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Journal Summary: Hepatitis E Virus Infection after Liver Transplantation

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In a recent prospective multicenter cross-sectional study, Samala et al studied the seroprevalence of hepatitis E virus (HEV) in waitlist and post-transplant patients in the United States. Large multicenter studies regarding HEV infection in the transplant cohort are lacking in the United States, and this prospective multicenter cross-sectional study described higher-than-expected HEV seroprevalence.[1] They studied 456 participants (224 had solid organ transplants, and 232 were on the waiting list). Subjects (above 18 years) after organ transplant and those on the waiting list matched for age, organ, as well as transplant center were enrolled. Organs transplanted include liver, intestine, kidney, and liver–kidney. Among post-transplant patients, those after 1 year of transplantation were included, as they were likely on a stable immunosuppressive regimen. Enrolment of transplant recipients was stratified based on the site and the number of years post-transplant: 1, 2, and more than 3 years.

The seropositivity of HEV infection for the whole study groups was 20.2%. The seropositivity was higher in the post-transplant group compared with the waitlist group. In the entire study group, HEV seropositive status was associated with higher age and organ transplantation. In the post-transplant group, older age, calcineurin inhibitor use, and history of graft hepatitis were associated with seropositivity. Authors suggested that HEV infection should be suspected in transplant recipients under evaluation with abnormal liver function tests (LFTs). However, they also noted that detection of HEV-RNA was rare, indicating that development of chronic HEV infection is not common in patients after organ transplantation in the United States. Other studies from the United States are usually limited retrospective studies and mainly included only kidney transplant patients.

HEV was discovered in 1978. It was initially described as epidemic non-A, non-B hepatitis. It usually causes acute hepatitis; epidemics are more common in low- and middle-income countries. HEV has been reported in many Western countries. It usually results in acute hepatitis in immunocompetent individuals but can result in chronic infection in approximately 60% of cases of immunocompromised individuals.[2] Its course and progression after orthotopic liver transplantation (LT) are difficult to identify and evaluate. Similarly monitoring and management options of chronic HEV infection in these patients are not clearly defined.

There is no clear data on the exact occurrence or clinical implication of HEV infection in patients after solid organ transplantation, including LT. This is mainly due to challenges in the serological diagnosis of hepatitis E infection. Existing assays show variability in performance and genotype determination. This largely results from marked antigenic variability and significant genetic diversity of different subtypes of HEV.[3] In patients after solid organ transplantation, serology-based diagnosis of chronic HEV is not very accurate. HEV-RNA testing in blood or feces is preferred method to diagnose chronic HEV infection, as serology-based testing may be falsely negative. When we reviewed studies from different regions in the world, the HEV-RNA positive status in post-LT patients varied from 0 to 7.7%. The reported prevalence of 7.7% is from a study from Thailand, which has a very high endemicity of hepatitis E infection.[4] Data from different parts of the world reveals that anti-HEV immunoglobulin G (IgG) seropositivity varied from 3.2 to 42% in the West[5–7] and from 2.9 to 53.3% in the East.[8,9] Similarly, anti-HEV immunoglobulin M (IgM) seroprevalence varied from

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0.35 and 4.1% in the West[5–7] to 0.05 and 10% in the East.[8,9] Similarly, HEV-RNA positive status varied from 0% and 1.4% in the West[5–7] to 0% and 7.7% in the East.[4,8,9]

Studies on the occurrence of HEV infection in post-LT patients with abnormal LFTs show a slightly different pattern. The prevalence of anti-HEV IgG in post-LT patients with abnormal LFTs varied from 3.4 to 4.3%.[10,11] The prevalence of anti-HEV IgM in post-LT patients with abnormal LFTs varied from 1.64 to 2.9%.[10,12] The prevalence of HEV-RNA in LT recipients having elevated LFTs ranged from 2.9 to 20%.[10,13]

The source of infection has varied from transfused blood products, consumption of food products, and indeterminate sources in different reports.[14,15] Risk factors were variably reported in different studies, such as age,[6] male sex,[6] and intensity of immunosuppression. Higher doses of both calcineurin inhibitors[4,16] and steroids[15] were associated with increased occurrence of HEV infection post-LT. Socioeconomic status, such as rural v/s urban areas, has been shown as a risk factor for HEV infection (more in rural areas).[17]

Different treatment strategies were used in the reported cases of HEV infection post-LT. Acute infection usually does not require treatment unless it proceeds to severe acute hepatitis or acute liver failure. In this scenario, treatment with ribavirin (RBV) has been tried with success. The persistence of HEV-RNA in blood or stool for 3 months establishes chronic infection. Chronic HEV infection can be treated with a reduction in immunosuppression doses in about one-third of cases. In some cases, reduction in immunosuppression doses and treatment with different agents like RBV, pegylated interferon, sofosbuvir, and valganciclovir were attempted. RBV is the most used drug in this setting. Markakis et al in their meta-analysis noted that transplant recipients who received RBV (combined with immunosuppression reduction or not) attained significantly higher sustained virological response (SVR) rates compared with those who received immunosuppression dose reduction alone (82.8 vs. 15.4%, respectively, $p < 0.001$). However, the SVR for transplant recipients who received RBV with or without immunosuppression reduction were comparable (87.5 and 82.4%, respectively, $p = 1.00$).[18]

Curing HEV in LT recipients is extremely important as untreated infection can lead on to liver fibrosis. Advanced liver fibrosis can lead on to cirrhosis and sometimes graft failure.[2] European Association for the Study of Liver guidance suggested that lowering immunosuppression (results in SVR in 30% of transplant recipients) should be the initial step in management of chronic HEV infection in post-LT patients. If SVR is not attained after lowering immunosuppression, RBV should be administered as single therapy for 3 months. If HEV relapses, another 6 months of RBV therapy is recommended. Failure to achieve SVR after the initial 3-month treatment or after 6-month treatment following relapse indicates pegylated interferon-alpha (►**Fig. 1**). Pegylated interferon-alpha should be used with great caution in post-LT patients as it has been associated with side effects, including acute graft rejection.[19]

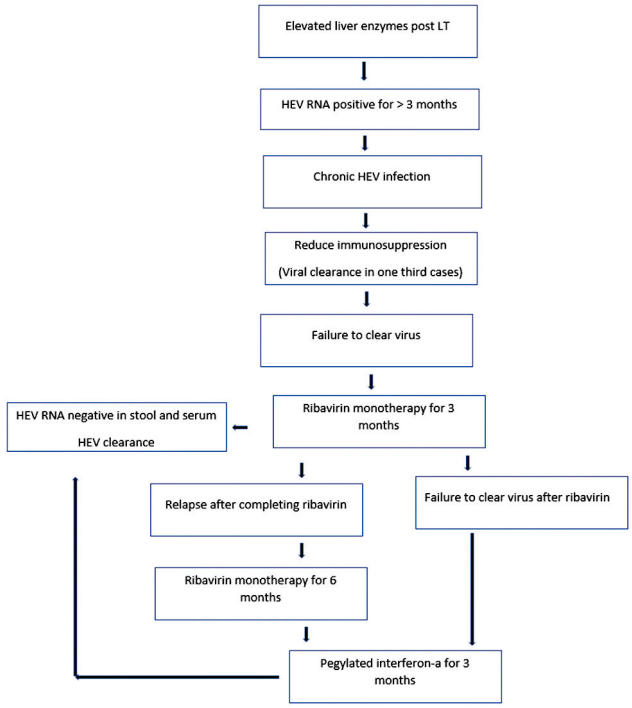

Fig. 1 Treatment of chronic HEV infection post-LT. HEV, hepatitis E virus; LT, liver transplant; RNA, ribonucleic acid.

In the study by Samala et al, the seroprevalence of both waitlist and post-transplant groups was described. There are no studies that had compared the waitlist and post-transplant prevalence of HEV infection. In this study, HEV seroprevalence was high, but the presence of HEV-RNA was less common and seen in only 0.4% of the entire cohort. This concurs with similar studies reported from the West (<2%) except for the study from Germany (20%) (►**Table 1**). The

Table 1 HEV infection after liver transplantation

Study, year (Ref)	Country	Study group (LT recipients)	Prevalence by RNA testing	Details
Pischke et al 2010[10]	Germany	Retrospective $n=$ 226 (156 with normal and 70 with elevated LFTs)	0.88%	Two patients had RNA + infection. First had interface hepatitis without fibrosis, second had cellular infiltrates and signs of rejection on liver biopsy
Pas et al 2012[20]	The Netherlands	Retrospective $n=$ 309	1.3%	Three of the RNA^+ patients had chronic infection and elevated LFTs

(*Continued*)

Table 1 (*Continued*)

Study, year (Ref)	Country	Study group (LT recipients)	Prevalence by RNA testing	Details
Galante et al 2015[21]	Germany	Cross-sectional $n = 287$	1.4%	HEV RNA$^+$ patients had significantly higher LFTs, all treated with RBV and cured. One relapse retreated with RBV
Inagaki et al 2015[8]	Japan	Cross-sectional $n = 1,893$	0.12%	RNA$^+$ patients had peritransplant transfusions with HEV+ samples
Koning et al 2015[22]	United States	Retrospective $n = 145$	0%	HEV RNA was negative in the cohort
Agarwala et al 2018[9]	India	Prospective $n = 30$	0%	None had HEV RNA detected, study from hyperendemic area for HEV
Darstein et al 2018[15]	Germany	Retrospective $n = 25$ (suspected rejection)	20%	Higher ALT levels, low AST/ALT ratio with HEV infection noted, HEV infection more frequent with glucocorticoid therapy
Sinakos et al2018[23]	Greece	Cross-sectional $n = 76$	1.3%	HEV RNA + patient had elevated LFTs and had received treatment for rejection
Soothill et al 2018[24]	UK	Cross-sectional $n = 490$	0.2%	Treated with RBV with 100% SVR
Reekie et al 2018[14]	UK	Retrospective $n = 262$	1.2%	Liver biopsy showed moderate chronic hepatitis with mild fibrosis in first and moderate mixed inflammation of portal ducts, moderate cellular rejection in second patient

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HEV, hepatitis E virus; LFT, liver function test; LT, liver transplant; RBV, ribavirin; SVR, sustained virological response.

study from Germany was specifically on a post-LT cohort with suspicion for rejection and had high LFTs as against most other studies that were done on usual post-LT cohort. The study by Samala et al highlights that unexplained hepatitis in post-transplant patients should be investigated for chronic hepatitis E infection.

In conclusion, HEV infection should be suspected in patients with unexplained elevation of LFTs post-LT after excluding the more common causes. The prevalence is higher in the East but continues to be identified in the West. HEV-RNA testing should be the basis for diagnosis of chronic HEV infection in post-transplant patients. Chronic HEV infection in post-LT patients remains low in the West. If diagnosed, immunosuppression reduction should be the first step, followed by treatment with RBV.

Ethical Considerations
No direct human subjects were involved in the preparation of this manuscript.

Authors' Contribution
All authors contributed equally to the preparation of this manuscript.

Data Availability
There are no data associated with this work.

Conflict of Interest
None declared.

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