are the roles of interferon-gamma (IFN γ , a specific inflammatory mediator) and macrophages (specialized white blood cells that kill and "clean up" damaged tissue and cells) in EPE?
- Why are so many horses exposed to *L. intracellularis*, but so few develop clinical infections?
- Why are there such drastic farm-to-farm differences in infection rates?
- What protective mechanisms do horses have against EPE?

Finally, Page offered his hypotheses regarding some of the questions that remain surrounding *L. intracellularis* and EPE:

- Horses residing at farms with a history of EPE have a greater risk of developing disease than foals residing at farms with no EPE history.
- Passively acquired antibodies (those the foal receives from his dam) do not have an effect on disease susceptibility.
- Mares do not play a role in the epidemiology of EPE on endemic farms.
- IFN γ production in response to *L. intracellularis* challenge is associated with resistance to the development of EPE.

Developing a Challenge Model

When Page began studying EPE, relatively little was known about the disease. One of his first accomplishments was developing a challenge model, which would allow veterinarians and researchers to study EPE in a controlled manner.

Page and his mentor, David Horohov, PhD, [designed a challenge model](#) whereby they administered *L. intracellularis*, isolated from a previous case of EPE, to six weanlings through a nasogastric tube. The team monitored the challenged weanlings daily for signs of EPE and collected fecal and blood samples for analysis at regular intervals. They also performed weekly ultrasounds to check for thickening of the intestinal walls, and they weighed the foals on a weekly basis. At the end of the study the group performed a necropsy on each of the weanlings, examining the small intestine for signs of *L. intracellularis* infection since this is where the bacteria typically infect the horse.

Of the six weanlings challenged with *L. intracellularis*, four contracted forms of EPE based on analysis of all of the data collected during the study. Page added that one of the foals was affected subclinically (the horse did not show any outward clinical signs of disease). The remaining two weanlings showed no signs of EPE, which is consistent with real-world cases where weanlings are exposed to the *L. intracellularis* but never develop EPE.

Validating an ELISA Test

Next, Page turned his attention to making it easier for veterinarians to accurately diagnose EPE. He and a team of researchers [developed a modified ELISA test](#) that detects antibodies to *L. intracellularis*—an easy-to-perform serologic assay able to detect the antibodies and, thus, *L. intracellularis* exposure. Using this test, the team evaluated the seroprevalence (the frequency of individuals in a population that have a particular element in their blood serum) of *L. intracellularis* among 337 Thoroughbred foals and weanlings residing on 25 Central Kentucky farms.

Page and his colleagues found an overall seroprevalence of 68%, with levels on individual farms ranging from 14-100%. Additionally, Page and colleagues found that all farm populations had evidence of *L. intracellularis* exposure, regardless of whether they had found previous cases of EPE. On average, the *L. intracellularis* seroprevalence was significantly lower on farms with no history of EPE cases than on those with confirmed or suspected EPE cases; and horses residing on farms with no history of EPE cases tended to have lower *L. intracellularis* antibody levels.

Role of Passively Acquired Antibodies

Next, Page described recent research surrounding the role of passively acquired antibodies in infection and immunity to *L. intracellularis*. His hypothesis was that these antibodies wouldn't affect a foal's immunity to the bacterium.

During the 2012 foaling season, Page and colleagues collected whole blood samples from mares and foals on 15 Central Kentucky Thoroughbred farms within 48 hours of parturition. They collected additional samples from the same foals on a monthly basis through February 2013 for analysis using their ELISA .

Page said the team classified all the horses as presumptive EPE, suspect *L. intracellularis* infection, seropositive, or seronegative. Some key findings from the recent study include:

- Of the 453 horses tested, 200 mares and 172 foals were seropositive at the time of parturition.
 - The overall seroprevalence was 56.4%, while farm-specific seroprevalences ranged from 11-80%.
 - By the time the foals reached two months of age, no *L. intracellularis* antibodies could be detected in their blood.
 - The team classified 11 horses as having "presumptive EPE" and 13 foals as having "suspect *L. intracellularis*" infections.
 - When it came to total protein and albumin levels, the presumptive EPE group had the lowest level of all groups, while there was no difference in the levels between the seropositive and seronegative groups.
 - There was a significant difference between age at weaning between seronegative and seropositive horses; the former group was weaned at 152 days old, on average, while the latter group was weaned at 144 days old, on average.
 - Colts were 5.3 times more likely to develop presumptive EPE than fillies.
 - Foals previously treated for a *Rhodococcus equi* infection were more likely to develop presumptive EPE than foals not treated for infections.
 - Foals weaned after August were less likely to develop presumptive EPE cases than foals weaned earlier.
- The team also made an interesting discovery regarding where the farms were located and what month had the greatest number of seropositive foals, Page said: Farms located in northern Fayette County had more seropositive foals in October; farms in Bourbon County and Jessamine County had the most seropositive foals in January; and farms in western Fayette and western Woodford counties had the most seropositives in November and December. Page said it isn't clear why this geographic separation occurs, but he's hoping to "get to the bottom of this."

The team has opted to continue the study for another year, and additional results should be available mid-2014.

Mares' Role in Epidemiology

Page also recently completed research focusing on whether mares play a role in disease development in foals. He and colleagues collected whole blood from 95 mares and 91 foals residing on one endemic farm within 48 hours of parturition and then every four weeks. They found that 42 mares were seropositive at parturition, and mares that were seropositive for more than five months through October had foals that were 5.667 times more likely to be seropositive between July and January compared to those mares with less than five months of seropositivity.

Other data demonstrated that nursing foals failed to seroconvert as a result of exposure to the bacterium during the same time period that their mares did, suggesting that mares may protect nursing foals from exposure. Based on the data he presented, however, we "can't rule out mares as playing a role in *Lawsonia* spread."

Future Research

Although Page and other researchers have made great strides in understanding *L. intracellularis* and EPE, there is still much to learn. Page said future research that would benefit the collective understanding includes challenge nursing and early weaned foals to see if mares provide protection, an assessment of risk factors and exam for reasons for geographic differences in seroconversion, and the use of recombinant proteins to identify antibody responses associated with EPE.