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EDITORIAL

Hepatitis E: Is it a blood-borne pathogen?

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Hepatitis E virus (HEV) infection is a common cause of acute hepatitis in several parts of the world, particularly developing countries where there is poor sanitation and environmental conditions.[1,2] In these endemic regions, HEV infection accounts for a considerable proportion of acute sporadic hepatitis. During hepatitis E outbreaks, the predominant route of transmission of HEV has been fecal-oral, in particular through consumption of contaminated drinking water.[3–5]

Infections that are transmitted by the fecal-oral route, namely hepatitis A, polio virus and rotavirus infection, frequently have a high rate of person-to-person transmission. However, surprisingly, person-to-person transmission of HEV infection is distinctly uncommon. During outbreaks of hepatitis E, secondary attack rates among household contacts of cases is only 0.7 to 2.2%.[1,2] Even when multiple cases occur in a family, these are usually related to a common water source.[6] We have recently shown person-to-person transmission to be uncommon in sporadic hepatitis E also.[7]

Vertical transmission of HEV infection from mother to infant is known. In one study, five of eight babies born to mothers with acute hepatitis E had HEV RNA in their blood specimens obtained at birth.[8]

Several hepatotropic viruses, namely hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) are transmitted primarily through the parenteral route. In contrast, hepatitis A and E are transmitted primarily by the fecal-oral route. Hepatitis A can rarely be transmitted through blood transfusion.[9] Generally, HEV is believed not to be transmitted through blood transfusions because viremia during infection with this virus lasts for only a short period.[10] Also, anti-HEV antibody prevalence rates among patients with hemophilia,[11] thalassemia, patients on hemodialysis and intravenous drug users are no higher than those in the general population.[12]

In this issue of the Journal, Khuroo *et al.*[13] provide data to indicate that HEV infection can be transmitted through blood transfusion. Their study had several components. First, they showed that serological evidence of HEV infection was more frequent among those who had received blood transfusions than among non-transfused controls. Second, they found that a small proportion of healthy blood donors had evidence of subclinical HEV infection and viremia. Third, individuals who had received blood from these donors with subclinical HEV infection developed evidence of HEV infection after transfusion. These data suggest (i) frequent existence of subclinical infection and viremia due to HEV among healthy persons residing in HEV-endemic regions, and (ii) the possibility of transmission of this virus through blood transfusions. These data raise several questions. Let us look at these one by one.

Are these data entirely novel? Individual pieces of information included in the paper by Khuroo *et al.*[13] have been reported previously. Mathur *et al.*,[14] using an in-house assay, found IgM anti-HEV antibodies in 244 of 2070 (11.8%) children residing in northern India and attending medical facilities for minor ailments, suggesting that subclinical HEV infection was frequent. However, they did not test these sera for HEV RNA. Arankalle *et al.*[15] found HEV RNA in sera from three of 200 blood donors in India; of these three donors, only one had detectable IgM anti-HEV antibodies. However, they did not follow-up the recipients of HEV RNA-positive blood. In another study,[16] Arankalle *et al.* tested serial sera from 37 IgG anti-HEV-negative transfusion recipients and found evidence of seroconversion to IgM and IgG anti-HEV in two patients; in contrast, none of the 34 non-transfused controls showed such seroconversion. However, the implicated donor blood units tested negative for HEV RNA, casting a shadow on blood transfusion as the route of transmission. Alternatively, this finding may reflect poor sensitivity of tests for HEV RNA. The current study by Khuroo *et al.*,[13] in contrast, provides data concurrently on all pieces of the puzzle. It thus represents a significant advance on the previously available data.

Do these data conclusively prove transmission of HEV through blood transfusion? Ideally, one would have liked the authors to show identity or close homology of genomic sequences of HEV isolates from the infected donor blood and from clinical specimens obtained from recipients with post-transfusion hepatitis

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E. Such studies have recently been used to prove transmission of HEV through consumption of undercooked meat infected with HEV.[17] However, even in the absence of such data, the evidence provided by the authors is fairly convincing.

Do the data reported by Khuroo *et al.*[13] have some inconsistency? In the prospective part of their study, nearly 4% of healthy blood donors (four of 107, including three with IgM anti-HEV) had HEV RNA (Table 1). In contrast, in the initial retrospective study, only two of 250 (0.8%) healthy controls and none of 115 healthy subjects with remote history of transfusion had detectable IgM anti-HEV and/or HEV RNA (Table 1). This significant difference (4/107 *vs* 2/365; $P < 0.05$, Fisher's exact test; EpiInfo, version 6) in frequency of subclinical HEV infection rates in the two phases of their study is somewhat puzzling. Even more disconcerting are a still wider range of IgM anti-HEV seroprevalence rates reported among healthy subjects in other studies from India, varying from as low as none of 412 blood donors[16] to 11.4% of healthy children.[14] These variations call for studies of a larger number of healthy subjects in HEV-endemic populations.

What is the clinical relevance of transmission of HEV infection through blood transfusions? Khuroo *et al.*[13] found HEV infection in three of their 22 susceptible transfusion recipients; of these three, one each had mild clinical hepatitis, subclinical alanine aminotransferase (ALT) elevation and no evidence of liver injury. In the study by Arankalle *et al.*,[16] of the two transfusion recipients who developed HEV infection, neither developed symptoms and one had ALT elevation. Thus, based on these limited data on five patients, post-transfusion hepatitis E was usually not a clinical problem. Furthermore, given the high rates of fecal-oral transmission of hepatitis E in disease-endemic regions, the parenterally acquired hepatitis E is likely to constitute only a minute proportion of all hepatitis E cases.

Do these data indicate the need to introduce screening measures to prevent transmission of HEV through blood transfusion? Currently, the answer will be 'no'. To introduce such measures, we need to be certain that post-transfusion hepatitis E poses a significant disease burden and that we have a method that reliably prevents such transmission. Various candidate screening tests for this purpose may include ALT levels, IgM anti-HEV and HEV RNA. ALT testing, although simple to perform, is unlikely to be effective. In the studies by Khuroo *et al.*[13] and Arankalle *et al.*,[16] ALT elevation was observed in only two of four and one of three donor blood units that contained HEV RNA, respectively. In another study, only 7% of IgM anti-HEV positive sera from healthy children had ALT levels exceeding twice the upper limit of normal.[14] Thus, ALT elevation is possibly too insensitive for this purpose. Furthermore, in a study from India,[18] 16.5% of blood units had ALT elevation, indicating that this test would lead to an unacceptably high rate of wastage of donated blood. HEV RNA testing is impractical in resource-poor HEV-endemic regions. Further studies are needed on the specificity of IgM anti-HEV assays in blood bank sera with a low prevalence of HEV infection.

Do the new observations alter our current understanding of hepatitis E? Possibly, yes. If confirmed by other groups, these findings may have a major impact on our understanding of HEV epidemiology. In an experimental animal model, subclinical HEV infection has been shown to be associated with excretion in feces of large quantities of viable virus, which is capable of transmitting infection to naïve animals.[19] This led to the hypothesis that repeated subclinical passage of HEV in humans and consequent shedding of large quantities of viable virus may represent a potential reservoir of HEV, somewhat akin to the situation with polio virus. The demonstration by Khuroo *et al.*[13] of subclinical HEV infection provides support for this hypothesis.

Khuroo *et al.*[13] found the IgG anti-HEV positivity rates to be relatively lower than would be expected from contemporaneous IgM positivity rates in various study groups (Table 1). After acute HEV infection, IgM antibodies persist for approximately 5 months. Although the exact duration of persistence of IgG antibodies is not known, these are believed to persist for several years.[1,2,20] Thus, one would expect the prevalence of IgG to be several fold higher than that of IgM. The relatively low ratio of IgG:IgM positivity rates observed by Khuroo *et al.* would suggest that IgG antibodies become undetectable fairly rapidly. Furthermore, frequent occurrence of HEV infections, both clinical and subclinical, among adults in HEV-endemic regions despite a high rate of subclinical HEV infection suggests absence of significant protection against reinfection. If this is true, attempts at eradicating hepatitis E through the development of an immunogenic vaccine may prove to be unsuccessful. In fact, in animal studies, the protective effect of a putative HEV vaccine has been found to be short-lasting.[21]

Another issue that will need to be answered is the possible mode(s) of acquisition of frequent subclinical HEV infection. This is particularly important because person-to-person spread has been shown to be infrequent in both epidemic and sporadic hepatitis E.[6,7]

Table 1 Frequency of various hepatitis E virus (HEV) markers in the study by Khuroo *et al.*[13]

Group	*n*	IgM anti-HEV or HEV RNA (%)	IgG anti-HEV (%)
Healthy controls in the retrospective study	250	2 (0.8)	10 (4.0)
Subjects with history of remote transfusion in retrospective study	115	0 (0)	9 (7.8)
Blood donors in the prospective study	107	4 (3.7)	11 (10.3)
Total	472	6 (1.3)	30 (6.4)

In conclusion, Khuroo *et al's* data on transmission of hepatitis E through blood transfusions represent an advance in our knowledge about the disease. However, larger studies are needed to determine the frequency of such transmission in disease-endemic regions. If such transmission is indeed found to be common, we will need to find out methods to prevent it. In addition, there is an urgent need to study in more detail the frequency and consequences of subclinical HEV infection, if we wish to fully understand the epidemiology of this 'E'nigmatic virus.

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