PORCINE HEMAGGLUTINATING ENCEPHALOMYELITIS VIRUS

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SUMMARY

Etiology

- Porcine hemagglutinating encephalomyelitis virus (PHEV) is a single-stranded, positive-sense RNA virus in the family *Coronaviridae*, genus *Betacoronavirus*. It usually causes vomiting and wasting disease and/or encephalitis in neonatal pigs. PHEV was first identified in the early 1960s in Canada and England.
- There is a single serotype of PHEV that contains several strains. Individual strains vary in virulence, and virus course coupled with host age may determine the extent of clinical disease.

Cleaning and Disinfection

- Exposure of PHEV to 37°C (98.6°F) results in loss of infectivity over a period of three days. PHEV, like other coronaviruses (CoVs), is highly stable when frozen and at low temperatures. In winter, PHEV can survive for extended periods of time. PHEV is relatively stable at pH 3.0, losing only 20% infectivity after 24 hours. The virus may lose infectivity at alkaline pH like other CoVs. Exposure to ultraviolet light for two minutes inactivates PHEV.
- Treatment of virus with 10 mM dithiothreitol results in loss of infectivity of PHEV isolated from cultured cells. Ether treatment also renders PHEV inactive. No information exists on susceptibility of PHEV to disinfectants. Disinfectants shown to be effective against other swine CoVs include iodides, quaternary ammonium compounds, phenols, phenol plus aldehyde, beta-propiolactone, ethylenamine, formalin, sodium hydroxide, sodium hypochlorite, alcohols, and accelerated hydrogen peroxides.

Epidemiology

- PHEV infection is found nearly worldwide. Serological evidence of infection has been found in pigs throughout Europe, the Americas, Asia, and Australia.
- PHEV can be found in both farrowing and finishing herds, though clinical disease mostly occurs in very young pigs. Pig-to-pig transmission results in persistence of PHEV in large herds, where few outbreaks are seen. Small herds are more likely to experience outbreaks of PHEV due to their inability to maintain enzootic infection.
- Swine are the only species in which PHEV naturally causes clinical disease. PHEV is not known to be zoonotic and poses no public health threat to humans.

Transmission

- PHEV is transmitted by aerosols, direct nose-to-nose contact, and contaminated fomites. Virus is present in oronasal secretions of infected pigs.

Infection in Swine/Pathogenesis

- PHEV can infect naïve pigs of any age. Clinical manifestations of PHEV, including vomiting and wasting and/or encephalomyelitis, are generally seen only in piglets less than 4-weeks-of-age. In one instance, however, PHEV was linked to respiratory disease in market-aged pigs at an agricultural fair.
- PHEV replicates primarily in the upper and lower respiratory tract with some replication occurring in the small intestine. Virus then travels to the central nervous system via peripheral nerves in one of three pathways: nasal mucosa and tonsils to trigeminal ganglia and trigeminal sensory nuclei; vagal nerves to the vagal sensory nuclei in the brainstem; or intestinal nervous plexus to the spinal cord.

Diagnosis

- Virus may be isolated from nasal swabs and identified by virus neutralization, hemagglutination, immunofluorescence, or hemadsorption plaque assay following inoculation of cultured cells.
- Virus antigen identification in tissues may be performed by the fluorescent antibody test (FAT), immunofluorescence, or immunohistochemistry.
- Viral RNA may be identified by reverse transcriptase polymerase chain reaction (RT-PCR), with or without nested PCR, in single or multiplex reactions targeting the HE, S, E, M, and N genes. Quantitative RT-PCR (qRT-PCR) targeting the N gene has also been described.
- PHEV-specific antibodies may be detected by serum virus neutralization (SVN) or by hemagglutination inhibition (HI) assays.
- Anti-PHEV antibodies and PHEV antigen have both been identified using the enzyme-linked immunosorbent assay (ELISA) and a lateral flow immunochromatographic strip. Neither are available commercially for detection of antigen or antibody.

Immunity

- PHEV-neutralizing antibodies are transferred in colostrum and milk from PHEV-seropositive sows to their offspring. Passive immunity lasts from 8–18 weeks-of-age.
- Neutralizing antibodies are first detectable between 6–9 days post-infection, very soon after the development of clinical signs.
- Consistent protection from clinical disease in suckling pigs is dependent on herd endemicity.
- Two vaccines, an inactivated PHEV and a DNA vaccine, have been described in mice. No vaccines have been described for use against PHEV in swine.

Prevention and Control

- Because of the ubiquitous nature of the virus, PHEV outbreaks occur in suckling pigs in herds that are not closed, resulting in high mortality among affected piglets and a potential high economic cost.
- PHEV outbreaks are of short duration, only affecting the birth cohort of the infected piglets that are born to seronegative sows. Ensuring that gilts and sows are PHEV seropositive prior to farrowing, thereby transferring protective neutralizing antibody to their piglets, may be the best way to prevent PHEV-induced clinical disease in suckling pigs until a vaccine becomes available. Alternatively, piglets born to non-immune sows can be inoculated with specific immune serum shortly after birth.

- Implementation of strict biosecurity can prevent PHEV from being transmitted via fomites.

Gaps in Preparedness

- No PHEV vaccines are currently available.
- The current seroprevalence of PHEV in the U.S. pig population is not known.

OVERVIEW

Porcine hemagglutinating encephalomyelitis virus (PHEV) is a member of the family *Coronaviridae*, genus *Betacoronavirus*. It is a single-stranded, positive-sense RNA virus that was first identified in 1962 in suckling pigs with encephalomyelitis in Canada. Shortly thereafter, it was determined that the same virus was causing disease characterized by vomiting and wasting in England. There is a single serotype of PHEV that consists of multiple strains of varying virulence. Individual strain virulence and virus course in tissues may determine the clinical signs exhibited by infected pigs. PHEV usually causes clinical disease in pigs less than 4-weeks-of-age born to seronegative sows. Both morbidity and mortality can reach 100% in a given litter.

Swine are the only species naturally susceptible to PHEV. No other reservoirs have been demonstrated, although the virus can be experimentally adapted to mice and Wistar rats. PHEV is not known to be zoonotic and poses no threat to human health. Experiments in mice and rats have revealed the neurotropism of PHEV and its spread from the peripheral to the central nervous system (CNS).

PHEV is found nearly worldwide throughout swine-rearing countries. The current seroprevalence of PHEV in U.S. swine is unknown; however, one of the earliest PHEV reports occurred in the U.S. in 1972. The paucity of reports of clinical disease ascribed to PHEV in the United States may indicate a high prevalence of seropositivity. Large swine herds are able to maintain endemic PHEV. Piglets born to seropositive sows are protected from clinical disease by colostral antibody throughout the time frame of susceptibility. Once maternal antibody wanes, pigs are susceptible to infection via aerosols, direct contact with infected pigs, or PHEV-contaminated fomites, yielding subclinical infection and the development of active humoral immunity.

Primary replication of PHEV occurs in the respiratory tract followed by infection of peripheral nerves and subsequent spread to the CNS. Infection of the gastrointestinal tract may also occur, leading to infection of the enteric nervous system and eventually the CNS via the vagus nerve. PHEV usually causes vomiting and wasting disease and/or encephalitis. One or more of the following signs may be observed: vomiting, constipation, wasting, respiratory signs, decreased weight gain, or neurologic signs including ataxia, stiffness, hyperesthesia, and posterior paralysis. Piglets that survive may require euthanasia at a later date due to the severe wasting that can occur. A typical clinical history includes the sudden appearance of nervous signs or vomiting and wasting in a small number of litters of the same age and within a few days of birth. Especially if coupled with litters that are born 14 days later or more remaining healthy, PHEV should be high on the differential diagnosis for the herd. Pigs greater than 4-weeks-of-age typically do not show any signs of disease. However, PHEV has been linked to respiratory disease in a marked-aged pig at an agricultural fair.

Virus isolation followed by fluorescent antibody test (FAT), immunofluorescence (IF), hemagglutination (HA), or hemadsorption plaque assay is possible. Immunohistochemistry (IHC) can be used for detection in tissue samples post-mortem. Both reverse transcriptase polymerase chain reaction (RT-PCR) and quantitative RT-PCR (qRT-PCR) have been described. Target genes include the HE, S, E, M, and N genes. Nested PCR may be used after RT-PCR to further amplify subgenomic RNAs for comparison to reference samples or sequencing. Appropriate diagnostic samples include oronasal secretions, tonsil swabs, inoculated cultured cells, and post-mortem tissue samples, including upper and lower respiratory tract, tonsils, brainstem, olfactory bulb, cerebrum and cerebellum, spinal cord, stomach, and intestine. The standard assay for detecting PHEV antibody is hemagglutination inhibition (HI). Enzyme linked immunosorbent assay (ELISA) and a lateral-flow immunochromatographic strip have also been described to detect serum antibody or antigen.

Two PHEV vaccines have been described and tested in mice for immunogenicity and protection following lethal virus challenge. The killed virus vaccine was highly effective at preventing infection in mice as was a combination of a DNA vaccine encoding the spike glycoprotein and the killed virus as a booster. No vaccines have been described in swine to date.

Prevention of PHEV-induced clinical disease currently relies on maintaining a swine herd that is seropositive for PHEV. Sows protect their vulnerable offspring passively through colostral antibody and this protection lasts for the duration of the age window of susceptibility. In herds that are PHEV-negative or that do not maintain a closed population, biosecurity is of the utmost importance to protect naïve litters from PHEV disease. New gilts and sows should be tested for antibody and for active virus shedding in nasal swab samples. Piglets born to non-immune sows can be inoculated with specific immune serum shortly after birth. Future efforts should focus on developing vaccines that allow protection of sucking piglets through passive immunity and allow producers to eliminate PHEV from herds, should they choose to do so.

LITERATURE REVIEW

1. Etiology

1.1 Key Characteristics

Porcine hemagglutinating encephalomyelitis virus (PHEV) is a single-stranded, positive-sense, RNA virus in the genus *Betacoronavirus*, family *Coronaviridae*.[1] It causes vomiting, wasting, and/or encephalomyelitis in pigs. Like other coronaviruses (CoVs), PHEV is enveloped and has prominent surface glycoproteins that protrude from the membrane. PHEV has a hemagglutinin-esterase (HE) gene that is responsible for its ability to hemagglutinate red blood cells, similar to related viruses such as bovine CoV and human CoV-OC43.[2] This is unlike coronaviruses in the genus *Alphacoronavirus*, including transmissible gastroenteritis virus (TGEV),[3,4] porcine epidemic diarrhea virus (PEDV),[4,5] and novel swine enteric coronaviruses (SeCoV),[4,6-9] as well as members of the genus *Deltacoronavirus*, such as porcine deltacoronavirus (PDCoV).[4,10]

1.2 Strain Variability

There is a single serotype of PHEV, containing several strains, all of which are serologically cross-reactive.[1] Sequence variations have been documented in the NS2 and NS4.9 genes, ORF1b, the S gene, and the 3´UTR by Lorbach et al,[11] and in the HE, S, E, M, and N genes by Dong et al.[12] and Li et al.[13] However, PHEV isolates remain quite similar overall.[11-14] The clinical presentation of PHEV in swine may depend on virus strain, age of infection, and course of viral replication and spread.[15] Interestingly, at least two SeCoVs have been isolated in pigs with vomiting and diarrhea that contained sequences from PEDV within a backbone of TGEV.[7,8] No PHEV recombinant viruses have been described.

2. Cleaning and Disinfection

2.1 Survival

Exposure of PHEV to 37°C (98.6°F) results in loss of infectivity over a period of three days.[16] PHEV, like other CoVs, is highly stable when frozen and at low temperatures.[17] In winter, PHEV can survive for extended periods of time.[17] PHEV is relatively stable at pH 3.0, losing only 20% infectivity after 24 hours.[16] The virus may also lose infectivity at alkaline pH values, as do other CoVs.[1] Exposure to ultraviolet light for two minutes inactivates PHEV.[18]

2.2 Disinfection

Treatment with 10 mM dithiothreitol results in loss of infectivity in PHEV isolated from cultured cells.[19] Ether treatment also inactivates PHEV.[16] No information exists on susceptibility of PHEV to disinfectants. Disinfectants shown to be effective against other swine CoVs include iodides, quaternary ammonium compounds, phenols, phenol plus aldehyde, beta-propiolactone, ethylenamine, formalin, sodium hydroxide, sodium hypochlorite, alcohols, and accelerated hydrogen peroxides.[1,20,21]

3. Epidemiology

3.1 Species Affected

Pigs are the only species in which PHEV causes clinical disease.[1] There has been no description of natural infection in birds or rodents. Experimentally, oral inoculation of rats and guinea pigs leads to seroconversion but no virus shedding.[22] Birds inoculated orally neither shed virus nor seroconvert. PHEV can be adapted to infect, cause illness, and kill mice within 2–3 days following intracerebral inoculation, irrespective of mouse age.[23] However, when inoculated intranasally, an age-dependent susceptibility to disease occurs in mice and rats, similar to pigs.[23,24] Spread of virus from peripheral nerves to the CNS occurs in pigs and experimentally infected mice and rats.[23,25,26]

3.2 Zoonotic Potential
PHEV is not known to be zoonotic and does not pose any public health threat to humans.[1] However, up to 91% homology has been reported between PHEV and human CoV-OC43.[13] A related bovine CoV has been documented in people in contact with infected calves.[27]

3.3 Geographic Distribution
PHEV can be found in most swine-producing regions of the world, including Europe, the Americas, Asia, and Australia.[1] The earliest reports of PHEV came from Canada (1958[28] 1962[29]), England (1969),[30] and the United States (1972).[31] The virus was documented in Belgian pigs in 1972[16] and in pigs from China and Taiwan in the late 1980s and early 1990s, respectively.[32] Fatal PHEV infection was reported in pigs from Quebec in 1998.[35] More recently, an outbreak of vomiting, wasting, and encephalomyelitis was attributed to PHEV in Argentina in 2006.[36] PHEV was further diagnosed as the cause of outbreaks in South Korean pigs in 2009 and 2010,[37] and in Chinese pigs in 2011[14] and 2014.[12,13]

3.4 Morbidity and mortality
PHEV morbidity is high in infected pigs less than 4-weeks-of-age born to seronegative sows. Mortality can reach 100% in diseased piglets and those that show wasting may require euthanasia.[1,38]

Serological evidence suggests that PHEV exposure is very common in many areas. Reported seroprevalence rates have included 31% in Canada,[39] 95% in Belgium,[34] 46% in Northern Ireland,[22] 49% in England,[40] 52–82% in Japan,[41] 7–82% in Jilin Province, China,[42] and 11–99% in the United States.[43]

In 2015, PHEV was identified in a clinically ill market-aged pig at a Michigan agricultural fair using next-generation sequencing.[11] Further testing showed that nearly 39% of pigs from 14 Michigan fairs were positive for PHEV via quantitative reverse transcription polymerase chain reaction (qRT-PCR).[11] Pigs at 14 Ohio fairs and 14 Indiana fairs were also tested for PHEV, though only 4% were positive via qRT-PCR.[11]

4. Transmission
PHEV is shed in nasal secretions. The virus is transmitted by direct nose-to-nose contact, aerosols, and contaminated fomites.[1,16] Pigs of all ages are susceptible to infection and serve as the source of virus for other naïve pigs. Virus is shed as early as one day post-infection (DPI) and continues for up to 10 DPI.[22] Transmission to naïve sows who recently farrowed leads to subsequent infection of the offspring through direct contact.[22] There is no intrauterine transmission of PHEV from sow to piglet.[22]

5. Infection in Swine/Pathogenesis
In pigs less than 4-weeks-of-age, the incubation period can vary from 4–7 days in experimental infections.[26] PHEV replicates primarily in the nasal mucosa, tonsils, and lungs. Virus spreads from the peripheral nervous system (PNS) to the CNS and may involve the trigeminal, inferior vagal, and superior cervical ganglia; intestinal nervous plexus; and the celiac and dorsal root ganglia in the lower thorax.[26] Virus may be found in the submucosal and myenteric nervous plexuses of the small intestine following infection of villus epithelium.[26] Vomiting and wasting disease caused by PHEV may result from infection of neurons within brainstem or the enteric nervous system, depending on virus strain.[16,25,26] Spread of virus, and associated clinical signs, may be strain specific.[26]

Viremia does not appear to be important in the development of clinical signs, though access to nerve pathways does.[25,44] Infection is acute and subsequently cleared in pigs. No chronic or carrier state of infection has been found in pigs,[22] although experimentally infected mice and rats are susceptible to chronic infection.[44,45] There is, however, evidence of subclinical encephalomyelitis being caused by PHEV in a pig.[22]

5.1 Clinical Signs

Pigs of all ages can be infected with PHEV but clinical disease is limited to pigs less than 4-weeks-of-age.[22] Disease is usually manifested as vomiting and wasting and/or encephalitis. Signs of disease include anorexia, constipation, vomiting, wasting, incoordination, ataxia, stiffness, hyperesthesia, posterior paralysis, respiratory distress,[46] and impaired weight gain.[29-31] Vomiting begins around 3–6 DPI[25,26,40] but by the time clinical signs are noted, virus may be difficult to isolate.[40] Diarrhea, though less common, has also been reported.[13]

In one instance, PHEV was identified in a market-aged pig with clinical respiratory disease at a Michigan agricultural fair.[11] High seroprevalence was later found in market swine at 14 different Michigan fairs. While uncommon, this presentation may reflect PHEV exposure in older but naïve swine populations, an atypical form of disease, or infection with a strain of increased virulence.[11]

5.2 Postmortem Lesions

PHEV causes few gross lesions.[31,47] Petechiae in the kidneys, thinning of the intestinal wall, and brain hemorrhage has been observed in suckling piglets with PHEV.[13] Histological lesions of viral encephalomyelitis are seen in the brain, medulla oblongata, cerebellar peduncles, olfactory bulb, and spinal cord.[1,48] These include perivascular mononuclear cuffing, the formation of glial nodes, and degeneration of neurons.[29] Lymphocytes expressing anti-PHEV IgG or IgM[48] may accumulate within the tunica media and adventitia of blood vessels and perivascular spaces[31] as well as within the glial nodes.[48] In the lungs, interstitial pneumonitis with macrophage, neutrophil, and lymphocytic infiltration of alveolar septae may be seen, as well as alveolar epithelial hypertrophy.[31] In the tonsil crypts, epithelial degeneration and lymphocyte infiltration can occur.[49]

6. Diagnosis

6.1 Clinical History

A sudden appearance of nervous signs or vomiting and wasting in a small number of litters of the same age, within a few days of birth in an otherwise healthy herd, may be indicative of PHEV. This is especially true if the infected litters are born within a few days of each other, and litters born 14 or more days after the sick piglets remain healthy.[22] Healthy piglets within an infected litter are also likely infected subclinically and may have brain lesions despite maintenance of health.[22] Additionally, as the respiratory tract is the primary site of replication for PHEV, respiratory symptoms may also be seen.

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens

Virus isolation is best accomplished in secondary pig thyroid (SPTh) cells or primary pig kidney (PPK), and a blind passage in cells may facilitate isolation.[29,50,51] The time of earliest virus isolation is between 1–3 DPI.[22] Virus can be isolated up to 9 DPI from respiratory tissues such as lung and nasal mucosa.[46] Virus may also be isolated fairly consistently from tonsils.[52] Loss of ability to isolate virus is coincident with appearance of neutralizing antibodies[31] and can occur concurrent with or soon after appearance of clinical signs.[25,40]

The fluorescent antibody test (FAT),[53] immunofluorescence (IF),[26] and immunohistochemistry (IHC)[45] can be used to identify antigen in tissues. Viral antigen can be identified in tissues beginning at one DPI.[26] IF,[46,54] hemagglutination (HA),[29] and hemadsorption plaque assays[54] can be used to identify virus antigen in tissue culture cells or cell supernatants that have been inoculated with tissue suspensions. IF and FAT consistently show PHEV antigen in neuronal perikarya and epithelial cell cytoplasm.[52] HA can be used to confirm the hemagglutinating properties of PHEV using chicken, mouse, hamster, or rat erythrocytes.[16,54]

RT-PCR and nested PCR have been described to identify PHEV infected tissue samples[38] using the N gene [37] and the HE, S, E, M, and N genes[12,13] for amplification. Additionally, a pan-coronavirus RT-PCR targeting the conserved polymerase gene has been shown to amplify PHEV.[56] Multiplex RT-PCR has also been used to determine that pigs were infected with PHEV rather than other porcine viruses known to cause similar clinical signs, including pseudorabies, classical swine fever, and porcine reproductive and respiratory syndrome (PRRS).[14] The PHEV genome has been sequenced[2] and may aid in design of probes for qRT-PCR. To date, qRT-PCR has been described targeting the N gene.[57,58]

An antibody sandwich enzyme-linked immunosorbent assay (ELISA) for detection of PHEV antigen has been described, as has a lateral flow immunochromatographic strip that is stable at room temperature for six months and for 12 months at 4°C (39.2°F).[55] Neither assay is commercially available.

6.3 Tests to Detect Antibody

Serum virus neutralization (SVN) and hemagglutination inhibition (HI) were originally used to identify seroconversion in experimental animals.[16] An ELISA to detect IgG antibodies against the PHEV HE protein has been described as has a lateral flow immunochromatographic strip designed to be shelf stable and allow early and rapid detection of seroconversion.[42]

6.4 Samples

To diagnose PHEV by virus isolation, samples should be taken within two days of the appearance of clinical signs.[25] Virus can readily be isolated from nasal and pharyngeal swabs, nasal mucosa, tonsils and lungs, the primary sites of replication of PHEV, as early as one DPI.[16] Virus may also be identified in the brain stem and or trachea after oronasal inoculation of pigs, depending on virus strain used.[16,22] Virus can be isolated for 3–10 DPI in saliva and nasal secretions irrespective of pig age.[16,22] Serum may be collected to monitor the development of neutralizing antibodies. Other tissues that may be diagnostic in some animals include olfactory bulb, cerebrum, and cerebellum,[23,26,48] spinal cord, stomach, and intestine.[52]

7. Immunity

7.1 Post-exposure

HI-antibodies first appear 6–7 DPI and serum-neutralizing antibodies are first detectable 7–9 DPI,[16,25,40] soon after the development of clinical signs[25] and coincident with histological changes in the CNS[48] and in tonsil crypts.[49] Antibody levels peak around 12 DPI.[40] PHEV-seropositive sows protect their piglets from disease through passive transfer of PHEV neutralizing antibodies in colostrum and milk.[22] Maternal antibody is detectable in their offspring for 8–18 weeks.[34,59] Gilts that received passive immunity as suckling pigs are unable to protect their offspring from PHEV disease unless they are subsequently infected and seroconvert.[22]

7.2 Vaccines

Two vaccines against PHEV have been experimentally tested in mice. An inactivated PHEV vaccine administered to mice with alum as an adjuvant elicited a high level of protection against live PHEV challenge.[60] The same authors simultaneously described a DNA vaccine encoding the spike glycoprotein. The DNA vaccine alone was protective against death following live virus challenge but did not prevent infection, whereas when administered as two injections of DNA vaccine followed by a booster of inactivated PHEV, mice were protected against infection and disease.[60] No information on vaccine studies in pigs is available.

7.3 Cross-protection

Antibodies to PHEV do not cross-neutralize any other porcine coronaviruses such as TGEV or PEDV.[61] The ability of infection with one PHEV strain to protect against another has not been established.

8. Prevention and Control

In animals greater than 4-weeks-of-age, PHEV infection generally does not cause clinical disease. However, mortality in piglets infected with PHEV can be as high as 100%.[1] In large, closed herds that maintain endemic PHEV, piglets are protected against infection by maternal antibody.[34] To prevent infection in smaller herds, where endemic infection cannot be maintained, a closed herd must be established or all animals entering the herd must be tested for PHEV. Piglets born to non-immune sows can be inoculated with specific immune serum shortly after birth.[1] Strict biosecurity measures must also be in place to prevent PHEV from entering the herd via fomites. Serious economic losses have been attributed to PHEV in China.

9. World Organization for Animal Health (OIE) Terrestrial Animal Health Code

PHEV is not covered in the 2017 OIE Terrestrial Animal Health Code. There are no recommendations on importation of swine or pork.[62]

10. Gaps in Preparedness

There is no PHEV vaccine available for use in pigs. As maternal antibody is protective against development of clinical disease in suckling pigs,[22] the prevalence of PHEV seropositive sows should be determined to gauge how vulnerable the U.S. swine population is to PHEV outbreaks.

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