

66965_Auto_Edited.docx

WORD COUNT

4672

TIME SUBMITTED

26-NOV-2021 06:43AM

PAPER ID

79298449

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 66965

Manuscript Type: REVIEW

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

Cheung *et al.* Transfusion-transmitted hepatitis E

11

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

Cheung CKM, Wong SH, Law AWH, Law MF. Transfusion-transmitted hepatitis E: what we know so far? *World J Gastroenterol* 2021; In press

Core Tip: Transfusion-transmitted hepatitis E virus (HEV) is an emerging global health concern. In immunocompromised patients, chronic HEV infection increases the risk of liver cirrhosis. The prevalence of viremia and anti-HEV immunoglobulin G in asymptomatic blood donors varies widely between countries but even low concentrations of HEV in blood components are infectious, and in most countries blood donations are not routinely screened for HEV. Treatment of persistent infection includes modification of the immunosuppressant regimen followed by ribavirin. The need for screening of HEV in all blood donations remains controversial. Strategies to reduce de novo HEV infection should also be emphasized.

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

5

HEV is a positive-sense, single-stranded RNA icosahedral virus belongs 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 *via* fecally contaminated water, but occasionally also by person-to-person and vertical transmission^[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 to 20 years, then falling rapidly to a lower rate of 0.2% and below in individuals older than 30 years^[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^[15,16]. The reported seroprevalence of HEV-3 ranged from 0.6% to 52.5% in Europe, 6% in USA, 3 to 16% in UK and up to 52% in some regions of France^[17]. HEV-3 and HEV-4 are zoonotic viruses which are frequently transmitted *via* food, close contact with animals, or transfusion of viremic blood units^[18].

CLINICAL FEATURES AND EXTRAHEPATIC MANIFESTATIONS

The incubation period following exposure to HEV ranges from 2 to 6 wk. HEV infection commonly takes a clinically silent, asymptomatic course with around 5% to 30% of infected individuals developing acute hepatitis^[19]. Symptoms of acute hepatitis include fever, malaise, anorexia, vomiting, followed by jaundice, tea-coloured urine, and hepatomegaly^[20]. It is then followed by a convalescent phase with gradual recovery within a few weeks in immunocompetent patients^[21]. Acute liver failure is rare and occurs more frequently in middle-aged/elderly patients^[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^[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^[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^[26]. It has been well

described in patients after solid organ or stem cell transplant, hematology patients receiving chemotherapy, or HIV-infected patients^[27-32]. The prevalence of anti-HEV IgG was about 11.6% and viral RNA was 2% in solid organ transplant recipients^[33]. In solid organ transplant recipients who were positive for HEV RNA, more than 60% developed chronic hepatitis^[33].

The natural history of chronic hepatitis E infection is not well understood^[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^[35]. Proliferation of, and cytokine production by, CD4+ and CD8+ T-cells were impaired in patients with persistent HEV viremia^[36]. Chronic hepatitis E leads to liver fibrosis and cirrhosis. Cases of HEV-related hepatocellular carcinoma have been reported^[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^[38]. Details of extrahepatic manifestations are shown in Table 1^[39-44].

PREVALENCE IN BLOOD DONORS

Viremia

The prevalence of HEV RNA in blood donors varies around the world. (Table 2)^[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%)^[49,70]. A meta-analysis of 10 studies from China showed a pooled prevalence of HEV RNA of 0.1%^[79]. The actual prevalence might have been underestimated 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* described anti-HEV IgG positivity in 60.5% of the tested donors in India and yet none of them were positive for HEV RNA ^[72]. 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 ($n = 11/50765$) 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 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.

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 immunocompromised 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 fresh 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 (4.80×10^5 IU *vs* 1.55×10^4 IU), the between-group difference was not statistically significant ($P = 0.1006$)^[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 overt hepatitis E, the mortality rate was 16% ($n = 8$), with liver-related death occurring in 4 patients^[164]. HEV could actively suppress the cellular immune response and increase levels of immunosuppressive interleukin-10 that may perpetuate chronic infection and subsequent liver damage^[165,166].

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/day, 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 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 UK, 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 Kamp *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 fulminant 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 multicentre 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. ² 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 ² 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. ⁴ 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. ⁴ 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 immunoaffinity 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.

10%

SIMILARITY INDEX

PRIMARY SOURCES

- 1** www.ncbi.nlm.nih.gov 111 words — 2%
Internet
- 2** www.science.gov 85 words — 2%
Internet
- 3** onlinelibrary.wiley.com 71 words — 1%
Internet
- 4** Gilles Delage, Margaret Fearon, Yves Gregoire, Boris M Hogema et al. "Hepatitis E Virus Infection in Blood Donors and Risk to Patients in the United States and Canada", *Transfusion Medicine Reviews*, 2019 64 words — 1%
Crossref
- 5** pubmed.ncbi.nlm.nih.gov 52 words — 1%
Internet
- 6** Daniel Todt, Toni Luise Meister, Eike Steinmann. "Hepatitis E virus treatment and ribavirin therapy: viral mechanisms of nonresponse", *Current Opinion in Virology*, 2018 24 words — < 1%
Crossref
- 7** Lisette Hauser, Anne-Marie Roque-Afonso, Alexandre Beylouné, Marion Simonet et al. "Hepatitis E transmission by transfusion of Intercept blood system-treated plasma", *Blood*, 2014 22 words — < 1%
Crossref

-
- 8 www.thelancet.com 17 words — < 1%
Internet
-
- 9 Zhou, Xinying, Robert A. de Man, Robert J. de Knecht, Herold J. Metselaar, Maikel P. Peppelenbosch, and Qiuwei Pan. "Epidemiology and management of chronic hepatitis E infection in solid organ transplantation: a comprehensive literature review : HEV in organ transplantation", *Reviews in Medical Virology*, 2013. 16 words — < 1%
Crossref
-
- 10 mts.intechopen.com 14 words — < 1%
Internet
-
- 11 www.mdpi.com 14 words — < 1%
Internet
-
- 12 Ashish C. Shrestha, Robert L. P. Flower, Clive R. Seed, Susan L. Stramer, Helen M. Faddy. "A Comparative Study of Assay Performance of Commercial Hepatitis E Virus Enzyme-Linked Immunosorbent Assay Kits in Australian Blood Donor Samples", *Journal of Blood Transfusion*, 2016 12 words — < 1%
Crossref
-
- 13 John R. Ticehurst, Nora Pisanic, Michael S. Forman, Carly Ordak et al. "Probable transmission of hepatitis E virus (HEV) via transfusion in the United States", *Transfusion*, 2019 12 words — < 1%
Crossref
-
- 14 Putu Prathiwi Primadharsini, Shigeo Nagashima, Hiroaki Okamoto. "Genetic Variability and Evolution of Hepatitis E Virus", *Viruses*, 2019 12 words — < 1%
Crossref

EXCLUDE QUOTES ON

EXCLUDE MATCHES

< 12 WORDS

EXCLUDE BIBLIOGRAPHY ON