Hepatitis E Virus

Disease Agent:

- Hepatitis E virus (HEV)

Disease Agent Characteristics:

- Family: *Hepeviridae*; Genus: *Hepevirus*
- Virion morphology and size: Nonenveloped, icosahedral nucleocapsid symmetry, spherical particles, 27-34 nm diameter
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~7.2 kb in length
- Physicochemical properties: Less stable to heat than HAV; most strains totally inactivated at 71°C for 20 min although a Mexican strain was moderately more resistant; stable to multiple cycles of freezing and thawing

Disease Name:

- Hepatitis E

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Low in the US but probably higher in other countries where transfusion-transmitted cases have been reported (Japan, the UK, France and potential transmissions in Saudi Arabia, India and Taiwan)
- Public perception and/or regulatory concern regarding blood safety: Moderate in the US
- Public concern regarding disease agent: Absent in the US

Background:

- A novel enterically transmitted hepatitis virus was initially suspected to be responsible for an explosive epidemic that was occurring in Kashmir in 1978. Serologic studies in 1980 distinguished this virus from hepatitis A virus both in this outbreak and in another large epidemic that occurred in Delhi in 1955-1956. The virus was subsequently visualized in the feces of an infected volunteer by immune electron microscopy in 1983 and was transmitted to Cynomolgus monkeys.
- HEV was cloned and sequenced in 1990.
- Chronic infection in immunocompromised patients was first reported in 2008.
- HEV is globally the most common cause of acute hepatitis with an estimated 20 million incident infections, greater than 3 million acute cases and 700,000 deaths per year. There are four mammalian genotypes and one serotype.
- Generally, genotypes 1 and 2 are more virulent than genotypes 3 and 4. The latter two genotypes infect humans, pigs and other animal species with genotype 3 associated with chronic hepatitis in immunosuppressed individuals.

Common Human Exposure Routes:

- Most large-scale epidemics of HEV are due to genotypes 1 and 2 and have been associated with fecally-contaminated water or food similar to what is observed in HAV.
- Genotypes 3 and 4 are zoonotic and typically are associated with sporadic food-borne transmission from consumption of meat products or viscera that are eaten raw or have not been cooked sufficiently to inactivate the virus, or by close environmental contact to an infected source. Such infections have most commonly been documented in Japan and Europe (e.g., bivalve mollusks, boudin noir, figatelli sausage, dinuguan).
- Transfusion transmission has been reported from infected donors presumably resulting from an extended asymptomatic viremic period.
- Person-to-person spread is relatively uncommon; sexual transmission is unproven.

Likelihood of Secondary Transmission:

- Very low, most likely from fecal shedding

At-Risk Populations:

- Endemic and epidemic in residents of Southeast and Central Asia plus Japan, Middle East, North and West Africa, Mexico, Brazil
- Travelers to these areas
- Sporadic cases occur in non-endemic regions
- Immunocompromised patients (solid organ transplant recipients, persons with HIV infections and patients with hematological malignancies) are at increased risk for HEV-related chronic hepatitis.
- Recipients of transfused blood products in endemic areas

Vector and Reservoir Involved:

- Mammalian genotypes: natural infections in humans (genotypes 1 and 2); human and zoonotic reservoirs (genotypes 3 and 4)
- Genotype 1 is found in Egypt, northern Africa and Sudan, India, Southeast Asia and China; genotype 2 is primarily present in Mexico and West Africa; genotype 3 is found in the US, South America, Europe and Japan and genotype 4 is in Japan and China.
- Zoonotic spread may occur from domestic swine or other domestic and wild animals (Sika deer, wild boar, rabbits, and mongooses) to humans through consumption of uncooked meat products or close environmental contact. Bivalve mollusks (mussels) also may be a source.

Blood Phase:

- HEV RNA has been detected in the blood of donors in Europe, Japan and China.
- Viremic phase of 4-6 weeks with nucleic acid being detected up to 112 days
- Longer duration of nucleic acid detection has been reported in immunocompromised organ-transplant recipients and in

patients with hematological malignancies undergoing treatment following acute HEV.

Survival/Persistence in Blood Products:

- No data on cellular components, but persists in frozen plasma as evidenced from two transfusion transmissions.

Transmission by Blood Transfusion:

- Blood from a hepatitis E viremic donor was transfused to a Rhesus monkey resulting in HEV transmission and clinical hepatitis, viremia and fecal shedding.
- Documented in endemic areas (e.g., Hokkaido in Japan) where at least 12 transfusion-transmitted cases have been identified, as well as transmissions in the UK and France, and potential transmissions in Saudi Arabia, India and Taiwan.
- In Hokkaido, Japan, HEV nucleic acid testing (NAT) was initiated in 2005 following detection of four cases of transfusion-transmitted hepatitis E. Through 2013, 231 NAT-reactive donors were identified among nearly 2 million donors for a frequency of 0.012%, predominantly with genotype 3. The NAT-reactive donors were mostly anti-HEV negative suggesting that they may have been in the early seronegative window period; the remaining NAT-reactive donors were mostly IgM anti-HEV reactive. Of donors with ALT levels over 200 IU/L, 1.1-2.8% were HEV-RNA positive. About half of the infected donors had elevated ALT levels during follow-up that resolved within 50 days. A history of consumption of meat products or viscera that are eaten raw or have not been cooked sufficiently to inactivate the virus was present in a significant number of the infected donors when compared to an uninfected donor subset.
- Anti-HEV IgG seroprevalence rates among 1939 blood donors at the US National Institutes of Health have ranged from 21.8% from donor samples collected in 2006 to 16.0% for those collected in 2012 (overall 18.8%); 0.4% were IgM anti-HEV positive, but no donor had circulating HEV RNA. Prevalence ranged from 3.4% in those 18-35 years old to 42.2% in those older than 65 years old. No transmission was observed among 362 prospectively followed blood recipients in a study that incorporated a linked donor-recipient repository; two suspect cases of anti-HEV seroconversion were investigated but neither could be confirmed as transfusion-related events.
- An IgG anti-HEV seroprevalence of 6.8% was found in German blood donors; seven of 69 had seroconverted (prior stored sample evaluated) during a 2-year interval for an incidence of 0.35% per year. HEV RNA could be recovered from the stored sample of three of the seven incident donors; none had elevated ALT levels in any sample including follow-up samples. One recipient of an RNA-positive unit was traced and was negative for IgG and IgM anti-HEV and HEV RNA 41 days following transfusion.
- Two transfusion transmissions from the same apheresis FFP unit (split into 3 components) occurred in one patient receiving a kidney transplant and in another receiving a liver transplant in France. These are notable because the FFP unit was treated by amotosalen and UVA light (Intercept). The third recipient died 2 days following transfusion; the two FFP recipients and the asymptomatic donor were infected by the same genotype 3f strain (homologous in both open reading frames 1 and 2).

Cases/Frequency in Population:

- Antibody prevalence in endemic regions is 16-52.5%. The prevalence of anti-HEV among qualified blood donors in Japan was reported as 3.4% (range: 1.8-5.6%) where over 200 cases of HEV RNA positive donors have been detected of which 31% were food-borne. Most cases occur in middle age to older males; isolates are genotypes 3 or 4 and are indigenous strains.
- The highest HEV seroprevalence rates reported to date have been in southwest France linked to the consumption of locally produced pork products containing uncooked or undercooked pork.
- Genotype 3 HEV RNA was recovered from Dutch blood donors at a rate of 0.037% in 2011-2012 with sequences closely related to isolates from patients and pigs in the area. Testing was performed on 40,176 donations in 459 pools of 48 or 480 donations from which 13 RNA-positive donors were identified. IgG antibody prevalence from testing an additional 5,239 donors was 27% (1,401 IgG positives) of which 3.5% (49) were also IgM positive. Four of the 49 IgM-positive donors were HEV RNA positive. Prevalence increased with age (13% in donors <30 years old and 43% in donors >60 years old). Viral loads ranged from <25 IU/mL to >100,000 IU/mL with RNA positivity extending from 27-58 days in seven followed donors. Intensive pig farming in the Netherlands is presumably responsible for viral amplification. HEV is most likely spread by contaminated meat and contaminated water used for irrigation.
- HEV seroprevalence in the US during 1988-1994 was 21% as measured in the 3rd NHANES survey. The highest prevalence was in the Midwest and metropolitan areas. This relatively high seroprevalence rate may reflect lower virulence of the genotype 3 strain that circulates in the US coupled with the fact that no confirmatory serology was performed. Correspondingly, clinical symptoms may be dose-dependent and patients may be exposed primarily to low doses of virus.
    - For US-born individuals, increased odds of HEV seropositivity were found among non-Hispanic whites, if a pet was in the home, or if liver and other organ meats were consumed more than once monthly. The incidence was also significantly higher in those who were born outside the US and who had a low poverty index. Gender and area of residence in the US were not significant factors.
- HEV infection is uncommon and infrequently recognized in the US. Symptomatic disease acquired domestically in

immunocompetent patients is rare. From 2005 to 2012, the US CDC has documented 26 clinical cases of HEV in the US from a total of 154 clinical cases of hepatitis that they were asked to examine for possible HEV with 15 acquired in the US and 11 acquired by travelers to endemic countries. Non-travelers were older (61 vs 32 years old), more likely to be anicteric (53% vs 8%), less likely to be of Southeast Asian ethnicity (7% vs 73%) and included more solid-organ transplant recipients (47% vs 0%). A selection bias cannot be excluded in the analysis of these data. Genotype 3 was identified from 8 nontravelers and genotype 1 and 4 from four travelers.

Incubation Period:

- Usually 3-8 weeks, but longer and shorter periods have been reported.

Likelihood of Clinical Disease:

- High during epidemics with genotypes 1 and 2 and among immunosuppressed patients residing in endemic areas who may develop chronic disease

Primary Disease Symptoms:

- Anicteric or icteric hepatitis
- Prodrome and clinical symptoms are indistinguishable from other forms of hepatitis: nausea, fever, vomiting, abdominal pain, anorexia, fatigue, jaundice

Severity of Clinical Disease:

- Severity in humans can range from inapparent disease to fulminant hepatitis.
    - In nonhuman primates, severity is related to dose.
- Atypical manifestations include chronic liver disease that can lead to cirrhosis in 10% within two years in immunosuppressed patients and fulminant hepatic failure in pregnant women.
    - High incidence of fetal wastage

Mortality:

- 0.2-4% overall except in pregnant women during third trimester where rates of 10-20% have been reported

Chronic Carriage:

- While no cases of chronic HEV have been reported among immunocompetent potential donors, acute hepatitis leading to chronicity and cirrhosis has been described in immunocompromised patients following solid organ transplant and in a patient undergoing chemotherapy for a T-cell lymphoma. Progression to cirrhosis can be rapid in these patients.

Treatment Available/Efficacious:

- Five to six months of ribavirin (600-1000 mg per day) may be effective in all genotypes with clearance in 1-2 months in most chronically infected patients. Dose reduction may be problematic so this should be avoided.
- Reduction in immunosuppression may be sufficient in liver transplant patients, but of limited value in heart and lung transplant patients.
- Tacrolimus appears to be associated with development of chronic HEV infection when compared to cyclosporine.

Agent-Specific Screening Question(s):

- None specifically for hepatitis E; however, questions from the Donor History Questionnaire concerning a history of clinical hepatitis and possible exposure to hepatitis viruses are applicable. These specific questions are as follows: Have you ever had hepatitis after the age of 11 years? In the past 12 months, have you lived with a person who has hepatitis?

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- IgG and IgM antibody assays have been developed but vary widely in sensitivity and specificity.
- Virus-specific nucleic acid detected by RT-PCR and transcription-mediated amplification (TMA) have been used diagnostically and in blood donor screening studies.
- Generally, ALT elevations are not predictive of HEV RNA status.

Currently Recommended Donor Deferral Period:

- The FDA requires an indefinite deferral for a clinical history of viral hepatitis after age 11 (regardless of the specific viral agent).

Impact on Blood Availability:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: the implementation of in-house HEV NAT in Hokkaido, Japan has had little impact on blood availability with prevalence in most countries <0.1%.

Impact on Blood Safety:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: the implementation of in-house HEV NAT in Hokkaido, Japan is likely to improve transfusion safety.

Leukoreduction Efficacy:

- None expected

Pathogen Reduction Efficacy for Plasma Derivatives:

- HEV would not be affected by the solvent-detergent process.
- Heat-inactivation by commercial plasma processes has not been evaluated, but the virus may be susceptible, based on recent thermal stability studies.
- No transmission of HEV has been documented from plasma derivatives although from 0%-0.022% of plasma donations from North America and Europe were found to contain HEV RNA.

Other Prevention Measures:

- Recombinant vaccines have been shown to be efficacious in animals and in phase III human clinical trials. The vaccines will have utility in endemic areas especially among females of child-bearing age, the military, in travelers to or workers in high-risk areas, and in immunocompromised patients at risk of acquiring HEV.
- Immune globulin collected from an endemic region has generally not been effective.
- Food can be rendered safe by cooking at 71°C (160°F) for 20 minutes. Avoid drinking water or ice of unknown purity, or consuming uncooked or partially cooked meat or bivalve mollusks and unpeeled fruits or vegetables.
- Two transfusion transmissions have been reported from Intercept-treated FFP.
- FDA licensed, solvent-detergent treated pooled plasma products (OctaPlas) are screened to reduce/eliminate HEV RNA.

Suggested Reading:

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