HEPATITIS E VIRUS

15.1 Disease agent

- Hepatitis E virus (HEV)

15.2 Disease agent characteristics

- Family: Hepeviridae; Genus: Orthohepevirus.
- Virion morphology and size: Nonenveloped, icosahedral nucleocapsid symmetry, spherical particles, 27–34 nm diameter; capsid likely consists of a single protein.
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~7.2 kb in length and contains 3 open reading frames.
- Physicochemical properties: Less stable to heat than HAV; most strains inactivated at 71°C for 20 min; stable to multiple cycles of freezing and thawing.

15.3 Disease name

- Hepatitis E

15.4 Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Low in the United States but higher in other countries where transfusion-transmitted cases have been reported and/or screening using NAT to identify infected donors implemented (Japan, the United Kingdom, France, Ireland, Spain, The Netherlands, Germany, Austria and Luxembourg).
- Public perception and/or regulatory concern regarding blood safety: Low/moderate in the United States.
- Public concern regarding disease agent: Absent in the United States.

15.5 Background

- A novel enterically transmitted hepatitis virus was initially suspected to be responsible for an explosive water-borne epidemic that occurred in Kashmir in 1978 resulting in 52,000 cases. Serologic studies in 1980 distinguished this virus from hepatitis A virus (HAV), both in this outbreak and in a similar large epidemic that occurred in Delhi in 1955–1956 with 30,000 cases. HEV 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. The virus cannot be efficiently grown in cell culture, and infectious cDNA clones are more commonly used.
- Chronic infection in immunocompromised patients was first reported in 2008.
- HEV is globally one of the most important causes of acute viral hepatitis with an estimated 20 million incident infections and 3.3 million symptomatic cases per year accounting for 70,000 deaths in 2022 (>3% of the mortality due to viral hepatitis) and 3000 stillbirths.
- There are five mammalian genotypes and one serotype.
- Generally, genotypes 1 and 2 are more virulent than genotypes 3 and 4. The latter two genotypes infect humans, swine, and other animal species, with genotype 3 associated with chronic hepatitis in immunosuppressed individuals. Both genotypes 3 and 4 have been associated with transfusion transmissions (and likely transplant transmissions).
- HEV is shed into feces as nonenveloped virions but circulates in blood in a membrane-associated, quasi-species enveloped form (eHEV) resembling exosomes. The eHEV form is more resistant to antibody neutralization and is most likely responsible for cell-to-cell viral spread.

15.6 Common human exposure routes

- Most outbreaks of HEV genotypes 1 and 2 occur in humans (epidemics and sporadic cases of hepatitis) and are associated with fecal-oral transmission from contaminated drinking water or food, particularly in India, Japan, East and Southeast Asia, North and West Africa. There is minimal person-to-person spread. Sexual transmission is unproven.
- HEV genotypes 3 and 4 are considered a zoonotic acquired from consumption of uncooked or undercooked meat products obtained from infected wild and domestic animals or from close environmental contact. Foods include bivalve mollusks, boudin noir, dinuguan or figatelli sausage. These genotypes also may be transmitted by transfusion and transplant.

15.7 Likelihood of secondary transmission

- Very low, most likely from fecal shedding
15.8 | 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 nonendemic regions.
- Pregnant women.
- 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, and in areas that are not endemic but have cases reported via ingestion from contaminated foods, particularly if screening blood donations for nucleic acids is not performed.

15.9 | 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, Mongolia, China, and Japan; genotype 2 is primarily present in Mexico and West Africa; genotype 3 is found in the United States, Canada, South America, Europe, and Japan and genotype 4 is in Japan (as identified in blood donors in Hokkaido).
- 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.

15.10 | Blood phase

- HEV RNA has been detected in the blood of donors in the United States, Canada, Europe, Japan, and China at frequencies ranging from <1:1000 to 1:17,000.
- Viremic phase of 4–6 weeks with nucleic acids detected up to 112 days.
- Longer duration of nucleic acid detection occurs in immunocompromised organ-transplant recipients and in patients with hematological malignancies undergoing treatment following acute HEV.
- Approximately 30%–50% of HEV-positive blood donations have a viral load <100 IU/mL, the infectivity of which is unknown.
- Estimates of the infectious dose resulting in transfusion-transmitted HEV is ~20,000 IU HEV RNA from a UK study, but lower infectious doses have been documented in Japan.

15.11 | Survival/persistence in blood products

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

15.12 | Transmission by blood transfusion

- Early documentation involved transfusing blood from an HEV-viremic donor to a Rhesus monkey resulting in HEV transmission and clinical hepatitis, viremia, and fecal shedding.
- Likely >100 transfusion transmissions in Japan and Europe prior to NAT screening; NAT has virtually eliminated cases in those countries that have implemented testing (recognizing that breakthrough infections can result depending on the component transfused and minipool size, if individual donation NAT is not performed; e.g., the United Kingdom). Potential transmissions also have been reported in Saudi Arabia, India, and Taiwan.
- NAT screening protocols are highly variable. Testing is done either individually or in minipools of 6 to 96 donations (the latter mostly for plasma for fractionation); two commercial technologies are being used for donation screening: either RT-PCR (Roche) or transcription-mediated amplification (TMA; Grifols).
- Since 2012, blood donation screening by NAT has been introduced in eight European countries (the United Kingdom, France, Ireland, Spain, The Netherlands, Germany, Austria, and Luxembourg) and Japan driven by prevalent infections, reported transfusion transmissions, and risk/benefit assessments favoring screening. This is despite knowledge that HEV exposure via diet far exceeds that of blood transfusion with the average reported rate of RNA reactivity of 1:1000 (but variable over time and country to country, and whether testing is performed individually or in minipools). The European CDC recommends that if screening of blood donations occurs, it should be accompanied by raising clinician awareness for strict dietary recommendations for patients at risk.
• The risk of transmission is related to viral dose (the product of the viral concentration and plasma volume). Data from the UK suggest that transmission is unlikely at a dose of <20,000 IU; however, transmissions have occurred at lower viral loads. The UK data suggest a transmission rate from an infected donor of at least 42%, resulting in persistent RNA-emia in 72% (with immunosuppression delaying or preventing seroconversion and viral clearance).

• In Japan, following 45 reported cases of transfusion-transmitted HEV occurring from 2002 to 2020 (most with viral loads >1000 IU/mL), NAT screening evolved from minipools of 20 from 2006 to 2014 in Hokkaido using an in-house test and finally to ID-NAT and nationwide screening in August 2020 using TMA (Grifols).
  - One-year later over 5 million donations were tested with 2804 (0.055% or 1:1783) NAT-reactive donors identified; 76% antibody-negative; 70% with ALT values <30 IU/L, thus representing early infections. The mean viral load, excluding those that were below the 95% limit of quantitation (~50% of the yield), was 204 IU/mL; 98.8% were genotype 3 and 1.2% genotype 4.
  - Since nationwide screening was implemented in 2020 (>2.5 years), no breakthrough cases of transfusion-transmitted HEV have been identified prospectively or via lookback of recipients of prior donations from test-positive donors. This is against a background of 270,000 new cases of HEV reported annually in Japan.
  - Using the lowest viral load of a donation that transmitted HEV (325 IU, which may be the lowest RNA dose documented to transmit), window periods by component (based on plasma volume) were estimated to range from 11 to 20 days. For an FFP unit (480 mL), HEV would be detectable by ID-NAT for 57.5 days.
  - From prior studies performed in Hokkaido, a history of consumption of meat products or viscera eaten raw or not cooked sufficiently to inactivate the virus was present in a significant number of the infected donors when compared to an uninfected donor subset.

• The first case of HEV transfusion transmission in France was reported in 2006. From 2006 to 2022, 41 high imputable cases were reported by the French Haemovigilance System, but none was associated with HEV-NAT screened plasma. Since the end of 2012, selective HEV RNA screening was performed to provide HEV-RNA negative plasma for at-risk recipients, first in pools of 96 (for SD plasma, as required by the European Pharmacopoeia using the RealStar RT-PCR kit from Altona Diagnostics), then starting in 2015, in minipools of 6 (RT-PCR; Roche).
  - During this time ~30%–40% of SD plasma was treated with amotosalen and UVA light (Intercept) including two documented HEV transmissions. After 2015, the use of SD plasma was discontinued in France. From the yield obtained from plasma NAT screening (2018–2021), the risk of introducing an HEV RNA-positive donation (unscreened) was estimated at 1:1682.
  - Universal NAT was introduced in March 2023 using a combination of minipools of 6 (Roche) for continental France and ID-NAT (TMA; Grifols) for overseas territories (and granulocytes in France).
  - 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 Intercept treated. 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).

• A recent HEV transfusion transmission from RBCs was reported in Spain involving an unscreened 25-day old red cell unit that transmitted HEV to a CML patient; however, the pooled buffy coat containing the platelets from the same donation as the transmitting red cell unit did not transmit (the pool was pathogen reduced with riboflavin and UV light); both the donor and red cell recipient had the same subgenotype (3f). The red cell patient cleared RNA by 46 days. The platelet recipient remained RNA, IgM and IgG nonreactive for 5 months.

• Among 1939 US blood donors at the NIH, anti-HEV IgG seroprevalence rates 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 linked to antibody-positive donors; two suspect cases of anti-HEV recipient seroconversion were investigated but neither could be confirmed as transfusion-related events.

15.13 | Cases/frequency in population

• A recent (2023) meta-analysis reviewing transfusion and exposure risk based on NAT and antibody
prevalence in blood donors (from 157 studies) indicated higher rates in Europe and Asia versus the United States (and Canada and Australia where routine screening is not done). On average, NAT reactivity ranged from 0.01% in the United States to 0.10% in Europe and 0.14% in Asia. However, NAT reactivity in Japan following 2.5 years of nationwide screening is 0.055%. Average seroprevalence ranged from 13% in the United States to 19% in Europe.

- The highest HEV IgG seroprevalence reported to date is 52.5% 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 (uncooked or undercooked pork).
- In Finland, HEV NAT was studied for 23,137 donations collected from March 2020–2021 tested individually (TMA; Grifols) which resulted in 4 positives (1:5784, 0.02%). All were IgM negative and subgenotype 3c consistent with national surveillance. IgG seroprevalence was 7.4% in HEV RNA negatives. Residual risk for severe disease was estimated at 1:1,377,000 transfused blood components, or 1 transmission every 6–7 years. No further testing has been reported.
- In Australia, one RNA-positive donation was identified (95% CI: 1:15,000 to 1:1.45 million) following HEV NAT of 74,131 donations collected in 2016; testing occurred in minipools of 6 (TMA; Grifols). The confirmed-positive donation had an estimated viral load of 180 IU/mL, which is below that typically associated with transfusion transmission. Using a transmission-risk model, the risk of an adverse outcome associated with HEV was estimated at 1:3.5 million components transfused.
- In the first US study using NAT for donation screening, 18,000 blood donations during 2013 were evaluated by individual donation testing (TMA; Grifols) with 2 positives identified (1:9500), one of which was IgM/IgG positive (viral RNA not detected; <10 IU/mL) and one antibody-negative with a viral load of 14 IU/mL; IgG prevalence was 7.7% and IgM prevalence 0.6%. These rates are significantly lower than the NIH study using different IgG and IgM assays. A subsequent larger study evaluated 101,489 blood donations from the United States and Canada (collected during 2015–2017) and tested individually using RT-PCR (Roche). US HEV RNA prevalence was 1:16,908 (95% confidence interval: 1:5786–1:81,987), whereas HEV RNA prevalence was 4-fold higher in Canada at 1:4615 (1:2579–1:9244) with Quebec having higher rates by 2.5-fold, although not significantly different than the rest of Canada (1:2920 [1:1417–1:7262] vs. 1:7581 [1:2961–1:27,825]). Viral loads in the United States and Canadian donors ranged from 20–3080 IU/mL; all were genotype 3. When recipient risk was stratified by underlying conditions for those considered high risk, risk was greatest for heart and lung transplant recipients (1:367,000 versus lowest for...
HEV seroprevalence in the general US population has been declining.

- During 1988–1994, IgG anti-HEV measured by the 3rd NHANES was 21%. High seroprevalence in the absence of clinical disease was hypothesized to be the result of low virulence of genotype 3, the lack of confirmatory testing, and that individuals may have been exposed to only low doses of virus.

- During 2009–2016, IgG prevalence in the United States was measured during NHANES at 6.1% overall (95% confidence interval: 5.6%–7%). The lowest rate occurred from 2013 to 2014 at 4.6% (3.7%–6%) but increased during 2015-2016 to 8.1% (7%–10%). Rates of IgM anti-HEV ranged between 0.5% and 1.6%.

- For US-born individuals, increased odds of HEV seropositivity were found among non-Hispanic whites in the earlier survey (1988–1994) but highest in Asians (12.8%) in the following surveys (2009–2016), if a pet was in the home, or if liver and other organ meats were consumed more than once monthly. Seroprevalence increased with age and was slightly higher in females. The highest prevalence was in the Midwest and metropolitan areas with increasing risk related to time spent outside of the US in an endemic country or for those who were at a low poverty level.

- HEV infection is uncommon and infrequently recognized in the United States. Symptomatic disease acquired domestically in immunocompetent patients appears rare. From 2005 to 2012, the US CDC has documented 26 clinical HEV cases from a total of 154 clinical hepatitis cases investigated for possible HEV; 15 were acquired in the United States and 11 acquired by travelers to endemic countries. Nontravelers 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%). Genotype 3 was identified from 8 nontravelers and genotype 1 and 4 from four travelers.

- No subsequent updates have been reported to the US CDC partly reflecting the fact that acute hepatitis E is not nationally notifiable (in contrast to hepatitis A-D).

- Los Angeles County, CA, conducted a population-based analysis of suspect acute hepatitis E cases reported from 2017 to 2019; 10 were confirmed (of 48 LA County residents reporting). A case definition included IgM anti-HEV and/or HEV RNA reactivity in those having symptoms compatible with viral hepatitis. Mean ALT values in cases were 1627 (range of 154–4693 IU/L) with 9 reporting a potential exposure. Recommendations included limiting HEV IgM anti-HEV testing to those only with symptoms of acute hepatitis in the absence of an alternate hepatitis etiology. False positivity could be further reduced if testing was limited to those with a potential risk factor via travel, food, or water.

15.14 | Incubation period
- Usually 15–60 days (mean 40 days)
- Virus excretion in stool has been demonstrated from 7 to 30 days after onset of jaundice.

15.15 | 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; higher for pregnant women in their second and third trimester.
- HEV infection is usually self-limiting; per the US CDC, the ratio of symptomatic to asymptomatic infection ranges from 1.2 to 1.13. In immunocompetent patients, most have no symptoms and jaundice is rare. ALT levels often range from 100 to 300 compared to >1,000 IU/L in immunocompromised patients.

15.16 | Primary disease symptoms
- Prodrome and clinical symptoms are indistinguishable from other forms of hepatitis: nausea, fever, vomiting, abdominal pain, anorexia, fatigue, jaundice, dark urine, clay-colored stool.
- Extrahepatic manifestations of HEV infection include arthritis, pancreatitis, aplastic anemia, neurologic, or autoimmune disease.
- HEV may masquerade as drug-induced liver injury (DILI). Among 2012 patients suspected of DILI, enrolled by the DILI Network between 2004 and 2020 with at least 6 months of follow up, 407 (20.2%) were reactive for HEV IgG and 18 (0.9%) for IgM. Of the latter, 8 were RNA positive. Seroreactivity was associated with older age and earlier enrollment in the cohort.

15.17 | Severity of clinical disease
- Severity in humans can range from inapparent disease to fulminant hepatitis.
In non-human primates, severity is related to dose. Atypical manifestations include chronic liver disease that can lead to cirrhosis in 15% within two years in immunosuppressed patients, and acute liver failure, fetal loss, and increased mortality in pregnant women particularly in their third trimester.

15.18 | Mortality

- 0.2%–4% (1% overall) except in pregnant women during the third trimester where case-fatality rates can range from 5% to 39%.

15.19 | Chronic carriage

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

15.20 | Treatment available/efficacious

- No specific treatment has been demonstrated to be effective in high-quality studies. Most cases are self-limiting while others may require hospitalization (i.e., in those with fulminant hepatitis or in symptomatic, pregnant women).
- 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.
- A higher degree of immunosuppression with a lower CD4 is a predictor of chronicity. Tacrolimus appears to be associated with development of chronic HEV infection when compared to cyclosporine A. A decrease in the dose and trough level has led to HEV clearance in one-third of the chronic group.

15.21 | Agent-specific screening question(s)

- None specifically for hepatitis E

15.22 | Laboratory test(s) available

- HEV infection should be considered in any person with symptoms of viral hepatitis who tests negative for hepatitis A-C or other hepatotropic viruses. Any symptomatic person who has traveled to an HEV-endemic area or outbreak area should be evaluated for HEV.
- No FDA-licensed blood donor screening test exists and there are no FDA-cleared diagnostic assays for use in the United States. Research tests are available; commercial laboratories will use research or laboratory-developed assays or those that are available outside of the US.
- IgG and IgM HEV-specific antibody assays have been developed but vary widely in sensitivity and specificity; IgM is most commonly used diagnostically generally having high sensitivity but lower specificity (including cross reactivity with EBV and CMV).
- Rapid antibody tests are also available.
- NAT from blood and stool, particularly during outbreak situations once HAV is ruled out; both RT-PCR (Roche) and TMA (Grifols) have been used for blood donation screening studies and routine diagnostics. HEV NAT has been multiplexed with HIV, HBV and HCV for blood donation screening as used routinely in Japan and evaluated in Spain (Grifols).
- Generally, ALT elevations are not predictive of HEV RNA status.

15.23 | Currently recommended donor deferral period

- No specific recommendations, but for comparison AABB recommends a deferral of 120 days following appropriately documented exposure to a community HAV outbreak that considers the potential for transmission from secondary HAV cases.

15.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable.
- Laboratory test(s) available: due to the high specificity of the available HEV NAT assays, along with relatively low
frequencies of HEV RNA-positive donors (~0.10% in most European countries that have implemented screening), the impact on blood availability is negligible.

15.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable.
- Laboratory test(s) available: the implementation of routine HEV NAT has improved blood safety as indicated by the near elimination of reported transfusion-transmitted HEV cases where rates of infection are deemed sufficiently high and screening has been implemented. Variability in preventing such cases is dependent on its use in the individual unit format versus that in minipools (which varies from 6 to 96 donations); however, the infectious dose remains controversial. Breakthrough cases following 24-member minipool NAT have been reported in the United Kingdom.

15.26 | Leukoreduction efficacy

- None expected.

15.27 | Pathogen reduction efficacy for plasma derivatives

- HEV is not eliminated 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% to 0.022% of plasma donations from North America and Europe were found to contain HEV RNA.

15.28 | 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.
- A vaccine has been licensed and available in China but not yet elsewhere. It is well-tolerated with an efficacy of 87% (95% CI: 71–94%). Because of one serotype, vaccines should be efficacious against all genotypes.
- Immune globulin collected from an endemic region has generally not been effective.
- Food can be rendered safe by cooking to 71°C (160°F) for 20 min. 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

13. Faramawi MF, Johnson E, Chen S, Pannala PR. The incidence of hepatitis E virus infection in the general population of the USA. Epidemiol Infect. https://doi.org/10.1017/S0950268810002177


