

**Authors**

**Hepatitis E virus**

Patrick G. Halbur, DVM, PhD; Chaiyan Kasorndorkbua, DVM, MS, Iowa State University  
Xiang-Jin Meng, MD, PhD, Virginia Polytechnic Institute and State University

Originally published as a National Pork Board Factsheet.

**Background**

Recent detailed reviews of hepatitis E virus (HEV) infection of humans and animals are available (Meng, 2000a, 2000b; Smith, 2001). Hepatitis E virus is the primary cause of enterically-transmitted, non-A, non-B, acute hepatitis in humans in several developing countries. The mode of HEV transmission is thought to be mainly by fecal-oral route and outbreaks in humans are usually associated with consumption of drinking water contaminated by feces. Mortality rate due to HEV infection in humans is typically less than 1%; however, mortality rates of nearly 20% have been reported in infected pregnant women in developing countries of Asia and Africa. However, attempts to reproduce fulminant hepatitis E in pregnant rhesus monkeys (Tsarev et al, 1995) and pregnant sows (Thacker et al, unpublished) were unsuccessful. HEV-induced disease is endemic in many developing countries particularly in Africa and Asia. Hepatitis E virus-induced disease is considered sporadic in humans in industrialized countries such as the U.S.

Recently, a novel strain of HEV, designated as swine HEV, was discovered in pigs in the U.S. (Meng et al., 1997). Swine HEV identified from a pig in the U.S. is genetically very closely related to the two U.S. strains of human HEV (US-1 and US-2) but is distantly related to other HEV strains worldwide. Seroepidemiological studies indicate that anti-HEV antibodies are widely distributed in humans, and domestic animals including pigs, cattle, sheep, goats, dogs, and rodents. These findings suggest that these animal species are likely infected by a strain(s) of HEV or a related agent, and that animals should be considered a possible reservoir(s) for HEV. So far, animal strains of HEV have been genetically identified from pigs (Meng et al., 1997), chickens (Haqshenas et al., 2001), and rats (Tsarev et al., 1998). Since swine HEV appears to be ubiquitous in pigs, there is concern for the potential transmission of HEV to human xenotransplant patients when the pig is used as an organ or tissue source. It appears that swine HEV is nonpathogenic in swine or humans, however, its pathogenicity under certain conditions such as immunosuppressive conditions in xenograft recipients and during pregnancy is not known.

**Agent**

Hepatitis E virus is a non-enveloped, single-stranded, positive-sense RNA virus. It is currently unclassified and designated in an unassigned genus as "hepatitis E-like viruses." Phylogenetic analyses of HEV isolates from various parts of the world indicate that there exist at least 5 different genotypes of HEV (Haqshenas et al., 2001): Asia-Africa (Burmese, Chinese, Indian, Nepalese, Pakistani strains), United States (the US-1, the US-2, and swine HEV strains), a variant Chinese strain of human HEV, avian HEV, and the Mexican strain. In Taiwan and United States, where both swine and human strains of HEV have been isolated, sequence analyses revealed that HEV isolates from pigs and humans were very closely related (Meng et al., 1998a, 1998b; Hsieh et al., 1999; Wu et al., 2001).

It appears there exists only one serotype of the virus. The protein expressed by ORF2 of human HEV is highly immunogenic and has been used as antigen in ELISA assays for serological diagnosis of HEV. The human HEV ORF2 antigen cross-reacts with swine HEV antibodies. Therefore, infections caused by swine HEV and human HEV can not be distinguished serologically.

## Pathogenesis

Experimental inoculation studies that describe the temporal pathogenesis of infection of pigs with swine and human strains of HEV have recently been published (Halbur et al., 2001). Experimental intravenous inoculation of pigs with swine HEV or with the US-2 strain of human HEV induced similar results. Both swine HEV and human HEV induced subclinical hepatitis in pigs. The only remarkable gross lesions were enlarged mesenteric and hepatic lymph nodes. Microscopic lesions associated with HEV infection included multifocal lymphoplasmacytic hepatitis. Ballooning degeneration of hepatocytes and hepatocellular necrosis was less frequently observed. Human HEV induced more severe and persistent lymphoplasmacytic hepatitis lesions in pigs compared to swine HEV; however, there was no significant elevation of hepatic enzymes or bilirubin levels in any of the experimentally infected pigs.

Intravenous inoculation of pigs resulted in viremia detectable by 1 week post inoculation and persisting for 3 weeks. The liver, small intestines, colon, and lymph nodes are thought to be sites of HEV replication based on RT-PCR assay of tissues from experimentally-inoculated pigs (Williams et al., 2001). Virus shedding occurs in bile and feces for 3-5 weeks. Anti-HEV IgG antibodies are detectable by 3 weeks post inoculation and persist for at least 8 weeks.

In a swine bioassay study (Kasorndorkbua et al., 2001), transmission of HEV was achieved by intravenous inoculation of naïve pigs with liver or feces from pigs previously infected experimentally with HEV. Efforts to transmit HEV through oral inoculation with various tissues and feces were unsuccessful, though pigs were successfully infected via I.V. route of inoculation. Thus the natural route of HEV transmission in pigs remains unclear.

## Epidemiological Features and Clinical Signs of Hepatitis E virus

Serological surveys indicate that HEV is ubiquitous in the U.S. swine population (Meng et al., 1997) and this is likely also the case worldwide. Recently, the prevalence of anti-HEV IgG in swine was assessed in two countries where human HEV is endemic (China and Thailand) and in two countries where human HEV is uncommon (Canada and Korea). Swine herds in all four countries were widely seropositive for anti-HEV (Meng et al., 1999). It has also been shown that anti-HEV prevalence in pig handlers is higher than that in normal blood donors (Meng et al., 1999; Meng et al., 2001, unpublished). However, since the antigens used in the serological assays can not distinguish infections caused by human HEV and other animal strains of HEV, it is not known if the pig handlers are infected by human HEV, swine HEV or other animal strains of HEV. More recently, strains of HEV of possible swine origins have been identified from patients in Spain and Japan (Pina et al., 1999; Takahashi et al., 2001). Hepatitis E virus is also widespread in rats in areas where exposure to pigs or pig feces is unlikely (Kabrane-Lazizi et al., 1999). Another recent study also demonstrated that human populations with occupational exposure to wild animals have higher anti-HEV prevalence compared to normal blood donors (Karetnyi et al., 1999). The high prevalence of anti-HEV in a number of other animal species, coupled with high prevalence of anti-HEV in human populations not at apparent risk of exposure to HEV, suggests that multiple sources of exposure to HEV may exist in the general U.S. population, as well as in specialty populations such as pig handlers.

Singular HEV infection of SPF pigs is subclinical. It is not known whether coinfection of pigs with HEV and other swine viruses and/or bacteria enhances disease.

## Diagnosis

Diagnosis of HEV based on clinical signs is not possible. Diagnosis is based on detection of swine HEV RNA in feces and sera by RT-PCR assay. Techniques for cultivation of HEV are not yet available. Serologic diagnosis by ELISA is the preferred method for detection of serum anti-HEV IgG or IgM response. A serological assay that can distinguish infections caused by swine HEV, human HEV or other strains of HEV is not yet available. The RT-PCR assay is useful to detect the presence of HEV RNA in serum, feces, and bile of

affected humans, laboratory non-human primates, pigs or other animals. Viremia persists for a relatively short period of time, therefore detection of the RNA in feces may be more reliable.

## Treatment and Prevention

HEV-free pigs have been derived from HEV-positive breeding herds by conventional segregated early weaning techniques (P. Halbur, unpublished data). Passive antibody appears to decay between 8-20 weeks of age and natural infection occurs shortly thereafter.

Cross species infection has been demonstrated in rhesus monkeys and a chimpanzee I.V.-inoculated with swine HEV, and in pigs I.V.-inoculated with the US-2 strain of human HEV (Meng et al., 1998). Evidence of cross-species infection of HEV raises potential public health concerns. The U.S.-1 strain of human HEV identified from a patient in Minnesota who has no history of travelling to endemic regions is genetically very closely related to the swine HEV identified from a pig in Illinois (Schlauder et al., 1998; Meng, 2000a, 2000b). A Taiwanese strain of swine HEV shared >97% nucleotide sequence identity with a human strain of HEV identified from a retired Taiwanese farmer (Hsieh et al., 1999). The ability of swine HEV to naturally infect other species is not known. Hygienic precautions should be in place when handling swine feces that potentially contain HEV. Extensive screening of donor pigs for HEV infection prior to xenotransplantation is also warranted.

## References

- Halbur PG, Kasorndorkbua C, Gilbert C, Guenette D, Potters MB, Purcell RH, Emerson SU, Toth TE, Meng X-J: 2001, Comparative pathogenesis of infection of pigs with hepatitis E viruses recovered from a pig and a human. *J Clin Microbiol* 39(3): 918-923.
- Kabrane-Lazizi Y, Fine JB, Elm J, Glass GE, Higa H, Diwan A, Gibbs CJ, Meng XJ, Emerson SU, Purcell RH: 1999, Evidence of widespread infection of wild rats with hepatitis E virus in the United States. *Am J Trop Med Hyg* 61:331-335.
- Kasorndorkbua C, Halbur PG, Thomas PJ, Guenette DK, Toth TE, Meng X-J: 2001, Use of a swine bioassay and a RT-PCR assay to assess the risk of transmission of swine hepatitis E virus in pigs. *J Virol Methods*, Submitted for publication.
- Karetnyi YV, Gilchrist MJ, Naides SJ: 1999, Hepatitis E virus infection prevalence among selected populations in Iowa. *J Clin Virol* 14:51-55.
- Meng X-J: 2000, Zoonotic and xenozoonotic risks of the hepatitis E virus. *Infect Dis Rev* 2(1):35-41.
- Meng XJ, Dea S, Engle RE, Friendship R, Lyoo YS, Sirinarumit T, Urairong K, Wang D, Wong D, Yoo D, Zhang Y, Purcell RH, Emerson SU: 1999, Prevalence of antibodies to the hepatitis E virus in pigs from countries where hepatitis E is common or is rare in the human population. *J Med Virol* 59:297-202.
- Meng X-J, Halbur PG, Haynes JS, Tsareva TA, Bruna JS, Royer RL, Purcell RH, Emerson SA: 1998, Experimental infection of pigs with the newly identified swine hepatitis E virus (swine HEV), but not with human strains of HEV. *Arch Virol* 143: 1405-1415.
- Meng X-J, Halbur PG, Shapiro MS, Govindarajan S, Bruna JD, Mushahwar IK, Purcell RH, Emerson SU: Genetic and experimental evidence for cross-species infection by swine hepatitis E virus. *J Virol* 72 (12): 9714-9721, 1998.
- Meng X-J, Purcell RH, Halbur PG, Lehman JR, Webb DM, Tsareva TS, Haynes JS, Thacker BJ, Emerson SU: 1997, A novel virus in swine closely related to the human hepatitis E virus. *Proc Natl Acad Sci (USA)* 94(18):9860-9865.
- Smith JL: 2001, A review of hepatitis E virus. *J Food Prot* 64 (4):572-586.
- Williams TPE, Kasorndorkbua C, Halbur PG, Haqsheas G, Guenette DK, Toth TE, Meng X-J: 2001, Evidence of extrahepatic sites of replication of hepatitis E virus in a swine model. *J Clin Microbiol*, In Press.

Reference to products in this publication is not intended to be an endorsement to the exclusion of others which may be similar. Persons using such products assume responsibility for their use in accordance with current directions of the manufacturer. The information represented herein is believed to be accurate but is in no way guaranteed. The authors, reviewers, and publishers assume no liability in connection with any use for the products discussed and make no warranty, expressed or implied, in that respect, nor can it be assumed that all safety measures are indicated herein or that additional measures may be required. The user therefore, must assume full responsibility, both as to persons and as to property, for the use of these materials including any which might be covered by patent.

This material may be available in alternative formats.

Information developed for the Pork Information Gateway, a project of the U.S. Pork Center of Excellence supported fully by USDA/Agricultural Research Service, USDA/Cooperative State Research, Education, and Extension Service, Pork Checkoff, NPPC, state pork associations from Iowa, Kentucky, Missouri, Mississippi, Tennessee, Pennsylvania, and Utah, and the Extension Services from several cooperating Land-Grant Institutions including Iowa State University, North Carolina State University, University of Minnesota, University of Illinois, University of Missouri, University of Nebraska, Purdue University, The Ohio State University, South Dakota State University, Kansas State University, Michigan State University, University of Wisconsin, Texas A & M University, Virginia Tech University, University of Tennessee, North Dakota State University, University of Georgia, University of Arkansas, and Colorado State University.