

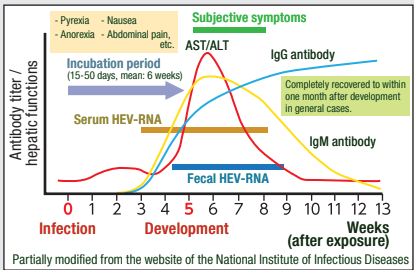
Hepatitis E Virus (HEV) Infection

A case of hepatitis E virus (hereinafter referred to as “HEV”) infection due to blood components for transfusion (see the reverse side) was reported at the 2017 5th Conference of the Committee on Blood Products of the Pharmaceutical Affairs and Food Sanitation Council held on January 31, 2018.

In this case, hepatic disorder appeared after the transfusion of Irradiated Red Blood Cells, Leukocytes Reduced in a patient under medication for multiple myeloma (female in her 80s); the stored sample was examined and it was found that the blood in the transfused component contained HEV. The hepatic disorder temporarily improved by discontinuation of the drug and the administration of liver-supporting therapy but flared up after resuming administration of the drug; thereafter the patient died due to fulminant hepatitis. The outcome of this case is considered to be due to multiple factors (advanced age, long-term administration of the drug, HEV infection).

HEV infections including this case are summarized as follows.

Characteristics of hepatitis E

Occurrence state	- Most cases have been reported in eastern Japan, and by prefecture, Hokkaido has the largest share. - There are mainly 4 genotypes that are transmitted to human. The HEVs native to Japan are genotype 3 (G3) and genotype 4 (G4), and the latter is most frequently observed in Hokkaido.														
Symptoms and typical clinical course	- The mean incubation period is 6 weeks. - In most cases the infection is cured without any symptoms. - Mild pyrexia, anorexia, nausea, and vomiting persist for several days during the initial phase of development, and abdominal pain, itching, skin rash, or arthralgia may be present. - Jaundice and hepatomegaly occur. - Only rarely does acute hepatitis become severe leading to fulminant hepatitis and death. - G4 infections are more likely to be severe than G3 infections.¹⁾  Partially modified from the website of the National Institute of Infectious Diseases														
Route of infection	Oral infection: Due to ingestion of insufficiently heated raw meat and intestines of swine, wild boars, and deer. (Advanced countries). Waterborne infection: Many cases of fecal-oral infection due to excreted virus in feces. (Developing countries) Transfusion infection: There have been 27 cases that have been reported in Japan since 2002, when the first case was reported, to 2017. (5 cases of persistent infection with organ transplantations and hematologic disease ^{2,3)}) [Breakdown of 701 cases of infection in Japan in cases notified as hepatitis E (with duplications)*1] <table><tr><td>Swine meat</td><td>Wild boar meat</td><td>Deer meat</td><td>Others (e.g., meat of unknown animal species, shellfish, water)</td><td>Unknown/not listed</td></tr><tr><td>121 cases (17%)</td><td>34 cases (5%)</td><td>32 cases (5%)</td><td>112 cases (16%)</td><td>411 cases (59%)</td></tr></table>					Swine meat	Wild boar meat	Deer meat	Others (e.g., meat of unknown animal species, shellfish, water)	Unknown/not listed	121 cases (17%)	34 cases (5%)	32 cases (5%)	112 cases (16%)	411 cases (59%)
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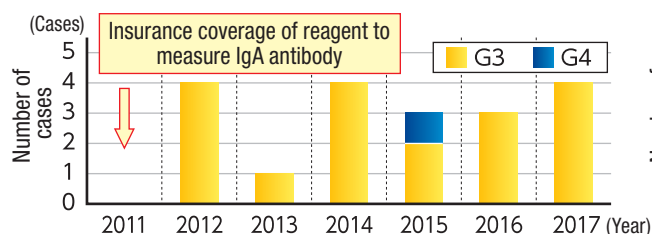
*1 From the National Institute of Infectious Diseases, National Epidemiological Surveillance of Infectious Diseases (NESID) (2012 to April 2016)

The Japanese Red Cross Society conducts a virus test (nucleic acid amplification test [hereinafter referred to as “NAT”]) on donated blood in Hokkaido where the positive rate is considered to be high, for the surveillance of HEV infections; blood with a positive result will not be used, and retrospective surveillance is conducted of patients who have donated blood within the last six months. Surveillance of HEV infections was also conducted in Tokyo in 2016. We continue to pay attention to the future direction and are discussing safety measures within the national council.

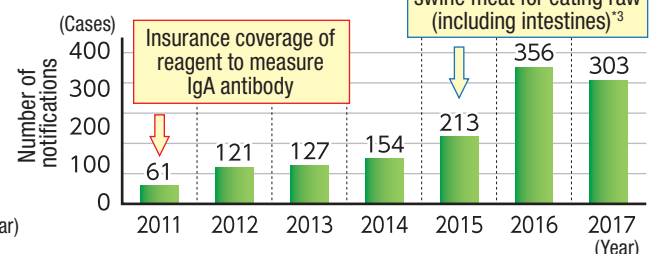
Changes in the number of cases of HEV infection due to transfusion (2011-2017)

There were 19 cases reported as suspected HEV infection due to transfusion from medical institutions to the JRC Blood Centers and identified as infection. Of these, one case was G4 infection, and the other cases were G3 infection.

Changes in the number of cases of HEV infection due to transfusion



(Reference) Changes in the number of notifications of hepatitis E^{*2}



*2 From National Institute of Infectious Diseases, IDWR year-based list and quick-look data

*3 Revision in the Specifications and Standards for Foods, Food Additives, etc. Under the Food Sanitation Act (Shokuan (Notification by Director of Department of Food Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) No. 0602-1 dated June 2, 2015 “Partial Revision in the Specifications and Standards for Foods, Food Additives, etc.”)

Case reported at the 2017 5th Conference of the Committee on Blood Products of the Pharmaceutical Affairs and Food Sanitation Council

- ◆ Patient: Woman in her 80s
- ◆ Primary disease: Multiple myeloma
- ◆ Clinical course: See the figure on the right
- ◆ Tests at the Japanese Red Cross Society

Blood of patient

Approx. 5 months predose: HEV-RNA (–), IgM antibody (–), IgG antibody (–)

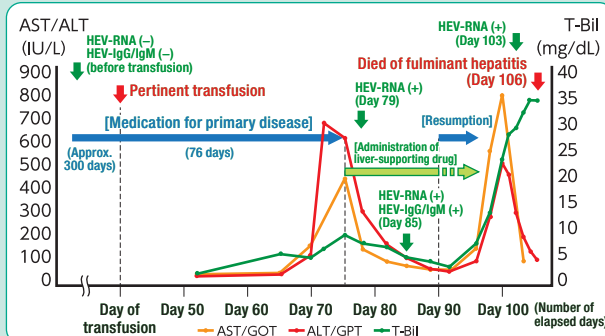
Day 85 postdose: HEV-RNA (+), IgM antibody (+), IgG antibody (+)

Day 103 postdose: HEV-RNA (+)

Stored sample of donor

One of the 19 stored samples of transfused blood was HEV-RNA (+).

The genome sequence of the HEV of the patient was consistent with that of the stored sample. (G3)



Precautions for the risk of infection with hepatitis viruses

- Blood components for transfusion may cause infection with hepatitis viruses such as HEV, hepatitis B virus (HBV) and hepatitis C virus (HCV), and these diseases may develop. For HBV and HCV, the package insert describes that tests for hepatitis virus markers before and after transfusion in patients should be performed if infection is suspected, and observation/monitoring of the clinical course of the patient should be performed. For HEV, conduct tests for hepatitis virus markers and follow-up monitoring of the patient as needed.
- Take appropriate measures if infection with the hepatitis virus is observed or any symptoms appear. Take into consideration the risks of infection with the hepatitis viruses and the possibility that the disease may become chronic in cases of immune system suppression due to treatment of the primary disease or for other reasons.
- Consider consultations with hepatologists at linked regional core centers for the treatment of liver disease about the test methods and treatment policy of HEV as needed.
- Blood components for transfusion conform to tests of HBV and HCV; however, there may be a risk of infection if the donor is in the window period, etc.
- Please provide information on any suspected cases of infection with the hepatitis virus to the Japanese Red Cross Society.

General precautions for the risk of infection

- Monitor the condition of the patient during transfusion as appropriate. Adequately monitor the patients for at least approximately five minutes after the start of transfusion, and monitor again after approximately 15 minutes have elapsed.⁴⁾
- Prepare emergency measures against the onset of adverse reactions during transfusion.
- Transfusion has risks of adverse reactions due to alloimmunization, etc. and infection with viruses, etc.; therefore it is performed only in case there is no alternative therapy and the efficacy outweighs the risk.⁴⁾
- It is determined that the necessity of transfusion and the risks of infections/adverse reactions due to transfusion should be understandably explained to patients or their families in writing and consent should be obtained if it is conducted.⁴⁾

Safety measures of the Japanese Red Cross Society

- We ask persons who have consumed raw meat and intestines of swine, wild boars, or deer, etc., which may be infected with HEV within a certain period of time, to refrain from blood donation.
- A notice regarding HEV is posted at blood donation venues. If a donor has been infected with HEV, it alerts that HEV may be transmitted to patients who will undergo transfusion.
- Interview with donors is thoroughly performed.
- We are discussing the conduct of the HEV test (NAT) on all of donated blood components in Japan.

[References]

- 1) Takahashi M, Okamoto H. Features of hepatitis E virus infection in humans and animals in Japan. Hepatology Research. 2014;44:43-58.
- 2) Satake M, Matsubayashi K, Hoshi Y, et al. Unique clinical courses of transfusion –transmitted hepatitis E in patients with immunosuppression. TRANSFUSION. 2017;57:280-288.
- 3) Transfusion Information 1610-148 “Cases of Infection Considered to be Highly Related to Blood Components for Transfusion – 2015”
- 4) Partial revision of “Guidance of Transfusion Therapies” and “Guidance of Use of Blood Components (PFSB Notification [Notification by Director General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare] No. 1112-12, dated November 12, 2014)

In case any of adverse reactions and/or infections related to transfusion of blood components, please notify the medical representatives of your local JRC blood center immediately. Please provide the residual products, the recipient samples, and any other related materials; it is helpful to investigate and/or identify the cause. For storage of residual products and the recipient samples, refer to the “Guidelines for lookback studies of blood products.”

Issued by:
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* For more information, please contact the medical representatives of your local JRC blood center.

For blood products and transfusion information
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