

E-xchange: Hepatitis E and the Risk of Plasma Products for Organ Transplant Recipients

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Hepatitis E virus (HEV) infection has recently been recognized as a relevant cause of hepatitis in immunocompromised individuals, both in Europe and North America.¹ Hepatitis E virus genotype 3 is a zoonosis and endemic in Western countries with pigs and wild boar being the main animal reservoirs.² Autochthonous HEV infections are much more frequent than previously thought. For example, a recent study estimated that more than 400 000 HEV infections occur in Germany every year—leading to an annual incidence of about 500 cases per 100 000 inhabitants.³ Even though the majority of these infections take a mild or even completely asymptomatic course in immunocompetent patients, HEV may be a particular threat for patients after organ transplantation. During the last 10 years, several reports were published describing cases of chronic hepatitis E in individuals after liver, kidney, heart, and lung transplantation. Importantly, persistent HEV infections can take rapidly progressing courses and liver cirrhosis may develop within few years. Moreover, HEV may also cause acute liver failure⁴ or acute-on-chronic liver failure in patients with preexisting liver diseases.⁵

Based on the emerging evidence that HEV represents a major hazard for organ transplant recipients, there should be consensus to protect patients at risk from HEV exposure—as far as possible. In this context, there is an ongoing debate on the safety of blood products. In Europe, between 1 of 800 and 1 of 4000 blood donors test HEV ribonucleic acid (RNA) positive.² Transmissions of HEV by blood products leading to severe or prolonged hepatitis in transplant recipients have been described in recent years. Still, the absolute risk for HEV transmission from different types of blood products, for example, red blood cells versus platelets versus fresh frozen plasma is not well defined. In this context, the article by Mallet and colleagues⁶ published in the current issue of Transplantation is of major interest. The investigators from Paris screened 263 kidney transplant recipients for HEV markers. It has to be highlighted that 3 samples per patient were tested

including 1 sample taken before transplantation allowing a rather robust determination of posttransplant HEV infections in this cohort. This is a particular strength of the manuscript because systematic pretransplant and posttransplant testings have rarely been performed in previous studies. A clear discrimination between pretransplant HEV immunity and posttransplant HEV de novo infections was possible. Within a mean follow-up of only 9.5 months after transplantation, already 9.1% of patients had acquired HEV markers. This finding is remarkable and clearly shows that kidney transplant recipients in France are frequently exposed to HEV. Importantly, several patients had also detectable HEV viremia and developed clinical hepatitis which required antiviral therapy with ribavirin. Subsequently, the authors investigated potential sources for HEV infection and identified plasma exchange as an independent risk factor for HEV infection and elevated liver enzymes. Plasma exchange was applied to 16% of the patients mainly to treat acute antibody-mediated rejection, to desensitize recipients from living donors or due to the presence of high titers of donor-specific antibodies on the day of transplantation. Finally, all blood donors of transfusions given to 3 patients with persistent HEV viremia were tested for HEV RNA and in 2 cases a plasma-borne transmission of HEV could indeed be proven by phylogenetic analysis. Overall, this is the first study that identified plasma exchange as vector for HEV and the authors suggest a 10-fold increased risk to acquire HEV by a single round of plasma exchange.

The study has several strengths but some limitations and open questions need to be considered. The retrospective nature of the study prevented testing of all blood products to define the absolute risk for HEV transmission in this setting. Passive transfusion of HEV antibodies may have occurred in some cases, and therefore, the acquisition of HEV markers may not have been HEV infections in all cases. Moreover, the study could not answer the important question if different pathogen-reduction methods may prevent HEV transmission. In the Mallet et al study treatment of plasma with amotosalen plus ultraviolet A (UVA) light (INTERCEPT) was not effective to avoid HEV infection but the role of methylene blue treatment is unclear. Moreover, solvent-detergent, riboflavin plus ultraviolet (UV) light or ultraviolet C (UVC) light have not been used. Another important clinical question could not be addressed due to the limited number of cases. Rejection episodes were more frequent in patients with HEV markers but these patients were also more likely to receive plasma exchange therapy. Still, it is well possible that HEV may trigger rejections as it can induce a potent type I interferon response.²

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What should be the consequences from the Mallet et al study and other recent reports on transfusion-associated HEV cases in organ transplant recipients? In clinical transplantation, all efforts to protect the recipient and the transplanted organ must be implemented. Knowing that blood transfusions and in particular plasma products represent a substantial risk for HEV transmission should lead to systematic screening programs. It is important to note that selection of blood donors by liver enzyme and HEV antibody testing is not sufficient. HEV RNA-positive blood donors rarely show elevated liver enzymes and can be even anti-HEV-negative.⁷ Thus, only direct testing of blood donors for HEV nucleic acid will reliably identify HEV RNA-positive donors and blood products. Several European countries, such as England, Ireland, or the Netherlands, have recently implemented blood donor HEV screening, whereas others are considering testing. Hepatitis E virus prevalences may differ between regions and but there is currently no conclusive evidence that the epidemiology of HEV infection is substantially different in North America as compared with Europe. Moreover, alternative pathogen-reduction methods should be explored for blood products because currently used approaches did not prevent transmission of nonenveloped viruses, such as HEV. In addition, it has to be noted that HEV infections may not only cause hepatitis but also autoimmunity and a variety of extrahepatic, in particular neurological disease manifestations.^{8,9} This yet widely ignored disease burden caused by HEV could also be reduced by avoiding transfusion-associated HEV infections. Finally, and probably most importantly, beyond blood donor screening, the most efficient way to prevent HEV infections would be to avoid consumption of undercooked pork and meat products. All transplant recipients should be strongly advised

to follow this recommendation. Hepatitis E is an emerging topic in transplantation medicine and hepatology. The European Association for the Study of Liver has just released first Clinical Practice Guidelines to guide physicians and patients in the management of this challenging infection in light of limited evidence.¹⁰

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