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Donor-derived Transmission of Hepatitis A Virus Following Kidney Transplantation: Clinical Course of Two Cases From One Donor

Jefferson M. Jones, MD,[1] Avinash Agarwal, MD,[2,†] Anne C. Moorman, MPH,[3] Megan G. Hofmeister, MD,[3] John C. Hulse, MD,[4] Max O. Meneveau, MD,[5] Tonya Mixon-Hayden, PhD,[3] Sumathi Ramachandran, PhD,[3] Christopher M. Jones, MD,[6] Stephanie Kellner, MPH,[7] Daniel Ferrell, MPH,[8] and Costi D. Sifri, MD[9]

Background. Donor-derived transmission of infections is a rare complication of kidney transplant. Hepatitis A virus (HAV) is a common cause of acute viral hepatitis worldwide, but donor-derived transmission to organ recipients has been reported in the literature only twice previously. The timeline for HAV incubation and clearance in transplant recipients is not well understood. **Methods.** In 2018, 2 kidneys and a liver were procured from a deceased donor resident of Kentucky, one of many states that was experiencing an HAV outbreak associated with person-to-person transmission through close contact, primarily among people who reported drug use. Both kidney recipients, residents of Virginia, subsequently developed acute HAV infections. We report the results of an investigation to determine the source of transmission and describe the clinical course of HAV infection in the infected kidney recipients. **Results.** The liver recipient had evidence of immunity to HAV and did not become infected. The donor and both kidney recipients were found to have a genetically identical strain of HAV using a next-generation sequencing-based cyber molecular assay (Global Hepatitis Outbreak Surveillance Technology), confirming donor-derived HAV infections in kidney recipients. At least 1 kidney recipient experienced delayed development of detectable hepatitis A anti-IgM antibodies. By 383 and 198 d posttransplant, HAV RNA was no longer detectable in stool specimens from the left and right kidney recipients, respectively. **Conclusions.** Adherence to current guidance for hepatitis A vaccination may prevent future morbidity due to HAV among organ recipients. http://links.lww.com/TXD/A548

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Donor-derived transmission of infections is an unfortunate complication of transplantation and viruses are among the most common infectious agents involved in these transmissions.[1] However, there have only been 2 reported cases

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[1] *Division of Healthcare Quality Promotion, National Center for Emerging, Zoonotic and Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.*

[2] *Division of Transplantation, Department of Surgery, UVA Health, Charlottesville, VA.*

[3] *Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA.*

[4] *University of Virginia School of Medicine, Charlottesville, VA.*

[5] *Department of Surgery, UVA Health, Charlottesville, VA.*

[6] *Division of Hepatobiliary and Transplant Surgery, Trager Transplant Center, University of Louisville, Louisville, KY.*

[7] *Central Shenandoah Health District, Virginia Department of Health, Richmond, VA.*

[8] *Rappahannock-Rapidan Health District, Virginia Department of Health, Richmond, VA.*

[9] *Division of Infectious Diseases and International Health, Department of Medicine, UVA Health, Charlottesville, VA.*

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Correspondence: Anne C. Moorman, MPH, Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA. (amoorman@cdc.gov).

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of hepatitis A virus (HAV) donor-derived transmission published in the literature, and the timeline for HAV incubation and clearance in transplant recipients is not well understood. The first reported case occurred in 2015 in a combined liver-small intestine-pancreas recipient.[2] The second, donor-derived HAV transmission to 2 kidney recipients, was reported in a 2022 clinical correspondence.[3]

HAV is highly transmissible from person to person, most commonly via the fecal-oral route; infection prevalence is largely dependent on socioeconomic factors and sanitation.[4] The hepatitis A vaccine (HepA vaccine) was first recommended in the United States in 1996, resulting in a steady decrease in cases until 2011, when the incidence plateaued for several years at approximately 1600 cases per year.[5] Before the recent outbreaks starting in 2016, US hepatitis A cases were largely attributed to travelers visiting endemic areas and food-borne outbreaks.[5] However, since 2016, widespread outbreaks associated with person-to-person transmission have been reported across the United States.[5,6] As of April 2023, more than 44 850 outbreak-associated cases were reported by 37 states since the outbreaks began.[6] These outbreaks are primarily affecting people who use drugs, experience unstable housing or homelessness, are currently or were recently incarcerated, or are men who have sex with men.[5]

In February 2019, following the report of a suspected donor-derived HAV transmission to the Organ Procurement and Transplantation Network (OPTN), another kidney transplant recipient sharing the same donor was also diagnosed with HAV infection. We report the results of an investigation to determine the source of transmission and describe the clinical course of HAV infection in the infected kidney recipients.

MATERIALS AND METHODS

Epidemiological Investigation

In the United States, all suspected, unanticipated donor-derived disease transmissions are reported to the OPTN for investigation by the Ad Hoc Disease Transmission Advisory Committee, which includes broad representation of the transplant and organ procurement communities, including ex officio representatives from the Centers for Disease Control and Prevention (CDC).[7] Cases of public health importance (eg, nationally notifiable infections, unknown syndromes, or multiple ill recipients) are referred to CDC for investigation to determine whether donor-derived disease transmission has occurred and to identify interventions to prevent further transmission events. A collaborative investigation between the University of Virginia Medical Center, state and local health departments, Kentucky Organ Donor Affiliates, and CDC was performed to determine the origin of the HAV infection in the index case and investigate potential transmission to other organ recipients.

Laboratory Testing

Serum specimens from the kidney transplant recipients were tested for HAV IgM antibody (anti-IgM) and HAV IgG antibody (anti-IgG) by chemiluminescent immunoassay (ARCHITECT HAVAB-M, HAVAB-G; Abbott Laboratories, Abbott Park, IL). Additional laboratory testing was performed at the CDC Division of Viral Hepatitis laboratory (Atlanta, GA). Quantitative HAV real-time polymerase chain reaction was performed on stored donor serum and stool and serum specimens from both kidney recipients using primers and probes targeting the 5′UTR. Testing for viral genetic relatedness among cases was performed using molecular sequencing. HAV from the donor and both kidney recipients was tested for genetic similarity of the 315 base-pair fragment of the VP1-P2B region of the HAV genome using a next-generation sequencing cyber molecular assay developed by CDC, named Global Hepatitis Outbreak Surveillance Technology.[8]

RESULTS

Donor-derived Hepatitis A Cases: Left Kidney Recipient and Right Kidney Recipient

The demographic characteristics and clinical course of the left kidney recipient (LKR) index case and right kidney recipient (RKR) are detailed in Table 1. To summarize, elevated liver enzymes were first detected in the LKR 19 d posttransplant accompanied by nausea, emesis, and diarrhea, likely representing the initial symptoms of HAV infection. An acute rise in alanine aminotransferase (ALT) and aspartate aminotransferase levels was first detected 57 d posttransplant. She had a positive HAV anti-IgM and negative HAV anti-IgG test on posttransplant day 50.

Routine laboratory testing of the RKR demonstrated an acute rise in liver enzymes 75 d posttransplant, accompanied 5 d later by many characteristic symptoms of acute HAV infection including malaise, emesis, and diarrhea. He was negative for HAV antibodies at 63 d posttransplant on testing prompted by the report of the positive index case. Hospitalized on posttransplant day 82, repeat HAV anti-IgM and HAV anti-IgG testing were both positive.

Both RKR and LKR received standard immunosuppression (Table 1). For both mycophenolic acid was held when diagnosed with acute HAV but resumed once symptoms improved and transaminases normalized.

The kidney transplant recipients were managed with supportive care and made a full recovery with no apparent negative impact on graft function. The household caregivers of both patients were counseled on HAV infection prevention practices and recommended to undergo postexposure vaccination.

Liver Recipient

The liver recipient was an adult male transplanted for cirrhosis and hepatocellular carcinoma and did not recall previous HepA vaccination or infection. He experienced no symptoms or signs of hepatitis and tested anti-HAV IgM-negative and IgG-positive 63 d posttransplant. Pretransplant HAV serology was not available.

Donor

The donor was an adult male who died of cardiac arrest from a possible pulmonary embolism. He did not have jaundice, vomiting, diarrhea, elevated bilirubin levels, transaminitis, or other symptoms or signs of hepatitis during his hospitalization before death and was not tested for HAV. Per next-of-kin interview, the donor had a fever shortly before death but no cause was identified. He used drugs daily, including methamphetamines, heroin, “pain pills,” and marijuana, and had been incarcerated within the year before death. The donor was a resident of Kentucky, a state experiencing a large outbreak of HAV among persons who use drugs at the time of the donor’s death.[5,6] Public health investigations did not

TABLE 1.

Demographic characteristics and clinical course of the LKR and RKR with donor-derived HAV infection

	LKR, index case	RKR
Demographics		
Age (rounded by decade[a])	50	60
Sex	F	M
Medical history		
Transplant indication	ESRD secondary to hypertensive nephrosclerosis	ESRD secondary to hypertension and type 2 diabetes mellitus
Previous hepatitis A vaccine?	Did not recall vaccination	Unknown
Laboratory data		
HAV anti-IgM	Positive (+) at day 50 posttransplant	Negative (–) at day 63 posttransplant, positive (+) at day 82 posttransplant
HAV anti-IgG	Negative (–) at day 50 posttransplant	Negative (–) at day 63 posttransplant, positive (+) at day 82 posttransplant
HAV RNA tests (**Table S1, SDC**, http://links.lww.com/TXD/A549)	Estimated HAV loads from serum and stool were 7.6 and 6.5 $\log_{10}$ IU/mL at 99 d posttransplant. Periodic tests of serum and/or stool remained positive through day 189 when values had decreased to 1.69 and 1.26 $\log_{10}$ IU/mL. The subsequent specimen collected at day 383 was negative for HAV RNA.	Estimated HAV load from serum was 7.62 $\log_{10}$ IU/mL at 85 d posttransplant. Periodic tests of serum and/or stool remained positive through day 176 when values had decreased to 1.17 $\log_{10}$ IU/mL in serum. The subsequent specimen collected at day 198 was negative for HAV RNA
Other pathogen testing	Negative for HBsAg, HCV NAAT at day 61 posttransplant. Negative for CMV NAAT at 61 d posttransplant	Negative for HBsAg and HCV antibody tests at day 82 posttransplant. Positive CMV serum viral load of 79 IU/mL at day 82 posttransplant
Liver enzymes, including AST and ALT, ALP, and Tbili	AST/ALT: Normal until 19 d posttransplant when began steadily increasing (Figure 1A). ALT and AST levels peaked at 1960 and 1056 U/L, respectively (Figure 1A) at day 61 posttransplant and trended down afterward. Tbili: Elevated at day 61 posttransplant and trended down afterward (Figure 1B). ALP: remained normal See Figure 1	AST/ALT: Elevated 26 d posttransplant and remained mildly elevated in subsequent months (Figure 2A). ALT and AST levels peaked at day 82 posttransplant at 1209 and 1049 U/L, respectively, and trended down afterward. Tbili: Elevated at 7.6 mg/dL day 82 posttransplant, peaked at 14.3 mg/dL on day 89 and trended down afterward (Figure 2B). ALP: elevated at 115 U/L at day 82 See Figure 2
Other testing		
Imaging studies	Liver ultrasound normal at 44 d posttransplant Magnetic resonance cholangiopancreatography normal at 61 d posttransplant	Liver ultrasound normal at 82 d posttransplant
Clinical history		
HAV risk factors[b]	None reported	None reported
Hospitalization history posttransplant	Hospitalization for kidney transplant, 4 d, uneventful Hospitalization from day 61 to 63 posttransplant for weight loss and ongoing intermittent vomiting; without diarrhea, abdominal pain, fever, jaundice, or hepatomegaly	Hospitalization for kidney transplant, 3 d, uneventful Hospitalization from day 82 to 87 posttransplant for progressively worsening malaise and acute liver injury
Symptom history posttransplant	Developed new onset nausea/vomiting 19 d posttransplant Developed diarrhea 19 d posttransplant, resolved after changing from myocyphenolate mofetil to mycophenolic acid Had experienced 20 lb weight loss by day 61 posttransplant	Developed malaise and anorexia posttransplant Developed vomiting, diarrhea, and a 40-pound weight loss by day 82 posttransplant hospitalization
Immunosuppressive and prophylaxis medication regimen posttransplant	Induction immunosuppression with methylprednisolone alone; antithymocyte globulin held as absolute lymphocyte count was 0 at the time of transplant. Maintenance medications included tacrolimus, prednisone; MPA was held due to leukopenia starting 61 d posttransplant. Valganciclovir for CMV prophylaxis. MPA was held when diagnosed with acute hepatitis A but resumed once symptoms improved and transaminases normalized	Induction immunosuppression with methylprednisolone and antithymocyte globulin. Maintenance medications included tacrolimus, MPA, and prednisone. Valganciclovir was held due to pancytopenia. MPA was held when diagnosed with acute hepatitis A but resumed once symptoms improved and transaminases normalized

[a]Age rounded to the nearest decade for deidentification purposes.

[b]HAV infection risk factors in the United States currently include contact with someone with HAV, travel to endemic regions, exposure to contaminated food, experiencing homelessness or unstable housing, men who have sex with men, illicit drug use, recent incarceration.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-IgG, IgG antibody; anti-IgM, IgM antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; ESRD, end-stage renal disease; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LKR, left kidney recipient; MPA, mycophenolic acid; NAAT, nucleic acid amplification testing; RKR, right kidney recipient; Tbili, total bilirubin.

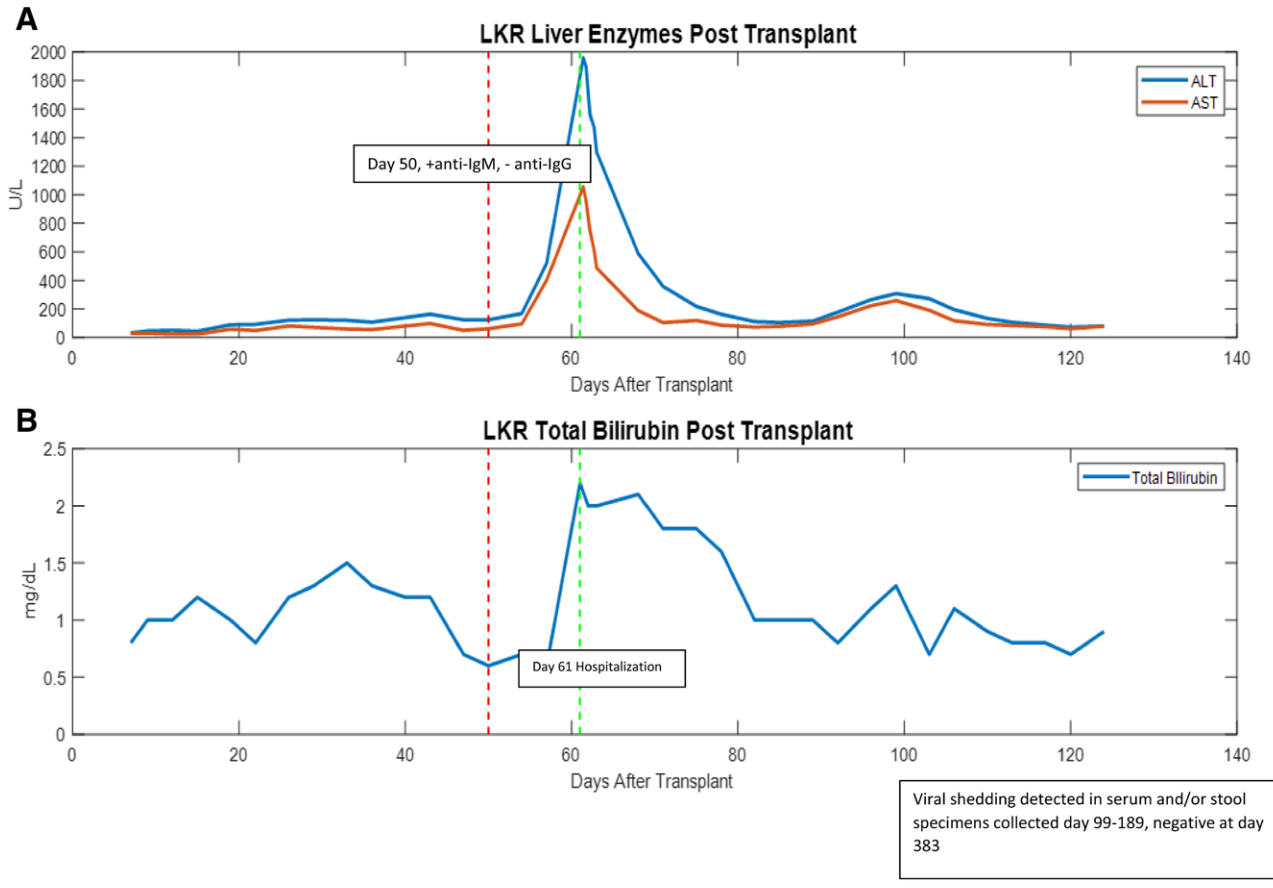

FIGURE 1. LKR clinical course, including (A) ALT and AST following transplant. B, Total bilirubin following transplant. Normal total bilirubin is 0.3–1.0 mg/dL. The red dashed line is posttransplant day 50 when she had a positive HAV anti-IgM and negative HAV anti-IgG. The green dashed line is the day she was admitted to the hospital for acute liver injury. ALT, alanine aminotransferase; anti-IgG, IgG antibody; anti-IgM, IgM antibody; AST, aspartate aminotransferase; HAV, hepatitis A virus; LKR, left kidney recipient.

identify any epidemiological links between the donor and kidney and liver recipients. Both kidneys and the liver were procured for transplantation.

Hepatitis A Viral Loads and Genomics

Global Hepatitis Outbreak Surveillance Technology sequencing of the donor and 2 kidney recipient HAV isolates showed all were infected with a genetically identical strain of HAV genotype IB. The quantitative HAV RNA result from a reserved donor serum specimen was 2 640 000 IU/mL. HAV RNA was detectable by quantitative HAV real-time polymerase chain reaction from serum and/or stool specimens of the LKR and RKR 189 and 176 d posttransplant, respectively. By 383 and 198 d posttransplant, HAV RNA was no longer detectable in stool specimens from the LKR and RKR, respectively (Table 1, **Table S1, SDC**, http://links.lww.com/TXD/A549).

DISCUSSION

Although transmission of HAV through blood transfusion has been reported, solid organ donor-derived HAV transmission has only been reported in the published literature twice to date, both since 2015.[2,3] The investigation described here identified genetically identical HAV RNA sequences in an organ donor and both kidney recipients, confirming donor-derived HAV transmission through kidney transplantation. Clinicians should adhere to current guidance for HepA vaccination, and consider HAV among recipients of donors who have risk factors and consider testing posttransplant if clinical signs or symptoms arise.

The mean incubation period of HAV is 28 d with a range of 15–50 d,[9] with development of IgM anti-HAV antibodies generally occurring 5–10 d before the onset of symptoms and persisting for up to 6 mo.[10] However, the development of positive anti-HAV IgM on posttransplant days 50 and 82 for the recipients, with negative testing at day 63 for the RKR suggests that immunosuppressed kidney transplant patients can have delayed appearance of anti-HAV IgM antibodies. Both kidney recipients were leukopenic at the time of their acute illness, likely as a consequence of immunosuppression. Leukopenia and transplant immunosuppression may have also contributed to the timing of the onset of their symptoms, which manifested with classic gastrointestinal symptoms about day 80 posttransplant for the RKR after several weeks of malaise. Both kidney recipients had rapidly rising aspartate aminotransferase and ALT levels (Figures 1A and 2A). Total bilirubin was also a useful clinical marker of HAV infection (Figures 1B and 2B) in these patients.

The liver recipient had no signs or symptoms of HAV infection. Possible explanations include not recalling prior vaccination or having had immunity from a previous unrecalled infection earlier in life, such as in childhood when many infections are asymptomatic. Given that the liver is the primary target of the hepatitis A virus, transplant-related transmission

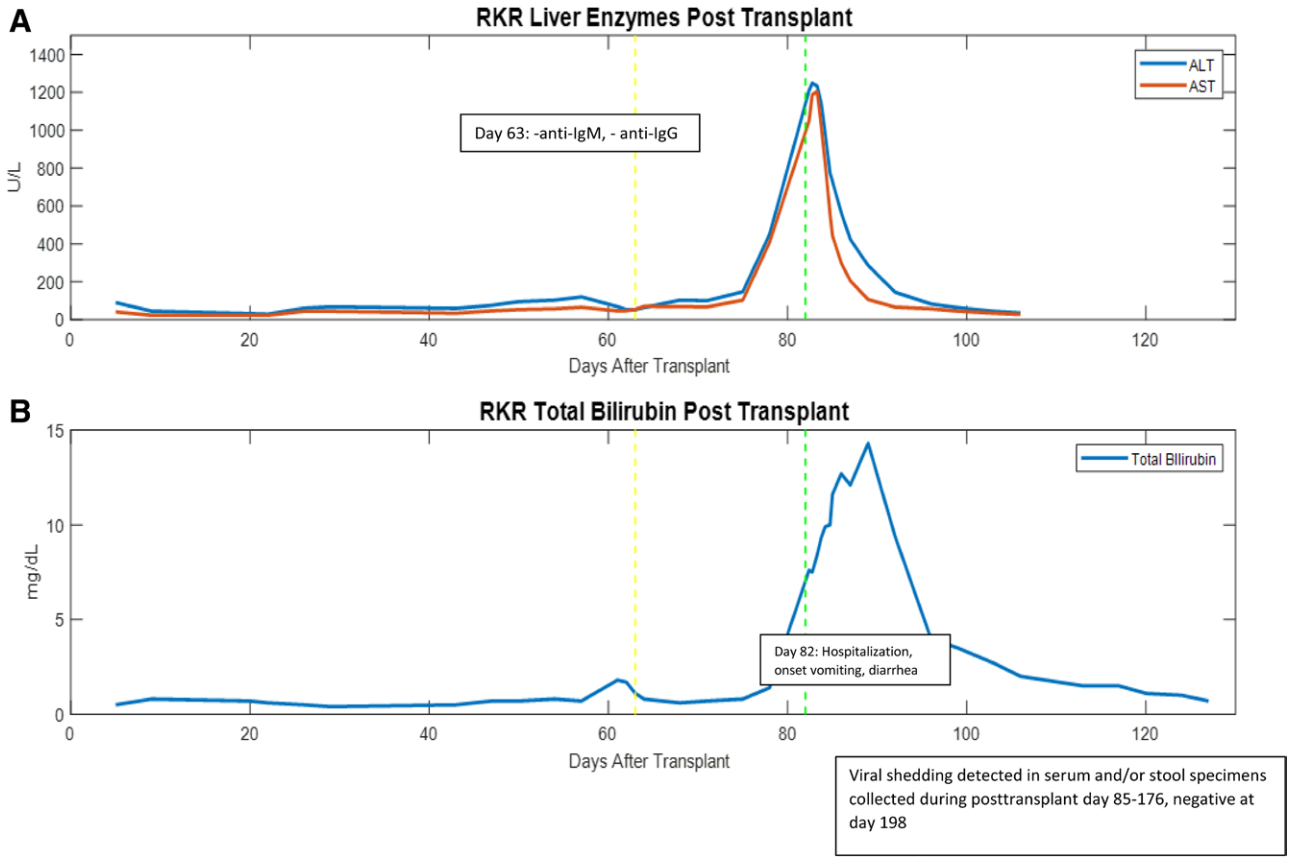

FIGURE 2. RKR clinical course, including (A) ALT and AST following transplant. B, Total bilirubin following transplant. Normal total bilirubin is 0.3–1.0 mg/dL. The yellow dashed line indicates 63 d posttransplant when he was HAV IgG/IgM negative. The green dashed line is 82 d posttransplant when he was admitted to the hospital for acute liver injury and tested HAV anti-IgM/IgG positive that day. ALT, alanine aminotransferase; anti-IgG, IgG antibody; anti-IgM, IgM antibody; AST, aspartate aminotransferase; HAV, hepatitis A virus; RKR, right kidney recipient.

would almost certainly have occurred without prior immunity. Asymptomatic or mild HAV infection is unlikely for this patient, because asymptomatic or mild infection is infrequent in all adults (including nonimmunocompromised adults) and loss of IgM during acute infection would be unusual.[9,10]

Hepatitis A is a self-limited disease that is usually successfully treated with supportive care alone. Approximately 0.2% of cases result in acute liver failure.[4] However, understanding of the clinical course of HAV infection in immunocompromised patients is limited. One study demonstrated that compared with HIV-negative patients, HIV-positive patients had a lower peak ALT at presentation (median, 1312 versus 2014 IU/L, $P = 0.003$).[11]

Currently, laboratory-based screening of organ donors for HAV infection is not recommended for several reasons. Testing for hepatitis A RNA is not currently commercially available. Screening of asymptomatic patients with HAV anti-IgM may have a positive predictive value as low as 11% in non-outbreak settings.[12,13] Additionally, there is a 15–45-d window period between exposure to HAV and the development of detectable HAV anti-IgM when a donor may be infectious but the infection is not yet detectable.[9] Finally, donor-derived HAV transmission has been very rare to date and routine laboratory-based screening for asymptomatic donors is unlikely to add additional safety at present. However, CDC and other public health partners will continue to monitor the occurrence of donor-derived transmission events and determine if additional risk mitigation strategies may be appropriate.

Current guidelines from several clinical organizations address HepA vaccination in solid organ recipients. American Society of Transplantation Infectious Diseases Community of Practice 2019 guidance recommends HepA vaccination for all adult solid organ recipients pre- or posttransplant and pediatric recipients posttransplant.[14] Infectious Disease Society of America guidance for vaccination of the immunocompromised host states that hepatitis A-unvaccinated, hepatitis A-undervaccinated, or hepatitis A-seronegative solid organ transplant candidates, particularly liver transplant candidates, should receive a HepA vaccine series.[15] Of note, high seroconversion rates after HepA vaccination in kidney transplant patients can be achieved, but a rapid decline of antibody titers over the course of 2 y has been observed in this population.[16,17]

Advisory Committee on Immunization Practices guidance for hepatitis A vaccination in the United States also recommends that among other groups, persons with chronic liver disease, who are at risk for severe outcomes from HAV infection, should receive HepA vaccine,[18] which may have prompted previous vaccination of the liver recipient. Advisory Committee on Immunization Practices guidance includes recommendations for HepA vaccination among those at risk for HAV infection in outbreak settings, including persons who use drugs or are experiencing homelessness, and suggests offering

HepA vaccine in jails and prisons as an effective strategy to reach persons at high risk for HAV infection.[18]

Organ donor-derived HAV infection might be underrecognized and underreported.[19,20] The incidence of HAV infections in the United States has been increasing since 2013 and the recent hepatitis A outbreaks in the United States are occurring primarily among people who use drugs.[6] During 2010–2017, the proportion of deceased donors with drug intoxication reported as the mechanism of death increased by approximately 200% and the proportion of donors with reported injection drug use has increased 500%, possibly indicating an increased risk of HAV infection among organ donors.[20] Recognition of risk factors among deceased organ donors and ongoing organ recipient monitoring is important to ensure that recipient infections are promptly diagnosed and managed. Suspected donor-derived HAV should be reported to the OPTN (Pathogens of Special Interest_07/05/2022 [https://optn.transplant.hrsa.gov/media/yyhnrkar/special_pathogens_list.pdf]). Adherence to current guidance for HepA vaccination may prevent future morbidity due to HAV infection among organ recipients.

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