Hepatitis E- Is it a risk to transfusion safety?

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Hepatitis E virus (HEV) has long been considered an enterically transmitted virus causing self-limiting acute viral hepatitis. The virus was first described in samples collected retrospectively in an outbreak of jaundice in 1955 in New Delhi.[1] The disease is endemic in many developing countries in Southeast and Central Asia, the Middle East, Central America and Africa, primarily due to contaminated drinking water. The disease causes large-scale epidemics of viral hepatitis in several developing countries and is the most common cause of acute sporadic hepatitis and occasionally fulminant hepatic failure in such countries. Pregnant females, patient's with pre-existing chronic liver disease and immunocompromised patients are at a much higher risk of developing hepatic failure.[2-4] Recently, it has been reported that worldwide HEV infection causes more than 3 million symptomatic cases of acute hepatitis E each year that result in approximately 70,000 deaths.[5] Although HEV hepatitis has been classically described as an acute illness, recently there have been reports of chronicity in immunosuppressed patients. Chronic infections are rare, and have been seen in solid organ transplant recipients.[6] Persistent infection may also occur in individuals with compromised immune systems including cancer patients undergoing chemotherapy, Human immunodeficiency virus (HIV)-infected patients, and individuals with drug induced liver failure and liver damage due to alcohol abuse.

Viremia in individuals infected with HEV is usually of a short duration with a brief incubation period followed by a symptomatic phase. There is also increasing evidence that asymptomatic infections constitute majority of the disease burden. The ratio of symptomatic to asymptomatic cases ranged from 1:2 to 1:13 in the developing world.[7] In recent years, studies have also shown asymptomatic viremia in blood donors which is suggestive of ongoing subclinical infection. Arankalle and Choube from Pune, India, have shown 1.5% (3/200) of blood donors to be positive for HEV RNA and suggested the possibility of transmission by transfusion.[8] Since then, many studies have shown that HEV RNA is present in the serum of healthy blood donors and there is a potential risk for transmission of HEV through blood.

Transfusion safety has been of paramount importance for the transfusion services and with time the transfusion safety has been constantly improving secondary to screening of blood and blood products with regular introduction of better tests. Currently screening of blood and blood products for HEV is not done and there are also no recommendations. But the question is largely unanswered whether parenterally transmitted HEV is a risk to transfusion safety.

The presence of anti-HEV IgG antibody has generally been taken as evidence of prior exposure to HEV. In developed countries, anti-HEV immunoglobulin G (IgG) prevalence rates range between 1% and above 20%. These appear to be higher than those expected from the low rate of clinically evident hepatitis E disease in developed countries, suggesting that subclinical or unrecognized infection is common.[9-12] Endemic regions have a very high seroprevalence. In India, the seroprevalence of HEV IgG has been reported up to 35%.[8,13] The seroprevalence of HEV in different countries is shown in Table 1. In India, seroprevalence of HEV rises with age peaking in young adults but studies from China, Japan, and Denmark have shown a continuous rise in prevalence with age with peaks at around 60 years or higher.

In one of largest studies by Gotanda *et al.*, out of 6,700 Japanese blood donors with elevated ALT, 479 (7.1%) were positive for anti-HEV IgG, including eight donors with anti-HEV IgM and seven donors with anti-HEV IgA. Among the nine donors with anti-HEV IgM and/or anti-HEV IgA, six had detectable HEV RNA. Three donors, including one without anti-HEV IgG, were found to be positive for HEV RNA.[14] Sakata *et al.*, have also shown the presence of HEV RNA in blood donors with elevated ALT levels.[15] Studies have thus shown that HEV RNA is present in the serum of healthy blood donors, and there is a potential risk for transmission of HEV through blood. There have been several instances of post transfusion HEV reported in developed countries including Japan, the United Kingdom, France, and Saudi Arabia.[16]

There are several high risk groups of patients, such as patients with chronic hemodialysis (CHD) who

are likely to develop transfusion associated hepatitis (TAH).[17] The previous studies done for seroprevalence have been unclear whether prevalence of anti-HEV antibodies in patients with CHD is higher than normal population. Study done by Sylvan *et al*., didn't find any increased seropositivity among patients with CHD as compared to healthy controls.[18] A study by Ayoola *et al*., indicated a significantly higher risk of acute HEV infection among patients on chronic haemodialysis although anti HEV IgG antibodies prevalence was not different.[19] A recent study by Harrrison *et al*., has shown a higher prevalence of anti-HEV IgG antibodies in CHD patients compared to normal controls and post renal transplant patients, which could be attributed to parenteral transmission.[20]

A current study by Reza *et al*., examined this possibility. They have shown that the prevalence of HEV antibodies was more than two times higher in the CHD patients, compared to the healthy controls. The difference was not significant. Furthermore, the authors examined the levels of alanine aminotransferase (ALT) in the CHD patients and the controls; there was no significant difference between the two. This is not unexpected as patients on CHD, are likely to have relatively lower alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels.[21] The study is, however, wanting in examining whether these CHD patients had IgM anti-HEV or IgG anti HEV and whether these patients had circulating HEV RNA. The transmission of HEV through blood transfusion is only likely to occur when patients are viremic. Furthermore, it is likely that the increased transfusion of blood and blood products may be the cause of increased seroprevalence rather than the chronic hemodialysis per se. Future studies in this direction would indeed be a great addition to the knowledge base.

The below Table 2 mentions the cases reported till date that have been proven as transfusion transmitted hepatitis E. The first case of transfusion transmitted HEV was reported from Hokkaido, Japan in 2004 when a Japanese male patient who developed acute hepatitis after receiving a transfusion of blood from 23 voluntary donors during open heart surgery.[16] Most reported cases were patients receiving multiple blood and blood products due to their underlying disease. Many cases are likely to go undiagnosed due to the general belief that hepatitis E is an enterically transmitted disease and can be asymptomatic, and thus these reported cases may represent only the tip of the iceberg.

Clinical relevance of transfusion-transmitted HEV is unclear. Studies from endemic areas have suggested the possibility of transmission through blood transfusion on retrospective evaluation in transfusion recipients. Khuroo *et al*., had shown a significantly higher prevalence of markers for acute HEV (anti-IgM and HEV RNA) in multitransfused patients (13/145) as compared to controls (2/250).[22] It was also shown that patients who were positive for HEV markers had received more transfusions, had a higher incidence of icteric disease and higher ALT levels. Arankalle and Choube from Pune and Irshad and Peter from Delhi have also shown a significantly higher prevalence of markers of acute HEV in transfusion recipients.[8,23]

The natural course of transfusion associated hepatitis E is not known but in high risk recipients like pregnant females, patient's with pre-existing chronic liver disease and immunocompromised patients, it is supposed to be associated with considerable morbidity and mortality. We are now well-aware of the entity of acute or chronic liver disease (ACLF), which has a very high mortality rate, and HEV is one of the most common insults leading to acute deterioration of the liver function and the irony is that the chronic liver disease may be previously undiagnosed in many patients.[4,24,25]

There has been a paradigm shift from Hepatitis E being considered as an enterically transmitted virus to a virus transmitted parenterally, and it is being also considered as a re-emerging infectious disease. It will be wise to consider hepatitis E as a risk to transfusion safety especially in high risk recipients due to two reasons, the first being that the HEV positive donor may be asymptomatic with normal AST/ALT and that the disease severity may be higher in the high risk individuals. In light of the current knowledge, at the presence or the absence of any effective vaccination or treatment, it will be worthwhile to introduce HEV screening for blood products in endemic areas and in high risk population considering the influence it can have on the disease course. HEV viremia is most commonly associated with IgM anti-HEV antibodies and less frequently with IgG anti-HEV antibodies. Screening for these antibodies should be introduced into clinical

Table 1: The seroprevalence of HEV in blood donors in different regions[8-12]

No.	Country	Year	Subjects studied	Seroprevalence
1	Netherlands	1993	1275	1.1
2	Italy	1994	948	1.0
3	Switzerland	1994	94	3.2
4	Spain	1998	863	2.8
5	NW Greece	1998	2636	0.2
6	India	1999	200	18.6
7	USA	2002	400	18.3
8	Japan	2002-3	5343	3.7
9	N France	2007	1998	3.2
10	Denmark	2008	461	20.6
11	China	2010	NA	32.6

Table 2: Proven cases of transfusion associated hepatitis E

No.	Country	Patient characteristic	Symptoms in transmitting donor	Confirmation of transmission
1	Japan	Open heart surgery	Asymptomatic	Genome sequencing
2	Japan	Chemotherapy for T-cell lymphoma	Asymptomatic	Genome sequencing
3	Japan	Chemotherapy for Non Hodgkin's lymphoma	Asymptomatic	Genome sequencing
4	Japan	Hemodialysis	Asymptomatic	Genome sequencing
5	United Kingdom	Cancer patient on chemotherapy	Flu-like symptoms	Genome sequencing
6	France	Chemotherapy for kidney cancer	Asymptomatic	Genome sequencing
7	Saudi Arabia (3 cases)	HEV infection post-transfusion in 3 of 22 recipients who received blood from 4 asymptomatic donors	All 4 donors asymptomatic and positive for HEV RNA	No Genomic sequencing

practice by the blood banks and wide scale implementation is likely to make it cost effective.

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