Transfusion-transmitted hepatitis E: What we know so far?

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Abstract

Hepatitis E virus (HEV) is a major cause of viral hepatitis globally. There is growing concern about transfusion-transmitted HEV (TT-HEV) as an emerging global health problem. HEV can potentially result in chronic infection in immunocompromised patients, leading to a higher risk of liver cirrhosis and even death. Between 0.0013% and 0.281% of asymptomatic blood donors around the world have HEV viremia, and 0.27% to 60.5% have anti-HEV immunoglobulin G. HEV is infectious even at very low blood concentrations of the virus. Immunosuppressed patients who develop persistent hepatitis E infection should have their immunosuppressant regimen reduced; ribavirin may be considered as treatment. Pegylated interferon can be considered in those who are refractory or intolerant to ribavirin. Sofosbuvir, a nucleotide analog, showed modest antiviral activity in some clinical studies but sustained viral response was not achieved. Therefore, rescue treatment remains an unmet need. The need for HEV screening of all blood donations remains controversial. Universal screening has been adopted in some countries after consideration of risk and resource availability. Various pathogen reduction methods have also been proposed to reduce the risk of TT-HEV. Future studies are needed to define the incidence of transmission through transfusion, their clinical features, outcomes and prognosis.

Key Words: Hepatitis E virus; Acute and chronic hepatitis; Immunosuppression; Blood transfusion; Transplantation

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Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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INTRODUCTION

Hepatitis E virus (HEV) was first discovered as an epidemic of non-A, non-B hepatitis in the 1980s[1], and has since become one of the major global causes of viral hepatitis. The World Health Organization estimated that HEV caused approximately 44000 deaths in 2015, and accounted for 3.3% of global deaths related to viral hepatitis[2]. A recent meta-analysis concluded that approximately 939 million of the global population have ever experienced HEV infection, and 15 to 110 million individuals have recent or ongoing infection[3]. The infection is generally self-limiting; however, it poses a threat to some vulnerable patients resulting in a significant burden of in-patient admissions, chronic infection, organ failure, and death[4]. The mortality rate can be greater than 20% in patients with chronic liver disease, cirrhosis, or pregnancy [4,5]. With a high HEV serological prevalence among the global population, the safety of blood products has become a public health concern. Herein, we review existing evidence on transfusion-transmitted HEV (TT-HEV), and the implications for screening of blood donations.

VIROLOGY

HEV is a positive-sense, single-stranded RNA icosahedral virus belonging to the genus Orthohepevirus within the Hepeviridae family[6]. Orthohepevirus A has eight distinct genotypes, of which HEV-1, -2, -3 and -4 infect humans[7]. HEV genotype C1, belonging to the species Orthohepevirus C, circulates in rats and can cause cross-species infection and sporadic zoonotic transmission to humans[8].

HEV exists in urine or feces as non-enveloped virions encased by a capsid. It circulates in blood in a membrane-associated, quasi-enveloped form (eHEV) which is considered to be less contagious[9]. The entry mechanisms for HEV are not well characterized, but once the genomic RNA is uncoated and delivered to the cytosol, the replication cycle is initiated[10]. The viral release that initiates subsequent infection requires multivesicular bodies through endosomal sorting complexes required for transport[11].

EPIDEMIOLOGY

The prevalence rates of HEV antibody are higher in developing countries than in developed countries[12]. The highest anti-HEV immunoglobulin G (IgG) seropositivity rate has been reported in Africa with a mean of 21.76%, followed by Asia (15.80%), Europe (9.31%), North America (8.05%), South America (7.28%), and Oceania (5.99%). In addition, the reported anti-HEV immunoglobulin M (IgM) seroprevalence rate was 3.09%, 1.86%, 0.79%, 0.22% and 2.43% in Africa, Asia, Europe, North America, and South America, respectively[3].
Among the four major genotypes that can infect humans, HEV-1 and -2 are mostly found in developing countries including Asia, Africa, Latin America, and Mexico. Infection is mainly transmitted \textit{via} fecally contaminated water, but occasionally also by person-to-person and vertical transmission\cite{13}. Hepatitis E occurs as outbreaks as well as sporadic cases of acute hepatitis, with the preponderance of cases among adolescents and young adults. When stratified by age, the estimated incidence of HEV-1 and -2 infection is roughly between 0.5\% and 1.0\% for ages 0 to 15 years, with rates increasing to between 1.0\% and 1.4\% for ages 15 years to 20 years, then falling rapidly to a lower rate of 0.2\% and below in individuals older than 30 years\cite{14}.

HEV-3 accounts for most of the autochthonous infection in developed countries while HEV-4 is mainly found in Asia and sporadically in Europe\cite{15,16}. The reported seroprevalence of HEV-3 ranged from 0.6\% to 52.5\% in Europe, 6\% in United States, 3 to 16\% in United Kingdom and up to 52\% in some regions of France\cite{17}. HEV-3 and HEV-4 are zoonotic viruses which are frequently transmitted \textit{via} food, close contact with animals, or transfusion of viremic blood units\cite{18}.

### CLINICAL FEATURES AND EXTRAHEPATIC MANIFESTATIONS

The incubation period following exposure to HEV ranges from 2 to 6 wks. HEV infection commonly takes a clinically silent, asymptomatic course with around 5\% to 30\% of infected individuals developing acute hepatitis\cite{19}. Symptoms of acute hepatitis include fever, malaise, anorexia, vomiting, followed by jaundice, tea-colored urine, and hepatomegaly\cite{20}. It is then followed by a convalescent phase with gradual recovery within a few weeks in immunocompetent patients\cite{21}. Acute liver failure is rare and occurs more frequently in middle-aged/elderly patients\cite{22}. Fulminant hepatitis with fatal outcome is uncommon, but has been observed in pregnant women or in patients with pre-existing liver disease. The development of fulminant hepatitis appears to be related to host-specific factors rather than virus genotype, variants, or specific substitutions\cite{23}. HEV superinfection may trigger liver decompensation in patients with chronic liver disease or cirrhosis, resulting in acute-on-chronic liver failure, which is associated with significant short-term mortality\cite{24,25}. Further research is needed to clarify the clinical features, course of illness, and prognosis of patients with decompensated cirrhosis who develop HEV infection.

HEV-3 and HEV-4 can persist in immunocompromised patients resulting in chronic infection, defined as viral replication lasting for more than 3 to 6 mo\cite{26}. It has been well described in patients after solid organ or stem cell transplant, hematology patients receiving chemotherapy, or HIV-infected patients\cite{27-32}. The prevalence of anti-HEV IgG was about 11.6\% and viral RNA was 2\% in solid organ transplant recipients\cite{33}. In solid organ transplant recipients who were positive for HEV RNA, more than 60\% developed chronic hepatitis\cite{33}.

The natural history of chronic hepatitis E infection is not well understood\cite{34}. In liver transplant recipients infected by HEV, histological analyses of liver biopsy revealed atypical morphology that is distinct from those in immunocompetent patients during early phases of infection\cite{35}. Proliferation of, and cytokine production by, CD4+ and CD8+ T-cells were impaired in patients with persistent HEV viremia\cite{36}. Chronic hepatitis E leads to liver fibrosis and cirrhosis. Cases of HEV-related hepatocellular carcinoma have been reported\cite{37}.

Although HEV predominantly infects hepatocytes, it may also affect other organs and present as extrahepatic manifestations. The mechanisms by which HEV can induce extrahepatic manifestations are not fully understood, but hypotheses include direct cytopathic tissue damage by extrahepatic replication, or immunological processes induced by an overwhelming host immune response\cite{39}. Details of extrahepatic manifestations are shown in Table 1\cite{39-44}.

### PREVALENCE IN BLOOD DONORS

**Viremia**

The prevalence of HEV RNA in blood donors varies around the world. (Table 2)\cite{45-78}. Most countries have a low prevalence of HEV viremia, ranging from 0.0013\% to 0.086\%. A relatively higher rate of viremia was reported in Germany (0.12\%) and China (0.281\%)\cite{49,70}. A meta-analysis of 10 studies from China showed a pooled prevalence of HEV RNA of 0.1\%\cite{79}. The actual prevalence might have been underes-
Table 1 Extrahepatic manifestations associated with hepatitis E virus infection

| System       | Extrahepatic manifestations                                                                 |
|--------------|---------------------------------------------------------------------------------------------|
| Neurological | Guillain-Barré syndrome (GBS)                                                                |
|              | Neuralgic amyotrophy                                                                        |
|              | Neuropathy                                                                                  |
|              | Bell’s palsy                                                                                |
|              | Encephalitis                                                                                |
|              | Transverse myelitis                                                                         |
|              | Myositis                                     |                                                                                           |
|              | Myasthenia gravis                                                                          |
|              | Pseudotumor cerebri                                                                        |
|              | Seizure                                      |                                                                                           |
| Renal        | Decrease glomerular filtration rate                                                         |
|              | Glomerulonephritis                                                                         |
|              | Nephrotic syndrome                                                                          |
|              | Mixed cryoglobulinemia                                                                     |
| Hematological| Thrombocytopenia                                                                           |
|              | Hemolytic anemia                                                                           |
|              | Aplastic anemia                                                                             |
|              | Hemophagocytic syndrome                                                                     |
|              | Monoclonal gammopathy of uncertain significance (MGUS)                                     |
| Others       | Thyroiditis                                                                                 |
|              | Pancreatitis                                                                               |
|              | Myocarditis                                                                                |
|              | Polyarthritis                                                                              |

Estimated as some studies included in the meta-analysis conducted RNA detection only in those donors who were positive for anti-HEV IgM or antigen[79].

The prevalence of HEV-3 and -4 is affected by dietary habits[80]. Consumption of raw pork tartare and undercooked pork liver may represent a relevant risk factor for HEV infection in Germany[49]. Regular consumption of pork meat and shellfish were also reported in the viremic donors in China[70].

Since 70% of infections with HEV-3 and -4 are asymptomatic[81], it can be difficult to identify infected blood donors, as viremia occurs primarily during the pre-icteric phase[82]. Katiyar et al[72] described anti-HEV IgG positivity in 60.5% of the tested donors in India and yet none of them were positive for HEV RNA. In India, human HEV is caused exclusively by the HEV-1 genotype, which causes brief hepatitis and seldom results in chronic infection[83,84]. The difference in endemicity between HEV genotypes may affect the propensity to cause symptomatic disease and viral persistence, which in turn influences the likelihood of viremia among blood donors.

Other factors influencing the reported prevalence of HEV viremia are the sensitivity and plasma pool size of the various nucleic acid test screening platforms used[85]. For example, 33 of 90 donations with a viral load of 20-750 IU/mL were positive when tested individually but missed in the pooled screening in a study by Hogema et al[57]. Delage et al[66] revealed a low prevalence (π = 11/50765) and viral loads of HEV-RNA in Canadian blood donors based on individual nucleic acid amplification techniques (NAT). They postulated that if pooled NAT was used, only two positive donations with viral loads > 1000 IU/mL would have been detected. The true frequency of viremia in blood donors in studies using pooled NAT could be underestimated due to a dilution effect. Vollmer et al[86] found that screening using individual NAT yielded an approximately 50% higher detection frequency compared with NAT of a mini-pool of 96 samples; nevertheless, samples exclusively positive for individual NAT had a
Table 2 Hepatitis E virus ribonucleic acid prevalence in donor, only studies include more than 1000 study subjects are included

| Ref.          | Country | Initial screening method | Number of donations screened | Number positive donations | Prevalence (95% CI) | HEV genotype: n/N | Median (range) viral load, IU/mL | Outcome of recipient |
|---------------|---------|--------------------------|------------------------------|---------------------------|---------------------|-------------------|----------------------------------|---------------------|
| Europe        |         |                          |                              |                           |                     |                   |                                  |                     |
| Fischer et al [45], 2015 | Austria | RT-PCR (plasma pool of 96 samples) with 95% LOD 11.6 IU/mL | 58915                       | 7                         | 0.012%             | 3: 7/7            | (2200 to 290000)                 | N/A                 |
| Vercouter et al [46], 2019 | Belgium | RT-PCR (plasma pool of 6 samples) with 95% LOD 18.6 IU/mL | 38137                       | 7                         | 0.018%             | N/A               |                                  | N/A                 |
| Harritshøj et al [47], 2016 | Denmark | TMA assay on individual plasma with 95% LOD 7.9 IU/mL | 25637                       | 11                        | 0.043% (0.02% - 0.07%) | 3 (in 2 samples) | 13 (unquantifiable to 920)       | (1) Look-back testing was performed in 7 recipients; all were tested negative for HEV RNA and anti-HEV IgM; (2) No recipient developed transaminitis; and (3) One patient had strongly positive anti-HEV IgG assay which may indicate recent HEV infection or secondary immune response by HEV re-exposure. |
| Gallian et al [48], 2014 | France  | RT-PCR (plasma pool of 96 samples) with 95% LOD 23 IU/mL | 53234                       | 22                        | 0.045% (0.043% - 0.047%). | 3c: 5/14; 3f: 8/14; 3 1/14 | (468 to 5155800)                | N/A                 |
| Westhölter et al [49], 2018 | Germany | RT-PCR (plasma pool of 24 samples) with 95% LOD 18.6 IU/mL | 18737                       | 23                        | 0.123%             | 3: 6/7            | (120 to 11200000)                | (1) Retrospective analysis of 4 viremic donors showed that they were HEV-positive in previous donations; (2) In 3 donors, testing of the previously donated blood in pools of 24 samples failed to identify viremic donations but were positive in unpoled samples; (3) Fourteen recipients had received HEV RNA positive blood products; (4) One immunosuppressed recipient tested positive for HEV RNA, developed acute on chronic liver failure, and died; and (5) One immunocompetent recipient developed acute self-limited episode of hepatitis E |
| Dreier et al [50], 2018 | Germany | RT-PCR with 95% LOD 4.7 IU/mL for FFP, platelet concentrates, and RBC supernatant; 95% LOD 8.9 IU/mL for RBCs. | 235524                       | 182                       | 0.077%             | 3: 4/4            | (< 25 to 69.4)                  | (1) Nine viremic donations were transfused to 6 different recipients; (2) Two recipients were immunocompromised (heart transplantation and leukemia); (3) Two recipients died shortly after transfusion for reasons other than HEV infection; and (4) None of the other 4 recipients developed acute HEV infection or had detectable HEV RNA / anti-HEV IgG |
| Corman et al [51], 2013 | Germany | RT-PCR (plasma pool of 96 samples mixed in metapools of 20) | 93955                       | 14                        | 0.015%             | 3: 14/14          | (3.1 to 4.8 Log10 IU/mL)         | N/A                 |
| Vollmer et al [52], 2012 | Germany | RT-PCR (plasma pool of 48 samples) with 95% LOD 4.7 IU/mL | 16125                       | 13                        | 0.081%             | 3: 13/13          | (13 to 68100)                  | N/A                 |
| Baylis et al [53], 2012 | Germany | RT-PCR (plasma pool of 96 samples) with 95% LOD 250 IU/mL | 18,100                      | 4                         | 0.022%             | 3                 | (3.26 to 5.35 Log10 copies/mL)   | Donations screened positive for HEV were excluded from pharmaceutical production |
| O Riordan et al | Ireland | TMA assay with 95% LOD | 24985                       | 5                         | 0.020%             | 3: 3/3            | (10 to 44550)                 | N/A                 |
| Author(s)                  | Year | Country | Methodology (Plasma Pool or Individual Plasma) | LOD (IU/mL) | Sensitivity (% and range) | 3c: positive/total | 3e: positive/total | 3a: positive/total | 2: positive/total | Other notes |
|---------------------------|------|---------|-------------------------------------------------|-------------|---------------------------|-------------------|-------------------|-------------------|-----------------|-------------|
| Cheung CKM et al          | 2016 |         |                                                 | 5.5         | (0.0065%-0.0467%)         | N/A               | N/A               | N/A               | N/A             |             |
| Spreafico et al           | 2020 | Italy   | TMA assay on individual plasma with 95% LOD 7.9 IU/mL | 0.0065-0.0467 | N/A                       | N/A               | N/A               | N/A               | N/A             |             |
| Spada et al               | 2018 | Italy   | RT-PCR, plasma pool and sensitivity varies according to anti-HEV IgG and IgM status | 0.0065-0.0467 | N/A                       | N/A               | N/A               | N/A               | N/A             |             |
| Hogema et al              | 2015 | Netherlands | RT-PCR (plasma pool of 96 samples) with 95% LOD 7.9 IU/mL | 0.0065-0.0467 | N/A                       | N/A               | N/A               | N/A               | N/A             |             |
| Slot et al                | 2013 | Netherlands | RT-PCR (plasma pool of 48 or 480 samples) with 95% LOD 25 IU/mL | 0.029-0.079 | 3c: 15/17; 3e: 2/17 | N/A               | N/A               | N/A               | N/A             |             |
| Grabarczyk et al          | 2018 | Poland   | TMA assay on individual plasma with 95% LOD 7.9 IU/mL | 0.035-0.079 | 3c: 2/3; 3e: 1/3 | N/A               | N/A               | N/A               | N/A             |             |
| Rivero-Juarez et al       | 2019 | Spain    | RT-PCR (plasma pool of 8 samples) with sensitivity 670 IU/mL | 0.035-0.079 | 3: 4/4 | N/A               | N/A               | N/A               | N/A             |             |
| Sauleda et al             | 2015 | Spain    | TMA assay on individual plasma with 95% LOD 7.9 IU/mL | 0.030-0.079 | 3f (in 1 sample) | N/A               | N/A               | N/A               | N/A             |             |
| Baylis et al              | 2012 | Sweden   | RT-PCR (plasma pool of 96 samples) with 95% LOD 250 IU/mL | 0.013-0.030 | 3 | N/A               | N/A               | N/A               | N/A             |             |
| Harvala et al             | 2019 | United Kingdom | RT-PCR (plasma pool of 24 samples) with 95% LOD 18.6 IU/mL | 0.026-0.030 | 3c: 112/149; 3e: 21/149; 3a: 1/149; 2 distantly related to 3h, and 1 clustered distinctly with 3a | N/A               | N/A               | N/A               | N/A             |             |
| Thom et al                | 2018 | United Kingdom | RT-PCR (plasma pool of 24 samples) | 0.040-0.040 | 3: 10/10 | N/A               | N/A               | N/A               | N/A             |             |
| Hewitt et al              | 2014 | United Kingdom | RT-PCR (plasma pool of 24 samples) | 0.035-0.035 | 3: 79/79 | N/A               | N/A               | N/A               | N/A             |             |

(1) Forty-three patients who had received blood components from HEV-infected donors were followed up; (2) The overall transmission rate was 42% (18 of 43 exposed patients); (3) One recipient developed clinical hepatitis and 4 recipients developed asymptomatic transaminitis; and (4) Four heavily
| Study                  | Country    | Methodology                                                                 | Samples | Detection Rate | Genotyping Success | LOD (IU/mL) |
|-----------------------|------------|------------------------------------------------------------------------------|---------|----------------|--------------------|-------------|
| Cleland et al [65], 2013 | United Kingdom | Nested PCR (plasma pool of 24 samples) with 95% LOD 201 IU/mL               | 43560   | 3.0069%        | N/A                | N/A         |
| Delage et al [66], 2013 | United States | RT-PCR on individual samples with 95% LOD 18.6 IU/mL                         | 50724   | 3.0059%        | N/A                | (23 to 1420) |
| Roth et al [67], 2013   | United States | RT-PCR (plasma pool of 96 samples) with 95% LOD 18.6 IU/mL                  | 50765   | 0.022%         | N/A                | (<10 to 3080) |
| Stramer et al [68], 2013 | United States | TMA assay on individual plasma with 95% LOD 7.9 IU/mL                       | 18829   | 0.011%         | N/A                | 14 IU/mL    |
| Xu et al [69], 2013     | United States | RT-PCR (plasma pool of 7 to 8 samples) with 95% LOD 200 IU/mL and nested PCR with 95% LOD 400 IU/mL | 1939    | N/A            | N/A                | N/A         |
| Baylis et al [53], 2012 | United States | RT-PCR (plasma pool of 96 samples) with 95% LOD 250 IU/mL                   | 51075   | N/A            | N/A                | N/A         |
| Wen et al [70], 2018    | China       | RT-PCR on individual plasma                                                  | 5345    | 0.281%         | N/A                | N/A         |
| Tsoi et al [71], 2019   | Hong Kong   | RT-PCR with 95% LOD 7.89 IU/mL                                                | 10000   | 0.023%         | N/A                | N/A         |
| Katiyar H et al [72], 2018 | India        | RT-PCR (plasma pool of 3 samples) with LOD 100 IU/mL                          | 1799    | N/A            | N/A                | N/A         |
| Minagi T et al [73], 2016 | Japan        | RT-PCR (plasma pool of 50 or 500 samples) with 95% LOD 152 IU/mL            | 620140  | 0.0058%        | N/A                | (<1.69 to 7.22 log10 copies/mL) |
| Intharasongkroh et al [74], 2019 | Thailand     | RT-PCR (plasma pool of 6 samples) with 95% LOD 53.5 IU/mL                    | 30115   | 0.086%         | N/A                | N/A         |
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| Others          | Country       | Methodological Details                                                                 | Sensitivity | Specificity | Limit of Detection | Limit of Accuracy | RBC | RNA | RT-PCR | N/A | N/A |
|-----------------|---------------|----------------------------------------------------------------------------------------|-------------|-------------|--------------------|-------------------|-----|-----|--------|-----|-----|
| Head et al[75], 2017 | Australia     | TMA (plasma pool of 6 samples)                                                          | 74131       | 1           | 0.0013%            | N/A               | 180 | N/A | N/A    | N/A | N/A |
| Shrestha et al[76], 2017 | Australia     | TMA assay on individual plasma with 95% LOD 7.9 IU/mL                                   | 14799       | 1           | 0.0068% (0.0002%-0.0376%) | 3                 | 15000 | N/A | N/A    | N/A | N/A |
| Hewitt et al[77], 2018 | New Zealand   | RT-PCR (plasma pool of 8 to 12 samples)                                                | 5000        | 0           | N/A               | N/A               | N/A | N/A | N/A    | N/A | N/A |
| Maponga et al[78], 2020 | South Africa  | TMA assay on individual plasma with 95% LOD 7.9 IU/mL                                   | 10000       | 1           | 0.01%             | 3                 | 79000 | All donations from donors with active HEV infection were discarded |

CI: Confidence interval; FFP: Fresh frozen plasma; HEV: Hepatitis E virus; Ig: Immunoglobulin; LOD: Limit of detection; RBC: Red blood cells; RNA: Ribonucleic acid; RT-PCR: Real time polymerase chain reaction; TMA: Transcription mediated amplification.

corresponding viral load of < 25 IU/mL. High-sensitivity individual NAT can yield false-positive results[55]. Whether the identification of low-level HEV-positive donors translates into clinical significance and whether a single individual NAT is adequate remain undefined.

**Antibodies**

In addition to direct detection of HEV RNA, another important indirect assessment of HEV burden is the prevalence of anti-HEV IgM and IgG in blood donors (Table 3)[45, 46,54-56,58,59,61,63,65,68,69,71,72,77,87-124]. HEV IgG prevalence increases with age which likely represents the cumulative effect of HEV exposure over a lifetime, especially as IgG antibodies can persist for decades[81]. The absence of detectable antibodies in donors was related to an increased risk of transfusion transmission of HEV[64]. However, the presence of anti-HEV IgG may not always be protective as multiple HEV reinfections could occur despite pre-existing antibodies[125]. Various HEV strains in serum are capable of replication in cell culture and generate infectious particles in the culture supernatant despite the coexistence of antibodies[126]. Anti-HEV IgM could be used to detect recent infection yet it failed to identify infected donors during the window period. For example, a meta-analysis of data from 28 countries found that only 26.6% of viremic blood units had positive anti-HEV antibodies[127]. In another study by Tedder et al[128], a significant portion of viremic individuals (n = 57/79) were seronegative at the time of donation. Anti-HEV IgM sometimes exhibits unexpectedly long persistence for up to 3 years after a self-limiting acute hepatitis E episode[129]. Only a minority of anti-HEV IgM-positive donors have detectable RNA[58,93,103,109]. All these findings suggest that detection of anti-HEV IgG or IgM alone may not provide effective screening of HEV in blood donors.
Table 3 Seroprevalence of hepatitis E in blood donors

| Ref.            | Country | Number of donations screened | Assay used                                      | Number of samples positive for HEV IgG antibodies | Anti-HEV IgG prevalence (95%CI) | Number of samples positive for HEV IgM antibodies | Anti-HEV IgM prevalence (95%CI) | Number of samples positive for HEV RNA in anti-HEV IgM positive | Viral load, IU/mL | Genotype |
|-----------------|---------|------------------------------|-------------------------------------------------|--------------------------------------------------|---------------------------------|---------------------------------------------------|---------------------------------|------------------------------------------------------------------|------------------|----------|
| Europe          |         |                              |                                                 |                                                  |                                 |                                                   |                                  |                                                                   |                  |          |
| Fischer et al[45], 2015 | Austria | 1203 (from HEV RNA negative donors) | Wantai                                         | 163                                             | 13.55% (11.6%-15.5%)           | N/A                                               | N/A                                           | 0                                                               | N/A              | N/A      |
| Vercouter et al [46], 2019 | Belgium | 356 (from HEV RNA negative donors) | Wantai                                         | 31                                              | 8.71% (6.20%-12.10%)           | 0                                                 | N/A                                           | 0                                                               | N/A              | N/A      |
| Miletić et al[57], 2019 | Croatia | 1036                          | 3 commercial ELISA assays were used, only findings with highest prevalence are shown | 209                                             | 20.17%                          | 46                                                 | 4.44%                                          | 0                                                               | N/A              | N/A      |
| Holm et al[88], 2015 | Denmark | 504                            | In-house NIH assay                              | 54                                              | 10.7% (8.2%-13.7%)             | N/A                                               | N/A                                           | N/A                                                             | N/A              | N/A      |
| Dimeglio et al [69], 2018 | France  | 300                            | Wantai                                         | 23                                              | 7.7% (4.9%-11.3%)             | 2                                                 | 0.6% (0.1%-2.4%)                                | 0                                                               | N/A              | N/A      |
| Juhl et al[90], 2013 | Germany | 1019                           | RecomWell assay and Western blot                | 69                                              | 6.8% (5.3%-8.3%)              | N/A                                               | N/A                                           | N/A                                                             | N/A              | N/A      |
| Dalekos et al [91], 1998 | Greece | 3016                           | Abbott assay and Western blot                   | 8                                               | 0.27%                          | 0                                                 | N/A                                           | N/A                                                             | N/A              | N/A      |
| O'Riordan et al [54], 2016 | Ireland | 1076                           | Wantai                                         | 57                                              | 5.3% (4.0%-6.8%)              | 2                                                 | 0.19%                                          | 0                                                               | N/A              | N/A      |
| Sprefico et al [55], 2020 | Italy   | 767                            | DiaPro                                         | 52                                              | 6.8% (5.1%-8.8%)              | 0                                                 | N/A                                           | 0                                                               | N/A              | N/A      |
| Spada et al[56], 2018 | Italy   | 10011                          | Wantai                                         | 869                                             | 8.7% (8.14%-9.25%)            | 46                                                | 0.4% (0.34%-0.61%)                              | 0                                                               | N/A              | N/A      |
| De Sabato et al [92], 2017 | Italy   | 170                            | Bio-Chain Institute and Western blot            | 15                                              | 8.82%                          | 3                                                 | 1.76%                                          | 0                                                               | N/A              | N/A      |
| Lucarelli et al [93], 2016 | Italy   | 313                            | Wantai                                         | 153                                             | 48.9% (43%-54%)               | 2                                                 | 0.6% (0.08%-2.3%)                              | 1                                                               | 100              | 3        |
| Puttini et al[94], 2015 | Italy   | 132                            | EIAGen HEV IgG kit                              | 12                                              | 9.1%                           | N/A                                               | N/A                                           | N/A                                                             | N/A              | N/A      |
| Author(s)                 | Country   | Lab   | Sample Size | Prevalence  | Methods                              | Anti-HEV       | Range | Titer | Sensitivity | Specificity |
|--------------------------|-----------|-------|-------------|-------------|--------------------------------------|----------------|-------|-------|-------------|-------------|
| Hogema et al [95], 2014  | Netherlands | Wantai | 513         | 11.31%      | N/A                                  | N/A            | N/A   | N/A   | N/A         | N/A         |
| Slot et al [58], 2013    | Netherlands | Wantai | 5239        | 26.7%       | 49                                   | 0.94%          | 4     | N/A   | Range: < 25 to 3700 | N/A         |
| Grabarczyk et al [59], 2018 | Poland    | Wantai | 3079        | 43.52%      | 39                                   | 1.27%          | N/A   | N/A   | N/A         | N/A         |
| Sauleda et al [61], 2015 | Spain      | Wantai | 1082        | 19.96%      | 13                                   | 1.20%          | 0     | N/A   | N/A         | N/A         |
|                         |            |        |             |             |                                      |                |       |       |             |             |
| Wantai                  |            |       |             |             |                                      |                |       |       |             |             |
| Mateos et al [96], 1999 | Spain      | Abbott assay and Western blot | 34 | 3.9% | 0 | N/A | N/A | N/A | N/A | N/A |
| Niederhauser et al [97], 2018 | Switzerland | Wantai | 3609        | 20.4%       | 737                                  | 4.9%           | N/A   | N/A   | N/A         | N/A         |
| Kaufmann et al [98], 2011 | Switzerland | Wantai | 550         | 4.9%        | 27                                   | N/A            | N/A   | N/A   | N/A         | N/A         |
| Thom et al [63], 2018    | United Kingdom | Wantai | 1714        | 6.1%        | 104                                  | 5.0%-7.3%      | N/A   | N/A   | N/A         | N/A         |
| Cleland et al [65], 2013 | United Kingdom | Wantai | 1559        | 4.7%        | 73                                   | 3.6%-5.8%      | 0     | N/A   | N/A         | N/A         |
| Beale et al [99], 2011   | United Kingdom | Wantai | 262         | 11.8%       | 31                                   | 1.5%           | 0     | N/A   | N/A         | N/A         |

**North America**

| Zafullah et al [100], 2018 | United States | Wantai | 5040 (from HEV RNA negative donor) | 11.29% | 146 | 2.90% | 0 | N/A | N/A |
| MP Biomedicals | 10.65% | 93 | 1.85%
| Wantai | 12.28% | 34 | 0.67%
| Wantai | 7.3% | 26 | 0.58% (0.39%-0.85%)
| Wantai | 18.8% | 8 | 0.4% (0.1%-0.7%)
| Wantai | 10% | 19 | 4.75%
| Wantai | 11.3% | 8 | 2.0% | 0 | N/A | N/A |

| South America |
|-----------------|
| Di Lello et al [101], 2020 | Argentina | DiaPro | 391 | 11.3% | 8 | 2.0% | 0 | N/A | N/A |
| Bangueses et al [102], 2020 | Uruguay | DiaPro | 400 | 10% | 19 | 4.75% | 3 | N/A | 3 |
| Asia         | Cambodia       | Wantai | 85   | 28.2% (23.4%-33.5%) | 3   | 1.0% (0.01%-1.8%) | 1   | 956 | 3 |
|-------------|----------------|--------|------|---------------------|-----|------------------|-----|-----|---|
| Chen et al[104], 2019 | China    | 4044  | 799  | 19.8% (18.6%-21.0%) | 43  | 1.1% (0.8%-1.4%) | 2   | N/A | 4 |
| Wen et al[70], 2018     | China   | 5345  | 1227 | 22.96%              | 38  | 0.71%            | 15  | N/A | N/A |
| Wang et al[105], 2017    | China   | 9069  | 2682 | 29.57%              | 131 | 1.44%           | 5   | N/A | N/A |
| Ma et al[106], 2015      | China   | 816   | 172  | 21.1%               | 4   | 0.5%            | 0   | N/A | N/A |
| Ren et al[107], 2014     | China   | 10741 | 2945 | 27.42%              | 109 | 1.01%          | 0   | N/A | N/A |
| Zhuang et al[108], 2014  | China   | 486   | 113  | 23.3%               | N/A | N/A            | N/A | N/A | N/A |
| Tsoi et al[71], 2019     | Hong Kong | 2000 | 315  | 15.8% (14.2%-17.4%) | 16  | 0.8%           | 0   | N/A | N/A |
| Tripathy et al[109], 2019 | India   | 2447  | 433  | 17.70% (16.23%-19.26%) | 5   | 0.20%          | 2   | N/A | 1 |
| Katiyar et al[72], 2018  | India   | 633   | 383  | 60.5%               | N/A | N/A            | 0   | N/A | N/A |
| Gajjar et al[110], 2014  | India   | 460   | N/A  | N/A                 | 22  | 4.78%          | N/A | N/A | N/A |
| Parsa et al[111], 2016   | Iran    | 700   | 42   | 6.0%                | 5   | 0.71%          | 5   | N/A | 1 |
| Hesamizadeh et al[112], 2016 | Iran    | 559   | 45   | 8.05%               | N/A | N/A            | N/A | N/A | N/A |
| Naeimi et al[113], 2015  | Iran    | 628   | 105  | 16.72%              | N/A | N/A            | N/A | N/A | N/A |
| Ehteram et al[114], 2013 | Iran    | 530   | 76   | 14.3%               | N/A | N/A            | N/A | N/A | N/A |
| Taremi et al[115], 2007  | Iran    | 399   | 31   | 7.8%                | N/A | N/A            | N/A | N/A | N/A |
| Takeda et al[116], 2010  | Japan   | 12600 | 431  | 3.42%               | N/A | N/A            | N/A | N/A | N/A |
| Shrestha et al[117], 2019 | Nepal   | 1845  | 773  | 41.9% (39.7%-44.1%) | 55  | 3.0% (2.2%-3.8%) | N/A | N/A | N/A |
| Authors          | Country     | Donors | Serology Kit                        | Samples Tested | Positive | CI    | False Negative | Reactivity | Other Assays |
|------------------|-------------|--------|-------------------------------------|----------------|----------|------|----------------|------------|--------------|
| Nasrallah et al  | Qatar       | 5854   | Wantai                             | 1198           | 20.46%   | 58% | 4              | N/A        | N/A          |
| Jupattanasin et al | Thailand   | 630    | EUROIMMUN test kit                  | 187            | 29.7% (26.2%-33.4%) | N/A | N/A | N/A | N/A | N/A |
| Africa           |             |        |                                     |                |          |      |                |            |              |
| Traoré et al     | Burkina Faso | 1497  | DiaPro and Wantai                   | 584            | 39%      | 13   | 0.87%          | N/A        | N/A          |
| Ibrahim et al    | Egypt       | 760    | N/A                                 | N/A            | N/A      | 3    | 0.39%          | 2          | N/A          |
| Meldal et al     | Ghana       | 239    | 4 commercial assays were used, findings reactive in; at least two serological assays are shown | 11             | 4.6%     | 14   | 5.9%          | 0          | N/A          |
| Lopes et al      | South Africa | 300   | Fortress Diagnostics                | 76             | 25.3%    | 0    | N/A            | N/A        | N/A          |
| Ben-Ayed et al   | Tunisia      | 426    | Globe; Diagnostics Srl ELISA        | 19             | 4.46%    | N/A  | N/A            | N/A        | N/A          |
| Others           |             |        |                                     |                |          |      |                |            |              |
| Hewitt et al     | New Zealand | 1013   | Wantai                             | 98             | 9.7% (7.9%-11.7%) | N/A | N/A | N/A | N/A | N/A |

ALT: Alanine aminotransferase; CI: Confidence interval; DSI: Diagnostic Systems Incorporated; ELISA: Enzyme-linked immunosorbent assay; HEV: Hepatitis E virus; NIH: National Institutes of Health.

Geographical variation, racial differences, and diverse study methodology and laboratory techniques all contribute to differences in HEV seroprevalence. More than one-third of donors had evidence of past HEV infection in Poland, India, Nepal and Burkina Faso[59,72,117,120]. Lucarelli et al[93] reported an unexpectedly high prevalence (48.9%) of anti-HEV IgG among 313 donors in central Italy. Eating raw dried pig liver sausage was the only independent risk factor for HEV IgG in their study, but the authors speculated that the uncontrolled expansion of the wild boar population had resulted in contamination of the soil and watercourses for people living in rural areas, and this may also have also contributed to the high prevalence of HEV[93].

Caution is needed when interpreting the HEV serology results because commercial kits for serological detection show marked variation in sensitivity and specificity. Despite the relatively high sensitivity of the IgM assay, the sensitivity of IgG detection kits is highly dependent on a patient’s immune status, being 80% to 90% in immunocompetent individuals, but falling dramatically to 15% to 45% in immunocom-
promised patients[130]. In a meta-analysis conducted in Europe, the pooled anti-HEV IgG seroprevalence rates determined by different commercial assays showed large variability with reported seroprevalence rates ranging from 2% to 17%[131]. Poor concordance of test results between the Wantai, Dia.Pro and MP Diagnostics HEV enzyme-linked immunosorbent assays (ELISA) were observed[132,133]. This may partly explain the broad ranges of anti-HEV IgG prevalence (5.3% to 48.9%) reported in Italy[55,56,92-94]. In contrast, most studies conducted in China used the Wantai assay and revealed a similar seroprevalence of around 20% to 30%. This assay is believed to be more sensitive than other commercial assays in detecting anti-HEV IgG[134,135].

**TRANSFUSION-TRANSMITTED HEPATITIS E**

HEV transmission via transfusion has been reported since 2004[136] and there has been increasing recognition of the risk of transmitting HEV by transfusion in recent years. Cases of TT-HEV are shown in Table 4[137-150]. Identical genomic sequences were identified in most infected patients and blood donors. Table 4 Likely only represents the tip of the iceberg as other probable or possible cases have been reported in the literature[151,152]. At the same time, patients with mild symptoms of hepatitis E may have gone undiagnosed. Physicians should stay vigilant for HEV infection in patients who have received a blood transfusion.

Although blood components that contain larger plasma volumes, principally frozen plasma and platelet components, are believed to transmit HEV more readily [64], a number of TT-HEV cases associated with red blood cell transfusion have also been described[138,140,141,143,144,148-150]. Red blood cell transfusion was a significant risk factor for HEV seropositivity in patients on hemodialysis in Croatia[153]. Twenty percent (n = 8/40) of multiply transfused thalassemia patients were anti-HEV IgG positive compared with 11.0% (n = 10/91) in blood donors[154]. In contrast, a study in Iran found anti-HEV antibodies in only 1.67% of patients with thalassemia, suggesting a low rate of TT-HEV in that country[155]. Results from these two studies in thalassemia patients were limited by the small sample size. Ankcorn et al[156] analyzed 1591 patients with hematologic malignancy and found that the more transfusions of non-HEV screened blood products the patients had received, the higher their likelihood of being IgG seroreactive was, suggesting HEV acquisition via transfusion in these patients.

A study by Hewitt et al[64] indicated that a viral concentration of between 407 and 257039 IU/mL in blood products was associated with TT-HEV, and that a high viral load in donors rendered infection more likely (P < 0.0001). However, this may not be true in immunocompromised patients. In a systematic review, Dreier et al[50] calculated the median transfused viral load in HEV-infected and non-infected immunocompromised patients. Although the transfused viral load was higher in the infected than the non-infected individuals (4.80 × 10^4 IU vs 1.55 × 10^4 IU), the between-group difference was not statistically significant (P = 0.1086)[50]. A potential reason for this finding is that a low viral concentration (150 IU/mL) of the blood component could already be infectious[140].

Most cases of TT-HEV occur in immunocompromised recipients, such as patients with hematologic malignancies, or recipients of solid organ or hematopoietic stem cell transplants. However, patients on simple immunosuppressants like corticosteroids and cyclosporine or even immunocompetent individuals are also at risk[157]. Massive transfusion increased the risk of HEV transmission in an immunocompetent trauma patient[158]. Spontaneous resolution, viral eradication by immunosuppressant reduction and/or ribavirin are possible[159] but occasionally there are cases which have progressed into chronic hepatitis, liver cirrhosis or multi-organ failure. Transfusion recipients are more vulnerable to chronic liver injury than the general population as a result of foodborne infection[140]. More than 60% (n = 56/85) of solid organ transplant recipients infected with HEV developed chronic hepatitis, with tacrolimus use as an independent predictive factor[160]. Pas et al[161] screened 1200 solid-organ transplant recipients in the Netherlands for HEV RNA and identified 12 patients with HEV infection. Nine of these 12 patients had been treated with a tacrolimus-based regimen postoperatively. In liver transplant recipients, graft hepatitis with rapid histological disease progression and requirement of re-transplantation due to liver cirrhosis has been reported[162,163]. The rapid progression of HEV infection to advanced fibrosis and cirrhosis has also been observed in individuals receiving kidney or heart transplants[33]. In 50 patients with hematologic malignancy and clinically
| Study                  | Number of patients | Comorbidity                                                                 | Blood component received (n) | Viral load of transfused blood product IU/mL | Genotype | Treatment | Outcome                                                                 |
|-----------------------|--------------------|------------------------------------------------------------------------------|-----------------------------|---------------------------------------------|----------|-----------|-------------------------------------------------------------------------|
| Okano et al [137], 2020 | 1                  | AML on chemotherapy                                                          | Plt                         | N/A                                         | 3b       | Nil       | Spontaneous resolution and developed HEV antibodies after cessation of chemotherapy for AML |
| Gallian et al [138], 2019 | 23                 | Solid organ transplant, n = 9; allogeneic hematopoietic stem cells transplant, n = 4; hematologic malignancies, n = 5; immunosuppressant, n = 2; immunocompetent, n = 3 | RBC n = 7; apheresis Plt n = 3; whole blood-derived pooled Plt n = 6; FFP n = 7 | Ranged from 1.14 × 10^3 to 31 × 62.10 | 3a, n = 1; 3c, n = 4; 3d, n = 16; 3e, n = 1; 4d, n = 1 | Ribavirin, n = 15 | Acute HEV infection, n = 8; spontaneous resolution, n = 4; ribavirin treatment, n = 3; immunosuppressant reduction, n = 1; chronic HEV infection, n = 14, all immunosuppressed; resolution with ribavirin, n = 10; resolution with immunosuppressant reduction, n = 4; One solid organ transplant recipient did not clear HEV infection despite ribavirin and died of multiorgan failure |
| Ledesma et al [139], 2019 | 2                  | Allogeneic BMT, n = 1; liver transplant, n = 1                             | Plt                         | 3 × 10^4                                   | 3e       | Ribavirin, n = 1 | The patient received BMT remained HEV-infected and IgM/IgG-negative until death; the patient with liver transplant was treated successfully with a course of ribavirin |
| Satake et al [140], 2017 | 19                 | Hematologic malignancies, n = 6; organ transplant, n = 2; systemic disease, n = 8; no major comorbidity, n = 3 | RBC n = 10; Plt n = 6; FFP n = 3 | Ranged from 1.5 × 10^7 to 5.3 × 10^8 | 4, n = 2 | N/A       | Two patients with malignant lymphoma and two who had received liver transplant developed chronic hepatitis E; the two liver transplant recipients were successfully cleared of HEV by ribavirin |
| Lhomme et al [141], 2017 | 3                  | Solid organ transplant                                                      | One patient received RBC; one patient received RBC and Plt; one patient received Plt and FFP | Ranged from 3.6 to 8.2 log IU | 3, n = 1; 3f, n = 2 | N/A       | N/A |
| Yamazaki et al [142], 2017 | 2                  | Hematologic malignancies treated with chemotherapy                          | N/A                         | N/A                                         | 3b       | N/A       | Did not become chronic hepatitis E |
| Belliere et al [143], 2017 | 1                  | Heart transplant                                                            | RBC                         | 1430 copies/mL                              | 3        | Ribavirin | Died from multi-organ failure despite treatment |
| Riveiro-Barciela et al [144], 2017 | 1              | Immunocompetent, admitted for disseminated infection                        | RBC                         | 75000                                       | 3        | Nil       | Spontaneous resolution |
| Hoad et al [145], 2017 | 1                  | Liver transplant                                                            | FFP                         | 947                                         | 3        | Ribavirin | Resolved with treatment |
| Matsui et al [146], 2015 | 1                  | AMI post CABG with hemorrhagic cardiac tamponade                            | Plt                         | 10^6 copies                                 | 3        | Nil       | Spontaneous resolution |
| Huzly et al [147], 2013 | 1                  | Immunocompromised                                                           | Apheresis Plt               | 30888-37273                                 | 3f      | N/A       | N/A |
| Coilly et al [148], 2013 | 1                  | Liver transplant                                                            | RBC                         | 3.5 log_{10}                               | 3c      | Ribavirin | Resolved with treatment |
| Boxall et al [149], 2006 | 1                  | Lymphoma on chemotherapy                                                    | RBC                         | N/A                                         | 3        | Nil       | Spontaneous resolution |
ALT: Alanine aminotransferase; AMI: Acute myocardial infarction; AML: Acute myeloid leukemia; BMT: Bone marrow transplant; CABG: Coronary artery bypass graft; FFP: Fresh-frozen plasma; HEV: Hepatitis E virus; Ig: Immunoglobulin; Plt: Platelet concentrates; RBC: Red blood cell.

**TREATMENT**

The management strategy for HEV infection should be determined by the clinical presentation. Currently, there is limited information in the published literature that describes the clinical features of TT-HEV, or the optimal approach to management. Acute TT-HEV infections are usually subclinical or mild, with no severe or fulminant cases reported[140]. Therefore, most acute HEV infections should be treated conservatively, while waiting for spontaneous clearance, although a short course of ribavirin may also be considered. In 21 patients with acute HEV infection who were at high risk of liver failure, receiving immunosuppressive therapy for an autoimmune disease or undergoing chemotherapy, a short course of ribavirin for up to 3 mo was associated with rapid virological response and normalization of liver enzymes[167].

The current practice for management of chronic HEV infection is mainly based on observational data[18]; Figure 1 shows a proposed algorithm for management. In patients who are on immunosuppressants, the first-line intervention should be a dose reduction or discontinuation of the immunosuppressive drug[168,169]. In solid organ transplant recipients, reducing the dose of immunosuppressive therapies that principally target T-cells can achieve HEV clearance in nearly one third of patients[160]. Most immunosuppressive drugs such as cyclosporine and tacrolimus increase HEV replication in vitro; mycophenolate mofetil is the only immunosuppressant agent demonstrated to have an anti-viral effect[170].

If modification of the immunosuppressant regimen is not possible or is unsuccessful, pharmacological agents such as ribavirin and/or pegylated interferon-alpha (peg-IFN) can be used[171]. In a meta-analysis that included 395 patients with chronic hepatitis E, ribavirin monotherapy for a median of 3 mo achieved sustained virological response (SVR) in 76% of patients[172]. The reported dose of ribavirin in the literature ranged from 29 to 1200 mg/d, and the duration from 1 to 18 mo. Data on the optimal treatment regimen are needed[173]. HEV RNA should be assessed in the serum and in the stool before treatment discontinuation[169]. A second course of ribavirin for 6 mo...
Figure 1 Recommended algorithm for management of transfusion-transmitted hepatitis E.

Acute transfusion-transmitted hepatitis E

- Monitor clinical symptoms, liver function and HEV RNA
- Reduce immunosuppressant if possible

Severe hepatitis with liver dysfunction

- Consider early ribavirin treatment

Preexisting chronic liver disease, receiving chemotherapy/immunosuppressive therapy

- Await for spontaneous clearance

- Yes
  - No treatment needed

- No
  - Chronic HEV infection

Ribavirin for 3 mo

Refactory to or intolerant of ribavirin

- HEV RNA in serum and stool positive

Ribavirin for 6 mo

- Persistent HEV infection or relapse

- HEV clearance

Pegylated interferon-alpha in patients with hematologic disorders, receiving hemodialysis, HIV, liver or kidney transplant recipients

can be attempted in cases of treatment failure\[172\]. HEV RNA concentrations decrease within the first week of initiating ribavirin therapy, and a greater reduction in viral load on day 7 is an independent predictor of SVR\[174\]. Ribavirin failure has been linked to the presence of certain single nucleotide variants (SNVs) and in-frame insertions in the hypervariable region of open reading frame (ORF) 1 in the HEV genome\[175\].

For those who are refractory to, or intolerant of, ribavirin, peg-IFN can be considered. Its efficacy has been documented in patients with hematologic disorders, patients receiving hemodialysis, and in combination with ribavirin in patients with HIV\[176-178\]. Close monitoring is needed if it is used in transplant recipients because of an increased risk of acute humoral and cellular rejection\[179,180\]. Peg-IFN was thought to be safe only in liver transplant recipients until recent case reports described its successful use in a kidney transplant recipient\[181-183\].

Sofosbuvir is a nucleotide analog shown to decrease replication of HEV-3 in vitro\[184\]. However, in clinical studies, only modest antiviral activity was observed and SVR was not achieved\[185-187\]. Rescue treatment for patients who are not eligible for, or not responding to, ribavirin and/or peg-IFN remains an unmet need.

HOW TO REDUCE TRANSFUSION-TRANSMITTED HEPATITIS E

The background risk of foodborne HEV transmission to both donors and recipients of blood products is not negligible. The transfusion-related risk of infection only exceeds the annual dietary risk when more than 13 individual donor components are transfused\[188\]. Strategies to reduce de novo infection, such as modifying eating habits and eliminating HEV from pigs and other animals that are used for food production are essential\[189\]. The one available vaccine (HEV 239, Hecolin, Xiamen, China) is licensed only in China, and has yet to play a fundamental role in global outbreaks or pandemic control\[190\]. Nonetheless, the transmissibility and disease phenotype may not be the same for a person who acquires the virus orally and a person who gets infected intravenously, as there may be some protection provided by the acidic environment of the stomach and the mucosal barrier in the gut\[191\]. The infectivity of the non-enveloped form is different to that of enveloped HEV\[9\]. Data reporting
outcomes of recipients of HEV-infected blood products are sparse[47,49,50,60,64]. Policies on screening HEV in blood products differ between countries. Universal screening was adopted in the United Kingdom, Ireland, and the Netherlands. Germany and France implemented targeted screening of donated plasma intended for use in high-risk patients[192]. In Japan, the use of nucleic acid-based screening is limited to Hokkaido[193]. Blood donors are not routinely tested for HEV infection in China including Hong Kong[70,71,194]. There has been much debate on mandatory HEV screening in blood donations[195]. Key questions, such as whether or not to screen, which laboratory assay to use, which donors to screen (universal or selective screening), and which types of blood components to screen should be assessed based on risk assessment, resource availability, health economics, and political or other influences. The answers may vary considerably by geographical location[169,196]. In areas where HEV is highly endemic, most donors and/or recipients have probably been exposed to HEV previously and would have positive IgG antibodies. Therefore, the decision on serological screening should also take into consideration the prevalence of HEV infection in that particular region.

All donors should answer a questionnaire about symptoms of clinical hepatitis and potential exposure to HEV prior to blood donation. Donation should be deferred in any donors with a history of clinical hepatitis[197]. Neither alanine aminotransferase (ALT) nor anti-HEV IgM testing correlate with the presence of HEV RNA, supporting the use of NAT for screening of blood donations[60,61,105]. A simulation study by Kampf et al[198] reported that testing for HEV RNA by NAT with a pool size of 96, and a 95% limit of detection of 20 IU/mL will result in an 80% reduction in expected HEV transmissions as well as of consequent chronic infections with severe complications. The risk of transmission could be reduced by 90% in NAT using a mini-pool of 24 samples[198].

If opting for selective screening instead of universal screening, a clear definition of at-risk patients is warranted[199]. Targeted screening should be contemplated for blood components that will be supplied to transplant recipients, or patients with hematologic malignancies or chronic liver disease, as these individuals are at high risk of developing fulminating hepatitis, acute on chronic liver failure, or chronic hepatitis. However, it is not yet clear whether patients with rheumatologic diseases, those on low-intensity immunosuppression, or elderly individuals should only receive HEV-negative blood products. A multicenter retrospective study in Europe including 21 rheumatology and internal medicine patients found that patients with rheumatoid arthritis who were receiving methotrexate or biologics were at risk of chronic hepatitis E infection[200]. However, another study in France did not find worse hepatitis E severity or increased risk of chronicity in 23 patients with inflammatory arthritis treated with immunosuppressants[201].

Patients co-infected with HIV with CD4+ count < 200/mm³ are at risk for persistent HEV infection[29]. In HIV patients with low CD4+ count, anti-HEV IgG seroconversion was delayed until immune reconstitution occurred[202]. A recent meta-analysis found that the HEV RNA positivity rate was significantly higher in transplant recipients than in HIV-positive patients [1.2% (95%CI: 0.9-1.6) vs 0.39% (95%CI: 0.2-0.7); P = 0.0011], possibly due to better immune status in the HIV-positive individuals using anti-retroviral therapy[203].

HEV-1 and -2 infections can take a fulminant course in pregnancy, resulting in liver failure, membrane rupture, spontaneous abortions, and stillbirths[204]. HEV-3 infection in pregnancy appears to be less virulent without significant maternal, fetal, or neonatal complications[205-207]. During pregnancy, a reduced cellular immunity and a high level of steroid hormones, in particular estrogen, progesterone, and human chorionic gonadotropin, influence viral replication/expression and possibly explain the disease severity[208]. The immune response could be influenced by HEV genotype, translating into different outcomes[209]. Ribavirin and peg-IFN are contraindicated in pregnancy due to concerns of teratogenicity[210]. Further studies are needed to clarify the risk of transmission of HEV to pregnant women via blood transfusion however, in view of the potentially serious disease course and absence of a safe treatment, pregnant women are a priority group for HEV-negative blood products.

Roth et al[67] evaluated the safety of plasma-derived medicinal products (PDMP) and found a very low prevalence of HEV RNA (0.002%) in plasma donors. Since viral reduction methods are used in the manufacturing processes of PDMP, these data do not support routine screening of all plasma pools intended for producing PDMP. Currently there is a lack of evidence to suggest that human serum albumin or coagulation factor concentrates are a major source of HEV infection[211,212].
The cost effectiveness of HEV screening of blood donations was analyzed in the Netherlands. Screening of whole blood donations in pools of 24 would prevent 4.52 of the 4.94 TT-HEV infections annually at a cost of approximately €310000 (Euro) per prevented chronic case. The estimated cost per incurable case prevented was 10-fold higher. Costs could potentially be reduced by 85% if only the blood products intended for use by immunocompromised patients were screened. Additional costs for selective screening may arise for logistic reasons and a possible increase in the number of blood products that expire before use. They concluded that preventing HEV transmission by screening of blood donations appears not excessively expensive compared with other blood-screening measures but the impact on disease burden may be small as only a minority of all HEV cases are transmitted by blood transfusion.[213]. Another economic analysis performed in North America found a very low estimated risk of TT-HEV infection risk leading to severe liver disease. When compared with no screening, the costs were $2.68 (USD) per component for a selective screening approach, and $6.68 per component for universal screening. The respective costs per quality-adjusted life-year gained were $225546 and $561810, respectively, which exceeded the threshold for what is considered as "cost-effective"[66].

In addition to screening, various pathogen reduction methods have been proposed to reduce risk of TT-HEV. Solvent/detergent treatment could not eliminate non-enveloped HEV in plasma[214]. Non-enveloped HEV is also resistant to the Intercept method, which combines a synthetic psoralen amotosalen HCl treatment with ultraviolet A light illumination to block the replication of DNA and RNA[215]. However, substantial viral reduction has been demonstrated during the manufacturing process of plasma products using immunosorbent chromatography, nanofiltration, cold ethanol fractionation and heat treatment[216]. Anti-HEV antibodies enhanced HEV removal by nanofiltration[217]. Furthermore, ultraviolet C light provided effective inactivation of HEV in platelet concentrates[218].

CONCLUSION

To conclude, TT-HEV is gaining attention worldwide. Although the overall prevalence of viremic blood donations is low, HEV can cause sinister consequences in immunocompromised recipients. Future studies are needed to define the incidence of transmission through transfusion, clinical features, outcomes, and prognosis. The decision on a screening policy in asymptomatic blood donors should be based on local risk assessment and health economics.

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