Porcine Pleuropneumoniae (Actinobacillus pleuropneumoniae, APP, Haemophilus pleuropneumoniae, HPP) – Pork Industry Handbook

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pork industry handbook

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Porcine Infectious Pleuropneumonia

(*Actinobacillus pleuropneumoniae*, App)

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Infectious porcine pleuropneumonia, caused by the bacteria *Actinobacillus pleuropneumoniae* (App), occurs throughout the world and in some cases can be a significant barrier to profitable pork production. On a herd basis, infection with at least one serotype of App is common and sporadic outbreaks of overt clinical disease, including frequent deaths, occur under the correct circumstances. App has been responsible for the depopulation of numerous herds, and its control was one of the motivations behind the development of early weaning and segregated rearing systems. Pigs (particularly sows and boars) are the major reservoirs of App within a herd. Introduction of clinically healthy infected replacement stock colonized with App are responsible for most of the transmission between herds.

Overt disease outbreaks of App may cause substantial economic losses because of deaths, treatment costs, and loss of performance (reduce daily gains and feed conversion rates). Vaccines are generally of limited value in the prevention and control of App. Preventing the introduction of App and the reliable control of disease outbreaks in infected herds requires the development and application of a well-planned and faithfully implemented health management system. To be effective, this approach must be based on an understanding of the various risk factors that contribute to the introduction and maintenance of App within herd, its transmission between various production stages, as well as the health and environmental factors that contribute to the occurrence of clinical disease.

Epidemiology and Mechanism of Disease

There are gaps in understanding how App causes disease as well as what combination of factors determine whether infection results in clinically apparent disease or merely colonization. On the other hand, there are a number of things that are well understood that are of value in the diagnosis, treatment, and prevention of App infection and disease.

Experimental evidence as well as characteristics of some disease outbreaks demonstrates that the ability of App to cause disease is dependent on the number of microorganisms the pig inhales, which under production conditions is related to the concentration of App in the environment/airspace. This dramatic dose-response relation between the number of App and the severity of disease means that a pig can become colonized, develop an immune response, and remain clinically healthy. A slightly higher level of exposure will result in severe clinical disease and mortality rates that can be as high as 50%.

The threshold exposure dose necessary to cause disease is reduced by concurrent infectious and stressful environmental and management conditions. The environmental load of App is influenced by the number of infected pigs that are actively shedding App which in turn relates to stocking densities, management, and environmental conditions such as humidity, air-changes, and temperature. Disease outbreaks may occur suddenly following a stressor such as rapid changes in environmental conditions or the movement or mixing of pigs. These factors are often the reason why the occurrence of App disease tends to take place at a specific stage of production or a specific location (problem barn or area within a barn). For the same reason, herds that have not suffered from clinical App disease and that are believed to be free of App, but are actually subclinically infected, can suddenly break with clinical disease following changes in production practices, environmental conditions, introduction of other diseases, or a decline in the level of App immunity within the herd.

App is unique in that it is a highly host-adapted primary respiratory pathogen that does not require defects in normal pulmonary defenses for it to cause pneumonia. This is reflected in the pathology where pulmonary lesions caused by App are

typically located in the top and back regions of the lung while the location of the pneumonia caused by bacteria that require reduced pulmonary defenses are nearly always front and bottom. It is clear that concurrent infection with a number of other microorganisms (particularly mycoplasma) increases the frequency of clinical disease in App-infected herds, perhaps by interfering with pulmonary defense mechanisms as well as by increasing the shedding rate of App carrier pigs via increased coughing.

Research over the past 20 years, particularly through the application of molecular biology, has provided a reasonable understanding of some of the virulence factors that App has which makes it a serious pathogen. App colonizes the upper respiratory track, particularly the tonsils, where it multiplies and is then inhaled into the lung resulting in pneumonia. With higher exposure doses and peracute disease, App may reach the lung directly without need to first colonizing the upper respiratory track. Once in the lung analysis demonstrates that App rapidly causes degeneration of alveolar macrophages and infiltrating neutrophils which is quickly followed by an inflammatory response. Virulence factors that have been identified include adhesions proteins, capsule, endotoxin, iron acquisition systems, and a number of toxins that activate and produce holes in the membranes of animal cells.

Under experimental conditions, the time between exposure and first clinical signs can be as little as four hours, with death occurring four hours later. In a clinical setting, it is often not possible to determine when exposure occurred but the time between first clinical signs of disease (which can be easily overlooked, see below) and death is often less than 12 hours. The rapid progress of App disease is often the most troubling to producers because when the pigs are checked at the end of the day they look healthy, only to find a large number of dead pigs first thing in the morning.

Recent advances in molecular biology plus the likelihood that the genome of App when sequenced in the near future, will undoubtedly provide answers to a number of important questions. These include the genetic basis for differences in virulence between serotypes of App, mechanisms that allow App to escape the immune system and persistently infect carrier pigs, and the characteristic of the passive immunity that prevents infection of piglets in early weaning systems. A more fundamental question is why, given the severity of the disease, are pigs the only animals that are susceptible?

Serotypes and Genotyping

There are 13 recognized serotypes of App and a number of serotype variants as well as strains that are not typeable. While all serotypes, including untypeable strains, have the potential of causing disease, some serotypes are more commonly associated with disease outbreaks. The basis for this higher degree of virulence is not completely understood but may be related to the production of more active toxins and the ability to cause disease at a lower exposure dose. Of the serotypes that most commonly occur in North America, serotypes 1 and 5 are the most virulent, followed by serotypes 7 and 3.

A number of genotyping procedures have been developed for App. These include both App specific, gene specific, and random DNA analysis methods. These procedures are particularly useful in confirming the identity of atypical App isolates, including biotype-2 strains and App-like strains. When evaluated by some procedures, the genotype of strains of the same serotype are remarkably similar which allows strains that are not serotypeable to be classified. This suggests that App strains are clonal in origin and that there is limited genetic exchange between serotypes. More stringent genotyping systems make it possible to recognize specific strains of the same serotype and conduct epidemiological investigations that track the transmission of App strains of the same serotype between herds and between different production stages within a single herd.

Clinical Signs and Necropsy Diagnosis

Infection with App and clinical disease can occur at any age, including older sows. Most clinical disease is recognized in growing-finishing pigs. The variability of clinical signs associated with App infection is much greater than is generally recognized. The most aggressive form of the disease is relatively easy to diagnose from the epidemiology and clinical signs which typically include high fever, coughing, abdominal breathing (thumping), cyanosis, bleeding from the nose, and rapid progression to death.

As the first few pigs develop disease, their coughing spreads App throughout the environment at relatively high concentrations. The disease can progress rapidly within the airspace such that up to 100% of the pigs become ill with mortality rates reaching 50%. Infection with *Actinobacillus suis* can mimic the clinical signs of an acute App outbreak. One of the key differences in *A. suis* outbreaks in finishing pigs is that morbidity is much lower (5% to 10%) but mortality can be nearly 100%.

It is important to recognize that most infections with App do not result in severe clinical disease. Following a sub-lethal level of exposure to App the clinical signs can be mild and include lameness, anorexia, lethargy, reluctance to move, and an infrequent deep non-productive cough that mimics the cough associated with mycoplasmal pneumonia. These milder clinical signs can be overlooked or confused with a number of other respiratory diseases and typically resolve without treatment in less than one week. In many cases, App infection is recognized only following serologic testing.

The gross and histopathologic lesions caused by App are helpful but should not be used to arrive at a definitive diagnosis because they can be confused with lesions caused by other bacteria, particularly *A. suis*, *Salmonella sp.*, *Haemophilus parasuis*, and secondary *Pasteurella multocida* infections following a mycoplasma or viral infection. Histological examination is particularly valuable in diagnosing concurrent infections (e.g. mycoplasma), the gross lesions of which are obscured by those caused by App. A histological lesion that is often overlooked is suppurative tonsillitis.

Classically, App lesions involve the dorsal regions of the diaphragmatic lung lobes and pleura. The lung lesions consist of one or more focal areas of severely consolidated and congested lung that is very firm and well delineated from the surrounding normal lung. The lesion may be covered by fibrinous pleuritis. Lesions may range in size from a few centimeters to involve the entire lung lobe. On a cut surface, the lesion has a meaty appearance and is composed of necrotic lung tissue and clotted blood. In terminal cases, blood-tinged foam and/or blood can be present in bronchi extending to the trachea, pulmonary septa may be thickened with edema, and mediastinal lymph nodes congested and edematous.

The lung lesions associated with App heal rapidly, leaving one or more small focal areas of interstitial fibrosis within the

lung that can be easily overlooked and pleural adhesions, neither of which is specific for App. Given the rapid rate of healing (weeks) and the nonspecific nature of the residual lesions, slaughter checks are only a reliable means of determining whether a herd is infected with App when disease occurs only a few weeks prior to slaughter.

Bacterial / Molecular Diagnosis

While a presumptive diagnosis of App can be made via the clinical and necropsy findings, it is critical to confirm the diagnosis by isolating and characterizing the causative organism. Isolation of App is important because it allows the selection of an effective antibiotic, the appropriate serologic test, and vaccines most likely to be effective.

Isolation of App is most successful when fresh tissues from acute cases are examined. Transport media does not adequately support the viability of App and other bacteria that are present in the lesion (e.g., *Pasteurella multocida*) may overgrow App when the tissue is not fresh. Large blocks of fresh lung tissue and tonsil that has been kept cold should be submitted directly to a laboratory that has experience isolating and identifying App. Attempts to isolate App from the lungs of pigs that are suspected of carrying App but do not have lung lesions have not been successful. In these cases, cultures of App from the cut surface of the tonsil have been more successful.

Confirming the identity of a suspect App isolate is generally possible using standard colony morphology and biochemical characteristics. The major difficulty relates to the differentiation of biotype 2 strains of App which do not require NAD from *A. suis*, urease negative strains of App from *H. parasuis*, as well as *A. lignieresii* and a number of App-like strains.

All App isolates should be permanently stored which will allow them to be genetically compared with subsequent isolates to see if the same strain is responsible for subsequent disease outbreaks, or whether a new strain has emerged or has been introduced into the herd. This is particularly important for App infected herds that are using segregated early weaning (SEW) systems to produce presumably App-free pigs for sale as replacement stock to other producers or as high-health status grower pigs.

A number of DNA-based molecular diagnostic techniques have been developed to improve the identification of App-infected carrier pigs, confirm the identification of App isolates, and to identify and distinguish between different strains of App of the same serotype. These assays are complex and should be preformed by experienced laboratories that have procedures in place that include the appropriate diagnostic safeguards and quality controls.

Serologic Diagnosis

Serologic testing is the cornerstone of efficient and cost effective App diagnosis, prevention, and control. This is because many App-infected pigs can appear healthy. Serologic testing is particularly helpful in assessing the relative risk of transmitting App between herds, between different production stages in the same herd, the design SEW systems that will reliably prevent transmission of App, and the value of medication and vaccination programs. Regardless of the serologic test selected, define a specific objective of the testing beforehand and sample a statistically valid percentage of pigs within the population of interest.

A number of serologic tests have been developed that detect serum antibodies to App specific antigens, including capsule, lipopolysaccharides (LPS), outer membrane proteins, and toxins. Complement fixation (CF) tests are generally not reliable because they are difficult to perform and suffer from a high degree of false-negative results. This causes them to function best in pigs that have only recently been infected. As such, a positive CF test can be trusted with a high level of confidence while a negative CF test result is of little value.

In contrast, the App ELISA (using highly purified capsule or long-chain LPS) are sensitive and specific with a false-positive and false-negative rate of approximately 3%, depending on the cut off point used by the laboratory. The ELISA are specific for each App serotype and thus may not be capable of detecting pigs that have been infected with untypeable strains or antigenic variants. In addition, vaccination with most vaccines will interfere with these assays.

The sensitivity and specificity of the toxin neutralization assay is similar to the ELISA but detects only those serotypes that produce the type-1 toxin (serotypes 1, 5, 9, 10, and 11). In addition, some but not all strains of *A. suis* produce a similar toxin that can result in false-positive results. Current vaccines do not induce toxin-neutralizing titers and, thus, do not interfere with the ability to detect vaccinated pigs that have been infected with App.

Therapy

The first response to diagnosing App disease is to begin antibiotic therapy. However, treatment failures are relatively common. Therapy for individual pigs requires the use of injectable antibiotics. A growing number of antibiotic resistant strains have been recognized and have been the basis of some treatment failures. Response to the correct antibiotic (penicillin, tiamulin, ceftiofur) can be rapid if given at an early stage of the disease, with subsequent deaths often related to dehydration and exhaustion. Feed antibiotics are not effective because App disease suppresses appetite and prevents effective plasma concentrations from being achieved.

All pigs in the airspace should be treated with injectable antibiotics for at least three days in App disease outbreaks that involve more than a few pigs. A treatment duration of 5 to 7 days may be necessary to prevent additional cases. All pigs in an affected group should be treated because of the short time between initial exposure and development of clinical disease.

Control and Prevention

The reliable control and prevention of App depends on the strategic application of basic principles of infectious disease control and prevention. Subclinical infections with App do not appear to result in significant increases in the cost of production. Healthy App-infected pigs can create a significant liability issue for herds that are selling replacement breeding stock or weaned or feeder pigs. Clinically affected pigs that recover from App disease can be very expensive to finish. In some cases, the cost of treatment and the poor performance of pigs that recover is greater than letting the disease run its course without treatment.

The first goal should be to create new herds that are App free, prevent the introduction of App into App-free herds, and prevent the introduction of another (perhaps more virulent) App strain into herds that are already infected. Pigs are the only known animal host of App and it cannot persist outside of the pig for extended periods of time. The major means of transmission of App between herds is via the introduction of App-carrier pigs.

The source herd of any replacement pigs should be rigorously tested by the most sensitive serological tests available to avoid introduction of App. Only pigs from herds where the sows are confirmed to be serologically negative from App should be accepted. In addition, a biosecurity system should be in place to prevent introduction of App by being carried between farms via people, equipment, and supplies.

Production practices and facilities-related factors are often responsible for causing App to move from a subclinical infection to overt disease in a herd. Thus, changes in management practices are often the most effective means of controlling and preventing additional App disease outbreaks in the long term. Recognized factors that increase the likelihood of clinical disease in App-infected herds include air quality, temperature (particularly rapid shifts), herd size, pig movement and commingling (particularly continuous flow production), population density, and the presence of concurrent infections. For example, in herds co-infected with App and mycoplasma, the use of mycoplasma vaccines can be sufficient to significantly reduce or prevent App-related disease.

In some cases, only relatively minor changes are necessary to avoid App disease outbreaks. Slight reduction in the pig density per pen, adding an additional day before barns are restocked, or tighter regulation of temperature variations may be sufficient to shift the infection from causing overt disease to being subclinical. However, once a herd is infected, successful control may require rather dramatic changes in production practices and the upgrading of facilities and equipment. Failing to make the necessary changes in production practices or to upgrade facilities may require that the herd be depopulated and replaced with App-free pigs.

Numerous vaccines have been developed against App. The most effective of these have not been produced commercially because of their high cost. Current vaccines may be helpful when carefully matched so the vaccine contains the same serotype of App that is causing disease within the herd. At their best, current vaccines may reduce the mortality rate but do not significantly reduce the infection rate and the development of App carriers. Vaccination of sows in the hope of increasing colostral immunity and reducing the chance of App transmission from the sow to piglet is not effective because vaccines do not adequately mimic the immunity acquired following infection. In particular, current vaccines do not induce neutralizing antibodies to the toxins produced by App which are believed to be responsible for much of the pathology. A number of modified-live App vaccines have been developed in the hope that they will confer the same degree of protection that follows recovery from infection. The general recommendation is to not rely on vaccines as a means of preventing or controlling App.

The prophylactic addition of antibiotics to feed or water to control App has occasionally been sufficient to tip the balance away from the occurrence of clinical disease. In particular, the addition of tilmicosin (Pulmotil®) as an antibiotic feed additive, has been successful in preventing clinical disease and perhaps infection because it accumulates within macrophages which aids in their ability to effectively kill App. However, tilmicosin does not eliminate App from carrier pigs. These pigs can still serve as a source of infection resulting in disease outbreaks once tilmicosin is withdrawn from the feed. Other water and feed delivered antibiotics may be helpful but generally are not a reliable means of App disease control.

The most dramatic development for reliable control of App has been the application of SEW production systems. The appropriate weaning age is dependent on the immunologic status of the sow herd. In sow herds with high antibody levels it is possible to wean at ages as old as 21 days while in sow herds with low titers or in which the gilt replacement rate is high, a younger weaning age may be necessary. Determining the correct weaning age requires serologic testing. The use of antibiotics or vaccines does not have a measurable influence on the weaning age necessary to reliably prevent App transmission between sow and piglet. It is clear that if piglets are weaned at an age prior to the time they become susceptible to being colonized with App from the sow, and raised under conditions that prevent exposure to App, it is possible to produce App-free pigs from an endemically infected sow herd.

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