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【 CASE REPORT 】

Acute Hepatitis E virus Subtype 3e Infection with Prolonged Jaundice Improved with Inchinkoto

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Abstract:
Hepatitis E virus (HEV) is a globally prevalent waterborne and zoonotic infection, with approximately 20 million infections occurring annually in developing and industrialized countries. Reported here are the details of a 73-year-old Japanese man who contracted HEV subtype 3e after consuming self-prepared pork liver from a domestically raised pig and presented with severe liver enzyme elevation. Conservative treatment, including hepatoprotective therapy and Inchinkoto, an herbal medicine, was administered for prolonged jaundice, and recovery was achieved. Owing to the long incubation period and nonspecific symptoms, routine HEV testing is crucial for the differential diagnosis of acute liver failure to provide appropriate management.

Key words: hepatitis E virus, acute hepatitis, subtype 3e, zoonotic infection, Inchinkoto

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Introduction

Hepatitis E virus (HEV) is a non-enveloped, single-stranded ribonucleic acid (RNA) virus that was initially discovered during the Soviet occupation of Afghanistan in the 1980s, following an outbreak of unexplained hepatitis at a military camp (1-3). Currently, HEV is predominantly observed as a waterborne disease in developing countries, and cases of zoonotic infections have also been identified in some industrialized nations. The World Health Organization (WHO) estimated that HEV caused 20 million infections annually, including 3.3 million symptomatic cases and 44,000 fatalities, in 2015 (4).

Based on a phylogenetic analysis, HEV is classified into eight distinct genotypes, among which HEV-1, HEV-2, HEV-3, and HEV-4 are responsible for human diseases. HEV-1 and HEV-2 are exclusively found in humans and are transmitted via the fecal-oral route, especially through contaminated water (5), with a prevalence noted in the Indian subcontinent, Southeast Asia, the Middle East, and Africa (3). In contrast, HEV-3 and HEV-4 infections are primarily associated with zoonotic transmission caused by close contact with an infected animal or the consumption of contaminated food products, with pigs most frequently implicated in such cases (6). Such infections have been reported in Japan and parts of Europe (e.g., Germany and France) following the consumption of undercooked deer meat, wild boar meat, pork liver sausage, or animal internal organs (7-11). Infections caused by HEV-3 or HEV-4 vary widely with respect to severity, ranging from clinically silent to fulminant hepatitis (12).

We herein report a case of acute hepatitis E caused by HEV subtype 3e infection in a healthy man in Japan who consumed pork liver from a domestically raised pig. Although hepatoprotective therapy led to an improvement in liver enzyme levels, jaundice persisted and subsequently improved following the administration of Inchinkoto.

Case Report

A 73-year-old man visited a local clinic with the chief complaint of a low-grade fever (approximately 37°C) and fatigue that had persisted for one week. Blood tests revealed elevated liver enzyme levels, and he was subsequently referred to our department for further evaluation. No comor-

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Table. Laboratory Data.

WBC	5,140 /μL	Creatinine	0.77 mg/dL
Neut	71.1 %	Sodium	136 mEq/L
Eos	1.2 %	Potassium	4 mEq/L
Baso	0.4 %	Chloride	106 mEq/L
Mono	8 %	Calcium	8.3 mg/dL
Lympho	19.3 %	HbA1c	5.3 %
RBC	4.78×10^6 /μL	CRP	4.84 mg/dL
Hemoglobin	16.5 g/dL	FT3	1.6 pg/mL
Hematocrit	46.5 %	FT4	1.9 pg/mL
Platelet	18.7×10^4 /μL	TSH	1.614 μU/mL
PT	51.7 %	HCV antibody	(-)
PT-INR	1.47	HBs antigen	(-)
APTT	43.1 s	HBs antibody	123 mIU/mL
D-dimer	3.7 μg/mL	HBc antibody	(-)
Total protein	6.7 g/dL	HBV DNA	(-)
Albumin	3 g/dL	HAV-IgM	(-)
Total bilirubin	24.1 mg/dL	HEV-IgA	(+)
AST	662 U/L	Antinuclear antibody	(-)
ALT	1,204 U/L	CMV-IgM	(-)
LDH	238 U/L	HSV-IgM	(-)
ALP	135 U/L	EB VCA-IgM	(-)
γ-GTP	440 U/L	EBNA	(+)
Amylase	43 U/L	Anti-mitochondrial antibody	(-)
Triglycerides	202 mg/dL	Immunoglobulin G	1,343 mg/dL
Total cholesterol	104 mg/dL	Immunoglobulin A	604 mg/dL
BUN	13.8 mg/dL	Immunoglobulin M	208 mg/dL

WBC: white blood cells, RBC: red blood cells, PT: prothrombin time, PT-INR: PT-international normarized ratio, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, CRP: C-reactive protein, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, HCV: hepatitis C virus, HBs: hepatitis B surface, HBc: hepatitis B core, HBV: hepatitis B virus, HAV-IgM: hepatitis A virus-immunoglobulin M, HEV-IgA: hepatitis E virus-immunoglobulin A, CMV-IgM: cytomegalovirus-immunoglobulin M, HSV-IgM: herpes simplex virus, EB VCA-IgM: Epstein-Barr virus capsid antigen-immunoglobulin M, EBNA: Epstein-Barr virus nuclear antigen

bidities were noted and the patient did not receive any regular medication. His daily alcohol consumption was approximately 1,000 mL of beer, and he had not undergone regular health check-ups. There was no history of transfusion or tattooing, and the patient had never traveled outside Japan.

Anthropometric measurements showed a weight of 61.9 kg, a height of 162 cm, and a body mass index of 23.6 kg/m^2. Physical examination revealed a conjunctival icterus and mild abdominal distension. The vital signs were stable: body temperature, 36.4°C; blood pressure, 145/111 mmHg; heart rate, 82 beats/min; respiratory rate, 16 breaths/min; and blood oxygen saturation, 98% on room air.

Laboratory test results indicated an elevation of aspartate aminotransferase (AST) to 662 U/L and alanine aminotransferase (ALT) to 1,204 U/L, while total bilirubin was markedly elevated to 24.1 mg/dL. Thyroid function tests and autoantibody screening showed no abnormalities, and hepatitis virus serology testing was negative for hepatitis A and C. Hepatitis B was indicative of a past infection pattern, whereas immunoglobulin A (IgA) for HEV was positive (Table). Based on these results, the patient was admitted to our hospital the same day for further evaluation and treatment. Hepatoprotective therapy with ursodeoxycholic acid 300 mg daily and taurine 3 g daily was initiated at the time of admission.

Abdominal ultrasonography revealed ascitic fluid accumulation on the liver surface and splenomegaly, with a maximum diameter of 140.6 mm. However, no signs of liver cirrhosis, intrahepatic masses, bile duct dilatation, or biliary obstruction were observed (Fig. 1). Similar results with abdominal contrast-enhanced computed tomography confirmed these findings, with no structural abnormalities in the liver (Fig. 2).

Further questioning revealed that the patient had consumed pork liver twice two months prior. It had been purchased locally and was self-prepared, although it originated from a pig raised in a different prefecture in Japan. Blood samples were collected on the fourth day of hospitalization and analyzed using Sanger sequencing at the Shimane Prefectural Institute of Public Health and Environmental Sci-

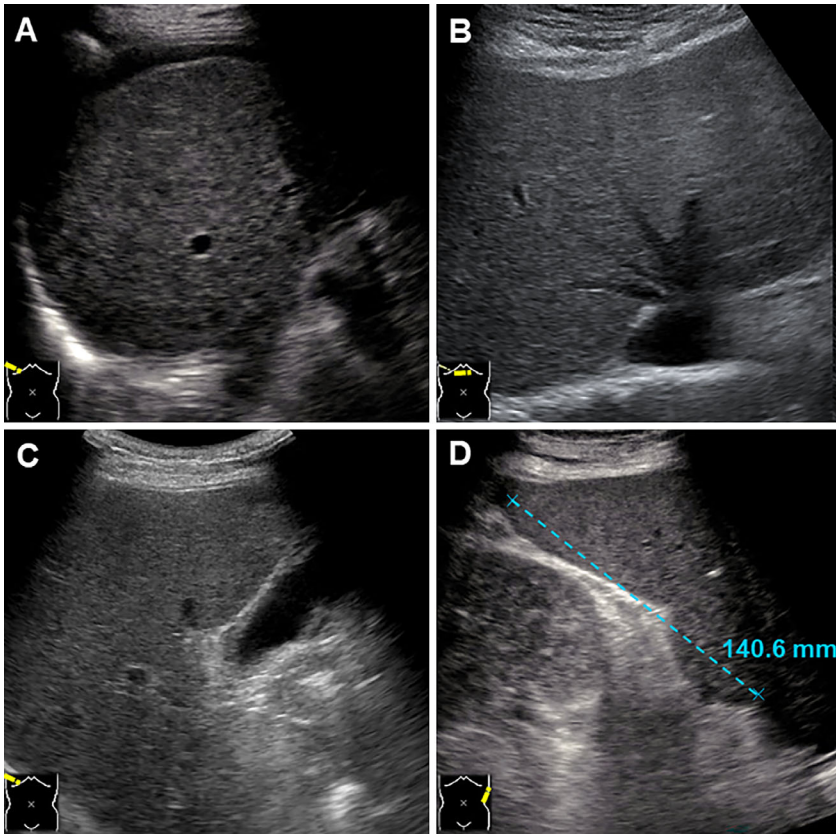

Figure 1. **Ultrasonography findings of the abdomen. Ascitic fluid accumulation on the liver surface was observed. No signs indicating liver cirrhosis, intrahepatic masses, bile duct dilatation, or biliary obstruction were detected (A-C). Splenomegaly with a maximum diameter of 140.6 mm was noted (D).**

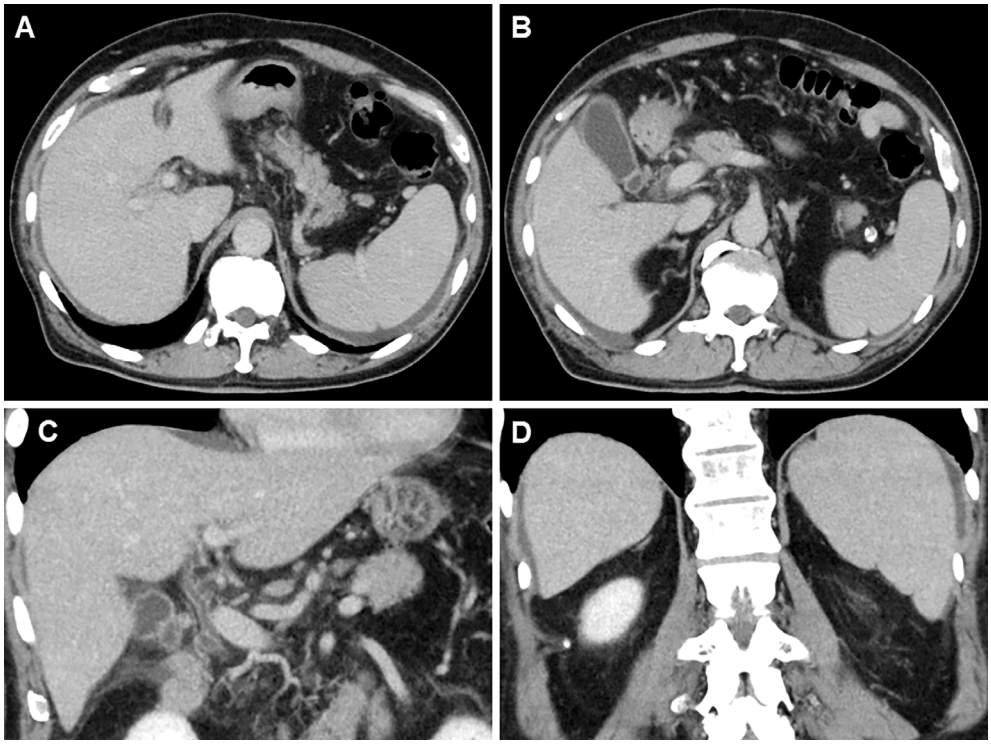

Figure 2. **Contrast-enhanced computed tomography findings of the abdomen. Ascitic fluid accumulation on the liver surface was observed. No signs indicating liver cirrhosis, intrahepatic masses, bile duct dilatation, or biliary obstruction were detected (A-C). Splenomegaly was noted (D).**

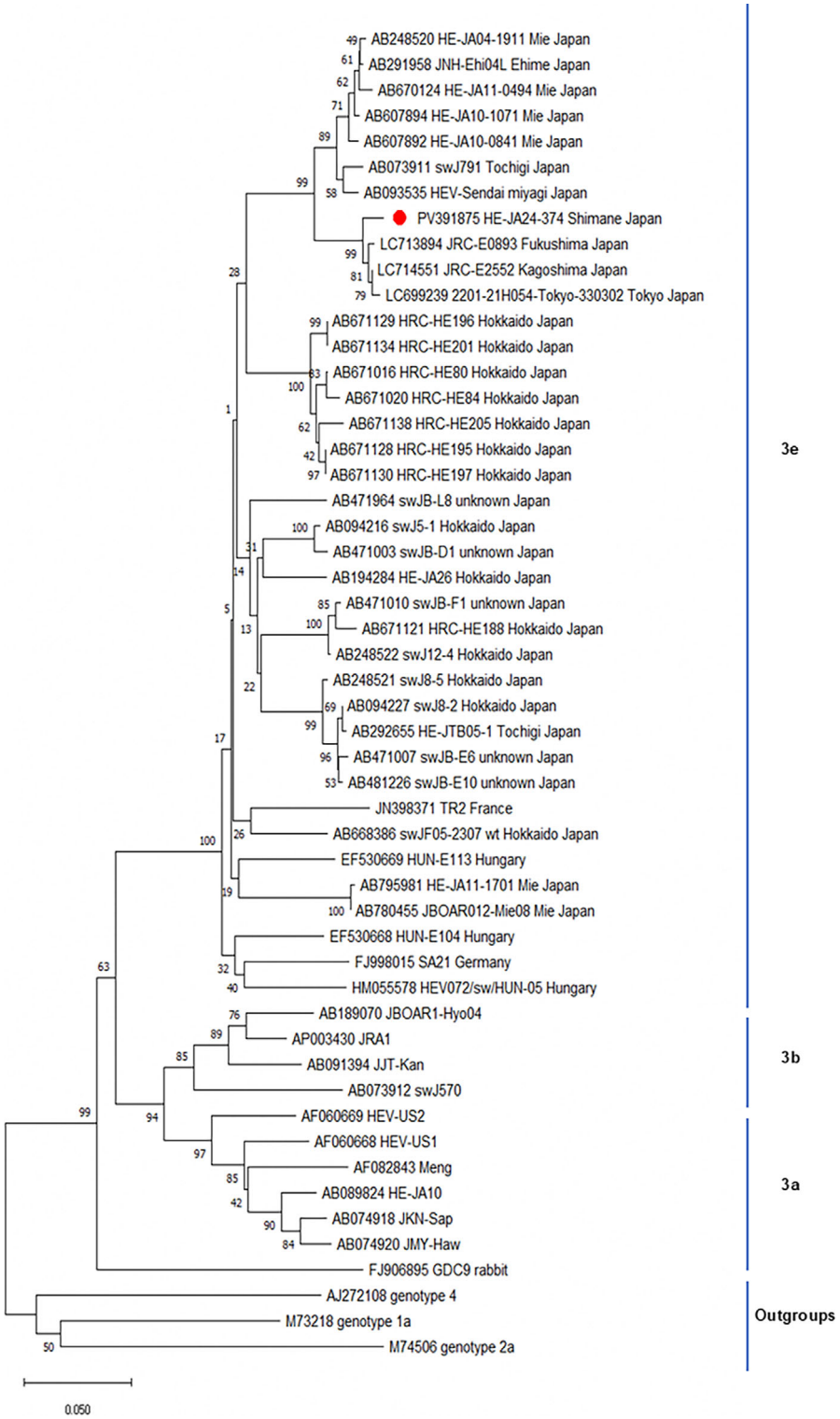

Figure 3. A neighbor-joining tree based on the 412-nucleotide (nt) open reading frame 2 (ORF2) sequences of the hepatitis E virus (HEV) strain obtained in this case, along with reference sequences of genotype 3 and outgroup isolates. Reference sequences are labeled with their accession numbers, followed by the isolate name and the prefecture and/or country where they were reported. The 3e strain isolated in this case is marked with a closed circle. The scale bar represents the nucleotide substitutions per site.

ence. The nucleotide sequence was identified as HEV subtype 3e, which was relatively similar to strains previously reported in Japan (Fig. 3). The diagnosis of acute hepatitis E was confirmed, and hepatoprotective therapy was continued. The liver enzyme levels began to improve after hospitalization and the initiation of hepatoprotective therapy. Additionally, Inchinkoto (13) at 7.5 g daily (Tsumura, Tokyo, Japan), a traditional Japanese herbal medicine, was administered for

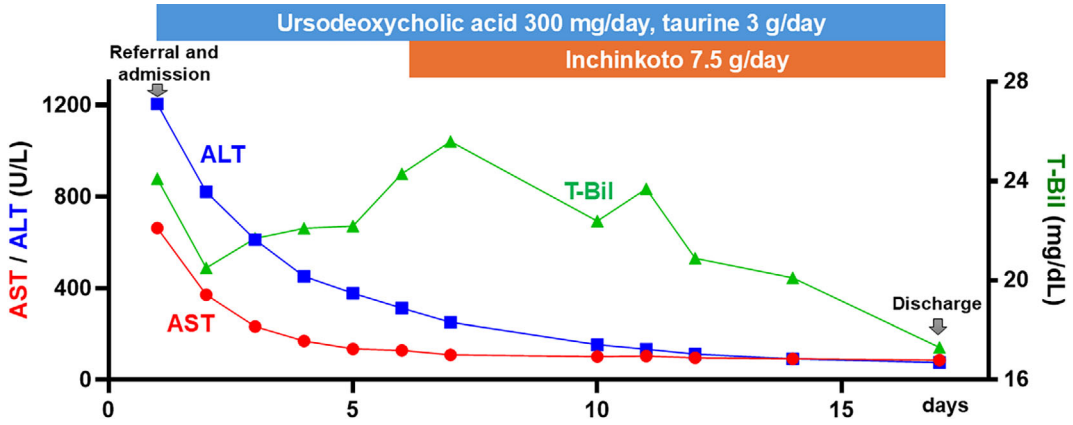

Figure 4. **Changes in liver enzyme (AST, ALT) and total bilirubin (T-Bil) levels following referral and admission. Hepatoprotective therapy with ursodeoxycholic acid at 300 mg daily and taurine at 3 g daily was initiated at the time of admission, and Inchinkoto at 7.5 g daily was administered for jaundice. Following liver enzyme level improvement, the patient was discharged on day 18.**

prolonged jaundice, and the total bilirubin level subsequently improved (Fig. 4).

HEV RNA was undetectable in the blood sample collected on day 12 of hospitalization, and the patient was discharged on day 18. Follow-up blood testing performed in the outpatient clinic confirmed improvements in liver enzymes (AST and ALT) and total bilirubin levels.

Discussion

HEV infection is not limited to developing countries, as HEV genotypes 3 and 4 have also been identified in some industrialized countries. A surveillance analysis conducted by the European Centre for Disease Prevention and Control in 2017 found an increase in the number of confirmed HEV cases in Europe over the last decade from 514 in 2005 to 5,617 in 2015 (14). However, it has not been confirmed whether this represents a true rise in HEV incidence or an increase in case detection due to growing awareness and expanded HEV testing (15).

HEV subtype 3e has been detected in Japan, Germany, France, Italy, and Hungary (16), with infections occurring following the consumption of undercooked organs from pigs, deer, and wild boars. One study noted that heating the liver at 88°C for five minutes or placing it in boiling water for five minutes can inactivate HEV and reduce the risk of transmission (17). However, the related data are limited. In the present case, infection was considered to have occurred through the consumption of a domestically raised pig liver and was presumed to involve a locally endemic viral strain. The patient prepared the food himself, and insufficient cooking may have contributed to the infection.

The incubation period for HEV infection ranged from 15 to 60 days (18). Consistent with this timeframe, the present patient had consumed pork liver approximately two months prior to symptom onset. While the majority of individuals spontaneously clear the HEV virus after acquisition, a small proportion (0.5-4%) become infected and develop acute liver failure (19), with risk factors including pre-existing liver conditions, such as chronic liver disease and malnutrition (20). Although our patient had no known underlying disease, he was a habitual drinker and did not undergo regular health check-ups, raising the possibility of an underlying alcohol-related liver dysfunction. Previous studies have proposed that excessive alcohol consumption should be considered an important risk factor for HEV infection as it contributes to the clinical expression of the infection and increases the severity of hepatitis (21).

Up to 60% of patients with acute HEV infection develop prolonged cholestasis, characterized by a persistent period of jaundice, a condition referred to as cholestatic hepatitis (22). The present patient exhibited a prolonged elevation of total bilirubin after disease onset; thus, Inchinkoto was administered for treatment. Inchinkoto is a traditional Japanese herbal medicine that has been reported to be effective against acute cholestatic hepatitis (23). The results of follow-up blood testing six months after onset confirmed the normalization of total bilirubin levels. To date, case reports in the Japanese literature have described the effectiveness of Inchinkoto in treating prolonged jaundice following HEV infection (24); however, this is the first report in English to document its efficacy.

The histological features of HEV infection include both cholestatic and classic patterns of acute viral hepatitis. The cholestatic form is characterized by bile stasis in the canaliculi and gland-like transformation of hepatocytes (25). Although a liver biopsy was considered in the present case, it was ultimately not performed because of the persistent presence of ascites throughout the hospitalization period.

HEV has a long incubation period of up to 60 days; thus, it is often difficult for patients to accurately recall situations possibly related to exposure, thus making a diagnosis based solely on medical history and symptoms challenging. A retrospective study conducted in the United States found that 3% of patients initially diagnosed with drug-induced liver injury were subsequently affected by acute hepatitis E (26).

Based on these factors, HEV should be considered during examinations and when making a differential diagnosis of acute liver injury, and routine HEV antibody testing should be performed regularly to ensure an accurate diagnosis and appropriate patient management.

The authors state that they have no Conflict of Interest (COI).

References

1. Balayan MS, Andjaparidze AG, Savinskaya SS, et al. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. Intervirology **20**: 23-31, 1983.
2. Tam AW, Smith MM, Guerra ME, et al. Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. Virology **185**: 120-131, 1991.
3. Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. Lancet **379**: 2477-2488, 2012.
4. World Health Organization. Hepatitis E Fact sheet [Internet]. [updated 2023 Jul; cited 2025 Feb 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e
5. Aslan AT, Balaban HY. Hepatitis E virus: epidemiology, diagnosis, clinical manifestations, and treatment. World J Gastroenterol **26**: 5543-5560, 2020.
6. Arankalle VA, Chobe LP, Joshi MV, Chadha MS, Kundu B, Walimbe AM. Human and swine hepatitis E viruses from Western India belong to different genotypes. J Hepatol **36**: 417-425, 2002.
7. Izopet J, Tremeaux P, Marion O, et al. Hepatitis E virus infections in Europe. J Clin Virol **120**: 20-26, 2019.
8. Tei S, Kitajima N, Takahashi K, Mishiro S. Zoonotic transmission of hepatitis E virus from deer to human beings. Lancet **362**: 371-373, 2003.
9. Li TC, Chijiwa K, Sera N, et al. Hepatitis E virus transmission from wild boar meat. Emerg Infect Dis **11**: 1958-1960, 2005.
10. Wichmann O, Schimanski S, Koch J, et al. Phylogenetic and case-control study on hepatitis E virus infection in Germany. J Infect Dis **198**: 1732-1741, 2008.
11. Colson P, Borentain P, Queyriaux B, et al. Pig liver sausage as a source of hepatitis E virus transmission to humans. J Infect Dis **202**: 825-834, 2010.
12. Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet **376**: 895-902, 2010.
13. Division of Pharmacognosy, Phytochemistry and Narcotics (DPPN), National Institute of Health Sciences of (NIHS) Japan, National Institutes of Biomedical Innovation, Health and Nutrition (NIBN). Standards of Reporting Kampo Products (STORK) ver. 5.2 [Internet]. [updated 2023 Nov; cited 2025 Mar 9]. Available from: http://mpdb.nibiohn.go.jp/stork/
14. Ricci A, Allende A, Bolton D, et al.; EFSA Panel on Biological Hazards (BIOHAZ). Public health risks associated with hepatitis E virus (HEV) as a food-borne pathogen. EFSA J **15**: e04886, 2017.
15. The Lancet. Growing concerns of hepatitis E in Europe. Lancet **390**: 334, 2017.
16. Borghi M, Graziani A, Marini D, et al. Case of fatal hepatitis related to HEV-3 infection in central Italy. Viruses **16**: 1869, 2024.
17. Feagins AR, Opriessnig T, Guenette DK, Halbur PG, Meng XJ. Inactivation of infectious hepatitis E virus present in commercial pig livers sold in local grocery stores in the United States. Int J Food Microbiol **123**: 32-37, 2008.
18. Chauhan A, Jameel S, Dilawari JB, Chawla YK, Kaur U, Ganguly NK. Hepatitis E virus transmission to a volunteer. Lancet **341**: 149-150, 1993.
19. Aggarwal R. Hepatitis E: clinical presentation in disease-endemic areas and diagnosis. Semin Liver Dis **33**: 30-40, 2013.
20. Hamid SS, Atiq M, Shehzad F, et al. Hepatitis E virus superinfection in patients with chronic liver disease. Hepatology **36**: 474-478, 2002.
21. Dalton HR, Bendall RP, Rashid M, et al. Host risk factors and autochthonous hepatitis E infection. Eur J Gastroenterol Hepatol **23**: 1200-1205, 2011.
22. Chau TN, Lai ST, Tse C, et al. Epidemiology and clinical features of sporadic hepatitis E as compared with hepatitis A. Am J Gastroenterol **101**: 292-296, 2006.
23. Ohwada S, Kobayashi I, Harasawa N, Tsuda K, Inui Y. Severe acute cholestatic hepatitis of unknown etiology successfully treated with the Chinese herbal medicine Inchinko-to (TJ-135). World J Gastroenterol **15**: 2927-2929, 2009.
24. Suzuki Y, Nishigaki Y, Takahashi K, et al. A case of autochthonous hepatitis E with a rare viral genotype (HEV-3f) and intractable jaundice. Kanzo (Acta Hepatol Jpn) **57**: 614-616, 2016 (in Japanese).
25. Asher LV, Innis BL, Shrestha MP, Ticehurst J, Baze WB. Virus-like particles in the liver of a patient with fulminant hepatitis and antibody to hepatitis E virus. J Med Virol **31**: 229-233, 1990.
26. Takahashi M, Kusakai S, Mizuo H, et al. Simultaneous detection of immunoglobulin A (IgA) and IgM antibodies against hepatitis E virus (HEV) Is highly specific for diagnosis of acute HEV infection. J Clin Microbiol **43**: 49-56, 2005.