HEPATITIS E VIRUS

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SUMMARY

Etiology

- Hepatitis E virus (HEV) is a non-enveloped RNA virus in the genus *Orthohepevirus* in the family *Hepeviridae.*
- There is a single HEV serotype but the genus *Orthohepevirus* contains four subgenera based on species affected. Within the subgenus *Orthohepevirus A,* there are at least seven different genotypes. HEV-3 and HEV-4 are zoonotic with swine serving as the reservoir host.

Cleaning and Disinfection

- Little is known about virus survival outside the host; however, HEV is thought to be somewhat stable in the environment since feces are an important source of infection.
- Heating pork products to an internal temperature of 71°C (160°F) for 20 minutes is required to completely inactivate HEV.
- HEV is potentially susceptible to disinfection with acids like acetic acid, aldehydes like glutaraldehyde, alkalis like sodium hydroxide, and oxidizing agents like Virkon-S.

Epidemiology

- HEV can be isolated from many different species including pigs.
- HEV is zoonotic. The severity of infection in humans varies from subclinical to fulminant hepatitis, along with reproductive effects. Pigs are the most important animal reservoir for genotypes capable of infecting people.
- The virus can be found in nearly every region in the world. Genotypic niches occur, with HEV-3 and HEV-4 occurring in the United States.
- In the United States, 80 to 100% of commercial swine farms show evidence of infection with HEV. Although morbidity can be high, especially in pigs 2–4 months of age, death is uncommon.

Transmission

- Most pigs acquire HEV via the fecal-oral route. The virus may also be transmitted in other ways, although more research is needed.

Infection in Swine/Pathogenesis

- HEV infections in swine are usually asymptomatic. Increased liver enzymes have been reported in experimental studies.

Diagnosis

- HEV is not cultivatable in cell culture.
- The most common and reliable assay for HEV detection is the reverse transcriptase polymerase chain reaction (RT-PCR). HEV antigen in tissues has also been detected using immunohistochemistry and in situ hybridization.
- Enzyme linked immunosorbent assays (ELISAs) have been developed for antibody detection, including one commercially available kit that detects antibodies to HEV-1 and HEV-3.

Immunity

- Most pigs become infected with HEV once maternal antibody wanes.
- A highly protective recombinant vaccine, *HEV 239*, has been developed for use in humans but has not been tested in swine.

Prevention and Control

- HEV is ubiquitous and difficult to detect. Standard biosecurity measures, including regular cleaning and disinfection, should be in place to limit fecal contamination of swine facilities.

Gaps in Preparedness

- Little is known about the pathogenesis of HEV, possible routes of transmission, and vaccine efficacy in swine.

OVERVIEW

Hepatitis E virus (HEV) causes asymptomatic infection in swine; however, it is a public health concern, causing acute hepatitis in humans of varying severity. HEV is a small, non-enveloped RNA virus in the family *Hepeviridae,* genus *Orthohepevirus.* The genus *Orthohepevirus* is subdivided into four subgenera that classify HEVs based upon species affected. *Orthohepevirus A* is the most clinically significant subgenera and has at least seven different genotypes. HEV-3 and HEV-4 are zoonotic with swine serving as the reservoir host.

HEV is ubiquitous and can be detected on swine farms worldwide. The virus is also zoonotic; the World Health Organization estimates that nearly 20 million HEV infections occur in humans each year. HEV has been detected in pig livers in grocery stores in Japan and the United States, figatelli (raw pork liver sausage) in grocery stores in France, wild boar meat, deer meat, and sewage water. Seroconversion has also been documented in people with occupational exposure to swine. Most severe human infections occur in pregnant women and can impact the outcome of the pregnancy. In pregnant women, mortality of 25% has been reported in HEV endemic regions.

HEV is not cultivatable in cell culture. Fecal samples are the primary source of HEV detection, although HEV RNA has been detected in serum, liver, bile, lymph nodes, and oral fluids of infected swine. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most common and reliable assay for viral detection. HEV antigen in tissues has been detected using immunohistochemistry and in situ hybridization. Enzyme linked immunosorbent assays (ELISA) have been developed and successfully used to detect anti-HEV antibodies.

Vaccines have been commercially developed for human use. The vaccine *HEV 239* has been shown to be 100% protective in human trials and can be used to prevent zoonotic, foodborne, and waterborne infections, especially in pregnant women. *HEV 239* vaccine has shown to be protective in rabbits when challenged with rabbit HEV and has shown cross-protective properties against other *Orthohepevirus A* genotypes. Efficacy of the vaccine *HEV 239* has not been evaluated in swine.

Further research is needed on the pathogenesis of HEV in swine, the modes of transmission in swine, vaccine efficacy in swine, and detection in finisher pigs to prepare for a potential outbreak and to prevent outbreaks from occurring.

LITERATURE REVIEW

1. Etiology

1.1 Key Characteristics

Hepatitis E virus (HEV) is a small, spherical, non-enveloped, positive-sense single stranded RNA virus with icosahedral capsid symmetry. It belongs to the genus *Orthohepevirus* in the family *Hepeviridae.*[1]

1.2 Strain Variability

Only a single serotype of HEV has been identified to date and great diversity exists between reported isolates.[2] The family *Hepeviridae* is divided into two genera, *Orthohepevirus* which contains HEVs that affect mammalian and avian species, and *Pescihepevirus,* which contains HEVs affecting cutthroat trout.[2] The *Orthohepevirus* genus is further divided into four different subgenera depending upon species affected. *Orthohepevirus A* contains HEVs of humans, pigs, wild boars, deer, mongoose, rabbit, and camel. *Orthohepevirus B* contains chicken HEV. *Orthohepevirus C* contains HEVs of rats, shrews, ferrets, and mink. *Orthohepevirus D* contains HEV isolated from bats.[2]

Within *Orthohepevirus A*, there are at least seven different genotypes. HEV-1 and HEV-2 are host-restricted to humans, while HEV-3 and HEV-4 are zoonotic with swine serving as the reservoir.[1] HEV-5 and HEV-6 have been found in wild boar in Japan, and HEV-7 has been found in dromedary camels in Dubai.[1] Prototypic strains of HEV-1 through HEV-4 are Burmese, Mexican, United States, and Chinese, respectively.[3] Each genotype is subdivided into many subgenotypes, the most important of which is HEV-3a. Two complete swine HEV strains of this subgenotype have been mapped, swKOR-1 and swKOR-2, and submitted to GenBank.[3] Rabbit HEV is most closely related to HEV-3, and shares 77–79% nucleotide similarity with HEV-1 through HEV-4.[4] It is possible that rabbit HEV may cause zoonotic infections.

The HEV genome consists of short noncoding regions on the 3’ and 5’ end, a poly-A tail, and three open reading frames (ORF). ORF-1 encodes nonstructural proteins and RNA-dependent RNA polymerase, and ORF-2 encodes immunogenic capsid proteins responsible for assembly and host interaction. ORF-3 encodes a small phosphorylated protein which binds to the hepatocellular cytoskeleton to form a complex with a capsid protein involved in cell signaling pathways and infectivity in vivo.[1] ORF-4 has been reported in ferret and rat strains.[5]

2. Cleaning and Disinfection

2.1 Survival

HEV is thought to resist inactivation by acidic and mild alkaline conditions in the intestinal tract.[5] Little is known about virus survival outside the host; however, since HEV spreads via the fecal-oral route the virus must be somewhat stable in the environment, similar to other hepatitis viruses.[6]

2.2 Disinfection

HEV is inactivated in pork products by adequate cooking.[5] Heating pork products to an internal temperature of 71°C (160°F) for 20 minutes is required to completely inactivate HEV.[7] Lower temperatures and/or shorter durations may not reduce HEV infectivity. In one study, pork livers heated to 191°C (376°F) for 5 minutes, or boiled in water for 5 minutes were found to contain infective HEV.[8] Similarly, incubation of pork livers at 56°C (133°F) for one hour did not reduce infectivity.[8] HEV in pork products remains infective when exposed to cooking temperatures of 56°C (133°F) for one hour, temperatures equivalent to rare to medium cooking conditions in restaurants.[8]

HEV is potentially susceptible to disinfection with acids like acetic acid, aldehydes like glutaraldehyde, alkalis like sodium hydroxide, and oxidizing agents like Virkon-S.[9]

3. Epidemiology

3.1 Species Affected

HEV has been isolated from a wide range of species. Those affected by *Orthrohepevirus A* include humans, pigs, wild boar, mongoose, and camel. *Orthrohepevirus B* affects chickens. Species susceptible to infection with *Orthohepevirus C* include rats, shrews, ferrets, and mink. *Orthohepevirus D* affect bats. Rabbits and cutthroat trout can also be infected with HEV.[2]

Anti-HEV antibodies have been detected in sheep, goats, cattle, dogs[2], and donkeys.[4] The virus has also been isolated from deer meat.[10] Pigs are the most important reservoir for HEV genotypes capable of infecting humans.[11]

3.2 Zoonotic Potential

HEV is a zoonotic disease. According to the World Health Organization, an estimated 20 million HEV infections occur each year, with over three million symptomatic cases and nearly 57,000 deaths.[12] HEV is a major cause of acute viral hepatitis in endemic countries, accounting for more than 50% of cases. Approximately two billion people live in endemic areas and are at risk of infection.[2] In these regions, HEV infection is primarily waterborne due to poor sanitation. HEV in industrialized countries has previously been linked to travel in endemic regions—like Mexico, the Middle East, and North and West Africa—however, genotyping indicates that most cases now appear to be foodborne.[2]

Human infections range from subclinical to fulminant hepatitis. Viremia is transient and clears by the time of onset of symptoms. Flu-like signs may be observed, along with hepatomegaly, fever, weakness, vomiting, and jaundice.[13] Middle aged and elderly men are most commonly infected, with a mortality rate of 1–4%.[2] Infections are most severe in pregnant women, with a mortality rate of 25% in endemic regions.[2] HEV infections during pregnancy can result in death of the mother and fetus, abortion, premature birth, or death of the newborn shortly after birth.[14] Vertical transmission has been reported in 33% of cases and HEV has also been detected in human colostrum.[14]

Difference in infection severity is poorly understood but presumed to be based on HEV genotype, viral load, coinfections, and immune status of host.[2] HEV-3 and HEV-4 are less pathogenic in humans compared to HEV-1 and HEV-2. HEV-2 has never been documented in a case of fulminant hepatitis, so HEV-1 may be the source of most severe infections in humans.[2] HEV-3 and HEV-4 from humans have experimentally infected pigs and HEV-3 and HEV-4 from swine have experimentally infected non-human primates.[15]

People with occupational exposure to swine, including veterinarians, slaughterhouse workers, and swine farmers, show increased serological evidence of exposure to HEV. Farm workers who worked with predominately young swine have demonstrated increased seroprevalence compared to slaughterhouse workers.[4] In one study, swine veterinarians in the United States were about 1.5 times more likely to be seropositive than other blood donors.[16] In another study, the seroprevalence of anti-HEV antibodies was 4.5 higher in swine producers from North Carolina compared to controls.[5] Similar results have been found in occupationally exposed people from Europe, Africa, and Asia.[17-20] However, several studies have documented no difference in anti-HEV seroprevalence between the occupationally exposed and controls.[21-23]

In addition to direct contact with pigs, zoonotic transmission of HEV also occurs through food. Acute HEV infections have been associated with consumption of contaminated, raw, or undercooked pig liver, deer, and boar meat.[13] Two percent of pig livers sold in Japanese grocery stores and 11% sold in United States grocery stores have tested positive for HEV RNA.[5,8] Figatelli (raw pork liver sausage) has been implicated as the source of sporadic cases of HEV in France, and HEV-3 RNA has been recovered from

supermarket-purchased figatelli samples.[24] In the same study, anti-HEV IgM antibodies were detected from 7 of 13 humans who consumed raw figatelli.[24] Shellfish, mussels, and oysters have also been implicated as sources of foodborne transmission of HEV due to marine pollution.[25]

Surface water can be contaminated by HEV virus shed in feces and serves as a major source of HEV infections in humans.[5,14] A study from Spain detected HEV RNA in the serum of humans who had acute hepatitis with no history of animal contact; the viral strain had 92–94% nucleotide similarity with HEV RNA detected from swine slaughterhouse sewage.[26]

Bloodborne transmission, human-to-human transmission, and vertical transmission have been reported in humans and are of emerging relevance.[2,13]

3.3 Geographic Distribution

Swine HEV was first reported in the United States in 1997.[15] Since then, it has been detected in nearly every swine production facility in the world.[15] Each genotype possesses geographic niches. HEV-1 isolates derive from and predominate in Asia and Africa. HEV-2 isolates predominate in Mexico. HEV-3 and HEV-4 contain isolates from the United States, Japan, New Zealand, Europe, China, and Taiwan.[27]

3.4 Morbidity and Mortality

Between 80 and 100% of commercial pig farms in the United States show evidence of infection with HEV.[15] Swine HEV has a high morbidity rate in pigs 2–4 months old. In Spain, 37% of pigs between 1–3 months of age show evidence of infection.[27] Seroprevalence increases with age. In China, 70–100% of adult pigs have been infected with HEV.[28] Seroprevalence in swine is significantly higher compared to other animals.[4] However, mortality in pigs is very low as infection is often subclinical.

4. Transmission

Transmission in swine is predominantly fecal-oral. By 12–15 weeks of age, most pigs are naturally infected and shedding HEV RNA in their feces.[27,31] Pigs less than three months of age exhibit higher HEV-RNA levels in feces compared to older animals, indicating young pigs may be an important source of viral shedding.[4] One pig shedding HEV virus in feces can transmit the virus to 0.15 pigs per day by direct contact.[31] Transmission via HEV-contaminated feces between adjacent pens is 30 times less effective than within-pen transmission.[31] In miniature pigs, experimental infection has been achieved via feces from an intravenously inoculated wild boar with HEV-3.[32] Contact with infected pigs or HEV-positive feces results in infection more easily than experimental oral inoculation.[30]

Additional modes of transmission probably occur in swine. In one study, the urine of three contact-infected pigs tested positive for HEV RNA by RT-PCR.[30] Aerosol transmission may also be possible.[30] Vertical transmission has been reported in pregnant rabbits infected with rabbit HEV, but has not been demonstrated in swine.[29] One study showed that neonatal rabbits born from HEV-infected rabbits were positive for HEV RNA in their feces from the very first passage of stool.[29] In one-week-old piglets seropositive for HEV, sequencing demonstrated that isolated strains were different than those isolated from sows.[27]

5. Infection in Swine/Pathogenesis

The pathogenesis of HEV in swine is largely unknown and information is limited. After fecal-oral infection of young swine (2–3 months old), shortly after maternal antibody wanes, viremia occurs lasting 1–2 weeks.[14] Fecal viral shedding occurs 1–2 weeks after inoculation, but may persist for up to eight weeks.[30] Infection has been reported in one-month-old pigs.[33]

After ingestion, the virus spreads to its target organ, the liver, where replication occurs.[5] Hepatic changes are minimal in swine. Extrahepatic sites of replication have been identified and include the small intestines, colon, and hepatic and mesenteric lymph nodes.[5] HEV RNA has been detected from the stomach, kidneys, salivary glands, tonsils, lungs and muscles of pigs inoculated intravenously with HEV-virus.[14,30] The virus is then excreted in feces and bile serving as a source of transmission to other pigs.

Rabbit HEV may replicate within the placental tissues of HEV-infected pregnant rabbits.[29]

5.1 Clinical Signs

Natural and experimental infections in swine are asymptomatic.[5] In one study, experimental intravenous infection of 3–4 week-old-pigs caused no overt clinical signs and no elevation of liver enzymes or hyperbilirubinemia.[34] Other studies have reported increases in liver enzymes in both experimental intravenous and contact inoculation.[32]

Pregnant rabbits infected with rabbit HEV have demonstrated increased infertility, increased incidence of miscarriage, and maternal death 6–7 weeks postpartum.[29] HEV in swine has shown no effects on litter size or preterm abortions in pregnant gilts; however, more examination is required.[30]

5.2 Postmortem Lesions

Postmortem lesions from HEV-infected swine are minimal and mild, and pigs exhibiting lesions are usually clinically normal.[5] Experimentally infected swine can exhibit mild to moderate hyperplasia of the hepatic and mesenteric lymph nodes from 7–55 days-post-infection.[30,34] Mild to moderate hyperplasia of Peyer's patches in the ileum has also been reported.[30] Multifocal lymphoplasmacytic hepatitis with focal hepatocellular necrosis is sometimes appreciable.[34] Severe hepatic swelling and vacuolization occurs between 7–27 days-post-infection. Slight subepithelial lymphohistiocytic cellular infiltrates in the gallbladder have been documented.[30] In one study, three intravenously inoculated pigs necropsied at 14 days-post-infection had lesions consistent with HEV. Liver samples from only one of the pigs was positive for HEV RNA by RT-PCR, but all were positive by RT-PCR for HEV-RNA in bile.[34] Another study showed that over 16% of swine negative for HEV by RT-PCR had microscopic hepatic lesions consistent with HEV infection.[33]

6. Diagnosis

6.1 Clinical History

Recognizing HEV infection in swine is difficult because of the absence of clinical signs. Any pig can be infected with HEV, and natural infection seems to most commonly occur at the time maternal immunity wanes in piglets around 7–9 weeks of age.[5]

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens

HEV nucleic acids traditionally have been detected using a semi-nested reverse transcriptase polymerase chain reaction (RT-PCR) assay.[35] Primers amplify a segment of the HEV ORF2 which encodes the immunogenic capsid protein.[1,33] A comparison has been done of two single-plex real-time RT-PCR assays and two duplex real-time RT-PCR assays for the detection and differentiation of HEV genotypes in swine.[36] One of the single-plex assays proved most effective in detecting HEV-3 and HEV-4, identifying 34-fold more positive samples compared to the duplex real-time RT-PCR assays.[36]

The most widely used assay for detection of nucleic acids in human HEV infections is a real time RT-PCR TaqMan assay which uses primers from ORF-3 and can detect genotypes HEV-1–4.[37] This assay can detect 0.12 PID_{50} swine HEV even in environmental samples, which is greater than the nested RT-PCR.[37]

HEV isolation is difficult; the virus is uncultivatable in cell culture.[5] However, recombinant capsid proteins can be expressed using *Escherichia coli,* containing a cloned capsid gene, and purified to hyperimmunize animals for diagnotics.[38] Immunohistochemistry has been used to detect HEV-3 antigens in tissues and characterize the type and severity of inflammatory process by binding to CD3 surface receptors on porcine immune cells.[32]Viral antigens have been detected using rabbit anti-HEV-3 hyperimmune serum using the recombinant capsid proteins.[32] In situ hybridization has also been used to detect HEV RNA in tissues.[33]

6.3 Tests to Detect Antibody

A commercially available ELISA has been developed. PrioCHECK® HEV Antibody ELISA kit uses HEV-1 and HEV-3 antigens encoded by ORF-2 and ORF-3 to detect antibodies. Sensitivity and specificity of the commercially available ELISA are both greater than 90%.[39] Other ELISA tests have been developed with specificity and sensitivity greater than 95% using capsid proteins antigens, anti-HEV serum, and rabbit anti-porcine IgG.[38]

6.4 Samples

6.4.1 Preferred Samples

The most common sample to detect HEV RNA from infected pigs is feces.[27] HEV RNA has been detected by RT-PCR in serum, bile, lymph nodes, liver, and oral fluids.[33]

6.4.2 Oral Fluids

HEV RNA has been detected in oral fluids of infected swine.[40] A 2014 report detected HEV RNA from oral fluid samples when incubated for less than 24 hours at 4°C (39°F) and 30 days at -20°C (-4°F) without the use of a stabilizing agent.[40] Use of stabilizing agents has shown to decrease the ability to detect HEV RNA from the samples. Therefore, it is unnecessary to stabilize oral fluid to detect viral RNA from swine.[40]

7. Immunity

7.1 Post-exposure

Pigs experimentally infected through contact develop anti-HEV antibodies in about 13 days; those inoculated intravenously develop them slightly earlier. Contact-infected pigs also become viremic approximately 13 days-post-infection. Virus may persist in the blood for nearly 11 days. HEV RNA can be detected in feces about 7 days-post-infection and can persist for 23 days.[30]

Maternal IgA, IgG, and IgM antibodies have been detected in suckling pigs.[27] In one study, nearly 77% of pigs were IgG positive and persisted until 9 weeks of age, almost 8% were IgA positive and persisted until 3 weeks of age, and about 15% were IgM positive and persisted until less than 12 weeks of age.[27] Once maternal antibodies waned, these pigs became naturally infected. Anti-HEV IgG antibodies were detected by 15 weeks of age and IgG-positive animals increased until the study ended.[27] After natural infection, anti-HEV IgM antibodies can be detected for 5–7 weeks, while IgA antibodies persists for about 4 weeks.[27]

7.2 Vaccines

A human recombinant bacterial expressed polypeptide vaccine based on ORF2 of HEV-1, *HEV 239*, is the world's first commercial vaccine against HEV infection, approved by China's State Food and Drug Administration in December 2011.[41] The polypeptide takes the form of a virus-like particle and presents immunogenic epitopes on its surface. The vaccine is reported to have shown 100% protective efficacy in men and women between 16–65 years of age without any unexpected side effects.[41]

A challenge study in rabbits using rabbit HEV and swine HEV-4 after immunization with *HEV 239* found that the vaccine was highly immunogenic in rabbits and prevented disease in all rabbits inoculated.[41] The rabbits were inoculated three times at two week intervals. The first immunization produced adequate titers to be protective. All immunized rabbits showed no viremia, fecal shedding, and no increase in serum ALT levels. Similar results have been reported from a challenge study using mice and rhesus monkeys.[42] This study shows the promise of *HEV 239* in providing protection in animals when challenged with different genotypes and could be used to reduce zoonotic transmission of HEV.[41]

HEV 239 has not been evaluated in swine. No vaccine is currently available for swine HEV.

7.3 Cross-protection

Common antigenic epitopes exist among human and avian HEV viruses, and cross protection does occur in primates following infection with different genotypes.[5] Vaccine-induced anti-HEV-1 antibodies have shown to be highly cross protective with HEV-4 and Rabbit HEV.[11,41] It is unknown whether the *HEV 239* vaccine also protects against HEV-3.

A single pig can become infected with at least two different strains of HEV, not simultaneously, during its lifetime probably due to movement to different housing facilities depending upon age and production stage.[27]

8. Prevention and Control

Concern exists about the potential transmission of HEV through spray dried porcine plasma. One study showed that the use of spray dried porcine plasma as a feed supplement in post-weaning pigs did not increase their risk for HEV transmission.[43] Nearly 100% of commercially available spray dried porcine plasma contained anti-HEV antibodies while only 22% were positive for HEV RNA by RT-PCR. The heating process of spray drying should inactivate HEV.[43]

Due to its ubiquity and difficulty in detection clinically, prevention of HEV may be difficult. Standard biosecurity measures should be in place, such as regular cleaning and disinfection. Feces should be removed from pens to prevent contamination.

Increased detection, especially in finisher pigs, could help prevent foodborne, zoonotic transmission of HEV. Pork should be cooked thoroughly to 71°C (160°F) for 20 minutes in endemic areas.[2]

There are no approved pharmaceutical treatments for HEV infections in swine.

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

HEV is not covered in the 2015 OIE Terrestrial Animal Health Code and there are no current recommendations on importation of swine or pork.

10. Gaps in Preparedness

HEV is the cause of subclinical infections in swine. HEV-infected swine are a source of zoonotic, foodborne, and waterborne disease of public health significance. Despite being extremely common in a wide range of hosts, details of HEV infection are largely unknown and remain to be investigated. Further research is needed on the pathogenesis of HEV in swine, the modes of transmission in swine, vaccine efficacy in swine, and detection in finisher pigs to prepare for a potential outbreak and to prevent outbreaks from occurring.

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