Epidemiology of Hepatitis E

Emerging Disease Notice

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Summary

- Hepatitis E virus (HEV) is ubiquitous in U.S. swine herds, but does not cause clinical illness in swine.
- Hepatitis E is a zoonotic disease risk and cross-species infection occurs. In 2003 in Japan, the first direct evidence of zoonotic transmission of HEV was documented in two outbreaks involving human consumption of raw wild boar liver and raw deer meat; one patient died.
- Xenotransplantation using swine tissues may pose a zoonotic disease risk.
- Up to 26 percent of persons in the U.S. have anti-HEV antibodies; the incidence of human cases of acute, clinically apparent hepatitis E in the U.S. is unknown but thought to be rare.
- HEV is prevalent in human and swine populations in other industrialized countries.
- Anti-HEV antibodies have been detected in a number of animal species including primates, rodents, domestic pigs, cattle, cats, chickens, dogs, sheep, and goats.
- Swine are infected at 1-3 months of age through fecal-oral transmission.
- Specific risk factors for on-farm and between farm transmission of HEV are unknown.
- HEV is prevalent in wild and domestic rodents in the U.S. HEV RNA has not been isolated from U.S. rodents and the genetic relatedness of rodent HEV to U.S. swine or human HEVs is unknown.

Researchers have hypothesized that hepatitis E (HEV) is a zoonotic disease, but direct evidence to support this claim has been lacking. New information documenting the zoonotic transmission of HEV was reported in 2003 from Japan . There, HEV was found in 1.9 percent of raw, packaged pork livers, human illnesses were epidemiologically linked to consumption of undercooked pork liver and consumption of raw deer meat and raw wild boar liver was responsible for outbreaks of hepatitis E (Tei 2003, Yazaki 2003, Mazuda 2003). The objective of this summary is to examine the epidemiology of hepatitis E as it pertains to animal and public health in the U.S. , given that HEV is now known to be

endemic in the U.S. and hepatitis E has been reported in U.S. citizens without history of travel to HEV endemic areas outside the U.S.

A fact sheet about hepatitis E virus is available from the National Pork Board (Halbur 2001b, www.porkscience.org/documents/Other/hepatitisevirusfacsheet.pdf). Recent reviews of hepatitis E virus include a summary of HEV seroepidemiology, molecular biology and vaccine development (Emerson 2003) and a comprehensive review by Meng (2003). A substantial amount of new information has been learned about hepatitis E since its discovery in the U.S. in 1997.

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Epidemiology of Hepatitis E

Hepatitis E virus (HEV) is the major etiologic agent of enterically transmitted non-A, non-B hepatitis in humans worldwide, and is a spherical, non-enveloped, single stranded RNA virus (Emerson 2003). HEV was formerly classified as a calicivirus, but has been reassigned as unclassified.

Until 1997, hepatitis E was thought to occur only in developing countries including Africa, central Asian republics of the former Soviet Union, Afghanistan , Bangladesh , Borneo, Burma , China , India , Mexico , Mongolia , Nepal , Pakistan , Thailand , Vietnam , and some parts of the Middle East (CDC 1993, Meng 1999, 2000). In these countries, the disease is a significant public health concern and is both endemic and epidemic, with human outbreaks generally associated with fecal contamination of drinking water. Hepatitis E generally results in asymptomatic or mild illness similar to Hepatitis A, except in pregnant women who experience up to 20 percent mortality (Chin 2000). Hepatitis E was not thought to be endemic in developed countries, including the U.S. , although early studies reported serum samples positive for anti-HEV antibodies (Dawson 1992, Thomas 1997, Redlinger 1998). The first reported human cases of acute hepatitis E in the U.S. were presumably attributed to travel to HEV-endemic areas (CDC 1993); however, in 1997, HEV was isolated from domestic swine and a U.S. resident with hepatitis and no travel history (Meng 1997, Kwo 1997, Schlauder 1998).

Since 1997, HEV has been documented in humans and swine in many countries previously considered nonendemic, including Argentina, Australia, Austria, Canada, Germany, Greece, Japan, Korea, the Netherlands, New Zealand, Spain, and Taiwan (Chandler 1999, Pina 2000, Schlauder 2000, Worm 2000, Garkavenko 2001, Purcell 2001, van der Poel 2001, Yoo 2001, Pei 2002, Meng 2003, Takahashi 2003, Teich 2003, Widdowson 2003). Based on nucleotide and protein sequencing of HEV isolates, 4 major genotypes have been described worldwide (Meng 2003, Emerson 2003). Genotype 1 includes Asian and African strains, genotype 2 includes a single Mexican strain, genotype 3 includes U.S. swine and human isolates, and genotype 4 includes strains from Taiwan , Japan and China (Meng 2003). The newly identified avian HEV from chickens may represent a 5th genotype or belongs to a separate genus (Huang 2002b). Additional genotypes may exist as other novel strains have not been completely sequenced and so cannot be definitively assigned to a genotype at this time. Overall, all HEV strains isolated thus far are genetically related and molecular studies of human and swine HEV isolates from

around the world have found that swine and human isolates from the same geographic region are more similar to each other than they are to swine or human HEV isolates from other regions (Clemente-Casares 2003, Hsieh 1999, Nishizawa 2003, Takahashi 2003, Meng 2003). Despite the variety of genotypes, only two serotypes of HEV have been reported to date. Serologic tests cannot distinguish between infection with different HEV genotypes (Emerson 2003).

Epidemiology in swine

HEV is ubiquitous in swine in the U.S. (Meng 1997, Halbur 2001b). In a seroprevalence study of swine from the midwestern U.S. , 100.0 percent of 15 herds had measurable anti-HEV antibodies (Meng 1997). In these herds, across all age ranges, 202 (71.4 percent) of 283 swine had IgG anti-HEV antibodies. In another U.S. study, clinical fecal and serum samples submitted to a veterinary diagnostic laboratory for non-HEV related reasons were tested for HEV viral RNA (Huang 2002). Samples originated from swine herds in 6 states (Arkansas, Iowa, Missouri, North Carolina, Oklahoma) and HEV RNA was detected in 20 (54.1 percent) of 37 swine herds and 34 (35.4 percent) of 96 pigs. Seroprevalence and RNA detection studies in commercial swine herds found HEV to be similarly prevalent in Australia , Canada , Korea , Japan , New Zealand , and Taiwan (Chandler 1999, Garkavenko 2001, Yoo 2001, Wu 2002, Choi 2003, Takahashi 2003).

Seroprevalence varies by age in swine herds. As reported in an article authored by Meng (1997), IgG anti-HEV antibodies were not detected in most pigs less than 2 months of age, but were found in 100.0 percent of swine aged 2-8 months, and in 85.4 percent of adult swine. Not all piglets are born seronegative; in a prospective study of a naturally infected commercial herd, only strongly seropositive sows passively transferred IgG anti-HEV antibodies to their piglets; however, antibodies waned by 8-9 weeks of age, at which point most piglets developed HEV infection and developed their own anti-HEV antibodies. Seronegative or only weakly seropositive sows had piglets that were seronegative. It is possible for swine herds to be free of HEV. In the seroprevalence study described above, a 16th herd that was specific pathogen free (SPF) was negative for anti-HEV antibodies (Meng 1997).

Transmission of HEV among swine appears to occur through a fecal-oral route of exposure at approximately 1-3 months of age, with a majority of animals exposed by 6-8 months of age (Meng 1997, Wu 2002, Takahashi 2003). In Taiwan , Wu (2002) found no evidence of viremia until two months of age, when pigs were moved to pens where there was increased opportunity for environmental fecal contamination. Specific risk factors for on-farm and between farm transmission of HEV, such as management practices and the role of rodents or other animals, are currently unknown.

Epidemiology in other animal species

Antibodies to HEV are prevalent in wild and domestic rodents in the U.S. ; serologic evidence of HEV infection was found in 26 rodent species in 14 states (Kabrane-Lazizi 1999, Favorov 2000). Seropositivity for a given rodent species ranged between 4.5-100 percent. To date, HEV has not been isolated from U.S. rodents, so the genetic relatedness of rodent HEV to other strains of HEV is

unknown. In addition to swine, chicken and primates, HEV has been isolated from deer (Tei 2003) and serologic evidence of HEV infection has been found in other species including cats, dogs, cattle, and sheep (Meng 2000, Purcell 2001, Kuno 2003).

Avian HEV is genetically related to but distinct from human and swine HEVs (Huang 2002b). Avian HEV appears to be prevalent in the U.S. ; a seroprevalence study of 76 chicken flocks located in California, Colorado, Connecticut, Virginia, and Wisconsin found anti-HEV antibodies in 71 percent of flocks and 30 percent of chickens. Avian HEV has been associated with hepatitis-splenomegaly syndrome in chickens.

Hepatitis E in Humans

Multiple serologic studies indicate that human infection with HEV is relatively common. The incidence of clinically apparent disease in humans in the U.S. is unknown but thought to be rare. Two cases of acute hepatitis E acquired in the U.S. have been reported (Kwo 1997, Tsang 2000). Because diagnostic testing is limited due to the lack of commercially available tests, and the disease is not nationally notifiable, illness due to HEV infection may be underdiagnosed and underreported in the U.S. In an Iowa study, 4.5 percent of 204 patients with acute non-A, non-B, non-C hepatitis tested positive for anti-HEV antibodies (Karetnyi 1999). In Japan , a retrospective study of 87 patients treated for acute hepatitis of previously unknown etiology, found that 12.6 percent had IgM anti-HEV antibodies and HEV RNA (Mizuo 2002). A survey of swine veterinarians and blood donors found that 26.4 percent of swine veterinarians and 18.3 percent of blood donors tested positive for antibodies to HEV (Meng 2002). Serosurveys conducted in Iowa, Maryland, California, Texas, and of a random sample of U.S. blood donors found 0.4-21.3 percent of persons tested positive for anti-HEV antibodies (Dawson 1992, Thomas 1997, Redlinger 1998, Karetnyi 1999, Smith 2002). In Iowa, healthy field workers from the Department of Natural Resources had a higher prevalence of anti-HEV antibodies, compared to blood donors (Karetnyi 1999). In Taiwan , seroprevalence was found to be 26.7 percent in swine handlers and 8.0 percent in control subjects (Hseih 1999). A study in Moldova found 51.1 percent of swine farmers and 24.7 percent of persons without occupational exposure to swine had anti-HEV antibodies (Drobeniuc 2001).

Risk Factors for Human Exposure to HEV

Hepatitis E is a zoonotic disease but risk factors for disease transmission to humans are largely unknown (Halbur 2003, Meng 2003). Exposure to swine or wild animals appears to be associated with the development of anti-HEV antibodies in humans, although seroconversion has been documented in individuals with no history of these exposures, indicating other sources of infection (Drobeniuc 2001, Halbur 2001, Meng 2002, Mizuno 2002, Meng 2003). Unfortunately, detection of anti-HEV antibodies through serologic testing provides no information about the HEV strain source; therefore, serology is of limited usefulness in identifying risk factors for disease transmission. New information from Japan has provided direct evidence that HEV is a zoonosis. Two outbreaks of hepatitis E occurred as a result of consuming infected raw sika deer meat and wild boar liver; one patient died (Matsuda 2003, Tei 2003).

Also in Japan , HEV was found in 1.9 percent of 363 packages of raw pork liver from grocery stores; one HEV isolate from packaged liver was an identical match to HEV isolated from a patient with hepatitis (Yazaki 2003). In contrast, Wu (2002) hypothesized that pork products may be of relatively low zoonotic risk to consumers because viremia appears to be rare in market aged swine.

In a study of 11 Japanese patients with hepatitis retrospectively diagnosed as hepatitis E, several patients reported no history of exposure to swine or rodents, two had occupational exposure to raw beef, pork and chicken meat and one patient was a swine farmer (Mizuo 2002). Huang (2002) raised the concern that swine fecal contamination of irrigation or coastal waters could contaminate produce or fish harvested for human consumption; however, HEV was not isolated from surface water adjacent to commercial swine facilities (Halbur 2003). Emerson (2003) has hypothesized that rodents would be a likely reservoir for HEV, given their wide distribution across a variety of human habitats. Additional studies are needed to identify the sources and risk factors for human exposure to HEV.

Clinical Illness in Animals

Hepatitis E virus infection does not cause clinical illness in swine. Experimental exposure of 2- to 4-week-old swine with human and swine HEV found no evidence of clinical disease or elevation of liver enzymes (Halbur 2001, Williams 2001). All infected swine developed anti-HEV antibodies; most within 27 days postinoculation. Experimentally inoculated swine did develop mild hepatic lesions consisting of enlarged hepatic and mesenteric lymph nodes, multifocal lymphoplasmacytic hepatitis and hepatocellular necrosis. Swine infected with the human HEV strain had more severe lesions than swine infected with the U.S. swine HEV strain (Halbur 2001). Experimental infection of pregnant gilts with HEV found no evidence of clinical disease in the gilts or piglets (Kasorndorkbua 2003).

Pathogenesis in Swine

In 2- to 4-week-old swine intravenously inoculated with a U.S. swine strain of HEV, viral RNA was detected in a variety of tissues between day 3 to 27 post-inoculation (Williams 2001). Positive tissues included liver, lymph nodes, colon, small intestines, stomachs, spleens, kidneys, tonsils, salivary glands, and lungs. Virus was not detected in blood after day 14 post-inoculation and was not detected in any tissue by day 55 post-inoculation. Similar results were found in a second group of swine inoculated with a U.S. human strain of HEV. Evidence was found that extrahepatic replication of HEV occurs in lymph nodes, colons, small intestines, and spleens for swine infected with swine HEV and additionally in stomach, kidneys, tonsils, and salivary glands of swine infected with human HEV (Williams 2001). Virus is shed in feces and bile for 3-5 weeks (Halbur 2001).

Prevention

Until more is known about the animal reservoirs and modes of transmission of HEV among swine and other animal species, and how HEV is transmitted to humans, it will be difficult to determine what, if any, preventive measures should be recommended in the U.S and other developed countries. In

developing countries, prevention of HEV relies primarily on the provision of clean water supplies and overall improved sanitation and hygiene. Vaccines currently under development may provide a means of prevention in the future.

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