Unique clinical courses of transfusion-transmitted hepatitis E in patients with immunosuppression

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BACKGROUND: The high prevalence of specific immunoglobulin G for hepatitis E virus (HEV) in Japanese people raises the possibility of a high incidence of HEV-viremic blood donors and therefore frequent transfusion-transmitted HEV (TT-HEV).

STUDY DESIGN AND METHODS: TT-HEV cases established in Japan through hemovigilance and those published in the literature were collected. Infectivity of HEV-contaminated blood components and disease severity in relation to immunosuppression were investigated.

RESULTS: Twenty established TT-HEV cases were recorded over the past 17 years. A lookback study verified that five of 10 patients transfused with known HEV-contaminated blood components acquired HEV infection. The minimal infectious dose of HEV through transfusion was 3.6×10^4 IU. Nine of the 19 TT-HEV cases analyzed had hematologic diseases. Only two cases showed the maximal alanine aminotransferase level of more than 1000 U/L. Two patients with hematologic malignancy and two liver transplant recipients had chronic liver injury of moderate severity.

CONCLUSION: The infectivity of HEV-contaminated components was 50%. Immunosuppression likely causes the moderate illness of TT-HEV, but it may lead to the establishment of chronic sequelae. Transfusion recipients, a population that is variably immunosuppressed, are more vulnerable to chronic liver injury as a result of TT-HEV than the general population is as a result of food-borne infection.

Sporadic hepatitis E that occurs in industrialized countries is a zoonotic or food-borne illness,[1,2] where humans are infected through the consumption of raw or undercooked meats or viscera from such animals as domestic pig, wild boar, deer, and rabbit.[3-5] Hepatitis E virus (HEV) of Genotypes 3 and 4 is responsible for this type of hepatitis E.

Nationwide studies indicated that the seroprevalence of HEV-specific immunoglobulin (Ig)G was 3.4% to 5.3% in Japan.[6,7] Based on this prevalence, it was estimated that

ABBREVIATIONS: JRC = Japanese Red Cross; TT-HEV = transfusion-transmitted hepatitis E virus.

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approximately 150,000 new HEV infection cases arise every year in Japan,[8] which raises the possibility of frequent blood donation during an HEV-viremic period, resulting in frequent transfusion-transmitted HEV (TT-HEV). We have, however, observed only a few TT-HEV cases since two TT-HEV cases were reported in 2002 and 2004.[9,10] Moreover, the incidence of hepatitis E in the general population is also low; only 120 to 220 cases have been reported annually over the past 3 years.[11] The apparent low incidences of hepatitis E and TT-HEV seemingly contradict the HEV seroprevalence in the general population that shows an age-dependent linear increase.

To explore whether blood screening using nucleic acid amplification testing (NAT) of donated blood is needed to prevent TT-HEV,[12,13] risk assessment for TT-HEV is essential, focusing on the following points: 1) the frequency of HEV-viremic blood donations, 2) the transmissibility of HEV by transfusion of HEV-contaminated blood, and 3) the magnitude of liver injury caused by TT-HEV. This study focuses on the latter two points, reviewing cases obtained from hemovigilance, as well as previously published cases.

MATERIALS AND METHODS

Hemovigilance system and lookback studies

Japanese Red Cross (JRC) blood centers are the sole facilities in Japan that deal with all processes from blood collection to blood delivery. The JRC hemovigilance system includes a complete blood archive obtained from all blood donations. On receiving information regarding suspected transfusion-transmitted infection from medical facilities, the JRC Central Blood Institute analyzes both archived blood samples from the implicated donations and patient samples. The JRC notifies the relevant medical facilities of the findings of these analyses and initiates lookback for transfused patients if necessary. This study was approved by the JRC ethical committee (2014-04). Patient data were reported to JRC in accordance with the Pharmaceutical and Medical Devices Act. The analysis and publication of those deidentified data were approved by the JRC ethical committee.

NAT and serologic analysis

The JRC Hokkaido Blood Center has developed an analytical in-house reverse transcription–polymerase chain reaction for the detection of HEV RNA in plasma.[9] This system was introduced in 2005 for screening donated blood for HEV RNA. Screening covered only the Hokkaido area because HEV was thought to be highly endemic to that area, particularly HEV with Genotype 4 that is believed in Japan to cause a more severe hepatitis than Genotype 3.[8] The screening system employed a 20-sample pool format, of which the 95% limit of detection for individual samples was 52.2 IU/mL (95% confidence interval, 35.5-93.0 IU/mL); accordingly, that for a 20-sample pool was 1044 IU/mL. In 2005, when the screening started, NAT results were not obtained until Day 5 after donation. Under this condition, the Hokkaido Blood Center was able to trace the clinical outcome of transfusion of HEV RNA–contaminated components that had been issued before NAT results were obtained. Since the implementation of real-time NAT in 2006, only HEV NAT–negative blood components have been issued in that area.

One of the domestic plasma fractionation factories in Japan (Japan Blood Products Organization) has conducted HEV RNA screening of plasma units delivered from the JRC since 2007, using its in-house system with a 50-sample pool format,[14] the sensitivity of which is 152 IU/mL for individual samples. When an HEV RNA–positive plasma unit was identified, the information was then sent to the JRC. The JRC reanalyzed the archived blood sample from the index donation and initiated lookback, if necessary, for patients transfused with the relevant blood component.

Analysis of patient samples or archived donor samples was conducted in the Hokkaido Blood Center and the JRC Central Blood Institute using the method described above. HEV genome sequences of ORF-1 (326 nucleotides, 123-448) and ORF-2 (412 nucleotides, 5987-6398) were compared between patient samples and archived samples from suspected donors using the methods previously reported.[9,15] HEV-specific IgG and IgM were measured using an enzyme-linked immunosorbent assay kit that uses an ORF-2 recombinant antigen derived from Genotype 4 HEV (Institute of Immunology, Tokyo, Japan).

Statistical analysis

Data were analyzed with computer software (SSRI, Excel Statistics, Version 8, Social Survey Research Information) for Windows (Excel 2007, Microsoft Corp.). Statistical analysis was performed using the Mann-Whitney U test, and differences with a p value of less than 0.03 were regarded as significant.

RESULTS

Collection of TT-HEV infection through hemovigilance

A total of 20 TT-HEV cases were established throughout Japan over the past 17 years, 12 of which were observed in the past 4 years. Nineteen cases with available data were evaluated in the current study, which included two TT-HEV cases previously reported from the JRC Hokkaido Blood Center[9,10] and six cases described in separate papers.[16-22] Thirteen of the 19 cases were males, and six were females. Their ages ranged from their 20s to their 80s.

TABLE 1. Clinical outcome of transfusion with HEV-contaminated components

Clinical outcome	Information source: Voluntary report	Information source: Screening NAT- or voluntary report–related lookback*	Information source: Plasma NAT-related lookback	Total
TT-HEV established	8	4	7	19
TT-HEV excluded	0	5	0	5
IgG positive	0	0	3†	3
ALT elevation	0	0	2‡	2
Unknown	0	2	9	11
Patient dead	0	5	9	14

* Outcome of the transfusion of cocomponents of TT-HEV–related donations and that of HEV-contaminated components verified by retrospective NAT screening are shown.
† Two patients showed positive HEV-specific IgG in their posttransfusion samples but no pretransfusion data were available. One patient showed specific IgG seroconversion but displayed no further evidence indicative of HEV infection.
‡ Two patients showed transient ALT elevation without any test results indicative of HEV infection.

TABLE 2. Establishment of TT-HEV infection

Patient*	Posttransfusion status: HEV RNA	IgM	IgG	Regions with sequence identity
1[17]	Positive	Negative	Conversion	ORF-1, ORF-2 (1 nt discordant)
2[16]	Positive	ID†	ID†	Whole sequence (7231 nts)
3[10]	Positive Genotype 4	Negative‡	Conversion	ORF-1,2
4	Positive	Positive	Conversion	ORF-1,2
5	Positive	Positive	Conversion	ORF-1,2
6[20]	Positive	ID	ID	ORF-1 (1 nt discordant), ORF-2
7[18,19]	Positive	Positive	Positive (pre- and post-)§	ORF-1,2
8[18,21]	Positive	Positive	Conversion	ORF-1 (2 nts discordant), ORF-2
9[9]	Positive Genotype 4	Positive	Positive	ORF-1
10	Positive	Negative	Conversion	ORF-1,2
11	Positive	Positive	Conversion	ORF-1,2
12[22]	Positive	Positive	Conversion	ORF-1,2
13	Negative‖	Positive	Positive	ND
14	Positive	ID	ID	ORF-1,2
15	Positive	Positive	Conversion	ORF-1,2
16	Positive	Negative	Positive	ORF-1,2
17	Positive	Positive	Conversion	ORF-1,2
18	Negative‖	ID	Conversion	ND
19	Positive	Positive	Conversion	ORF-1,2

* Patients 10, 12-16, and 18 were verified through plasma NAT-related lookback.
† "IgM ID (indeterminate)" or "IgG ID" indicates negative result(s) from a very few sample tests and does not mean negative results throughout the clinical course.
‡ "IgM negative" indicates negative results from multiple sampling throughout the clinical course.
§ HEV-specific IgG was positive both before and after transfusion.
‖ HEV RNA testing was done only once after transfusion. These two cases were considered as probable TT-HEV cases.
ND = not done; nt = nucleotide.

Eight cases were initially reported by physicians (Table 1) with the diagnosis of either hepatitis E or viral hepatitis. Eleven cases were verified through lookback, three of which were uncovered via retrospective NAT screening in Hokkaido. One case was disclosed by voluntary report-related lookback. The remaining seven cases were verified by lookback initiated from plasma NAT screening. Hepatitis E or even liver dysfunction had not been suspected for most cases disclosed by lookback.

Establishment of TT-HEV infection

Blood components that caused TT-HEV were red blood cells (n = 10), platelet (PLT) concentrates (n = 6), and fresh-frozen plasma (FFP, n = 3). Because only blood with an alanine aminotransferase (ALT) level of not more than 60 U/L qualifies for use as a blood product in Japan, all 19 donations responsible for the TT-HEV cases had ALT levels of not more than 60 U/L at the time of their blood donation.

Table 2 shows the details of test results that substantiated the establishment of TT-HEV in the 19 cases. HEV RNA was demonstrated in posttransfusion samples of 17 patients, in all of whom sequence identity of the ORF-1 and/or 2 between the archived donor blood sample and the patient blood was confirmed. Two cases were determined to be probable TT-HEV because of the absence of

HEV RNA in the posttransfusion samples; one patient (Patient 13 in Tables 2 and 3) developed transient hepatitis 1 month after transfusion. He was HEV-specific IgM- and IgG-positive after transfusion. Another patient (Patient 18) developed hepatitis 2 months after transfusion and later showed IgG conversion. Both patients had little possibility of acquiring HEV infection other than through blood transfusion during their continued hospitalization. Patient 7 possibly acquired reinfection because she was HEV specific IgG positive before transfusion and IgM positive after transfusion. Patients 3 and 9 were infected by HEV Genotype 4, and infection of both of these patients occurred in Hokkaido. The remaining 17 patients were infected by Genotype 3.

Infectivity of blood components contaminated with HEV

The viral concentration of the components that caused TT-HEV ranged between 1.5×10^2 and 5.3×10^6 IU/mL. The total viral load in components ranged between 3.6×10^4 and 1.1×10^8 IU (Fig. 1) with the factorial median being 6.2×10^5 IU. Five patients, who were transfused with HEV-contaminated components but who were not infected, were identified through lookback (Table 1). The total viral load in those components ranged between less than 2.0×10^4 and 2.6×10^5 IU (Fig. 1). All components with a total viral load of more than 1.0×10^6 IU caused TT-HEV. Two of the 19 responsible donations were HEV specific IgG positive. We assessed the infectivity of HEV RNA-contaminated components when transfused into patients based on the results of lookback. In this analysis, data derived from plasma NAT screening including the two probable TT-HEV cases were excluded. Lookback for those cases was conducted more than 1 year after blood collection because of the plasma quarantine period where, in most cases, we were unable to retest patients or conduct precise examination of clinical records of patients for HEV. On the other hand, we included one TT-HEV case that was not included in this analysis because this case was verified from the JRC lookback study. Overall, 10 blood components with known HEV RNA contamination had been transfused. Of patients transfused with these components, five patients (Patients 3, 11, 17, and 19 and a case excluded in this paper) acquired TT-HEV (Table 1); therefore, the infectivity of HEV RNA contaminated blood components was 50%.

There was no statistical difference in the viral load infused between eight patients with intense immunosuppression (six with hematological disorders [Patients 1-6] plus two with liver transplantation [Patients 7 and 8]) and nine others without such immunosuppression (Patients 9-12, 14-17, and 19) excluding the two probable cases (median, 9.0×10^5 and 4.4×10^5 IU, respectively).

Kinetics of viremia and ALT during the hepatitis course

We assessed the length of viremia in 10 patients who were tested multiple times for HEV RNA. The median viremic period in the typical transient hepatitis cases ($n = 6$) was 44 days (range, 24-76 days). Four cases that showed a viremic period of more than 100 days were all heavily immunosuppressed patients; one patient (Patient 1) with acute promyelocytic leukemia accompanying disseminated intravascular coagulation and sepsis, one Burkitt lymphoma patient (Patient 6) with sustained hypogammaglobulinemia, and two liver transplant patients (Patients 7 and 8).

We assessed the severity of hepatic injury by evaluating maximal ALT levels during the hepatitis course (Table 3). The two probable cases were included in the following analysis dealing with ALT levels. The maximal ALT levels of 16 (84%) of the 19 cases were more than 100 U/L; nine cases (47%) had levels of more than 500 U/L, and two (11%) had levels of more than 1000 U/L. Their median ALT level was 486 U/L (range, 39-1665 U/L). Except for two cases with chronic liver injury as described below, most other cases showed prompt normalization of ALT levels after the ALT peak. The maximal ALT levels of two cases infected with Genotype 4 were 1665 and 673 U/L. Liver injury caused by TT-HEV is, thus, generally mild. There was no tendency of maximal ALT levels to increase with increasing total viral load infused (Fig. 2).

There was no difference in the maximal ALT levels between the eight heavily immunosuppressed patients (Patients 1-8) and the other 11 patients (median ALT values, 548 U/L vs. 486 U/L, respectively). Three of the four patients with the highest ALT levels (Patients 9, 10, and 17) were not being treated with immunosuppressants, while two patients with liver transplantation showed low maximal ALT levels (315 and 93 U/L, respectively). The time from the implicated transfusion to the date with peak ALT was significantly longer in the cases with intense immunosuppression (Patients 1-8) than in those without such immunosuppression (Patients 9-19) (median, 126 days vs. 54 days; $p < 0.03$). Six cases (Patients 3, 5-7, 10, and 18) showed a bimodal elevation of ALT levels (Fig. 3). The first and second peaks of ALT levels in those patients were observed between 17 and 69 days and between 49 and 969 days posttransfusion, respectively.

HEV hepatitis with chronic liver injury

There were two chronic TT-HEV hepatitis cases with liver histology showing mild fibrosis. One case was a patient with Burkitt lymphoma (Patient 6)[20] who received an HEV-contaminated blood transfusion while heavily immunosuppressed due to chemotherapy. After the first ALT peak (347 U/L) on Day 58, she showed a linear increase from 33 to 395 U/L over 2 years, possibly with a

TABLE 3. Underlying diseases and maximal ALT levels of patients with transfusion-transmitted HEV infection

Patient*	Year of transfusion, age (years), sex	Underlying diseases	Total viral load infused (IU)	Maximal ALT (U/L) (days after transfusion)	Remarks
Heavily immunosuppressed					
1[17]	2011, 27, female	Acute promyelocytic leukemia with DIC and sepsis	3.6×10^4	972 (220)	Very late onset of hepatitis
2[16]	1999, 21, male	Malignant lymphoma Pancytopenia Marrow transplantation	1.2×10^6	832 (117)	Sustained liver dysfunction Moderate hepatic fibrosis by histology
3[10]	2004, 64, male	Non-Hodgkin's lymphoma PBSCT	2.4×10^5	673 (59)	Genotype 4 HEV Bimodal ALT elevation
4	2015, 67, male	Hodgkin's lymphoma	2.0×10^7	646 (105)	
5	2015, 52, female	Multiple myeloma Autologous PBSCT	4.8×10^5	449 (110)	Bimodal ALT elevation
6[20]	2011, 37, female	Burkitt lymphoma Persistent low gammaglobulinemia	2.1×10^6	395 (969)	Chronic hepatitis with moderate fibrosis Bimodal ALT elevation Incomplete viral clearance with ribavirin
7[18,19]	2012, 61, female	Primary biliary cirrhosis Liver transplantation	6.7×10^5	315 (17)	Sustained viremia Bimodal ALT elevation Chronic hepatitis with mild damage by transient elastography HEV cleared by ribavirin
8[18,21]	2014, 41, male	Nonalcoholic steatohepatitis with hepatocellular carcinoma Liver transplantation	3.6×10^6	93 (178)	Sustained viremia Chronic hepatitis with mild hepatic injury HEV cleared by ribavirin
Cases with systemic diseases					
9[9]	2002, 67, male	Annuloaortic ectasia Valve replacement surgery	6.1×10^5	1665 (37)	Genotype 4 HEV
10	2008, 74, male	Epidural abscess, ARDS, sepsis, and acute renal failure	3.2×10^5	1336 (23)	Bimodal ALT elevation
11	2012, 81, female	MDS	5.6×10^4	811 (64)	
12[22]	2011, 70, male	MDS Pneumonia and lung abscess	4.0×10^4	736 (37)	
13	2008, 82, male	Advanced prostate cancer Radiation and hormone therapy	1.1×10^8	486 (33)	Probable TT-HEV case
14	2012, 72, male	DM nephropathy Unstable angina AC-bypass surgery	4.4×10^5	379 (91)	
15	2011, 55, female	Myelofibrosis ITP (under prednisolone therapy)	6.6×10^4	224 (125)	
16	2008, 66, male	Gastric cancer Maintenance dialysis	5.6×10^5	39 (54)	No ALT elevation
No accompanying systemic diseases					
17	2005, 72, male	Angina	5.3×10^6	972 (65)	
18	2011, 77, male	Abdominal trauma (intestinal perforation)	5.1×10^4	229 (69)	Bimodal ALT elevation Probable TT-HEV case
19	2005, 58, male	Angina	1.2×10^6	61 (48)	

* Patient number corresponds with that in Table 2.
AC-bypass = aortocoronary bypass; ARDS = acute respiratory distress syndrome; DM = diabetes mellitus; DIC = disseminated intravascular coagulation; ITP = immune thrombocytopenic purpura; MDS = myelodysplastic syndrome; PBSCT = peripheral blood stem cell transplantation.

sustained high level of viremia (Fig. 4). Blood testing for HEV that verified HEV viremia was first conducted on Day 878, which led us to consider that the incubation time was likely to have been much shorter. Administration of ribavirin over the following 8 months could not totally eradicate HEV RNA. The second case was a patient with malignant lymphoma (Patient 2)[16] who had chronic hepatitis with an ALT level of 832 U/L on Day 117. HEV viremia was first verified on Day 171. This patient developed a progressively increasing liver injury during the pancytopenic period. He did not generate HEV-specific IgG.

Two more patients with liver transplantation were diagnosed with chronic hepatitis E with slight to moderate liver damage. One of these was a patient in her 60s (Patient 7)[18,19] who had a viremic period of more than 141 days, with an HEV level of 10^2 to 10^6 IU/mL. She developed liver dysfunction with two ALT peak levels: one of 315 U/L on Day 17 and one of 127 U/L on Day 136. Transient elastography verified mild liver stiffness. The second patient (Patient 8)[18,21] showed a linearly increasing ALT level from 10 to 98 U/L over 8 months with a constant HEV viremia of more than 10^5 IU/mL (Fig. 4). Both cases

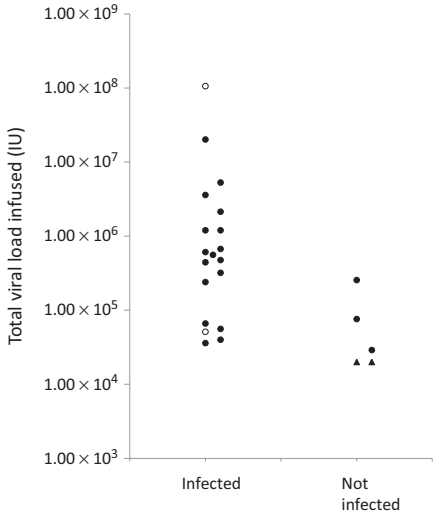

Fig. 1. Establishment of TT-HEV in relation to total viral load contained in the components infused. (○) Probable TT-HEV cases; (▲) cases in which the HEV concentration was below the detection limit by quantitative assay. Viral loads for these cases are placed at the possible highest point of HEV load.

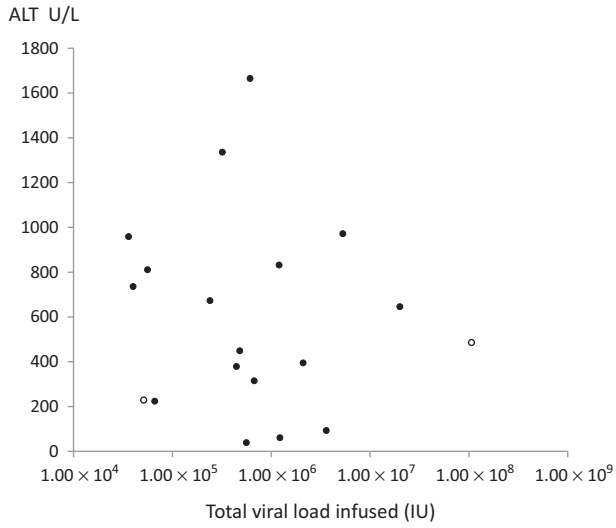

Fig. 2. Correlation between the total HEV load infused and the highest level of ALT in the transfused patients. The horizontal axis indicates the total HEV viral load contained in the transfused blood component. (○) Probable TT-HEV cases.

were successfully cleared of HEV by ribavirin administration.

DISCUSSION

We described 19 established TT-HEV cases that had occurred over the past 17 years. All blood donors responsible for these TT-HEV cases were asymptomatic with a low ALT level (≤60 U/L). The lowest total HEV load in a component that caused TT-HEV in this study was 3.6×10^4 IU. If this amount of virus were transmitted by transfusion with a component of the largest plasma volume (i.e., 480 mL of FFP in Japan), the viral concentration would be 75 IU/mL. If total exclusion of donations with the potential of causing TT-HEV is required, the sensitivity of the NAT system for blood screening should therefore be at least 75 IU/mL. In contrast, a report from Germany describes TT-HEV by the transmission of 7056 IU of HEV.[23] The difference in the component type, that is, apheresis PLTs in the German case and FFP in our case, may partly explain the discrepancy between that report and ours. Possible lower infectivity of FFP compared with that of PLTs has been suggested for hepatitis B virus;[24] thus, the process of freezing and thawing plasma may somehow result in deterioration of virus integrity, leading to lowering of the infectivity of FFP. Notably, in this study, all components with a total viral load of more than 1.0×10^6 IU caused TT-HEV. If this amount of virus (1.0×10^6 IU) were to be transmitted by transfusion with the component with the least plasma volume (20 mL, RBCs), donated blood with HEV at a concentration of more than 5×10^4 IU/mL would have a high risk of causing TT-HEV.

Two components positive for HEV-specific IgG caused TT-HEV, suggesting that specific IgG in these components is incapable of preventing TT-HEV. Hewitt and colleagues[25] also identified three infectious donations that were specific IgG positive. We also found a possible HEV reinfection case where her pretransfusion sample was IgG positive.[19] Thus, the potency of specific IgG as a viral neutralizing agent is questionable in the transfusion-transmitted infection setting. The envelope-like layer surrounding the HEV capsid may hinder the access of specific IgG to neutralizing epitope(s) on HEV.[26-28] In the possible reinfection case (Patient 7), the first ALT peak appeared as early as on Day 17 posttransfusion, possibly as a second reaction.

We deduced the infectivity of HEV-contaminated blood components to be 50% through lookback study, a value close to that reported by Hewitt and colleagues (42%).[25] In both studies, however, the infection group included cases without overt illness. Most TT-HEV cases disclosed in our lookback study had not been recognized by physicians until notified by the JRC. Also, considering that passive hemovigilance tends to collect cases with apparent symptoms, it is likely that the majority of TT-HEV cases are asymptomatic or of low clinical significance.

TT-HEV cases in this study included eight severely immunosuppressed patients and eight patients with serious systemic illnesses. Only two of the 19 cases showed maximal ALT levels between 1000 and 2000 U/L, and the

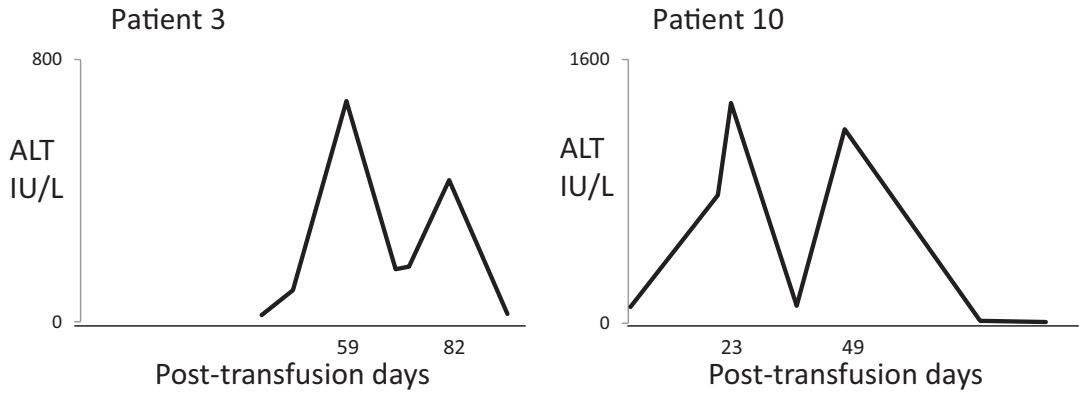

Fig. 3. Bimodal elevation of the ALT level during transfusion-transmitted hepatitis E in two patients. Two of the six cases with bimodal ALT elevation are shown. The vertical axes show the ALT level (U/L). Note that the scale for the ALT level differs among the cases. The horizontal axes show the posttransfusion days, where each indicated number is a date with a peak ALT level. The patients' underlying diseases are as follows: Patient 3 = non-Hodgkin's lymphoma with peripheral blood stem cell transplantation; Patient 10 = sepsis and acute respiratory distress syndrome.

rest of the cases showed low to moderate levels between less than 40 and 1000 U/L. Moreover, two heavily immunosuppressed patients (Patients 1 and 7) had periods with no ALT elevation even with a viremic period of several months (data not shown). It was also found that disease onset was significantly delayed among the eight heavily immunosuppressed patients. These observations indicate that liver injury observed in TT-HEV cases is brought about by the immunologic response to HEV[29-31] and that transfusion recipients may show milder and delayed liver injury. These milder phenomena may occur because of the possible lack of a powerful immunologic attack compared to that staged by otherwise healthy individuals who exhibit clinically overt hepatitis due to HEV infection through an oral route.

Although most patients showed a single episode of liver injury as indicated by ALT levels, six patients showed bimodal elevations of ALT levels during the clinical course. It may be difficult to explain these clinical courses based only on the function of adaptive immune systems such as CD4/8+ T cells or adaptive cytokine production. Indeed, a role for innate immunity involving NK cells[32] or Toll-like receptors,[33] or even direct HEV cytopathy,[34] has been proposed. The slowly increasing ALT levels over an extended period with sustained high-level viremia that were shown by three patients (Patients 6 and 8 and possibly Patient 2) may be the result of mechanisms other than cytotoxic T-cell activity. Biphasic liver injury has been reported to occur in 6% to 10% of cases of HAV hepatitis.[35]

Liver injury in 15 patients eventually resolved, whereas in four patients it took the form of chronic liver injury. These four patients were all under intense immunosuppression. The rate at which liver injury became chronic in our study was 21% (4/19), which is lower than the 60% reported among recipients of solid organ transplantation.[36] The difference in the target patient populations, that is, all transfusion recipients versus solid organ recipients, may explain this discrepancy. Taking into consideration the risk of chronicity that is limited to a small portion of transfusion recipients, the transfusion community must consider the issue of the implementation of HEV NAT screening of donated blood. A high frequency of viremic donors, a seemingly very low incidence of overt TT-HEV hepatitis, the moderate nature of the hepatitis, and the high cost of NAT screening are the complicating factors to be considered.[25] Of note, HEV or the carrier state is mostly treatable with ribavirin.[37,38] In countries with high endemic HEV, blood screening would be of less significance with lower cost-effectiveness because patients are frequently exposed to HEV-contracting risks other than blood transfusion in their daily life. In contrast, in countries with low to intermediate HEV endemicity, the issue of TT-HEV may become a public concern as a transfusion-related side effect. If this is the case, selective screening of blood to be used for transfusion of immunocompromised patients would be one potential solution with reasonable cost-effectiveness, although the logistics for product delivery would be problematic. At any rate, screening of patients for HEV infection who are at risk of becoming chronically infected is the first and most important step to be taken in the clinical setting before implementation of blood screening.

In addition to organ-transplanted patients, patients with hematologic diseases with immunosuppression accounted for nearly half of the overt TT-HEV cases in this study. Acute TT-HEV hepatitis generally takes the form of subclinical to intermediate illness, with no severe or

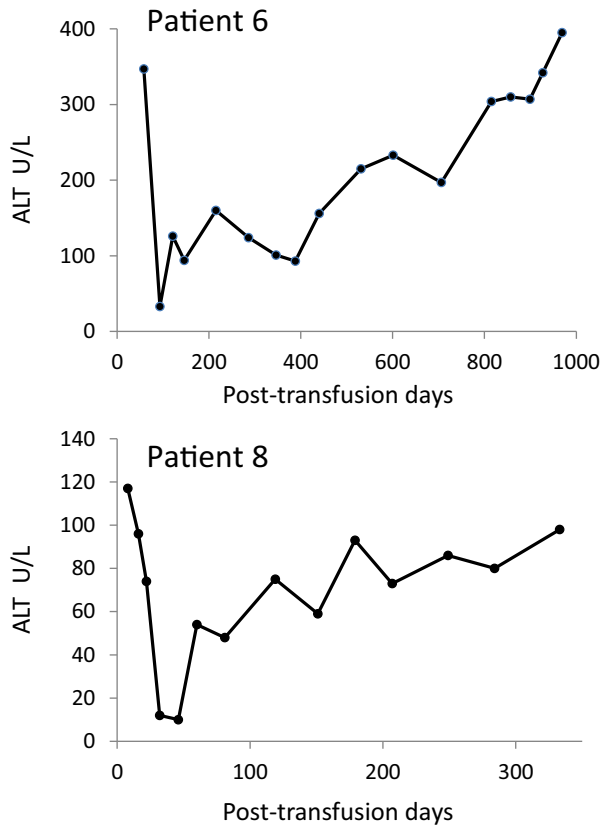

Fig. 4. Linearly increasing ALT levels in two patients with chronic liver injury due to HEV infection. Patient 6 = a female patient with Burkitt lymphoma. HEV viremia was first detected on Day 878 posttransfusion. HEV load in the blood sample of Day 927 was 5×10^6 IU/mL. Patient 8 = a male patient with liver transplantation. HEV viremia continued at a level of more than 1.0×10^5 IU/mL for 8 months. In both cases, ribavirin was later administered, resulting in incomplete and complete eradication of HEV in Patients 6 and 8, respectively.

fulminant cases having been reported. Transfusion recipients, a population that is variably immunosuppressed, are more vulnerable to chronic liver injury as a result of TT-HEV than the general population is as a result of foodborne infection.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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