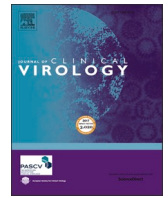




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Nosocomial transmission of hepatitis E virus and development of chronic infection: The wider impact of COVID-19

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ABSTRACT

Background: Transmission of hepatitis E virus (HEV) within the healthcare setting is extremely rare. Additionally, the development of chronic HEV infection in association with severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) infection and/or its immunomodulatory therapy has not been reported previously.

Aims: To describe the investigation and management of a nosocomial HEV transmission incident during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Epidemiological and molecular investigation of two individuals hospitalised with COVID-19 who were both diagnosed with HEV infection.

Results: Findings from our investigation were consistent with transmission of HEV from one patient with a community-acquired HEV infection to another individual (identical HEV sequences were identified in the two patients), most likely due to a breach in infection control practices whilst both patients shared a bed space on the intensive care unit (ICU). Chronic HEV infection requiring treatment with ribavirin developed in one patient with prolonged lymphopaenia attributable to COVID-19 and/or the immunomodulators received for its treatment. Further investigation did not identify transmission of HEV to any other patients or to healthcare workers.

Conclusions: The extraordinary demands that the COVID-19 pandemic has placed on all aspects of healthcare, particularly within ICU settings, has greatly challenged the ability to consistently maintain optimal infection prevention and control practices. Under the significant pressures of the COVID-19 pandemic a highly unusual nosocomial HEV transmission incident occurred complicated further by progression to a chronic HEV infection in one patient.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has placed unprecedented demands on all aspects of healthcare, including staffing, resources and space. Critical care settings have been particularly affected as they have surged capacity and adapted working practices to cope with the unprecedented influx of people requiring intensive care, which has greatly impacted on the ability to consistently maintain optimal IPC practices. Recent reports of Carbapenem-producing Enterobacteriaceae (CPE) transmission in the intensive care unit (ICU) setting [1], increased rates of catheter-related bloodstream infections [2] and evidence of nosocomial transmission of severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) [3] highlights the IPC challenges being faced during the pandemic.

The widespread use of immunosuppressive therapy for COVID-19 has also led to the emergence of other unusual pathogens e.g. COVID-19 associated pulmonary aspergillosis [4] and mucormycosis [5]. To our knowledge, there have been no reports on the impact of SARS-CoV-2 infection or its therapy on the natural course of hepatitis E virus (HEV) infection, nor on the potential for HEV to be transmitted in a nosocomial setting under the exceptional circumstances created by the COVID-19 pandemic.

HEV is a 7.2 kilobase, non-enveloped RNA virus belonging to the *Hepeviridae* family [6]. Eight HEV genotypes are known to exist with

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genotypes 1 to 4 typically infecting humans [7]. Genotype 3 is the predominant HEV genotype in Europe and the United States with consumption of undercooked and processed pork deemed to be a major route of acquisition but genotype 3 HEV RNA has also been detected in shellfish, therefore considered to be another potential source of human infection [8]. HEV has also been transmitted through transfusion of blood products including plasma, red blood cells and platelets, indicating that parenteral transmission can occur [9,10]. Although coincidental household infections do occur, confirmed person-to-person transmission is very rare. There have been a very small number of reports of HEV outbreaks in the hospital setting whereby possible nosocomial HEV transmission has been suggested [11,12]. However, the HEV diagnoses in these cases were typically based on serological investigations without molecular sequencing analysis to confirm nosocomial transmission.

Following a 2 to 10 week incubation period (median 5 to 6 weeks), acute HEV infection is typically a mild, self-limiting illness. However, in rare instances, chronic HEV infection defined as a viraemia of >3months, can develop although this occurs almost exclusively in immunocompromised patients (e.g., solid-organ transplant recipients and haematopoietic stem cell recipients) [13].

We describe an incident of confirmed nosocomial transmission of HEV during the coronavirus disease 2019 (COVID-19) global pandemic and the development of chronic HEV infection in the index case following immunomodulation.

2. Patient one

A 69 year old male with a medical history of hypertension, asthma, obstructive sleep apnoea and benign prostatic hyperplasia was admitted to King's College Hospital (KCH), a large tertiary teaching hospital in South London, UK on 30 January 2021 with COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR). He was admitted to a medical ward and received treatment with high-flow oxygen, remdesivir (a viral RNA-dependant RNA polymerase inhibitor), steroids (dexamethasone), tocilizumab (a recombinant humanised interleukin-6 receptor antagonist/monoclonal antibody) and amoxicillin/clavulanic acid. However, he continued to deteriorate and was admitted to the ICU on day 6 of admission. He spent two months on the ICU (04 February to 12 April 2021) during which time he was intubated and ventilated and continued receiving treatment for COVID-19. He was stepped down from the ICU to a medical ward on day 72.

Approximately 2 and a half months into his admission, his liver function tests (LFTs) became acutely deranged. A viral hepatitis screen on day 111 (21 May 2021) revealed an acute HEV infection; HEV IgM positive, HEV IgG negative and HEV RNA 1,074,985 IU/mL. HIV serology (HIV type 1 & 2 antibody/HIV-1 p24 antigen) was negative. Retrospective testing of serial serum samples (collected for testing other blood parameters) stored in the laboratory from earlier in his admission revealed that he was first HEV RNA positive 11 weeks after hospital admission (15 April 2021). A serum sample collected 12 days prior to this sample was HEV RNA negative. This was therefore consistent with a hospital acquired HEV infection and an investigation was commenced into the possible source. The serum HEV RNA level peaked at >5,000,000 IU/mL (the upper limit of quantification of the assay) then subsequently fell to 3982 IU/mL on day 123 (02 June 2021), with a corresponding normalisation of his LFTs at discharge from hospital on day 130 (09 June 2021). Outpatient review confirmed complete resolution of his acute HEV infection.

3. Patient two

A second male aged 69 years with a medical history of ischaemic heart disease, hypertension and alpha-thalassaemia was admitted to KCH on 02 March 2021 with COVID-19 (just over 1 month after patient 1 was first admitted). On day 7 of admission he was transferred to the

ICU where he was intubated and ventilated, received remdesivir, dexamethasone, tocilizumab and antibiotics. He progressively improved and after over 2 months on the ICU he was transferred to a medical ward on day 88 (28 May 2021). He had mildly deranged, fluctuating LFTs since admission, however, approximately 2 months into his admission this derangement became more marked. A viral hepatitis screen on day 91 (31 May 2021) demonstrated evidence of a current HEV infection; HEV IgM indeterminate, HEV IgG negative, HEV RNA >5,000,000 IU/mL. A faecal sample was also HEV RNA positive (>5,000,000 IU/mL). HIV serology was negative. Retrospective testing of stored serum samples indicated a community-acquired HEV infection; a serum sample collected on the day of hospital admission had an HEV RNA load of 266,204 IU/mL. He had been viraemic for at least 3 months, consistent with a chronic HEV infection. Although he ate pork, the source of the HEV infection remained undetermined. In 12 months preceding this hospital admission he had no prior hospital admissions and had not received any blood products or undergone any invasive procedures.

On day 107 (16 June 2021) he was started on treatment for a chronic HEV infection with oral ribavirin (400 mg twice daily) and his serum HEV RNA level began falling once treatment was initiated. He was discharged from hospital on day 109 (18 June 2021) with follow up in the hepatitis clinic. Despite a sharp decline in his serum HEV RNA levels following the initiation of ribavirin, HEV RNA was positive at below the lower limit of quantification (positive at <50 IU/mL) at the end of the initial 12 week course of ribavirin. Ribavirin therapy was therefore extended for a further 12 weeks and the outcome of this extended treatment course is currently awaited. Fig. 1 illustrates the trends in LFTs, serum HEV RNA and peripheral blood lymphocyte count for both patients.

4. Investigation of the transmission incident

Following the diagnosis of HEV infection in the second patient, further investigation into the various locations of the two patients during their admissions revealed that due to the heightened demands for ICU beds during the COVID-19 pandemic they shared a 2-bedded space (intended for a single patient only) on the ICU for a 7 day period from 17 March to 23 March 2021. Both patients were intubated and fully confined to their beds over that period thus had no direct physical contact with each other. Patient 1 was first viraemic 4 weeks after the two patients first shared the bed space on ICU (therefore within the 2 to 10 week incubation period for HEV) and given their very close proximity on the ICU we highly suspected at this stage that HEV had been transmitted from patient 2 (with community acquired HEV infection) to patient 1 via a breach of standard infection control practices.

Serum samples from both patients collected in late May 2021 were sent to the UK Health Security Agency (UKHSA) Reference Laboratory for HEV sequence analysis. Analysis of a 1.3 kilobase region of the open reading frame 2 (ORF 2) of the HEV genome found identical sequences therefore consistent with nosocomial transmission. The sequences were consistent with an HEV genotype 3 subtype f infection as illustrated by the phylogenetic tree in Fig. 2. There were no other sequences in the national UKHSA database found to be identical to the sequences from our two patients.

Prior to the diagnosis of HEV infection in patient 2, various potential sources of HEV acquisition for patient 1 were considered including blood transfusions and haemodialysis. Further investigation revealed that patient 1 had not undergone dialysis prior to becoming viraemic excluding this as a potential source but he had received 10 units of packed blood cells over a 2 month period on the ICU. Our nurse consultant in Blood Transfusion was contacted and their team identified all the packed red cells that he had been transfused in the 10 weeks preceding his HEV viraemia. The national NHS Blood and Transplant service was then informed of the incident in order to initiate a process of testing the individual blood donor stored aliquots (+/- recall of blood donors). We subsequently suspended the blood transfusion investigation

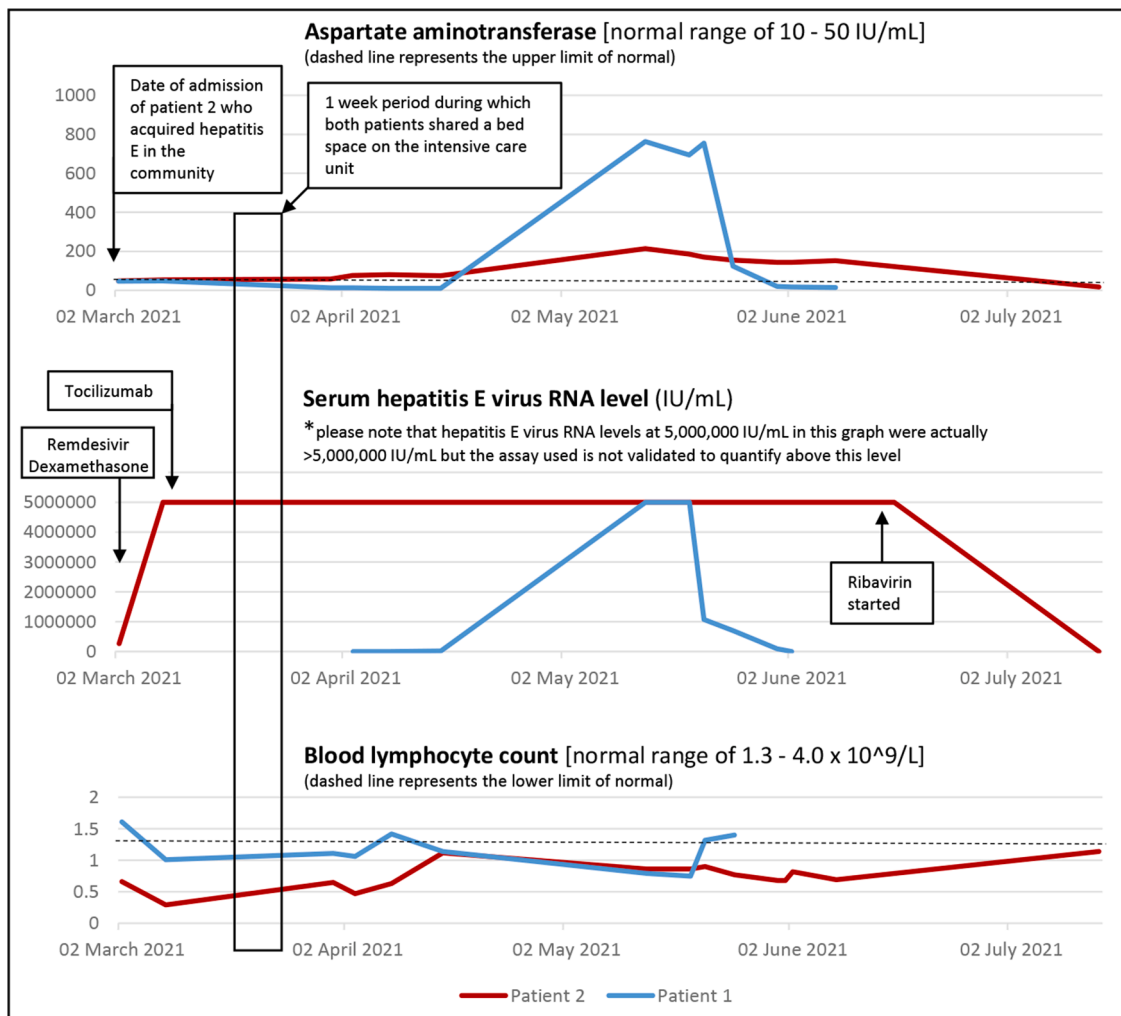


Fig. 1. Serum aspartate aminotransferase, serum hepatitis E virus RNA levels and peripheral blood lymphocyte counts for the two patients with hepatitis E virus infection.

once we discovered that patient 2 was the likely source of transmission.

5. Investigation of contacts

A contact tracing exercise was initiated to identify any other patients who had shared a bed space with either of the two confirmed HEV cases on the ICU. Three patients were identified; all three tested HEV IgM, IgG and RNA negative at more than 10 weeks (the maximal incubation period) after their potential exposures.

Ninety seven staff were identified (of whom 2 were pregnant and none were known to be immunocompromised) who provided direct clinical care to either of the two confirmed HEV cases on the ICU or the medical ward whilst they were infectious. Twenty staff attended for testing and none demonstrated evidence of current or past HEV infection. The remaining 77 untested staff members were re-contacted but elected not to attend for testing.

One of the two patients had recovered from COVID-19 but remained in hospital for further rehabilitation and volunteered (prior to being diagnosed with HEV) for participation in a formal medical student clinical examination. A doctor within our department was an examiner in that session and on returning to the department, to his surprise discovered that the patient had just been diagnosed and notified to the public health team with an acute HEV infection. The medical school had ensured all students wore personal protective equipment as a precaution and as a result, none had to be followed up.

6. Discussion

We report an incident of nosocomial transmission of genotype 3f HEV between two patients in the ICU both admitted with severe COVID-19. The pressures of the COVID-19 pandemic on ICU bed capacity thereby necessitating increased numbers of patients within pre-existing areas augmented the nosocomial transmission risks. Following their individual HEV diagnoses both patients were cared for in single-bed rooms with dedicated sanitary facilities and staff were required to wear surgical masks, gloves and plastic aprons as minimum protection (pregnant staff were excluded from caring for both patients). Strict handwashing with soap and water was reinforced. Both patients were also notified to the public health team.

Although the specific mode of HEV transmission could not be established, it most likely occurred via a staff member possibly due to a faecal/blood contaminated glove or blood/faecal contamination of shared equipment. As patients in the ICU typically have single dedicated staff providing care over an extended period, potentially fewer glove changes may have taken place, particularly given the enhanced personal protective equipment being worn due to COVID-19. Interestingly, in recent years most HEV infections in the UK have belonged to subtypes 3c and 3e [14]. HEV subtype 3f infections are very infrequent in the UK but are more commonly described in France or Spain [14]. Neither the index patient nor his close/household contacts had a history of travel abroad in the preceding one year which highlights the need for consideration of

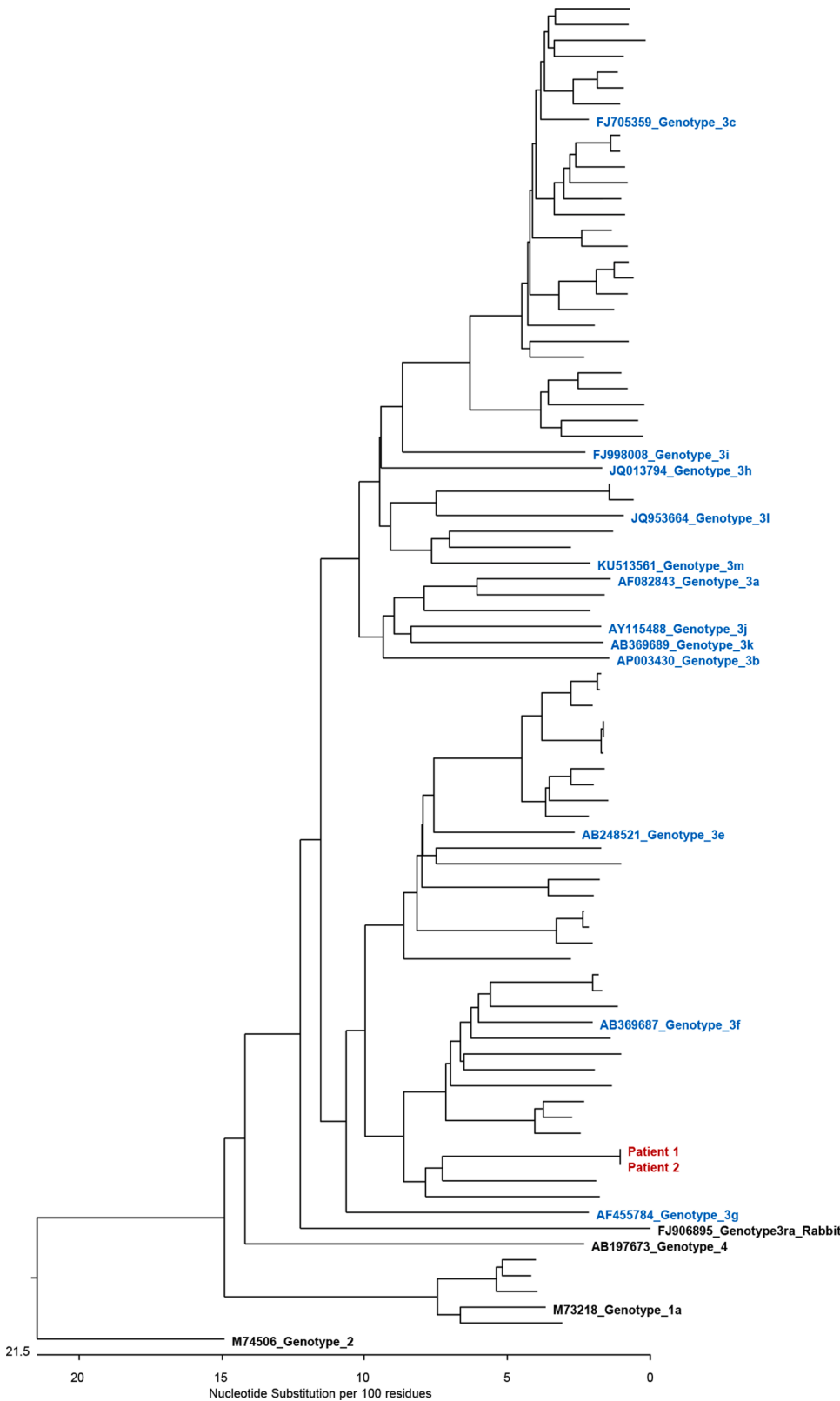


Fig. 2. Phylogenetic tree demonstrating sequences across the 1.3 kilobase region of hepatitis E virus (HEV) open reading frame 2. Sequences in black/bold indicate the HEV genotypes 1, 2, 4 and the rabbit; sequences in blue/bold indicate the genotype 3 subtypes. The sequences from samples collected from the two HEV-infected patients are shown in maroon/bold and are identical and cluster within the genotype 3f sequences. The unlabelled branches denote sequences generated from samples from patients across England with HEV-infections in the same time period as patients 1 and 2.

HEV infection even in asymptomatic patients with mildly deranged LFTs and without a history of travel. Of note, the one previously reported nosocomial HEV incident in which transmission was confirmed by sequencing, occurred on a haematology ward in France whereby a 33 year old man being treated for acute leukaemia acquired genotype 3f HEV from a 44 year old man with lymphoma and chronic HEV infection

being cared for on the same ward [15]. Enteric transmission through a lapse in strict hygiene precautions was postulated as a possible mode of transmission. In a previously reported nosocomial HEV outbreak in a hospital in Pakistan, transmission was thought to have occurred through sharing of intravenous infusion sets, however molecular analysis was not performed [11]. In another reported nosocomial HEV incident in South

Africa, HEV transmission was suspected (no molecular analysis performed) to have occurred from a pregnant patient with jaundice and diarrhoea to two nurses and a doctor who had all been exposed to the patient's faeces, blood and liquor [12].

Interestingly, neither of our two patients had a history of jaundice, the most common clinical feature of acute HEV infection occurring in up to 75% of cases [16]. This was possibly related to the effects of COVID-19 and its treatment on their immune response. Studies show that patients admitted to the ICU with COVID-19 exhibit dramatic reductions in T cell counts, particularly CD8 T lymphocytes [17]. Amongst T cell populations, CD8 T lymphocytes play a crucial role in immune responses against genotype 3 HEV infections through profound infiltration of the liver and stimulation of the release of antiviral cytokines directed against well-preserved regions of the HEV genotype 3 ORF2 [18]. Given that both patients were lymphopenic during the earlier stages of their HEV infection their CD8 T lymphocyte response against HEV and the degree of hepatocyte infiltration by CD8 T cells may have been significantly diminished potentially accounting for the absence of jaundice. This is supported by a recent study which found that symptomatic genotype 3 HEV infections were characterised by heightened recruitment of highly cytotoxic CD8 T cells into the liver whereas in asymptomatic infections significantly lower CD8 T cell responses were observed [18].

Although a chronic HEV infection prior to hospital admission cannot be completely excluded in patient 2, it is likely that he had an acute HEV infection at the time of hospital admission which established chronicity in view of a profound and prolonged lymphopenia attributable to COVID-19 and its treatment with tocilizumab and steroids. Both viral and host factors are considered to determine the chronicity of HEV infection [19]. Viral factors include genotype, zoonotic potential and adaptability to a given host. Other than single case reports of genotype 1 and genotype 7 HEV infections, most chronic HEV infections belong to genotype 3 [19]. Important host factors include the immunocompetence and nutritional status of the patient, and data indicate that HEV genotype 3 infections predominantly affect older individuals [20], possibly related, at least in part to the fact that the CD8 T cell compartment is affected by ageing [18]. In individuals receiving immunosuppressive therapy, the type of drug is considered to be a major determinant of chronicity with calcineurin inhibitors (e.g. cyclosporin A and tacrolimus) and mTOR inhibitors (e.g. sirolimus) being reported to pose a higher risk [19]. Although there are reports in patients with autoimmune disease of chronic HEV infection associated with the use of biological agents such as rituximab [21] and adalimumab [22], this is the first report to the best of our knowledge of the development of chronic HEV infection due to the immunomodulation associated with COVID-19 and/or tocilizumab.

Patient 2 was treated with oral ribavirin as per the European Association for the Study of the Liver (EASL) guidelines which for chronic HEV infection recommends reduction of immunosuppression in the first instance but if unsuccessful or not possible then oral ribavirin therapy is recommended for 12 weeks. The course may be extended if HEV RNA remains detectable in serum and/or faeces at the end of the initial treatment [23]. Ribavirin (a competitive inhibitor of the cellular inosine monophosphate dehydrogenase) is the most extensively studied drug in chronic HEV infection and although it has been suggested that it inhibits HEV replication via depletion of cellular guanosine triphosphate (GTP) pools [24], its precise mechanism of action against HEV is unclear. A systematic review found that 64% of subjects treated for chronic HEV infection with ribavirin achieved cure [25].

7. Conclusion

We report transmission of HEV within the healthcare setting, an extremely rare event. In addition, due to the lymphopenia associated with COVID-19 and the immunosuppressive treatment received, one patient developed a chronic HEV infection requiring antiviral treatment.

This incident highlights the IPC-related challenges of the COVID-19 pandemic, particularly within the ICU setting where demands have been drastically heightened. It also reinforces the importance of testing for HEV infection in non-endemic regions and demonstrates the unusual manifestations of HEV in the setting of COVID-19 and with the widespread use of immunomodulators.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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