



Screening of blood donations for hepatitis E virus

Executive summary

Transfusion of blood products (cellular and plasma) is a frequent, potentially life-saving medical treatment. The safety of blood products has been a concern during the last 5 decades. Subsequently, testing for HIV, HBV and HCV has been implemented in most countries world-wide. There is emerging evidence that also the hepatitis E virus (HEV) can be transmitted by transfusion of different types of blood-derived products. As HEV infection can cause severe acute and chronic liver disease as well as a variety of non-liver disease manifestations, the aim of this policy statement from the European Association for the Study of the Liver (EASL) is to inform policy makers about the possibility of preventing transfusion-transmitted HEV infection by screening blood donations for HEV RNA.

Key messages and recommendations

Recent studies revealed that HEV viremia in asymptomatic blood donors in Europe is more frequent than previously assumed. Approximately 0.04-0.12% of blood donations are HEV RNA positive by nucleic acid testing (NAT) (1). This is far more frequent than HBV-, HCV- or HIV-positive blood donations. While testing of blood products for these three pathogens is universally accepted, testing for HEV is still under debate in several European countries. Various reports have demonstrated the potential severe complications caused by transfusion-transmitted HEV infection (2, 3). EASL recommends that blood donations should be tested for HEV by NAT to prevent transfusion-transmitted HEV infection.

Problem statement

Hepatitis E is an infectious inflammation of the liver caused by the hepatitis E virus (HEV) (4). Eight different HEV genotypes have been described, including the four major genotypes (gt) 1-4 (5). Genotypes 1 and 2 are the HEV variants present in resource-limited areas with reduced hygienic conditions and are mainly transmitted by contaminated drinking water (4, 5)(6). HEV gt 3 and 4 are present in industrialized countries and cause HEV infections in annually 0.5% of the general population. Evolution to chronic hepatitis E is possible in immunocompromised individuals. Transmission of HEV gt 3 is mainly foodborne by infected pork, fruit or vegetables. It is possible for HEV gt 3 and 4 to be transmitted *via* HEV containing blood products. (2)

The vast majority of acute HEV infections are asymptomatic and fewer than 1% develop symptomatic hepatitis E. However, in rare cases acute HEV infection can progress to acute or acute-on-chronic liver failure. Furthermore, HEV gt 3 (and 4) infections can result in chronic hepatitis E in

approximately 50% of transplant recipients (8). Chronic hepatitis E can progress to liver cirrhosis, resulting in liver failure with life-threatening complications (8). The prevalence of chronic HEV infections in European solid organ transplant recipients is approximately 1%; it varies between countries and continents (8, 9).

HEV infection is also associated with several extrahepatic manifestations, mainly neurological or immunological diseases (10)(11). Patients with extrahepatic manifestations can be asymptomatic, with normal ALT.

Currently there is no approved antiviral treatment for acute or chronic HEV infections. Ribavirin, which has been approved for chronic hepatitis C, can be effective in patients with chronic hepatitis E and leads to HEV clearance in approximately 90% of treated patients (12, 13). However, ribavirin is associated with side effects such as hemolysis, and the dose has to be reduced in patients with chronic kidney disease.

There is no approved vaccine for the prevention of HEV gt 3 infection in Europe. Thus, preventive measures are restricted to improving hygiene, avoiding raw pork products and testing of blood donations.

However, the relevance of blood product-transmitted HEV gt 3 infections in Europe is still under debate in many countries. England, Ireland, the Netherlands and Switzerland have implemented regular testing of all blood donations for HEV. In other countries, this decision is still pending. The controversial discussion not to implement screening of blood donations is based on the relative risk of acquiring HEV *via* blood products versus the risk of foodborne HEV infection. A mathematical model, which allows a comparison of the risk for HEV acquisition by dietary exposure versus the risk of acquiring HEV by unscreened blood products (14) found that the risk of HEV exposure only exceeds the annual dietary risk when more than 13 individual donor components are transfused. However, this mathematical model does not account for possible different clinical consequences caused by either orally administered HEV particles still having to pass the gut/blood barrier in contrast to intravenously injected particles reaching the blood stream without any barrier.

Up to now several European studies have determined the frequency of HEV viremia in blood donations. In Europe, the prevalence of HEV RNA tested by NAT varies from 0 to 1/814 (Table 1). The largest study, performed in the United Kingdom (3), documented a ratio of 1/2850 blood donations positive for HEV. The likelihood to develop clinically relevant hepatitis E after transfusion of an HEV-contaminated blood product was determined to be 42%.

Studies from the Netherlands and from Scotland demonstrated that the number of positive donations increased significantly over time (15, 16). The most recent German study documented an HEV RNA prevalence of 0.12% (23/18,737) in blood donors (1), which was higher than previous studies from Germany (Table 1).

So far it is not known which viral load in blood products is sufficient to cause HEV infection (19). The present literature demonstrates a significant variation regarding the infectious dose causing hepatitis E (19). Thus, the method and mode of testing is discussed. Serological anti-HEV tests

frequently fail to detect HEV viremia in blood donors (1). Antigen assays do not show an adequate sensitivity for the detection of gt 3 infections. Furthermore, the optimal pool size for HEV NAT testing is still under debate. A single sample testing of blood donations would surely warrant the highest possible safety. However, this seems to be uneconomical. In line with the countries who have established general HEV testing (Ireland, United Kingdom, the Netherlands, Switzerland), a pool size of 16 to 48 samples seems to be adequate. In line with these regulations the German responsible authority, the Paul-Ehrlich-Institute, decided in June 2018 that NAT-based screening of all blood donations in Germany will start in September 2019. A limit of detection of 2000 IU/ml will be regulated by law. However, all recommendations and rules in countries prescribing general testing are based on theoretical reflections and not on robust data. Thus, further investigations are necessary to determine the optimal pool size and PCR conditions.

De Vos et al. calculated the cost-effectiveness of the screening of blood products for HEV and stated that preventing HEV transmission by screening of blood donations appears not excessively expensive compared to these other blood screening measures (20). Within their simulation model they calculated that one prevented chronic HEV infection costs approximately € 310,000. However, their interpretations rely on mathematical models based on various proceedings [What do you mean by proceeding in this context?] and assumptions. Real-life data regarding the cost-effectiveness and the need of screening blood products for HEV are still missing.

Recommendations

In Europe 0.04-0.12% of blood donations are HEV RNA-positive. The frequency of HEV RNA-positive blood products shows variations in Europe. It has been shown that HEV contaminated blood products were the reason for acute and chronic HEV infections.

EASL recommends that blood donations should be tested for HEV RNA by NAT. To prevent acute HEV infections and extrahepatic manifestations, HEV screening ideally includes all blood donations. If general HEV screening is not feasible, at least a selective screening should be performed for blood products used in immunocompromised patients such as organ transplant recipients. The NAT method should detect all major genotypes, most importantly gt 3. The NAT methods should be sensitive enough to detect an HEV RNA concentration of ≤ 2000 IU/ml. Routine HEV RNA screening of pools of 24 using a highly sensitive NAT method may be sufficient to detect viremia that leads to HEV infection.

Table 1: Prevalence of viremic blood donations in Europe

Country	Pool size	Samples	Results	Author	Comment
Italy	Up to 10	10.011	0/10.011 (0%)	Spada et al. 2018 (21)	
Scotland	24	43560	1/14520 (<0.01%)	Cleland et al. 2013 (22)	
Sweden	Up to 96	95835	1/7986 (0.01%)	Baylis et al. 2012 (23)	
England	48	42.000	1/7000 (0.01%)	Ijaz et al. 2012 (24)	
Germany	Up to 96	93.955	Absolute numbers not available (0.02%)	Corman et al. 2013 (25)	Estimation of the frequency of pooled samples
Ireland	Individual testing	24.985	1/4997 (0.02%)	O'Riordan et al. 2016 (26)	
Germany	Up to 96	18.100	1/4525 (0.02%)	Baylis et al. 2012 (23)	
Germany	96	18.100	1/4525 (0.02%)	Baylis et al. 2012 (23)	
Spain	Individual testing	9.998	1/3333 (0.03%)	Sauleda et al. 2015 (27)	
United Kingdom	24	225.000	1/2850 (0.04%)	Hewitt et al. 2014 (3)	
Scotland	24	94.302	1/2481 (0.04%)	Thom et al. 2018 (16)	Evidence for an increase of prevalence in comparison with a cohort collected from 2004-2008
France	Pools of 96	53.234	1/2218 (0.05%)	Gallian et al. 2014 (28)	
The Netherlands	96 or 192	59.474	1/1440 (0.07%)	Hogema et al. 2016 (15)	Evidence for an increase of prevalence
Poland	Individual testing	12.664	1/1266 (0.08%)	Grabarczyk et al. 2018 (29)	
Germany	48	16.000	1/1250 (0.08%)	Vollmer et al., J Clin Microbiol. 2012 (30)	
Germany	24	18.737	1/814 (0.12%)	Westhoelter et al. 2018 (1)	

References

1. Westholter D, Hiller J, Denzer U, et al. HEV positive blood donations represent a relevant infection risk for immunosuppressed recipients. *J Hepatol* 2018. doi: 10.1016/j.jhep.2018.02.031.
2. Pischke S, Hiller J, Lutgehetmann M, et al. Blood-borne Hepatitis E Virus Transmission: A Relevant Risk for Immunosuppressed Patients. *Clin Infect Dis* 2016;63:569-70. doi: 10.1093/cid/ciw309.
3. Hewitt PE, Ijaz S, Brailsford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. *Lancet* 2014;384:1766-73. doi: 10.1016/S0140-6736(14)61034-5.
4. Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. *Gastroenterology* 2012;142:1388-1397 e1. doi: 10.1053/j.gastro.2012.02.014.
5. von Wulffen M, Westholter D, Lutgehetmann M, Pischke S. Hepatitis E: Still Waters Run Deep. *J Clin Transl Hepatol* 2018;6:40-47. doi: 10.14218/JCTH.2017.00030.
6. Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology* 2012;55:988-97. doi: 10.1002/hep.25505.
7. Naik A, Gupta N, Goel D, Ippagunta SK, Sharma RK, Aggarwal R. Lack of evidence of hepatitis E virus infection among renal transplant recipients in a disease-endemic area. *J Viral Hepat* 2013;20:e138-40. doi: 10.1111/jvh.12027.
8. Behrendt P, Steinmann E, Manns MP, Wedemeyer H. The impact of hepatitis E in the liver transplant setting. *J Hepatol* 2014;61:1418-29. doi: 10.1016/j.jhep.2014.08.047.
9. Inagaki Y, Oshiro Y, Tanaka T, et al. A nationwide survey of hepatitis E virus infection and chronic hepatitis E in liver transplant recipients in Japan. *eBiomedicine* 2015:epub ahead of print.
10. Pischke S, Hartl J, Pas SD, Lohse AW, Jacobs BC, Van der Eijk AA. Hepatitis E virus: Infection beyond the liver? *J Hepatol* 2017;66:1082-1095. doi: 10.1016/j.jhep.2016.11.016.
11. Dalton HR, van Eijk JJJ, Cintas P, et al. Hepatitis E virus infection and acute non-traumatic neurological injury: A prospective multicentre study. *J Hepatol* 2017. doi: 10.1016/j.jhep.2017.07.010.
12. Pischke S, Hardtke S, Bode U, et al. Ribavirin treatment of acute and chronic hepatitis E: a single-centre experience. *Liver Int* 2013;33:722-6. doi: 10.1111/liv.12114.
13. Kamar N, Izopet J, Tripon S, et al. Ribavirin for chronic hepatitis E virus infection in transplant recipients. *N Engl J Med* 2014;370:1111-20. doi: 10.1056/NEJMoa1215246.
14. Tedder RS, Ijaz S, Kitchen A, et al. Hepatitis E risks: pigs or blood-that is the question. *Transfusion* 2017;57:267-272. doi: 10.1111/trf.13976.
15. Hogema BM, Molier M, Sjerps M, et al. Incidence and duration of hepatitis E virus infection in Dutch blood donors. *Transfusion* 2016;56:722-8. doi: 10.1111/trf.13402.
16. Thom K, Gilhooly P, McGowan K, et al. Hepatitis E virus (HEV) in Scotland: evidence of recent increase in viral circulation in humans. *Euro Surveill* 2018;23. doi: 10.2807/1560-7917.ES.2018.23.12.17-00174.
17. Gupta BP, Lama TK, Adhikari A, et al. First report of hepatitis E virus viremia in healthy blood donors from Nepal. *Virusdisease* 2016;27:324-326. doi: 10.1007/s13337-016-0331-y.
18. Parsa R, Adibzadeh S, Behzad Behbahani A, et al. Detection of Hepatitis E Virus Genotype 1 Among Blood Donors From Southwest of Iran. *Hepat Mon* 2016;16:e34202. doi: 10.5812/hepatmon.34202.
19. Dreier J, Knabbe C, Vollmer T. Transfusion-Transmitted Hepatitis E: NAT Screening of Blood Donations and Infectious Dose. *Front Med (Lausanne)* 2018;5:5. doi: 10.3389/fmed.2018.00005.
20. de Vos AS, Janssen MP, Zaaier HL, Hogema BM. Cost-effectiveness of the screening of blood donations for hepatitis E virus in the Netherlands. *Transfusion* 2017;57:258-266. doi: 10.1111/trf.13978.
21. Spada E, Pupella S, Pisani G, et al. A nationwide retrospective study on prevalence of hepatitis E virus infection in Italian blood donors. *Blood Transfus* 2018;1-9. doi: 10.2450/2018.0033-18.
22. Cleland A, Smith L, Crossan C, et al. Hepatitis E virus in Scottish blood donors. *Vox Sang* 2013;105:283-9. doi: 10.1111/vox.12056.
23. Baylis SA, Gartner T, Nick S, Ovemyr J, Blumel J. Occurrence of hepatitis E virus RNA in plasma donations from Sweden, Germany and the United States. *Vox Sang* 2012;103:89-90. doi: 10.1111/j.1423-0410.2011.01583.x.
24. Ijaz S, Szypulska R, Tettmar KI, Kitchen A, Tedder RS. Detection of hepatitis E virus RNA in plasma mini-pools from blood donors in England. *Vox Sang* 2012;102:272. doi: 10.1111/j.1423-0410.2011.01554.x.
25. Corman VM, Drexler JF, Eckerle I, Roth WK, Drosten C, Eis-Hubinger AM. Zoonotic hepatitis E virus strains in German blood donors. *Vox Sang* 2013;104:179-80. doi: 10.1111/j.1423-0410.2012.01638.x.

26. O'Riordan J, Boland F, Williams P, et al. Hepatitis E virus infection in the Irish blood donor population. *Transfusion* 2016;56:2868-2876. doi: 10.1111/trf.13757.
27. Sauleda S, Ong E, Bes M, et al. Seroprevalence of hepatitis E virus (HEV) and detection of HEV RNA with a transcription-mediated amplification assay in blood donors from Catalonia (Spain). *Transfusion* 2014. doi: 10.1111/trf.12929.
28. Gallian P, Lhomme S, Piquet Y, et al. Hepatitis E virus infections in blood donors, France. *Emerg Infect Dis* 2014;20:1914-7. doi: 10.3201/eid2011.140516.
29. Grabarczyk P, Sulkowska E, Gdowska J, et al. Molecular and serological infection marker screening in blood donors indicates high endemicity of hepatitis E virus in Poland. *Transfusion* 2018;58:1245-1253. doi: 10.1111/trf.14531.
30. Vollmer T, Diekmann J, Johne R, Eberhardt M, Knabbe C, Dreier J. Novel approach for detection of hepatitis E virus infection in German blood donors. *J Clin Microbiol* 2012;50:2708-13. doi: 10.1128/JCM.01119-12.

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