

Hepatitis E virus infections in people with multiple myeloma: an emerging challenge in the era of immunotherapeutic approaches

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Abstract

Hepatitis E virus (HEV) is an under-recognized cause of viral hepatitis, with rising incidence in high-income countries largely driven by zoonotic transmission. Patients with multiple myeloma (MM) are especially vulnerable to HEV, yet there have been no recommendations for antiviral treatment or on its impact on the management of myeloma treatment. Here, we describe 7 patients (5 males, 2 females) with MM who were diagnosed with HEV infection at a tertiary care center in Western Europe within less than one year. All cases were confirmed by positive HEV RNA PCR in peripheral blood. Although no instances of fulminant hepatitis were observed, HEV prompted clinically relevant interruptions: autologous stem cell transplantation was postponed, lymphocyte apheresis for CAR T-cell manufacturing was delayed, and bispecific antibody regimens were suspended for up to five months. Ribavirin was initiated in 4 cases. The 3 patients undergoing T-cell-redirecting therapies, including one with prior ciltacabtagene autoleucel and 2 on bispecific antibodies, progressed to chronic infection despite ribavirin treatment. One patient, despite clearing HEV from peripheral blood, developed persistent vertigo and tested positive for HEV RNA in cerebrospinal fluid, indicating neuroinvasion. As the largest reported cohort of MM patients with HEV infections and the first to document chronic infection during treatment with T-cell-redirecting therapies, this study emphasizes the urgent need to increase awareness of HEV as an emerging threat, refine screening protocols at baseline or during unexplained aminotransferase flares, and to establish standardized therapeutic strategies in the era of novel immunotherapeutic approaches.

Introduction

Hepatitis E virus (HEV) is a significant yet frequently under-recognized cause of viral hepatitis globally, with an estimated 20 million new infections annually and approximately 44,000 deaths in 2015 alone.¹ HEV, also known as *Paslahepevirus balayani*, a member of the Hepeviridae family, is transmitted via various routes depending on geographic and socio-economic conditions. In low-income countries, HEV is primarily transmitted through contaminated water, with genotypes 1 and 2 responsible for large outbreaks. Conversely, genotypes 3 and 4 are more common in high-income nations due to zoonotic transmission through undercooked pork or offal.^{2,3} HEV IgG seroprevalence among adults in Germany was estimated to be almost 17% in a nationwide study conducted in 2012.⁴ Environmental contamination

through excretions from infected pigs, wildlife, and humans is a recognized potential source of HEV infections. A preliminary German study detected HEV RNA in wastewater and river water, and these findings correlate with subtypes previously identified in patients from the same region.⁵ Additionally, transmission through blood products has been reported, posing a particular risk for hematologic patients undergoing transfusions.⁶ However, since January 1, 2020, mandatory routine testing for HEV in blood products in Germany has significantly reduced this risk.⁷ In immunocompetent individuals, HEV generally presents with a spectrum from asymptomatic courses to, in rare cases (0.5-4%), fulminant hepatitis.⁸ Cases of fulminant hepatitis leading to acute liver failure or acute-on-chronic liver failure occur in patients with pre-existing liver disease or during pregnancy.^{9,10} Furthermore, immunosup-

pressed patients (such as solid organ transplant recipients, HIV-infected individuals, or patients who have undergone hematopoietic stem cell transplantation) are at significant risk of progression to chronic hepatitis E, which carries a long-term risk of liver cirrhosis.^{6,11-14}

The course of HEV infection in patients with hematologic malignancies remains poorly understood and clinically challenging. Limited data underscore the importance of reporting cases to better understand the specific challenges of managing HEV in hematologic patients, including its effects on treatment modifications and patient outcomes. In published, retrospective cohort studies involving hematologic patients with HEV infection, an HEV-related mortality rate of 5-8% has been reported. Acute hepatitis in these vulnerable patients was associated with an acute liver failure rate of 8-11% and a progression to chronic infection rate ranging from 37% to 62%.^{6,13,15,16} Across all reported cohorts, approximately half of the patients received ribavirin treatment, with HEV clearance rates ranging from 27.0% to 79.2%. Ribavirin treatment was associated with reduced mortality and tended to lower chronicity rates, mainly when initiated within 12 to 24 weeks after the HEV diagnosis.^{6,16} The current European Conference of Infections in Leukemia (ECIL) guidelines on viral hepatitis, which will be updated soon, address the management of HEV infections in hematologic patients, including the feasibility of off-label ribavirin treatment for both acute and chronic HEV infection.^{6,17,18}

Reported data on required modifications of antitumor therapy vary widely. von Felden *et al.* noted that 12% of patients experienced treatment adjustments due to hepatitis E, including delays in planned autologous hematopoietic stem cell transplantation (ASCT).⁵ In contrast, Ghandili *et al.* reported therapy modifications in 60% of cases, including delays of 6-8 weeks in administering high-dose chemotherapy and ASCT.¹⁶ Therapy modifications can significantly impact disease control and prognosis, making it critical to understand how often they are needed and which strategies are most effective.

Patients with multiple myeloma (MM), the second most common hematologic malignancy, are particularly vulnerable due to their immunocompromised state and the prolonged use of highly immunosuppressive therapies, including CD38 antibodies, proteasome inhibitors, immunomodulatory agents, high-dose dexamethasone, and medications targeting B-cell maturation antigen (BCMA). Additionally, these patients are often at an increased risk of ribavirin-induced anemia because of their advanced age and concomitant medications, further complicating treatment decisions and management strategies.

In this retrospective cohort study, we report a series of HEV cases among MM patients occurring in a notably short period between March 2024 and January 2025. This is unusual, as previous cohorts reported only a few cases of hepatitis E in MM patients, typically over much longer periods.¹⁶ We

describe how treatment adjustments were made, balancing the risks of delaying cancer therapy against the need to manage HEV infection effectively. This study also highlights an unusual case involving a strictly vegan patient, underscoring the need to consider alternative transmission routes beyond the consumption of contaminated meat. This paper is also the first to report 3 cases of chronic HEV infection in MM patients receiving T-cell-redirecting therapies.

Methods

Study design and data collection

This is a retrospective analysis of 7 patients (5 males, 2 females) aged 48 to 78 years, who were diagnosed with HEV infections between March 2024 and January 2025. All patients were identified through positive HEV RNA PCR results from blood samples obtained at the university outpatient clinic of a tertiary center (University Medical Center Hamburg-Eppendorf, Hamburg, Germany), where approximately 300 MM patients are treated on an outpatient basis annually.

HEV PCR testing was performed for elevated transaminase levels (5 patients) or as part of routine screening prior to lymphocyte or stem cell apheresis (2 patients). Clinical information, including treatment details and disease characteristics, was abstracted from the patients' electronic health records. Electronic medical records were reviewed to assess baseline patient characteristics, laboratory findings, including liver enzyme levels and HEV RNA levels, as well as treatment details and outcomes.

Data cutoff was March 31, 2025. The assessment of toxicities followed the Common Terminology Criteria for Adverse Events, version 5. Myeloma remission status was assessed according to the International Myeloma Working Group (IMWG) criteria.¹⁹ Figures were created with GraphPad Prism version 9 for macOS, GraphPad Software, Boston, MA, USA. Monocentric data acquisition was conducted in accordance with local requirements as per the Hamburg Hospital Act (HmbKHG) §12. Data collection complied with local legal requirements, and was reviewed and approved by the Ethics Committee of the Medical Council of Hamburg (Approval: 2025-300583-WF). The ethics committee waived the requirement for informed consent, as only anonymized data were analyzed and published.

Virological assessments

HEV RNA detection was performed using the automated Cobas® HEV assay on the Roche Cobas 6800 platform (Roche Diagnostics, Mannheim, Germany) in accordance with the manufacturer's instructions. Peripheral blood samples were tested for clinical HEV detection, with a lower limit of approximately 20 IU/mL.

In addition to blood, HEV RNA was also assessed, when available, in urine, stool, and cerebrospinal fluid (CSF)

samples to confirm systemic infection and investigate the presence in extrahepatic tissue. Stool samples, when collected, underwent pretreatment to extract viral RNA before analysis, following protocols validated for Cobas® HEV performance. HEV RNA in CSF was tested only in cases where neurological symptoms suggested potential neuroinvasion. Sustained virological response (SVR) was defined as the absence of detectable HEV RNA in peripheral blood across two consecutive samples taken at least four weeks apart, with additional confirmation from HEV RNA-negative results in stool, urine, or CSF where available. In patients receiving antiviral therapy, virological monitoring was performed at baseline, during treatment, and at follow-up to assess treatment efficacy and detect any recurrence of viremia.

Results

Patient characteristics

HEV infection was detected after a median of 46.7 months (range, 4.4–177.3 months) following the initial MM diagnosis. At the time of acute HEV diagnosis, 6 patients were receiving active anti-myeloma therapy, while one patient had undergone BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy with ciltacabtagene-autoleucel (cilta-cel) six months earlier. Five of the 7 patients had received multiple prior lines of therapy (range, 1–6). Detailed patient characteristics are summarized in Table 1.

Virological findings

Patients were asymptomatic except for atypical vertigo in one patient. HEV infection was detected after routine blood tests showed elevated liver transaminases. Median glutamate-pyruvate transaminase (GPT) and gamma-glutamyl transferase (GGT) levels at diagnosis were 200 U/L (range, 19–1,220 U/L) and 340 U/L (range, 16–901 U/L), respectively. Median HEV RNA viral loads in EDTA-anticoagulated whole blood samples, as determined by PCR, were 48,865 IU/mL (range, 363–20,577,850 IU/mL). Concomitant infections with other hepatitis viruses or herpesvirus reactivations were ruled out through comprehensive serological and PCR testing. Characteristics of HEV infection and HEV-related laboratory parameters are shown in Table 2.

Up to the time of this report, 3 patients (cases #3, #6, #7) achieved spontaneous viral clearance after 16–36 days without the use of ribavirin, all of whom subsequently maintained SVR. In case #3, CD38 antibody-based MM treatment was paused for a total of 26 days without affecting the remission status (ongoing stringent complete response). In cases #6 and #7, treatment with lenalidomide maintenance and bridging therapy with isatuximab/carfilzomib/dexamethasone has remained paused for 44 and 46 days, respectively, to allow for the resolution of HEV infection. No changes in remission status have occurred.

Three patients (cases #1, #4 and #5), all of them receiving

T-cell-redirecting therapy, one with a history of treatment with cilta-cel (6 months prior) and 2 with ongoing treatment with bispecific antibodies targeting BCMA and GPRC5D, developed chronic infection, confirmed by persistent viremia detected by HEV PCR for more than three months despite ribavirin. Bispecific antibody treatment was interrupted for five months (case #4) and three months (case #5).

Patient #4 developed severe treatment-refractory vertigo at the time of HEV diagnosis, which was subsequently linked to the detection of HEV RNA in the CSF. The vertigo persisted despite clearance of HEV from peripheral blood under ribavirin treatment, indicating neuroinvasion. Cytomorphological and immunophenotypic CSF analyses, as well as MRI, showed no evidence of cerebral extramedullary myeloma manifestation. In this patient, at the time of initial diagnosis of HEV infection, a reactivation of a formerly known immune thrombocytopenia (ITP) was observed despite a history of splenectomy performed 15 years ago. Concurrently with the decline in viral load, platelet recovery was noted, indicating HEV infection as the underlying cause of ITP relapse. At the time of this report, the vertigo is still ongoing. Given the clinical course, persistent viral replication and chronic infection of the central nervous system is suspected.

The clinical course and laboratory parameters of the individual patients are presented in Figure 1 for patients who received ribavirin treatment and in Figure 2 for patients who have not been treated with ribavirin.

Ribavirin treatment and adverse effects

The decision as to whether to initiate ribavirin treatment was made by infectious disease specialists according to the criteria proposed in the ECIL guidelines and the guidelines of the European Association for the Study of the Liver (EASL).²⁰ Specifically, HEV infections lasting longer than three months were interpreted as chronic, and chronic courses were treated with ribavirin whenever feasible. In cases of acute HEV infection, the urgency of antiviral therapy was assessed. Upfront ribavirin treatment was initiated in highly immunocompromised patients undergoing T-cell-redirecting therapy (cases #1, #4, #5) or quadruplet induction therapy with planned autologous stem cell transplantation (ASCT) (case #2), while in the other 3 cases (cases #3, #6, #7), the initial course of infection was monitored, leading to spontaneous viral clearance without antiviral therapy.

Initial doses ranged from 800 mg to 1,000 mg daily during the 3-month induction phase, depending on tolerability. The treatment was generally well tolerated, except for 3 patients with grade 3 anemia requiring red blood cell transfusions. In patients who developed chronic HEV infection, a maintenance dose of 200 mg once daily was administered.

Impact of hepatitis E virus infection on myeloma treatment

Active myeloma treatment was interrupted in all patients

Table 1. Patient characteristics and clinical course of hepatitis E virus infections.

#	Time of HEV diagnosis	Age at onset of infection years	Potential transmission	Time of MM diagnosis	Current myeloma treatment	Chronology of previous lines of treatment	Myeloma remission status, IMWG	Symptoms related to HEV Infection	Ribavirin treatment	HEV outcome, blood-based PCR	Myeloma treatment modifications
1	March 2024	59	Raw minced pork	March 2017	None	1. VCD and high-dose MEL 2. KRd and high-dose MEL 3. DaraPd 4. Kd 5. ACE 6. BCMA-CAR-T (Jan 2023)	VGPR	Asymptomatic, tested due to high liver enzymes	Yes	Chronic infection	None
2	July 2024	64	Raw minced pork	March 2024	IsaVRd	None (first-line ongoing)	VGPR	Asymptomatic, tested before cell separation for ASCT	Yes	Relapse after transient clearance	Paused treatment for 6 weeks, no change in MM remission status
3	August 2024	57	Raw minced pork	October 2020	Dara/Imid/Dex	1. VCD, high-dose MEL, LEN maintenance	sCR	Asymptomatic, tested due to high liver enzymes	No	Sustained virological response	Paused treatment for 26 days, no change in MM remission status
4	August 2024	68	Unknown (vegan)	March 2021	GPRC5D T-cell engager	1. DaraVTd, 2x high-dose MEL and LEN maintenance 2. IsaKd 3. PACE	CR	Vertigo, tested due to high liver enzymes	Yes	Chronic infection: CNS	Paused treatment for 3 months, no change in MM remission status
5	September 2024	78	Unknown	March 2010	BCMA T-cell engager plus Imid/Dex	1. Vd and high-dose MEL 2. DaraRd 3. EloPd	sCR	Asymptomatic, tested due to high liver enzymes	Yes	Chronic infection	Ongoing pause in treatment, no change in remission status
6	December 2024	57	Unknown	December 2020	IsaKd as bridging before CAR-T cells	1. VRd, 2x high-dose MEL and Imid maintenance	VGPR	Asymptomatic, tested before lymphocyte apheresis	No	Remission	Paused treatment for 3 months, lymphocyte apheresis postponed for 11 weeks
7	January 2025	48	Unknown	August 2022	Imid maintenance	1. DaraVTd, 2x high-dose MEL	VGPR	Asymptomatic, tested due to high liver enzymes	No	Remission	Paused treatment for 4 weeks, no change in remission status

Continued on following page.

Clinical and treatment-related characteristics of the 7 patients, including time of hepatitis E virus (HEV) infection diagnosis, age at onset, potential transmission source, multiple myeloma diagnosis and treatments, remission status, HEV-related symptoms, ribavirin treatment, outcome, and treatment modifications. ACE: doxorubicin, cyclophosphamide, etoposide; ASCT: autologous stem cell transplantation; BCMA: B-cell maturation antigen; CAR: chimeric antigen receptor; CNS: central nervous system; CR: complete response; Dara: daratumumab; Imid: immunomodulatory drug; DaraPd: daratumumab, pomalidomide, dexamethasone; DaraRd: daratumumab, lenalidomide, dexamethasone; DaraVTd: daratumumab, bortezomib, thalidomide, dexamethasone; Dex: dexamethasone; EloPd: elotuzumab, pomalidomide, dexamethasone; GPRC5D: G protein-coupled receptor class C group 5 member D; IMWG: International Myeloma Working Group; IsaKd: isatuximab, carfilzomib, dexamethasone; IsaVRd: isatuximab, bortezomib, lenalidomide, dexamethasone; Kd: carfilzomib, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone; LEN: lenalidomide; MEL: melphalan; MM: multiple myeloma; PACE: cisplatin, doxorubicin, cyclophosphamide, etoposide; PCR: polymerase chain reaction; sCR: stringent complete response; VCD: bortezomib, cyclophosphamide, dexamethasone; Vd: bortezomib, dexamethasone; VGPR: very good partial response; VRd: bortezomib, lenalidomide, dexamethasone.

Table 2. Baseline and peak laboratory parameters and immune function markers in multiple myeloma patients with hepatitis E virus infections.

#	Initial blood laboratory parameters					Peak blood laboratory parameters					Parameters of immune function at HEV diagnosis				
	Viral load IU/mL	GPT U/L	GOT U/L	GGT U/L	Bilirubin mg/dL	Viral load U/mL	GPT U/L	GOT U/L	GGT U/L	Bilirubin mg/dL	IgG g/L	CD3 ⁺ T cells 1/ μ L	CD4 ⁺ T cells 1/ μ L	CD8 ⁺ T cells 1/ μ L	B-cell count 1/ μ L
1	8,038,222	691	227	340	0.8	32,923,561	374	227	312	0.8	5.33	930	547	384	0
2	543	19	10	16	0.3	3,524	28	10	29	0.5	2.55	320	232	87	33
3	4,357	1,220	90	266	2.9	4,357	1,220	90	266	2.9	7.99	580	NA	NA	NA
4	342,483	187	161	778	1	418,909	222	219	798	1.2	2.76	3,354	630	2,569	38
5	20,577,850	136	118	901	0.8	20,577,850	136	118	901	0.8	6.19	1,543	452	981	0
6	363	326	75	31	0.5	363	326	75	31	0.5	10.58	352	200	121	290
7	48,865	200	67	606	0.6	48,865	374	67	606	0.6	4.22	1,054	302	459	124

Baseline and peak blood laboratory parameters, as well as immune function markers, in multiple myeloma patients diagnosed with HEV infection. GGT: gamma-glutamyl transferase; GOT: glutamate-oxaloacetate transaminase; GPT: glutamate-pyruvate transaminase; IgG: immunoglobulin G.

under active therapy for at least 26 days and up to five months due to concerns regarding liver toxicity and HEV-associated risks.

One patient (case #2) acquired HEV infection during induction with isatuximab, bortezomib, lenalidomide, and dexamethasone and achieved transient viral clearance after 24 days of ribavirin. The infection caused a 6-week delay in cyclophosphamide mobilization and subsequent ASCT, accompanied by a rise in serum free light chains that did not meet IMWG progression criteria. Although the patient remained HEV RNA-negative during high-dose melphalan and ASCT, relapse was detected on day +121 post ASCT by blood-based HEV RNA PCR, coinciding with elevated GPT and GGT. Ribavirin was re-initiated at 800 mg/day; HEV RNA became undetectable by week 8. At data cutoff, confirmation of SVR by repeat testing was pending.

Notably, in patient #6, who received isatuximab / carfilzomib / dexamethasone as bridging therapy before CAR T-cell treatment, planned lymphocyte apheresis needed to be postponed for almost three months due to the diagnosis of HEV infection and the risk of a subsequent product contamination.

Despite these treatment interruptions, HEV-related deaths

or changes in remission status have not yet been observed. Additionally, no HEV-associated acute liver failure or chronic liver disease has been documented to date.

Discussion

The paradigms of MM therapy have radically evolved in recent years, leading to significantly improved patient outcomes. However, these advances come at the cost of profound immunosuppression, caused both by the disease itself and by intensive, prolonged immunosuppressive treatments. Despite the high incidence of HEV infection in the Western world, detailed data on the course of infection and outcomes in patients with hematologic malignancies, particularly MM, remain scarce. This study highlights the challenges and clinical implications of managing HEV infections in MM patients, a population uniquely vulnerable due to their immunocompromised state and extensive exposure to immunosuppressive therapies. In our cohort, acute HEV infections were often asymptomatic or presented with only mild hepatic involvement, detected incidentally through routine blood tests. Although elevated liver en-

zymes and high viral loads were common, severe hepatic complications like acute liver failure did not occur. However, relevant delays in MM treatment were observed due

to HEV infection, including the postponement of an ASCT in one patient (case #2), a delay in lymphocyte apheresis prior to CAR T-cell therapy in another patient (case #6), and

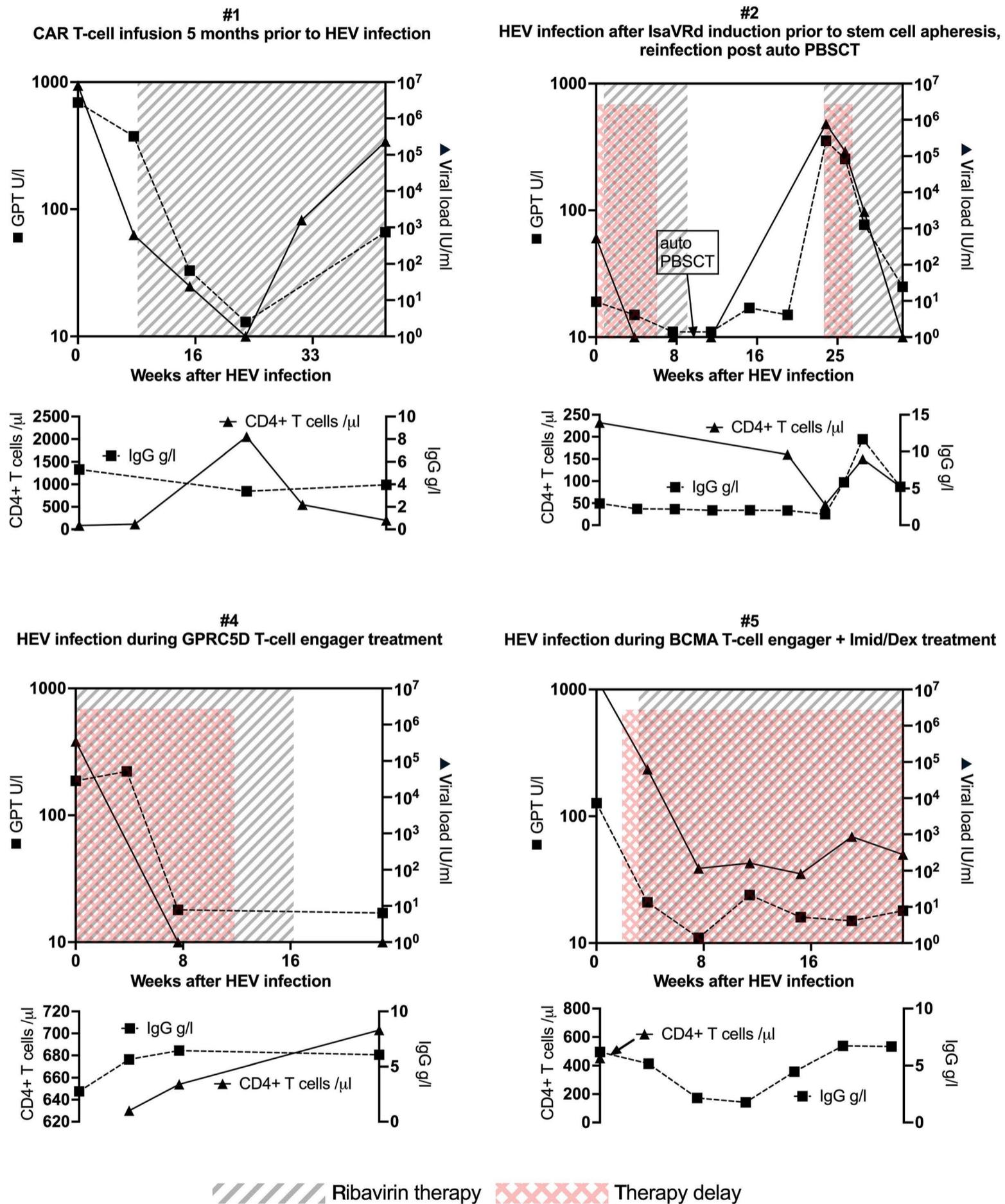


Figure 1. Clinical course and laboratory parameters of hepatitis E virus infection in 4 multiple myeloma patients (cases #1, #2, #4, #5) treated with ribavirin. Glutamate-pyruvate transaminase (GPT) levels (black squares) and hepatitis E virus (HEV) viral load (black triangles) are shown in relation to ribavirin treatment (gray shaded area) and therapy delays (pink shaded area). Lower panels depict CD4⁺ T-cell counts and immunoglobulin G serum levels over time. autoPBSCT: autologous peripheral blood stem cell transplantation; BCMA: B-cell maturation antigen; CAR: chimeric antigen receptor; Dex: dexamethasone; GPRC5D: G protein-coupled receptor class C group 5 member D; GPT: glutamate-pyruvate transaminase; IgG: immunoglobulin G; Imid: immunomodulatory drug.

therapy interruptions of three to five months in patients receiving bispecific antibodies (cases #4 and #5). Three patients (cases #1, #4 and #5), all of them undergoing novel T-cell-redirecting therapies, developed chronic HEV infection, underscoring its potential severity in this highly immunocompromised subgroup.

Importantly, the observed case yield of 7 infections among approximately 300 MM outpatients within less than 12 months likely underestimates the true burden of HEV in this population. Testing was performed only in patients with

elevated transaminases or before planned apheresis. We, therefore, speculate that the real incidence is higher, as asymptomatic infections would have remained undetected.

Transmission

In 3 out of 6 patients, the consumption of raw minced pork was reported as a potential source of HEV infection, suggesting a foodborne origin. Previous studies support this possible transmission route, having detected HEV RNA in various commercial pork products, including 20% of liver

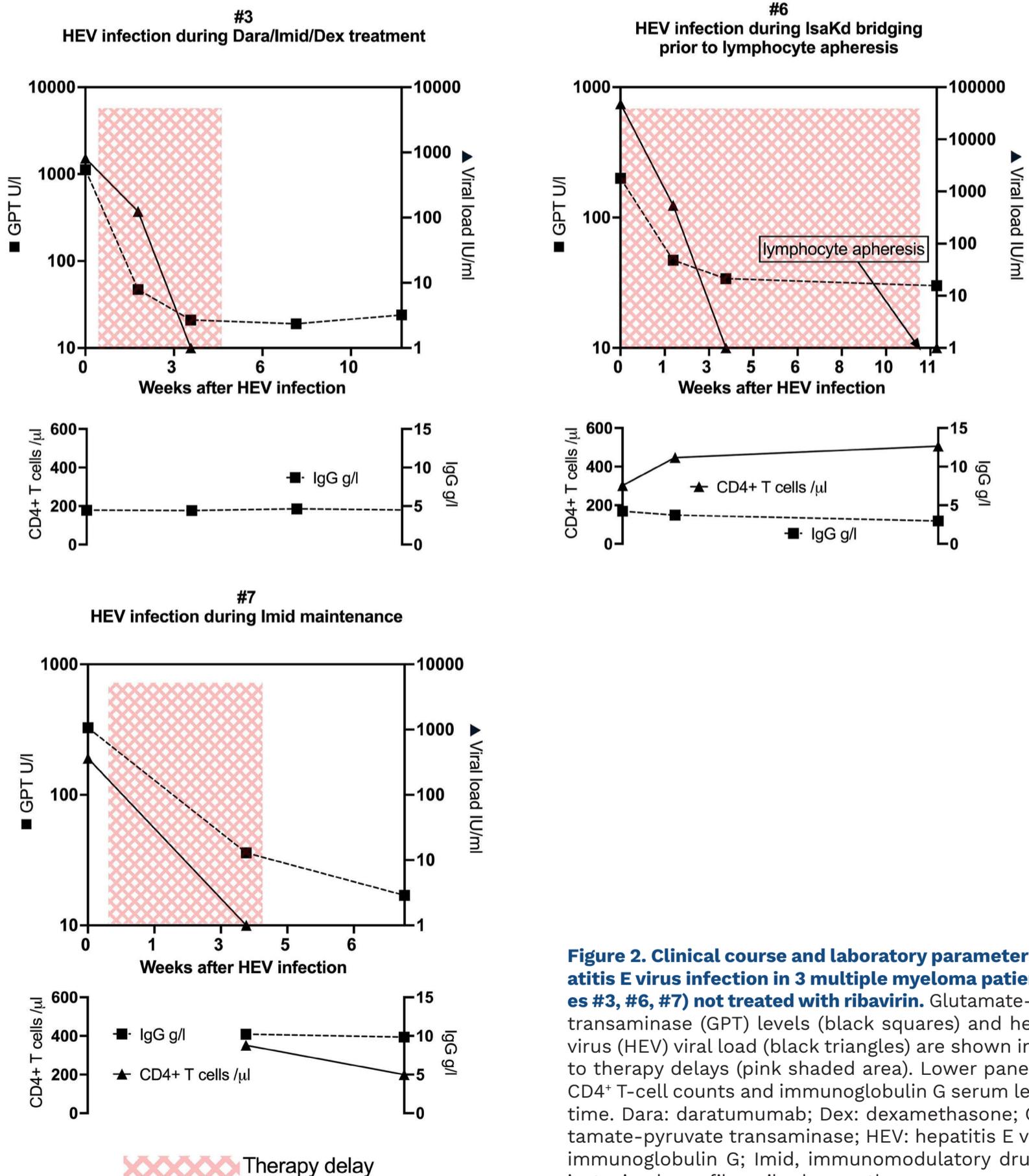


Figure 2. Clinical course and laboratory parameters of hepatitis E virus infection in 3 multiple myeloma patients (cases #3, #6, #7) not treated with ribavirin. Glutamate-pyruvate transaminase (GPT) levels (black squares) and hepatitis E virus (HEV) viral load (black triangles) are shown in relation to therapy delays (pink shaded area). Lower panels depict CD4⁺ T-cell counts and immunoglobulin G serum levels over time. Dara: daratumumab; Dex: dexamethasone; GPT: glutamate-pyruvate transaminase; HEV: hepatitis E virus; IgG: immunoglobulin G; Imid, immunomodulatory drug; IsaKd: isatuximab, carfilzomib, dexamethasone.

sausages purchased from supermarkets in Berlin, Germany, almost half of pork pâtés sampled in Canada, and 4% of pork livers from butcher shops and supermarkets in southern Germany.²¹⁻²³

However, the sources of infection in the remaining patients are unclear. Transmission through contaminated blood products can be ruled out due to routine HEV PCR testing in Germany, and none of the patients had a history of international travel prior to the diagnosis of HEV infection. The occurrence of HEV infection in a vegan patient suggests alternative transmission routes beyond dietary exposure to undercooked pork or offal, potentially through contaminated food products exposed to infected manure or fertilizers. In Germany, HEV-3 RNA is frequently detected in urban surface waters, with identified subtypes sometimes matching those found in local patients, supporting environmental circulation.⁵ This hypothesis is supported by findings from case-control studies, which identified associations between HEV infection and the consumption of raw vegetables and fruits. An association was also identified with contact with wastewater, indicating that environmental contamination may mediate transmission, including in individuals who do not consume pork (e.g., in the case of our vegan patient).²³⁻²⁵

Neuroinvasion and extrahepatic manifestations

The detection of HEV in cerebrospinal fluid in one patient with refractory dizziness and vertigo, along with the reactivation of immune thrombocytopenia (ITP), highlights the potential for extrahepatic manifestations of HEV. While neuroinvasion and immune dysregulation by HEV are rare, cases of thrombotic thrombocytopenic purpura, glomerulonephritis, Guillain-Barré syndrome, neuralgic amyotrophy, and acute pancreatitis have been described in recent literature.²⁶⁻²⁸ Although acute and chronic infection with hepatitis A, B and C are a well-characterized cause of ITP,^{29,30} our work suggests that HEV may also be the underlying trigger. In line with 3 case reports describing acute HEV infection as the cause of ITP in a young and otherwise healthy girl from India,³¹ a 34-year-old male,³² and a 72-year-old French woman,³³ all of them without any history of prior hematologic illness, the observed recovery of thrombopoiesis with HEV load reduction underlines the causal link between HEV infection and reactivation of ITP in our patient as well, warranting further investigation into the interplay between HEV and hematologic conditions.

B-cell depletion, T-cell exhaustion, hypogammaglobulinemia, and hepatitis E virus infection risks

CD20-directed therapies, such as rituximab, have been significantly associated with the development of chronic HEV infection, likely due to the impact of B-cell depletion on the immune system's capacity to control HEV.¹⁶ This effect is similar to the role of B-cell responses in hepatitis B and C control; indeed, various B-cell-directed therapies are

known to increase the risk of hepatitis B reactivation.^{34,35} In contrast, Ingwersen *et al.* reported sustained viral responses in a patient with B-cell chronic lymphocytic leukemia who, despite profound hypogammaglobulinemia, maintained normal CD4⁺ T-cell counts.¹⁷ This finding suggests that while B-cell response may not be the only essential factor for viral clearance, CD4⁺ T-cell presence could be more critical. Further supporting this, lymphopenia and low CD4⁺ T-cell counts have been associated with chronic HEV infections in solid organ transplant recipients.¹⁴ Observations in HIV/HEV-co-infected patients similarly indicate that HEV clearance is associated with higher CD4⁺ T-cell counts. Additionally, in patients with low CD4⁺ T-cell counts, the time from solid organ transplantation to HEV diagnosis was shorter, with these patients more likely to develop chronic hepatitis E.¹⁴ Ingwersen *et al.* also observed that recovery from CD4⁺ lymphopenia and an increase in CD4⁺ T-cell counts correlate with viral response, likely reflecting recovery from T-cell exhaustion.¹⁷

In our cohort, 3 out of 7 patients received novel T-cell engaging immunotherapies that may induce T-cell exhaustion, such as bispecific T-cell engagers (TCE) or CAR T-cell treatment, which could have heightened the risk of HEV infection due to profound humoral and cellular immune suppression.

Intravenous immunoglobulin (IVIG) supplementation, routinely administered in the context of T-cell-engaging immunotherapies to address immunoglobulin deficiency, helps reduce the risk of severe infections in this highly immunocompromised population. However, it is not clear if IVIG supplementation could reduce the likelihood of chronic HEV infection. Immunoglobulin products have been found to contain anti-HEV antibodies capable of neutralizing HEV antigens, suggesting the possibility of a passive seroprotection provided by anti-HEV antibodies in IVIG products.³⁶ However, in our patient cohort, 2 patients (cases #3 and #5) received routine IVIG supplementation (30 grams monthly) with immunoglobulin G plasma levels well above 4 g/L before HEV diagnosis, suggesting a limited efficacy in preventing infection.

Navigating ribavirin treatment

The management of HEV infection in immunocompromised patients presents a significant therapeutic challenge. Two key considerations underscore the need for timely initiation of ribavirin off-label treatment in this context.

Challenges in HEV treatment guidance - Ribavirin treatment has been shown to reduce mortality and lower chronicity rates. Although spontaneous but unpredictable HEV clearance may occur in some cases, this outcome cannot be reliably anticipated.⁶ Prolonged viremia not only increases the risk of chronic infection but may also interfere with planned therapeutic schedules for the underlying tumor disease if spontaneous viral clearance does not occur.¹⁵ Currently, there are no established guidelines regarding the

optimal timing for initiating ribavirin therapy, reliable predictors of treatment response, or the recommended duration needed to achieve a sustained virological response. Additionally, it remains uncertain whether and when immunosuppressive therapy can be safely resumed during ribavirin treatment. Ribavirin dosing poses further challenges due to inter-individual differences in drug metabolism, the lack of routine therapeutic drug monitoring, and the frequent occurrence of anemia among responders.^{20,37,38}

Avoiding delays in oncologic therapies - HEV infection poses a risk of acute or chronically evolving hepatitis, which can delay or even disrupt critical oncologic therapies. Delays in cancer treatment while awaiting viral clearance can compromise disease control, particularly in patients with progressive myeloma and poor prognostic indicators. Such delays may influence the long-term prognosis of these patients.

In this case series, HEV-related delays significantly impacted myeloma therapy, including the postponement of an ASCT, delays in lymphocyte apheresis prior to CAR T-cell therapy, and interruptions exceeding three months during bispecific antibody treatment targeting BCMA. However, the impact of HEV-related treatment delays extends beyond this study. von Felden *et al.* reported that 33.3% of hematopoietic stem cell transplant recipients with HEV required reductions in immunosuppressive therapy, a modification linked to a mortality rate of 28.6%.⁶ Such findings emphasize the potential for HEV infection to precipitate adverse outcomes, not only through its direct effects but also by forcing alterations to critical oncologic or immunosuppressive treatments.

Mechanisms of ribavirin treatment failure in chronic hepatitis E virus infection

In heavily pretreated patients, particularly those exposed to T-cell-redirecting therapies, ribavirin failure is biologically plausible via three, often overlapping, mechanisms.

Firstly, T-cell exhaustion, affecting both the CD4⁺ compartment (with low CD4⁺ counts associated with chronic HEV in solid-organ transplant recipients) and HEV-specific T cells that, under persistent antigen exposure, acquire PD-1^{high} CD127^{low} exhausted phenotypes with waning CD8⁺ responses, reduces antiviral pressure, and may contribute to virological non-response.^{14,39}

Secondly, HEV can persist in extrahepatic sanctuary compartments, such as renal epithelium, peripheral blood mononuclear cells, the CNS, and bone marrow. In these compartments, ribavirin penetration or intracellular phosphorylation may be suboptimal, permitting low-level viral replication, subsequent rapid viral rebound and dissemination into other organs upon discontinuation of treatment.⁴⁰⁻⁴²

Thirdly, pharmacokinetic limitations frequently arise in this clinical context. Dose adjustments of ribavirin are often required due to renal impairment, common among MM patients. Additionally, ribavirin-induced hemolytic anemia

frequently necessitates dose reductions. Both factors reduce systemic exposure to the active nucleoside analogue, thus increasing the likelihood of virological non-response.⁴³ Finally, prolonged sub-therapeutic exposure to ribavirin can facilitate the gradual emergence of resistance-associated substitutions in the HEV RNA-dependent RNA polymerase, most commonly Y1320H, K1383N, and the replication-enhancing G1634R mutations. These mutations can confer resistance to ribavirin or enhance viral fitness, and have been identified in up to one-third of patients experiencing virological relapse after treatment cessation.⁴⁴

Recommendations for preventive measures and testing

Preventing HEV infections among patients undergoing treatment for hematologic malignancies requires a combination of dietary precautions, kitchen hygiene, and proactive medical management. Although there are no official recommendations advising immunocompromised patients to avoid consuming undercooked meat completely, we, like the Robert Koch Institute (RKI), support the recommendation that meat be heated to $\geq 71^{\circ}\text{C}$ for at least 20 minutes to inactivate HEV.⁴⁵ Additionally, adequate kitchen hygiene should be observed to prevent cross-contamination.

Early diagnosis is critical for preventing complications, including liver damage or interference with ongoing therapy. For patients undergoing treatment for MM, a high degree of vigilance is required in cases of an otherwise unexplained increase in liver enzymes, which should prompt PCR-based blood testing. This is especially important for patients on T-cell-directing therapies, as our study has demonstrated a high risk of chronic HEV infections, including a CNS manifestation, in this patient population. These findings align with recent reports highlighting the increased susceptibility to opportunistic infections, such as cytomegalovirus (CMV) infections and reactivations, in MM patients undergoing treatment with bispecific antibodies and CAR T cells.^{46,47} Due to this emerging issue, the International Myeloma Working Group (IMWG), the European Myeloma Network (EMN), and an international expert consensus panel have recently published consensus guidelines on managing infections in myeloma patients undergoing T-cell-redirecting therapies. (See summary in Table 3.)⁴⁸⁻⁵⁰ These recommendations have been expanded by our group's proposal to incorporate HEV into routine preventive algorithms.

Our findings indicate that close infection monitoring in these patients should be expanded beyond the usual screenings for hepatitis B, hepatitis C, HIV, and CMV to include HEV. Given the high risk of chronic HEV infections observed in this patient population, systematic screening should be incorporated into routine monitoring protocols, such as at initial MM diagnosis and prior to initiating T-cell-redirecting therapy, and in the event of rising liver enzyme levels, to ensure early detection and timely intervention.

To the best of our knowledge, we here report on the largest cohort of MM patients treated with state-of-the-

Table 3. Guidance on viral infection management in T-cell-redirecting therapy.

Virus	Baseline screening	Prophylaxis	Routine monitoring	Diagnostics for suspected infection	Intervention for confirmed infection/reactivation
HSV/VZV	Anti-HSV IgG+IgM, anti-VZV IgG+IgM	Acyclovir or valacyclovir; vaccination against VZV	None	DNA PCR (blood, focal lesions, CSF)	Acyclovir (IV) or valacyclovir (therapeutic dose)
CMV	Anti-CMV IgG+IgM; CMV-PCR can be considered	Not as routine	Consider if positive at baseline	Blood-based DNA PCR	CMV-directed antivirals (valganciclovir, ganciclovir, foscarnet) as per guidelines
EBV	EBV DNA PCR can be considered	None	Can be considered, e.g., fatigue, fever	Blood-based DNA PCR	Rituximab can be considered
SARS-CoV-2	Nasopharyngeal swab (PCR) in cases of suspected infection	Immunization	None	Nasopharyngeal swab (PCR or antigen test)	Remdesivir or nirmatrelvir/ritonavir as per local guidelines
Influenza		Yearly immunization			Oseltamivir, baloxavir or zanamivir
RSV		Immunization			Symptomatic
HIV	HIV antigen/antibody screening test	Not as routine	If indicated	Blood-based HIV RNA PCR if screening test positive	cART
Hepatitis B	HBsAg+anti-HBc IgG; HBV PCR if HBsAg or anti-HBc positive	Entecavir, tenofovir or lamivudine	HBV DNA PCR if positive for HBsAg or anti-HBc	HBV DNA PCR	Entecavir, tenofovir or lamivudine
Hepatitis C	Anti-HCV IgG+IgM; HCV PCR if positive for anti-HCV IgG/IgM	Antivirals according to genotype and availability	HCV RNA PCR if positive for anti-HCV IgG/IgM	HCV RNA PCR	Antivirals according to genotype and availability
Hepatitis E	Anti-HEV IgG+IgM; HEV RNA PCR if positive for anti-HEV IgG/IgM	Unclear	HEV RNA PCR if positive for anti-HEV IgM or positive for HEV RNA PCR at baseline	HEV RNA PCR, e.g., in cases of increased LFT or neurological symptoms	Off-label ribavirin for chronic infection; benefits of pre-emptive ribavirin unclear

Guidance on baseline serological screening, prophylactic strategies, routine monitoring, diagnostic work-up in suspected infections, and therapeutic interventions for relevant viral in patients receiving T-cell-redirecting therapies. Recommendations are adapted from current expert consensus, documents and international guidelines, supplemented by our proposed strategy for additional hepatitis E virus (HEV) screening. Compiled according to the EMN Consensus Report,⁵⁰ IMWG Guidelines for Bispecific Antibodies,⁴⁹ Consensus Recommendations from an International Expert Panel,⁴⁸ and expanded by our group's proposal to include HEV. anti-HBc: hepatitis B core antibody; cART: combination antiretroviral therapy; CMV: cytomegalovirus; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; IgG: immunoglobulin G; IgM: immunoglobulin M; IV: intravenous; LFT: liver function tests; PCR: polymerase chain reaction; RNA: ribonucleic acid; RSV: respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VZV: varicella zoster virus.

art regimens (including T-cell-redirecting therapies) at a tertiary center in Western Europe who were diagnosed with concomitant HEV infections within a notably short period of less than 12 months. The detection of 7 cases among approximately 300 MM outpatients during this period likely underestimates the true burden of HEV in this population, as testing was restricted to patients with elevated transaminases or prior to planned apheresis. The actual incidence is probably higher, given that asymptomatic infections would have remained undetected. Importantly, we report on the first 3 cases of chronic HEV infection in patients with MM, all occurring in patients receiving T-cell-redirecting therapies. While this study highlights favorable outcomes, with no cases of fulminant

hepatitis or acute liver failure following timely diagnosis and management, it also revealed significant delays in oncologic treatments like CAR T-cell therapy or ASCT, as well as treatment interruptions with unclear prognostic implications. These findings underscore the need for increased awareness of the rising incidence of HEV infections in hematologic patients, alongside improved diagnostic protocols and standardized therapeutic strategies. Future research should aim to refine antiviral therapies, elucidate transmission routes, and explore the broader implications of HEV infections on treatment modifications and outcomes in hematologic malignancies in the era of emerging immunotherapeutic approaches such as CAR T-cell therapy and bispecific T cell engagers.

Disclosures

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Contributions

MA-B and RK designed the research, analyzed and interpreted data, visualized the data, and wrote the paper; MA-B, SP, WA, SP, LL, JA, SC, JSZW, CS, AK, KW, CB and RK contributed and interpreted data. All authors revised and edited the manuscript, and approved the final version for publication.

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Data-sharing statement

The data presented in this study are available on request from the corresponding author.

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