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Transfusion-Transmitted Hepatitis E and Implications for Blood Donation Screening: A Narrative Review

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Abstract

Hepatitis E, which is caused by infection with the hepatitis E virus (HEV), is common in places with poor sanitation. HEV belongs to the Hepeviridae family, genus Orthohepevirus, and is an RNA virus. Over the past 19 years, cases of HEV transmitted by transfusions have been reported. Growing apprehension regarding the transmission of hepatitis E virus (HEV) through blood transfusions has emerged as a burgeoning global health concern. Individuals with compromised immune systems who contract HEV may experience a protracted infection, elevating their susceptibility to the development of liver cirrhosis and, ultimately, facing mortality. HEV can be transmitted at even relatively low blood levels of the virus. The usefulness of HEV testing on all blood donors is still up for debate. Some countries have implemented universal screening of HEV after taking risk and resource availability into account. The key approach for prevention is the HEV NAT screening. Alternative approaches, such as NAT testing for all or portion of blood donations individually or in a small pool, are being investigated. Future research is required to determine the incidence of HEV transmission by transfusion as well as its clinical characteristics, prognosis, and consequences. This article reviews the available data on transfusion-transmitted HEV, summarizes the prevalence of HEV infections among blood donors, and discusses the significance of these findings for blood donor screening. The review is based on a structured literature search using electronic databases, including Medline, Embase, Scopus, PubMed, Directory of Open Access Journals, and Web of Science. The literature search was accomplished in the databases already stated above using the keywords (HEV OR Hepatitis E Virus), (Blood Transfusion), (Transfusion-Transmitted), (Blood Safety), AND (Donor Screening).

Key Words: Hepatitis E, Blood, Transfusion, Screening

Introduction

In recent times, viral infections have emerged as a significant threat to global public health. RNA viruses have taken the forefront as the primary cause behind the majority of newly emerging viral diseases. One such single-stranded, non-enveloped RNA virus that causes hepatitis E is the hepatitis E virus (HEV). During the 1980s, an outbreak of non-A, non-B hepatitis led to the initial identification of this virus.[1] Outbreaks of hepatitis E virus (HEV) are commonly triggered by contaminated water sources, and the virus is primarily transmitted through oral-fecal routes. The prevalence of HEV is strongly associated with the socioeconomic status of the affected community.

The prevalence of HEV is significantly underestimated, and there is a lack of awareness among healthcare professionals about this disease.

Consequently, routine screenings for hepatitis E are seldom conducted in hospitals across the majority of countries worldwide, leading to both underdiagnosis and misdiagnosis of the condition. The hepatitis E virus presents a growing concern in the context of blood safety. The discussion surrounding the potential hazards and the importance of addressing hepatitis E virus infections resulting from contaminated blood donations has become a prominent subject of discussion within the field of transfusion medicine.

Aim of Review

This article's goal is to reflect on the current epidemiology of the hepatitis E virus, its prevalence in blood donors, and transfusion-transmitted hepatitis E. Finally, it discusses

the implications of HEV screening in blood donors, especially in a developing country like Pakistan. Studying the HEV epidemiology in blood donors and reviewing the transfusion-transmitted cases of HEV will accelerate the formulation and subsequent implementation of evidence-based control policies intended to prevent the transmission of HEV through blood transfusions.

Method of Review

This review is based on a comprehensive exploration conducted through electronic databases such as Medline, PubMed, Embase, Scopus, the Directory of Open Access Journals, and Web of Science. The aim was to meticulously extract peer-reviewed and pertinent publications, thoroughly assess their findings, identify knowledge gap, and propose directions for future research and action. Both prospective and retrospective studies were included. The literature search was accomplished in the databases already stated above using the keywords (HEV OR Hepatitis E Virus), (Blood Transfusion), (Transfusion-Transmitted), (Blood Safety), AND (Donor Screening). Words were searched as both keywords and appropriate subject headings for particular databases. The literature search resulted in 86 articles; including original articles, review articles, and survey reports, of which 64 were incorporated in this article. Non-English language studies were removed from the results.

HEV Virology

Scientists in HEV virology investigate how the virus infects host cells, replicates within them, and causes hepatitis E infections. Understanding HEV virology is crucial for developing diagnostic tests, treatments, and preventive measures against hepatitis E. The HEV belongs to the Hepeviridae family and the genus *Orthohepevirus.* There are eight genotypes of HEV, with genotypes 1 to 4 known to affect humans. The HEV genome has open reading frames abbreviated as ORF and include (i) ORF1 encoding nonstructural (functional) proteins including RNA-dependent RNA polymerase and methyltransferase, (ii) ORF2 encoding the viral capsid protein, and (iii) ORF3 encoding a functional ion channel that plays a crucial role in the release of viral particles.[2] The two endemic genotypes 1 and 2 (of the four main HEV genotypes) infect humans and are liable for waterborne outbreaks. Genotypes 3 and 4 of the hepatitis E virus (HEV) are linked to zoonotic HEV infections, which can be transmitted to humans through contact with infected animals or by consuming raw or insufficiently cooked shellfish or pork that has been contaminated with the virus.[3] HEV entry pathways are poorly understood, although the replication cycle starts as soon as the genomic RNA is carried to the cytosol and uncoated.[4]

Clinical Signs and Symptoms

Following HEV exposure, the incubation period can last anywhere between two and six weeks. Typically, HEV infection is clinically latent and asymptomatic, with 5 - 30% of infected people suffering acute hepatitis.[5] Fever, malaise, anorexia, and vomiting are signs of acute hepatitis, which is then accompanied by jaundice, tea-coloured urine, and hepatomegaly, among others. In immunocompetent patients, it is subsequently followed by a quiescent period with gradual recovery over the course of a few weeks.[6] Acute liver failure is uncommon and mostly affects middle-aged or older people. Although fatal cases of fulminant hepatitis are rare, they have been reported in individuals with pre-existing liver illnesses or in pregnant women. Instead of the genotype, variations, or specific substitutions of the virus, host-specific variables seem to be more closely linked to the occurrence of fulminant hepatitis.[7] The infection is typically self-limiting, but some vulnerable people are at risk, which results in a large burden of inpatient hospitalizations, chronic infection, organ failure, and loss of life.[8] Individuals with chronic liver disease, cirrhosis, or pregnancy may have a mortality rate of more than 20%.[9]

Epidemiology

HEV is the most prevalent cause of acute viral hepatitis globally and the fifth recognized hepatitis virus after types A, B, C, and D. In contrast to developed nations, developing countries exhibit higher incidence rates of HEV antibodies.[10] With a mean of 21.76%, Africa has the highest anti-HEV IgG seropositivity rate, followed by Asia (15.80%), Europe (9.31%), South America (7.28%), and Oceania (5.99%). Additionally, the reported HEV IgM prevalence rates in Africa, Asia, Europe, North America, and South America were 3.09%, 1.86%, 0.79%, 0.22%, and 2.43%, respectively.[11] According to the World Health Organization, HEV was responsible for 3.3% of all viral hepatitis deaths worldwide in 2015, killing over 44,000 people. According to recent estimates, approximately 20 million new cases of HEV occur annually, with approximately 20% of these cases exhibiting symptoms.[12] Hudu *et al.,* estimated that there are 6.5 million symptomatic incidences of this disease, with a case-death rate of 160,000 per year and over 2,700 stillbirth cases in Asia alone.[13] Globally a high number of sporadically

transmitted hepatitis E cases occur in contrast to epidemic cases of hepatitis E. According to a recent meta-analysis, 15 - 110 million people worldwide have a current or continuing HEV infection, and over 939 million people worldwide have ever encountered HEV infection.[14]

However, despite these troubling statistics, the prevalence of hepatitis E remains grossly underreported. Physicians are not well-informed about the illness. As a result, in the majority of countries around the world, routine disease checks are rarely done in hospitals, resulting in the under- and misdiagnosis of hepatitis E. Additionally, a scarcity of research studies exist regarding the epidemiology of hepatitis E, particularly in developed countries. This reinforces the initial notion that hepatitis E primarily prevails in economically poor regions. Nonetheless, contemporary research on HEV has prompted a reevaluation of the understanding of its epidemiology. These studies have unveiled additional insights into this enigmatic virus while also raising further unresolved queries. Presently, HEV is recognized as an emerging disease with the potential to jeopardize global public health.

HEV and Blood Transfusions

Transfusions and transplants involving blood and blood components have been documented to transmit HEV.[14] Because the majority of HEV infections are without symptoms, it is likely for reactive blood donors to donate blood while having viraemia. Acute phase viraemia in HEV patients normally lasts for 6 to 8 weeks. Nucleic acid testing (NAT) has found a high frequency of viraemic donors, up to 1:726, in numerous European states.[15] The number of transfusion-transmitted HEV infections reported to date has been extremely low, most likely as a result of underreporting and underrecognition. HEV first acquired relevance as a transfusion-transmitted infectious pathogen in 2004. Erythrocytes, platelet concentrates, pooled granulocytes, and fresh frozen plasma samples have all shown evidence of HEV transmission.[16] Public health professionals are now concerned about the safety of blood products due to the increasing serological prevalence of HEV in the world's population and research showing reactivity in healthy blood donors.[17] In retort to the threat raised by HEV to blood products, Ireland and England have each executed universal or selective (screening of donations for immunocompromised patients) screening of blood donations for the incidence of HEV RNA, and other countries are contemplating doing the same. This article reviews the available data on transfusion-transmitted HEV, summarizes the epidemiology of HEV infections among blood donors, and discusses the significance of these findings for blood donor screening.

HEV Prevalence in Blood Donors

Different regions of the world have different prevalence rates of HEV in blood donors. Most regions have a modest prevalence of HEV viraemia, ranging from 0.0013% to 0.086%, according to a meta-analysis of 34 research.[18] A comparatively greater rate of viraemia was seen in Germany (0.12%)[19] and China (0.281%).[20] According to the German study, eating raw or undercooked pork liver may be a significant predictor for HEV infection. The viraemic donors in China also reported regularly consuming hog meat and shellfish. The combined prevalence of HEV RNA was 0.1% according to a meta-analysis of 10 Chinese studies. Because several of the studies included in the meta-analysis only tested donors who had anti-HEV IgM or antigen positivity, the true prevalence may have been misrepresented.[21] Since viraemia mostly occurs during the pre-icteric period, it can be challenging to detect infected blood donors since 70% of HEV-3 and -4 infections are asymptomatic.[22] In India, 60.5% of the tested donors had anti-HEV IgG positivity, but none of them had HEV RNA positivity.[23] The HEV genotype 1, which results in transient hepatitis and infrequently leads to chronic infection, is the only one responsible for human HEV infections in India.[24] The risk of viraemia among blood donors is influenced by the variation in endemicity between HEV genotypes, which in turn determines the tendency to induce symptomatic disease and viral persistence.

The sensitivity and size of the plasma pool of various NAT-screening systems employed are further factors affecting the reported prevalence of HEV viraemia.[25] A viral load of 20-750 IU/mL in 33 of 90 donations, for instance, tested positive when screened individually but was overlooked by the pooled screening.[15] Based on individual NAT, Delage *et al.,* found that Canadian blood donors had a low prevalence (n = 11/50,765) and viral levels of HEV-RNA.[26] They hypothesized that only two reactive donations with viral loads of more than 1,000 IU/mL would have been found if pooled NAT had been utilized. A dilution effect may cause research using pooled NAT to underestimate the true prevalence of viraemia in blood donations. According to Vollmer *et al.,* screening using individual NAT produced a detection rate that was almost 50% higher than that of NAT of a mini-pool of 96 samples, although samples that were solely positive for individual NAT had viral loads that were lower than 25

IU/mL.[27] Individual NAT (Nucleic Acid Testing) with a high level of sensitivity can potentially yield false-positive results. Additionally, it remains uncertain whether identifying low-level HEV-positive donations has clinical significance or whether a single individual NAT is adequate for this purpose.

The frequency of antibodies to HEV (IgM and IgG) in blood donors is a crucial indirect measure of HEV burden in addition to the direct assessment of HEV RNA (already discussed). Given that IgG antibodies can last for decades, the fact that HEV IgG prevalence rises with age presumably denotes the aggregated effect of HEV exposure over a lifespan.[28]

The risk of HEV transmission through blood transfusion was higher in donors without detectable antibodies.[29] However, it is important to note that repeated HEV reinfections may still occur despite pre-existing antibodies, suggesting that the existence of anti-HEV IgG will not always be protective.[30] Anti-HEV IgM can be employed to identify infected donors during the window period, but it is ineffective in detecting recent infections. For instance, a meta-analysis of data from 28 countries found that only 26.6% of blood bags containing the HEV virus showed the presence of anti-HEV antibodies.[31] All of these findings imply that screening for HEV in blood donors may not be as efficient when anti-HEV IgG or IgM are detected as screening markers.

Different HEV antibody prevalence estimates are caused by geographic variation, racial variation, different research methodologies, and various laboratory assays. Given the observable discrepancies in sensitivity and specificity among commercial serological screening kits, caution should be exercised when interpreting the outcomes of HEV serological tests.

Although the IgM assay exhibits relatively high sensitivity, the effectiveness of IgG detection kits is largely contingent on the immune status of the patient, with sensitivity rates ranging from 80% to 90% in immunocompetent individuals and declining to 15-45% in immunocompromised patients.[32] The pooled anti-HEV IgG seroprevalence rates assessed by various commercial assays in a meta-analysis carried out in Europe showed significant variation, with reported seroprevalence percentages ranging from 2% to 17%.[33] A study from Italy has observed a poor correlation between test findings from various HEV enzyme-linked immunosorbent tests (ELISA) kits.[34] This may help explain the wide variations in anti-HEV IgG prevalence recorded in Italy (5.3% to 48.9%).[35]

HEV and Transfusion-Transmitted Cases

Since 2004, there have been documented cases of HEV infection resulting from blood transfusions, and in recent years, the potential for HEV transmission through transfusions has garnered increasing attention. The genomic sequences of the majority of the infected patients and corresponding blood donors were found to be identical, leading to the reporting of a total of 86 cases (Table I) of HEV that were transmitted by transfusion. These 86 cases (from 20 studies) just reflect the tip of the iceberg, as other likely or plausible cases have been documented in the research studies.[36] At the same time, it's possible that patients with hepatitis E who only had minor symptoms remained undetected.

As evident from Table I, some cases of transfusion-transmitted HEV connected to red cell concentrates transfusion has also been recorded, despite the fact that blood components with larger plasma quantities, primarily fresh frozen plasma and platelet concentrate, are thought to transmit HEV more easily. In Croatia, receiving red blood cell transfusions was a major risk element for developing HEV seropositivity in haemodialysis patients.[56] A Brazilian study reported that anti-HEV IgG positivity was found in 20% (n = 8/40) of repeated transfused thalassaemia patients compared to 11.0% (n = 10/91) in blood donors.[57] In comparison, research in Iran discovered anti-HEV antibodies in just 1.67% of thalassaemia patients, indicating a low prevalence of transfusion-transmitted HEV there.[58] According to a study by Hewitt *et al.,* high-level viraemia in donors made infection more probable (P 0.0001) and a viral concentration of between 407 and 257,039 IU/mL in blood products was related to transfusion-transmitted HEV.[29] In people with impaired immune systems, this might not be the case.

The majority of transfusion-transmitted HEV cases, as shown in Table I, involved immunocompromised patients, such as patients with haematological malignancies or those who had received organ or haematopoietic stem cell transplants. Patients on basic immunosuppressants like corticosteroids and cyclosporine, as well as people who are immunocompetent, are also at risk.

There are currently different ways of improving - blood safety against HEV. Potential countermeasures include immunization of patients at risk, which is not yet available and is unproven against intravenous challenge, pathogen inactivation of blood components, which may not yet be

adequately effective for some non-enveloped viruses like HEV, and testing of blood donations, which is a readily accessible intervention but not commonly used due to effectiveness constraints and costs. Individuals who run the risk of suffering serious consequences are still at risk of contracting transfusion-transmitted HEV infection without implementing such precautionary strategies.[59]

When there are certain patient groups at risk of infection from blood transfusions, there is a strong case for screening donations for all potential pathogens. The group of individuals that are recognized as being at risk for transfusion-transmitted HEV (recipients of organ and haematopoietic stem cell transplants, as well as immunosuppressed patients) is significantly smaller, but they may receive a significant amount of transfusions, increasing the likelihood of exposure and, consequently, the risk of infection.

If the possibility of transfused patients being exposed to dietary sources is not completely removed, the justification for screening blood donations for HEV RNA becomes debatable. Similarly, certain diseases spread by transfusions that affect immunosuppressed people, including parvovirus B19, are nevertheless tolerated and unchecked. However, despite prolonged community contact with transfusion patients, laboratory screening of certain infections (such as cytomegalovirus) has been used in transfusion practices. Therefore, it would appear that the danger of HEV exposure outside of a transfusion may not be a major factor in the choice to conduct HEV RNA screening of blood donors. Prior to giving blood, all donors are required to complete a questionnaire concerning clinical hepatitis symptoms and possible HEV exposure. Any donors with a past record of clinical hepatitis should avoid donation. The utilization of NAT for blood donor screening is supported by the fact that neither anti-HEV IgM testing nor alanine aminotransferase (ALT) testing corresponds with the detection of HEV RNA.[60] NAT might lower the likelihood of transmission by 90% by employing a mini-pool of 24 samples.[61]

In the Netherlands, the cost-effectiveness of blood donation HEV screening was examined. Screening 24 pools of whole blood donations would prevent 4.52 of the 4.94 transfusion-transmitted-HEV infections each year at around 310,000 Euros for each chronic case avoided. The anticipated cost per preventable incurable case was ten times greater. Only screening blood products designated for use by immunocompromized individuals might possibly lower costs by 85%. They came to the conclusion that screening blood donors to prevent HEV transmission does not appear to be overly expensive when compared to other blood-screening procedures, but the impact on disease burden may be minimal because only a small percentage of HEV cases are transmitted through blood transfusions.[62] In Germany, there is ongoing preparation to implement mandatory testing of all blood donations for Hepatitis E virus (HEV) following the recommendation of the esteemed Paul-Ehrlich-Institute.[63] Other countries, including Ireland, the UK, Japan, and the Netherlands, have already instituted a nationwide HEV RNA universal screening of blood donations.[55,59] In Switzerland, the screening of all blood products for HEV using nucleic acid testing commenced in November 2018.[64] In contrast, blood authorities in Greece, Portugal, Italy, France, and Spain are currently engaged in evaluating the feasibility and potential implementation of similar measures.[59] This step towards HEV testing underscores the growing importance of safeguarding the blood supply from infectious agents to ensure public health and safety.

Based on an evaluation of the risk of transfusion-transmitted HEV in the vulnerable community, blood donations should be screened for HEV. Additionally, thorough information on the prevalence of hepatitis E in patients receiving HEV-negative blood products and those who get unscreened blood components is essential to estimate the absolute advantage of screening. Both the expenses and the advantages must be considered. One of the important challenges affecting the cost-effectiveness of regular screening is determining the optimal sensitivity level for NAT testing (, i.e. pool size).

Conclusion

HEV is the most prevalent cause of acute viral hepatitis globally and the fifth recognized hepatitis virus after types A, B, C, and D. Most infections occur in developing countries. Different regions of the world have different prevalence rates of HEV in blood donors. Transfusions involving blood and blood components have been documented to transmit HEV, 86 such cases have been reported from 20 original research studies. Global awareness of HEV transmitted through blood transfusions is growing. Despite the low general incidence of HEV in blood donations, HEV can have hazardous effects on recipients who have compromised immune systems. Notwithstanding the ambiguities surrounding the prevalence of HEV, screening blood donations for HEV RNA is undoubtedly being considered in a number of countries. Based on a local assessment of HEV risk and health economics, a screening policy for asymptomatic blood donors must be chosen.

Table I: Transfusion-Transmitted Cases of HEV

Author and Year	Country	No. of patients	Transfused Blood Component	Comorbidity
Mitsui *et al.,* 2004[37]	Japan	4	Red cell concentrates	Haemodialysis
Matsubayashi *et al.,* 2004[38]	Japan	1	Fresh frozen plasma	Open-heart surgery
Boxall *et al.,* 2006[39]	UK	1	Red cell concentrates	Lymphoma
Colson *et al.,* 2007[40]	France	1	Red cell concentrates	Rhabdoid tumor
Matsubayashi *et al.,* 2008[41]	Japan	1	Platelet concentrates (aphaeresis)	Non-hodgkin's lymphoma
Coilly *et al.,* 2013[42]	France	1	Red cell concentrates	Liver transplant
Huzly *et al.,* 2013[43]	Germany	1	Platelet concentrates (aphaeresis)	Immunocompromised
Hewitt *et al.,* 2014[29]	UK	18	- Red cell concentrates = 4 - Platelet concentrates (pooled) = 4 - Platelet concentrates (aphaeresis) = 7 - Fresh frozen plasma = 2 - Pooled granulocytes = 1	- Cardiac surgery - Gastrointestinal bleeding - Sepsis - Myelodysplastic syndrome - Aplastic anaemia - Metastatic cancer - Acute renal failure - Non-hodgkin's lymphoma - Acute myeloid leukaemia - Failed transplant - Multi organ transplant
Matsui *et al.,* 2015[44]	Japan	1	Platelet concentrates	Rethoracotomy for haemostasis
Hoad *et al.,* 2017[45]	Australia	1	Fresh frozen plasma	Liver transplant
Barciela *et al.,* 2017[46]	Spain	1	Red cell concentrates	Immunocompetent
Belliere *et al.,* 2017[47]	France	1	Red cell concentrates	Heart transplant
Yamazaki *et al.,* 2017[48]	Japan	2	Data not available	Haematological malignancies
Lhomme *et al.,* 2017[49]	France	3	- Red cell concentrates - Red cell concentrates with platelet concentrates - Platelet concentrates with fresh frozen plasma	Organ transplant
Satake *et al.,* 2017[50]	Japan	19	- Red cell concentrates = 10 - Platelet concentrates = 6 - Fresh frozen plasma = 3	- Haematological malignancy = 6 - Organ transplant = 2 - Systemic disease = 8 - No comorbidity = 3
Westhölter *et al.,* 2018[51]	Germany	2	- Red cell concentrates = 1 - Platelet concentrates = 1	- Acute-on-chronic liver failure complicated by Pseudomonas septicemia - Cardiac surgery
Ledesma *et al.,* 2019[52]	UK	2	Platelet concentrates	- Allogeneic bone marrow transplant = 1 - Liver transplant = 1
Gallian *et al.,* 2019[53]	France	23	- Red cell concentrates = 7 - Platelet concentrates = 3 (aphaeresis) - Platelet concentrates = 6 - Fresh frozen plasma = 7	- Haematological malignancy = 5 - Organ transplant = 9 - Allogeneic stem cell transplant = 4 - Immunosuppressed = 2 - Immunocompetent = 3
Okano *et al.,* 2020[54]	Japan	1	Platelet concentrates	Acute myeloid leukaemia
Harvala *et al.,* 2022[55]	UK	2	Platelet concentrates	- Aplastic anaemia and portal hypertension - B-cell lymphoma

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