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Hepatitis E virus as a transfusion transmitted infection-current status

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ABSTRACT

Objectives: Hepatitis E virus (HEV) infection is growing worldwide and presents a new threat to the blood transfusion services across the world. The present review tries to explore how the transfusion medicine community is responding to the threat.

Materials and Methods: The major papers and important case reports were culled from PubMed, Science Direct, Embase related to this infection, and transfusion medicine since 2005 were explored and relevant articles were discussed with emphasis on epidemiology, infection, prevalence in donor population, susceptible recipients, prevention, and future development.

Results: There are eight genotypes of this virus with different host, transmission biology, and clinical infection. Chronic infections are more common with Genotype 3 and Genotype 4 which are prevalent in Europe and transmitted by pig and meats cooked from this animal. Genotype 5 and 6 has not yet been linked to human transmission. Genotype 1 and Genotype 2 cause epidemic form of this infection and are common in developing countries. Immunosuppressed and chronic liver disease patients get chronic or severe infection. Pregnant ladies develop fulminant hepatitis with high mortality. The virus is transmitted by blood products but severe infection is uncommon. Many European countries, USA, Canada are using Nucleic Acid Testing (NAT) based technology to screen their donors as Individual Donor-NAT or Minipool NAT with varying efficiency. Large part of the world as yet has not taken any active measure to contain this infection through transfusion. A vaccine is available, effective but is not widely used as more studies are needed. Cross immunity does happen between genotypes and presence of immunoglobulin G antibody in blood protects against serious infection. Alanine transaminase level corresponds with viremia in asymptomatic but infected individuals.

Conclusion: The HEV is an emerging but important threat to transfusion medicine service. Important information regarding this infection is still lacking. However, there is a need to develop robust safety algorithm to counter this threat and make transfusion safer.

Keywords: Hepatitis E virus, Various genotypes, Transfusion transmission, Epidemiology, Acute and chronic liver disease, Pathogen inactivation

INTRODUCTION

Many different types of infections can be transmitted through transfusion of blood and blood products. Some of these transmission are more theoretical and some have already been established to be of important health concern.[1,2] Depending on the risk, various such organisms have been classified as Red, Orange, Yellow, and white risk.[1] At present, of the viral infections,

Hepatitis B, Hepatitis C, and human immunodeficiency virus (HIV)-1&2 are universally screened in donated blood across the world both serologically and in large part of the world also technically more involving and more costly Nucleic Acid Testing (NAT) testing is used.[3] The list for different viruses which could shown to be transmitted by transfusion are increasing already added to the list is human t-lymphotropic virus 1 and West Nile virus in USA. Many other viruses have been shown to be transmitted through transfusion either sporadically,[4] or during epidemics, for example, Dengue.[5] Often this transmission of known viruses like hepatitis A happens through failure of virus inactivation process.[4,6] Two viruses which had been red flagged but not yet widely screened for in blood donors or blood are dengue and hepatitis E virus (HEV).[1,7-9] Present review involves description of the scenario and need for screening of HEV in blood donors and in the blood products along with appraisal of risk in the event of transfusion of infected product.

MATERIAL AND METHODS

The data base in Pubmed/Science Direct/Embase were searched from January 2001 to June 2022 with following headings in association with HEV-epidemiology, complications, transfusion transmission, chronic and acute disorder, serology, NAT testing, liver enzymes, viremia, inactivation of virus. Main focus was review articles, clear transfusion transmission data, donor infectivity data, testing for the infection, and guidelines. The relevant material from these review articles was collated for the present review.

Epidemiology of HEV

HEV has a worldwide distribution [Figure 1].[10] Twenty million persons are affected with this virus every year in epidemic and sporadic form with 60,000 mortality.[11]

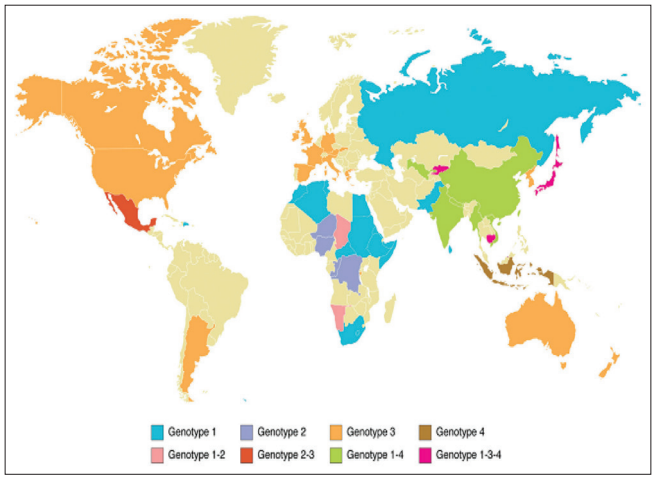

Figure 1: Distribution of Hepatitis E genotype across the world. (Re-used with permission from Pérez-Gracia[10]).

Seroepidemiology shows from around 2–80% positivity of immunoglobulin G (IgG) in different parts of the world with lowest level of 1.4% in a Californian study.[12] There are eight genotypes of the virus identified of which Genotype 1 and Genotype 2 are associated with acute epidemic form of the disease and are mainly restricted in Indian subcontinent and South-east Asian countries.[11-13] Genotype 3 and 4 are transmitted through Pork and are sporadically found in European countries and in USA. These genotypes can cause acute hepatitis but has the potential to cause chronic liver disease particularly with Genotype 3 and 4. Genotype 5 and Genotype 6 has been demonstrated in wild Boars and has not been associated with human disease. Genotype 7 and Genotype 8 have been demonstrated in camels and camelids. Recently, this Genotype 7 were reported to cause human transmission and chronic disease in the immunosuppressed.[14] HEV not only cause hepatitis but in a proportion of cases may cause various extra hepatic pathology [Table 1][15] and chronic hepatic pathology.[16]

Table 1: Non-hepatic manifestations of genotype 1 or 2 hepatitis E virus infection.

Gastrointestinal tract:
Acute pancreatitis
Renal manifestations:
Membranous/membranoproliferative glomerulonephritis
Autoimmune phenomena
Henoch-Schönlein purpura
Crypglobulinaemic glomerulo nephritis
Nephrotic syndrome
Monoclonal paraproteinaemia
Myocarditis:
Hematological manifestations:
Hemolysis
Thrombocytopenia
Hemophagocytic syndrome
Aplastic anemia
Lymphoma
CD30+cutaneous T cell Lymhoma
Cryoglobulinaemia
Central and peripheral nervous system manifestation:
Cognitive dysfunction
Meningoencephalitis
Aseptic meningitis
Pseudotumor cerebri
Seizure
Neuralgic amyotrophy
Vestibular neuritis
Myelitis
Myesthenia gravis
Oculomotor palsy
Brachial plexopathy
Myositis
Nerve palsies
Peripheral demyelinating polyneuropathy.

Epidemiologic characteristic of this infection in developed and developing countries has been presented in [Table 2].

HEV and liver disease

Normally Genotypes 1 and 2 which cause both epidemic and sporadic form of Hepatitis E is largely a water borne disease with faeco-oral route of transmission is the major cause of acute hepatitis.[17,18] This is self-limited and only 1–2% infected patient develop clinical infection. Hence largely, it is subclinical disease in immunocompetent host.[18-20] However, the disease becomes very severe in pregnancy leading to acute fulminant hepatitis with 30–40% mortality and increased fetal loss.[21] In patients who have chronic liver disease, this infection may cause acute decompensation of liver function. With Genotype 3 and Genotype 4 virus, the disease is transmitted through pork meat and a proportion of patient particularly those who are immunocompromised, solid organ transplant patients on immunosuppressive drugs may develop chronic hepatitis and some of them continue to excrete viruses in the stool for indefinite period of time.[22] Genotype 7 and 8 which cause infection in camels have recently been found to cause chronic liver disease with Genotype 7 in immunocompromised patients.[23] In cell culture studies, HEV was not found to be cytopathogenic but in autopsied patients with fulminant hepatitis or from liver biopsy specimens in patients with this infection the pathogenic effect of this virus on liver appeared to be immune mediated.[24,25]

HEV as a transfusion transmitted disease

HEV has a reasonably long incubation period varying between 2 and 10 weeks with a median of 4 weeks when the viruses are demonstrable in blood in asymptomatic individuals. Highest level of viremia is reached just before clinical symptoms and increased transaminases level in the blood. During this asymptomatic period, the viruses could be transmitted if blood is collected during that period.

Table 2: Epidemiology of Hepatitis E virus infection in developing and developed countries.

Seroprevalence: Low <15 year, rise rapidly between 15 and 30 year; Increases with age with peak between 30 and 50 year **Incidence:** Developing Nation: 64/1,000 patient-year in Bangladesh; 42/1,000 patient-year in Egypt. Developed Nation: 30/1,000 patient-year in South of France; 7/1,000 patient-year in USA **Outbreaks:** No: sporadic, small groups from a food point source. Yes; thousands of cases **Attack rate:** 1 in 2: asymptomatic in 67-98% **Person-to-person spread:** Very limited **Seasonality:** Yes; outbreaks occur at times of flooding/monsoon **Mortality rate:** 0.5–3%.
Modified from Dreier *et al*.[44]

Seroepidemiology of the virus has shown that there is steady increase in seropositivity rate from 15 years to 40 years and males have higher seropositivity than females; this is the age group with which large number of blood donors overlaps. As there are multiple modes of transmission of this virus depending on viral genotype, geographical location of the population and lifestyle, season of the study, food and water hygiene of the area, it has become difficult to assess the transfusion risk of transmission of the virus. Multiple studies across the globe with seroepidemiology and carriage of viral ribonucleic acid (RNA) in asymptomatic blood donors have shown variable frequency of the viral RNA in donor population.[26-35] On the average one in 2900 donors carry this virus donate it in their blood;[36] in India it could be as high as one in 36.[8] As 98–99% of these infections are asymptomatic hence unless looked for with proper tracing records of the blood products it is not possible to quantify the risk. However, data collected so far suggests viral transmission through transfusion definitely occur but the risk is low.[4,36] Moreover, as the population who receives the blood has antibody to this virus in variable proportion of cases, the risk of virus induced hepatitis is further minimized.[32] It has often been argued that demonstration of RNA in variable amount does not necessarily mean that the infective virion is present in blood. However, recent study has also shown circulating virus particle in real life donor plasma[37,38] From the transfusion transmitted Hepatitis E cases, it is now generally understood that the virus withstand refrigeration and freezing for at least 4 weeks and being a non-enveloped and small virus, it is moderately resistant to heat and solvent detergent treatment.[39] This is a signal to plasma industry that the infectivity of the virus of the plasma pools. However, large pool of plasma does two things to mitigate this from happening - (1) a large pool of plasma dilutes the virus unless many contributors in the pool is infected, (2) presence of IgG antibodies in the population reduce the infectivity of the pool. Virus inactivation studies also showed variation and heterogeneity in the rate of inactivation of the viruses in plasma pools.[40,41]

In real life virus transmission, it has been shown that presence of IgG antibody to the virus mitigates the risk of infection and there is cross reactivity of the antibody across the genotypes.[42,43]

Infective dose of the virus

As the virus is associated with the plasma component of the blood, plasma remains the major source of infection. However red cell concentrates which contain small amount of plasma has been shown to transmit the virus. It has generally been shown <19000 iu of the virus does not cause infection and more than 520,000 iu of virus cause infection irrespective of immune status of the host.[32,44-46] Hence, it

can be seen that with low level viremia, red cell concentrate is unlikely to transmit the infection unless the viral load is very high but with plasma containing products, that is, fresh frozen plasma (FFP), concentrates, single donor platelet, pooled random donor platelet, pooled cryoprecipitate all could cause the infection if the recipient is susceptible, that is, IgG negative and immunoglobulin M (IgM) negative.

In modern transfusion medicine set up, many patients who are pregnant, immunosuppressed due to their disease, on medication with immunosuppressing agents due to various reasons or had solid organ transplantation and related pathology, very small sized neonates, and chronic liver disease patients receive blood or plasma products due to various reasons. In these patients, HEV can cause serious acute and chronic liver disorder and many non-hepatic symptoms already referred to.[21,28]

Moreover, due to globalization of food industry, increased international travel and massive population displacement in different parts of the world created situations where this virus transmission in healthy donors can only increase. Hence, hepatitis E screening of some type in blood products needs to be initiated sooner than later.

HEV in blood donors

HEV antibody has been demonstrated in variable number of populations from different parts of the world. It is usually much lower in developed European Countries and in United states. However, here, autochthonous transmission of Genotype 3 and Genotype 4 virus in asymptomatic donors pose a different kind of problem. Because if transmitted in susceptible immune compromised host, it has higher propensity to cause persistent infection, chronic liver disease and extrahepatic symptoms, transfusion of blood, and blood products surely pose a risk of hepatitis E infection in these patients. Evaluation of donors for RNA and serology in these donors show different prevalence of circulating RNA in these donors[16,44] [Tables 2 and 3]. With increase in age the RNA positivity as well as seropositivity of the donors also increases [Table 4].[45]

Table 3: HEV-RNA prevalence in blood donors.

Country	Method	Samples	Results	References
Ghana	Individual testing	239	0/239	Meldal *et al*. 2013
United States	Individual testing	1939	0/1,939	Xu *et al*. 2013
Canada	Pools of 48	13,993	0/13,993	Fearon *et al*. 2017
Australia	Pools of 6	74,131	1/74,131	Hoad *et al*. 2017
United States	Pools of 96	128,020	1/32,005	Roth *et al*. 2017
United States	Individual testing	18,829	1/9,500	Stramer 2014
Germany	Pools of 96	18,100	1/4,525	Baylis *et al*. 2012
Spain	Individual testing	9,998	1/3,333	Sauleda *et al*. 2014
U. K.	Pools of 24	225,000	1/2,850	Hewitt *et al*. 2014
France	Pools of 96	53,234	1/2,218	Gallian *et al*. 2014
Netherlands	Pools of 96	59,474	1/1,440	Hogema *et al*. 2016
Germany	Pools of 48	16,000	1/1,250	Vollmer *et al*. 2012

Adapted from Aggarwal and Goel.[15] HEV: Hepatitis E virus, RNA: Ribonucleic acid

Table 4: HEV reactivity rates in Irish blood donors according to age groups.

	Donations screened negative	HEV RNA (+)	HEV RNA (+), % (donation rate)
18–24 years	28,386	12	0.042 (1:2,367)
25–34 years	54,493	13	0.024 (1:4,193)
35–44 years	66,397	15	0.023 (1:4,427)
45–65 years	130,603	19	0.014 (1:6,875)
Total	279,879	59	0.021 (1:4,745)

Modified from Boland *et al*.[47] HEV: Hepatitis E virus, RNA: Ribonucleic acid

Should we screen our donors or recipients for HEV and susceptibility to infection on transfusion?

There is definite evidence of circulating RNA as well as virus particle in donors blood, a good number of evidence from different countries that the transmission of the hepatitis do happen through transfusion of infected blood products and risk of severe disease increases in pregnancy and in immunosuppressed patients. There is also evidence unlike some of the transfusion transmitted hepatitis viruses suh as Hepatitis B and Hepatitis C, presence of IgG in blood of a immunocompetent person gives him partial immunity and in acute epidemic setting majority of the population have asymptomatic infection; hence capable of transmission through blood donation. If hepatitis does happen it is mostly mild and recovers on its own except in pregnant ladies in third trimester of pregnancy. Fairly effective hepatitis E vaccine is likely to be available soon.[48] Evaluating all these parameters HEV-RNA screening of blood units either as Individual Donor-NAT (ID-NAT) or Minipool NAT has already been initiated in several European countries.[44,45]

However, in large part of the world, Hepatitis E related transfusion risk is considered to be low, negligible or a debatable issue.[41,49-51] However, a variable number of donors

on the average across the world carries HEV RNA without associated antibody. They are at greatest risk of transmitting the virus and cause disease in non-immunized, immune suppressed and pregnant patients who also receives a substantial amount of red cell and other blood product transfusion with high plasma content risking them for real infection.

What then should be the strategy for screening?

Straight forward and democratic way of screening without raising any conflicts of interest should be NAT screening of all blood units as we do for other transfusion transmitted viruses i.e. HIV-1&2, HBV and HCV. Then of course, a major discussion will be whether it should be ID-NAT or minipool NAT of different sample sizes depending on perception of virus load and frequency of positivity in the population. In general, studies have shown ID- NAT detects this virus in 50% more donors[49] than minipool NAT particularly those who have low viral load yet may be able to transmit the infection if high volume plasma infusion is given. Both the techniques are currently employed in several European countries[49] As plasma is the main source of transfusion transmitted hepatitis E infection, plasma containing products such as platelet concentrates, FFP, Cryo poor plasma, cryoprecipitates, and plasma-based concentrates all can transmit the infection even when the viral load in these products are low. Red cell concentrates which contains minimum amount of plasma (<15 mL) have also transmitted HEV.[50] As this virus is a non-enveloped one and in plasma a proportion of these viruses remains non-enveloped, solvent detergent technology does not inactivate the virus easily.[41] Similarly, heat sensitivity of this virus in usual plasma heat treatment condition has not been established with certainty making screening for this virus is essential at least for some blood products.

So what are the ways HEV transmission causing serious damage to recipients can be minimized? (1) testing every unit of blood using NAT based or loop mediated amplification[51] or using ID-NAT format or minipool format. Pool size may be decided on past data on frequency of this infection in voluntary donors; (2) testing all blood units for IgG/IgM as positive units even if they transmit infection the infection is likely to be subclinical or mild; (3) combine option 1 and 2; and (4) surrogate liver function test (alanine transaminase, ALT) may be added as used to be done before because the peak viremia in this disease closely corresponds with ALT levels. Moreover, donors with high ALT are at risk of transmitting other infections and provides the opportunity of counseling the donor for other liver disorders and subsequently referring the donor to competent clinical center; (5) if sensitive antigen testing serology is developed they may be combined with other modes or may be used alone; (6) testing the susceptible/pregnant/immunosuppressed recipient for seroimmune status against HEV before transfusing the product. Here, the donors may/may not be tested for the virus or serostatus. The menu as described above can be combined in a different ways to suit the country's finance and risk of transfusion transmitted Hepatitis E as well as the number of susceptible recipient population in the country. Suitable algorithm for testing can be developed and improved over time in each country. Here, artificial intelligence-based decision-making and algorithm for donor recipient testing may optimize the risk-benefit of such decision-making process.

DISCUSSION AND CONCLUSION

HEV is another hepatitis virus which was flagged of 12 years back that it could be transmitted through transfusion.[1] It is neither easy nor desirable to provide a single prescription for the whole world how to minimize its transmission and its consequences. Clear evidence exists for devastating consequences of infection; non-existence of a vaccine to be used widely for the population, serology combined with NAT testing could be the way to go (like, HIV infection). A large part of the world's transfusion community could not embrace it even for other infections because of many logistic and financial reasons.

In that case another infection which has different genotypes infecting different parts of the world, differential immune status in both donor and recipients, largely subclinical infectious outcome, unknown dynamics of the virus infection and transmission in many of its infective cycle and clear existence of chronicity of infection, acute liver failure and many non-hepatic disabling manifestation of the disease in a small subset of infected patients and not so small subset of infected but pregnant patient, dictates a very nuanced approach to the problem till more details about the infection through transfusion and its morbidity in the recipient emerges. Moreover, the infection can spread by fecal oral route as well as through infected livestock (pork and camel) and its meat. Many other animals host both in sylvatic and non-sylvatic conditions are increasingly reported. Each country should carefully investigate and document its transfusion associated hepatitis patients to build a risk profile of transfusion transmission for the country.

Vaccines are in the horizon (e.g. HEV239/Hecolin is first marketed in China, then Pakisthan) but not extensively available clinically. Infection with this virus does produce immunity or even when immunity wanes it modulates the infection to a milder degree but it is not always so.

The greatest impact of infection by this virus falls on pregnant ladies in their third trimester of pregnancy. In a year across the world, 140 million children are born and at least so many

mothers become pregnant. About 2–3% of pregnant mothers on an average need Red Cell transfusion and this percentage are higher in many developing countries and cause of transfusion is often severe anemia and the product given is often whole blood. These pregnant women are at great risk of contracting HEV infection as majority of them come from developing world. About 60% of the pregnant ladies so infected develop the infection while 30–40% of them develop fulminant hepatitis and hepatic failure; of these about 30% eventually die. Many of them deliver premature new born; often with still born babies.

A back-of-the-envelope calculation with 140 million new borns, at least that many pregnancies, per year across the world (UNICEF 2021), 2–3% require transfusion of at least two units of red cell preparation, and 1 in 3000 blood units being RNA positive for hepatitis virus (in a developing country it could be as low as 1 in 36–1 in 1800 donations).[52] Now, 60% developing the infection means 190,000 mothers get the infectious blood unit, 114,000 gets the infection, 45,000 develop fulminant hepatitis and 14,000–21,000 mothers die from this infection with much more higher consequences related to prematurely born and new born. This number is likely to be much higher for developing countries where severe anemia as well as HEV infection is much more common.

Another obvious group where this infection could prove serious is those with cirrhosis of liver or with chronic liver disease.[53] These are also the patients who often needs blood product transfusion and such patients are progressively increasing in number across the world. Immunosuppressed patients, patients with various hematological malignancy, and patients with solid organ transplantation are all at very high risk of development of chronic infection with this virus, specially viruses with Genotype 3 and Genotype 4.[54]

There are many questions associated with screening of blood and blood products as a national program. Some countries have already started universal screening of the virus.

Plasma is an important source of infection and considering resistance of this virus to solvent detergent inactivation and ability of the heat to neutralize the virus after long exposure means these two procedures alone may not clear more than 6–7 log of the viruses. Nano filtration and immune-nanofiltration with filter pore size <20 nm may be required to achieve satisfactory results and as large pool of plasma used in plasma industry except albumin and immunoglobulin all fractions are liable to pass the infection hence needs to be screened. NAT tested blood has been shown to be associated with low transmission of this virus.[55]

However, world is still divided whether universal screening of blood is required for HEV is required or not.[56-58] The hesitancy comes from still unknown dimension in the pathogenesis and morbidity of this infection, more infections are contracted by fecal oral route and food, increasing cost and time required for testing of these products and logistics of its integration in the already overburdened transfusion service. Many developing countries are not in a position to add another nucleic acid amplification technology for another virus when they have not yet been able to implement universal NAT testing for common transfusion transmitted virus infection.[59]

Improvement of environmental sanitation, vaccination against the virus (at least in susceptible recipients), developing dual inventory where susceptible population can get virus negative NAT tested blood all can be considered in any country depending on the epidemiology of the virus and cost considerations. However, there are ethical and logistic difficulties in maintaining multiple inventories for different recipients. Many questions relating to this virus transmission through transfusion route have been discussed elsewhere.[60]

Pathogen inactivation technology, though available, does not inactivate this virus reliably by all available techniques and is still difficult to apply for cellular products for all the viruses. Although significant advances have been made and the state of the advances in the field is reviewed elsewhere.[63] Hepatitis E and other non-enveloped and some enveloped viruses have been shown to be reliably removed from cellular products like platelet concentrates using only ultraviolet C band radiation.[61,62] However, this product has not yet been fully developed for RBC. Many of these pathogen inactivation systems are utilized in many transfusion centers of the world and eventually may become the final safety layer against known and unknown viruses and bacteria that slips into transfusable blood products.

Donor questioning and screening which is the hall mark of safe blood transfusion program, unfortunately does not reliably determine the infective carriers of this virus who are largely asymptomatic and does not have high risk behavior (eating pork or camel meat cannot be considered as high risk behavior). As having IgG against Hepatitis E both in donors as well as recipients protect against serious infection even when the blood is RNA positive and serum glutamate pyruvate transaminase level as surrogate marker correlate with viremia may be combined to provide HEV safe transfusion to susceptible patients.

Many of the recent advances and challenges related to HEV infection some of which touches the areas of transfusion medicine have been discussed elsewhere.[28,63,64]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Dr. Prakash Kumar Mandal is the Editor-in-Chief of the journal, Dr. Kanjanksha Ghosh is the Patron of the Journal.

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