Updated Pathway to Micro-elimination of Hepatitis C Virus in the Hemodialysis Population

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Chronic hepatitis C virus (HCV) infection continues to be transmitted to hemodialysis (HD) patients within HD facilities globally. The goal of the World Health Organization to micro-eliminate HCV infection from the HD population by the year 2030 is not on target to be achieved. Obstacles to eliminate HCV in HD settings remain daunting due to a complex system created by a confluence of guidelines, legislation, regulation, and economics. HCV prevalence remains high and seroconversion continues among the HD patient population globally as a result of the HD procedure. Preventive strategies that effectively prevent HCV transmission, treatment-as-prevention, and rapid referral to treatment balanced with kidney transplant candidacy should be added to the current universal precautions approach. A safer system must be designed before HCV transmission can be halted and eliminated from the HD population.

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In 2016, the World Health Organization (WHO) established a goal to eliminate chronic hepatitis C virus (HCV) as a major public health threat by 2030.1 Two years later, the “micro-elimination” of HCV among high-risk subpopulations, including patients receiving HD, was proposed to accelerate global HCV elimination.2 In response to this proposal, we are suggesting some refinements to the existing guidelines for screening and treating HD patients for HCV, as part of an overall strategy for micro-elimination of HCV in this vulnerable population. Hemodialysis facilities will remain high-risk environments for HCV transmission as long as infected and susceptible patients are undergoing treatment concurrently.3 This risk can be reduced by meticulous adherence to infection control practices. We also advocate the use of HCV-RNA tests for earlier detection of HCV viremia, along with use of the direct-acting antiviral (DAA) agents for treatment of infected patients.

PROGRESS TOWARDS ELIMINATION OF HEPATITIS B AND C

Respiratory infections, such as influenza and coronavirus, spread rapidly and broadly. In contrast, blood-borne infections, such as chronic hepatitis B virus (HBV) and HCV, spread slowly, and the infections have been heavily concentrated among people with known risk factors.

The attempts to eliminate HBV are following a 3-pronged approach: (i) to immunize all susceptible people; (ii) to suppress the HBV in those currently infected; and (iii) to interrupt transmission routes. Thanks to the existence of an effective vaccine against HBV, efforts to eliminate HBV are on track. Targeted prevention has successfully controlled chronic hepatitis B virus (HBV) infection transmission among HD patients, with dramatic declines in overall prevalence in the United States (US) from 7.8% in 1976 to 3.8% in 1980, and post-vaccine availability to 0.9% in 1999 and has since remained stable4–6 (Figure 1).
There is not yet an effective vaccine against HCV, and the first drug therapies to become available against HCV had limited efficacy and were poorly tolerated. For that reason, public health efforts focused mainly on interrupting transmission through improved hygiene at HD facilities. Thanks largely to these efforts, the prevalence of HCV infection among HD patients declined significantly in the years before the introduction of DAAs (Figure 1). There is still room for improvement. Of the 18 healthcare-associated HCV outbreaks investigated by the US Centers for Disease Control and Prevention (CDC) between 2005 and 2013, 39% occurred in HD facilities,7 and between 2008 and 2019, more than 50% of all healthcare-associated outbreaks reported to the CDC occurred in HD facilities.8 The prevalence of HCV is high among individuals starting HD, and the risk of seroconversion increases with time on HD.9,10 Most of these seroconversions result from transmission within the dialysis clinic, whereas some represent infections acquired in the community. The spontaneous clearance of HCV infection among HD patients is low.11

**RISK FACTORS FOR HCV TRANSMISSION**

**General Population**

Hepatitis C virus is mainly a blood-borne infection. In affluent countries, the main risk factors include history of HD (the longer the duration of dialysis, the higher the risk), prior blood transfusion, prior organ transplantation, residence in endemic communities, hemophiliacs born before 1992, male sex, Black race, HIV infection, substance abuse, HBV infection, and glomerulonephritis-induced end-stage renal disease (ESRD).9,12,13 Other documented routes of HCV transmission include perinatal,14 injection drug use, and high-risk sex among men who have sex with men.15,16 The prevalence of HCV is higher in resource-poor countries and settings, where substandard sterile processes in healthcare environments, home births, trauma, and poor living conditions are associated with unsanitary water and limited electric supplies, which hamper sterilization and increase risk of HCV transmission.17

**Healthcare Workers**

Anti-HCV prevalence among dialysis staff is similar to that in blood donors18,19 and the risk of acquiring HCV is considered to be no higher than for other healthcare workers. Consequently, routine HCV testing of HD staff members is not recommended.20 Notwithstanding, HD patients and healthcare workers are at risk for HCV-contaminated blood and bodily fluids exposure. Recent studies of healthcare workers in the United States and the European Union found a 0.1% to 0.3% risk of HCV transmission following sharps-related or needlestick injuries and higher following hollow-bore needle-injuries.21–25 The patient source viral load and host factors that determine the risk for HCV transmission include the viral concentration levels per unit of blood volume, inoculum volume, anti-HCV medications or antibodies, ambient conditions, age of the blood on the needle or injurious device, and tissue injury depth.26

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**Figure 1.** Annual hepatitis prevalence in the hemodialysis population. DAA, direct-acting antiviral; HCV, hepatitis C virus; HD, hemodialysis.
Hemodialysis Patients
In addition to general population risk factors, a history of HBV or HIV infection is an independent risk factor for HCV infection in HD patients. The global anti-HCV prevalence among patients starting HD and <120 days HD duration is 5%, 5-fold higher than in the general population. The risk of seroconversion increases with time on HD. A prospective multicenter study of 2744 long-term HD patients followed between 1999 and 2003 using HCV-RNA found a 0.33% annual incidence of new infections and reinfections within HD facilities. Similar rates were found in 2002 among the HD population in the United States. Accordingly, of the 468,091 HD patients in the United States at the end of 2017 and the 2.24 million globally in 2012 to 2015, approximately 1545 and 7392 individuals, respectively, acquired a new HCV infection each year. Many of these patients are undiagnosed during the acute stage of infection.

Transmission risk relates directly to a HD facility’s HCV prevalence. An early study demonstrated no apparent risk factor in 38% of newly diagnosed patients and no new HCV infections occurring in HD facilities without anti-HCV–positive individuals. Later studies demonstrated, using molecular virology data from molecular phylogenetic analysis and viral genome sequencing, a predominance of the same strain among new infections and reinfections within dialysis facilities. These data and the clustering of seroconversion in dialysis facilities concurrently dialyzing HCV-infected and susceptible at adjacent stations suggest medical error with breaches in infection control within a dialysis facility.

**INFECTION CONTROL PRACTICES**

Implementation of universal precaution measures and those to decrease contamination has decreased HBV and HD transmission in dialysis units. The most common breaches identified in HCV outbreak investigations are substandard cleaning and disinfection of equipment and environmental surfaces, followed by blood contamination of the patient care environment or medical devices, handling of blood specimens near medication preparation and cleaning supply areas, use of a mobile cart to deliver injection medications or to transport supplies, failure to rigidly enforce universal precautions and standard infection-control measures, such as sharing multi-dose vials, failure to change gloves between patients, touching machines without gloves or glove change, improper vascular access care, or failure to perform proper hand hygiene between tasks or patients.

A few reports found that the failure to adequately clean and disinfect high-touch surfaces on dialysis machines between patients, increases risk of HCV transmission. Dialyzer membranes and HD ultrafiltrate have not been shown to be associated with transmission of HCV. An alteration in pore size or disruption of membrane integrity, such as may occur with the dialysis process itself, dialyzer reprocessing, or filter assembly, could theoretically permit passage of the HCV virus. HCV-RNA polymerase chain reaction detection in dialysate may reflect viral RNA fragments, rather than the infectious virus.

Some individuals could be members of more than 1 at-risk subpopulation at the time of starting dialysis. The cornerstone of HD facility transmission control is process safety, which includes the following: (i) the accurate and early identification of the HCV-infected reservoir using regularly scheduled HCV-RNA screening; (ii) the implementation and optimization of bedside HD safety processes via peer- and HD facility–driven leadership and public health and regional oversight; and (iii) capitalizing on technological support opportunities (Figure 2).

**SCREENING FOR HCV**

**HCV-RNA**

Table 1 shows the challenges in interpreting the results of HCV tests. The goal of HCV testing for HD patients should be to detect active infections. HCV-RNA tests are best for that purpose. Qualitative HCV-RNA testing done with polymerase chain reaction nucleic acid amplification detects viremia with 96% to 98% sensitivity and 98% to 99% specificity as early as 1 to 2 weeks post-acute infection. A reactive result is often followed by a quantitative test, such as reverse-transcription polymerase chain reaction, transcription-mediated amplification, or branched DNA testing, which detects viral load as low as 10- to 15-IU/ml limits. All HCV-RNA assays are calibrated by the World Health Organization HCV international unit standard to enable global comparability. An HCV core protein-detecting immunoassay can be done in areas where nucleic acid testing is not available, but may detect HCV less reliably with HBV co-infection or in persons with HCV genotypes 4, 5, and 6, respectively, more commonly found in the Middle East and Central Africa, South Africa, and Asia.

Hepatitis C viremia levels fluctuate by the viral stage of replication and host immune response level. For example, viral load is highest before antibody development, then declines, sometimes to undetectable levels, at the time of seroconversion, followed by a return to detectable levels. Repeated sampling and testing with HCV-RNA are necessary for high-risk
populations such as HD patients to identify HCV viremia (Figure 2).

Anti-HCV Antibody

Anti-HCV antibody tests have high positive predictive value when used for high-risk patients such as HD patients. However, it may take up to 6 months after infection for the patient to have a positive antibody test result. For this reason, the antibody tests have low negative predictive value for HD patients. Also, a patient will continue to have positive antibody test results even after the viral infection is cleared, either naturally or as a result of treatment.

Testing Protocols

Given that the HCV-RNA tests are a good indicator of viremia, we suggest heavier use of the RNA tests than is recommended by the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Figure 3). The current KDIGO guidelines recommend HCV testing by hepatitis C antibody (anti-HCV) serological screening at HD facility admission, followed by scheduled incidental infection surveillance with monthly serum alanine aminotransferase (ALT) levels and biannual anti-HCV. After prompt review, recommendations include anti-HCV for a newly elevated ALT, HCV-RNA PCR testing in the event of a newly reactive anti-HCV, referral for care if HCV-RNA is detected, and notifying the local public health agency to initiate a source and cause investigation. Current guidelines recommend that patients with past and cleared HCV viremia documented by the presence of HCV-RNA, with or without treatment, have HCV-RNA levels every 6 months. We suggest, instead, quarterly HCV-RNA testing in HD facilities dialyzing viremic patients and biannually in HD units without HCV-RNA-positive patients.

TREATMENT OF HCV INFECTION

Dialysis Patients

The 3 major classes of DAA, when used in concert, effectively block various steps in the HCV replication cycle and include inhibitors of the NS3/NS4A protease, NS5A complex, and NS5B polymerase. Greater than 90% of patients achieve a sustained viral response (SVR) or “cure,” defined as undetectable HCV-RNA level at 12 weeks following completion of therapy with DAA combinations, pangenotypic or designed for HCV genotype, and tailored to CKD level and liver disease. Unlike older interferon-based therapies, DAA treatment is safe and effective in patients with ESRD. Furthermore, a recent large prospective cohort study (without reported renal function data) of 9895 patients who attained cure with DAA showed decreased HCV-associated all-cause, hepatocellular carcinoma, and hepatic mortality. After 33.4 months of treatment, there was lower all-cause mortality when adjusted for multiple variables (hazard ratio = 0.48, confidence interval = 0.33–0.70) and lower risk for the development of hepatocellular carcinoma. When HCV-associated cryoglobulinemic glomerulonephritis is moderate to severe, the addition of directed
immunosuppressive therapy to DAA treatment may avert ESRD among CKD and kidney transplant recipients. Early data are encouraging that DAA cure will result in reductions of mortality, mixed cryoglobulinemia, non-Hodgkin’s B-cell lymphoma, and glomerulonephritis similar to those observed with older interferon-based therapies \(^5^3,^5^4\) particularly if treatment is started early in the disease process. \(^5^5—^5^8\) Such survival benefit is likely applicable to the HD population. \(^5^9,^6^0\) Most patients tolerate DAA extremely well. \(^6^1\) Patients with advanced liver failure, concomitant HBV infection, or decompensated cirrhosis should be monitored for rare risk of liver failure. \(^6^2,^6^3\)

### Patients Awaiting Kidney Transplants

Transplantation in HCV-infected ESRD patients is the preferred management, independent of donor HCV status. \(^6^4\) Studies demonstrate improved survival of HCV-infected patients with transplantation over dialysis. \(^6^5,^6^6\) A significant challenge to performing outcomes research in wait-listed HCV-positive dialysis patients is that neither of the national registry data systems, the Organ Procurement and Transplantation Network or the US Renal Data System, includes HCV serostatus for wait-listed patients despite the need for a more complex pre-transplantation medical assessment. That notwithstanding, a 2019 retrospective cohort study of adult long-term dialysis patients treated by a U.S. national dialysis provider between 2004 and 2014 found that of the 7.2% of patients who were HCV positive, the rate of death was higher, and the rate of entry onto the wait-list was lower, than for those who were seronegative. Once wait-listed, the rate to kidney transplantation was similar between seropositive and seronegative dialysis patients. \(^6^5\) Wait-list time for transplantation exceeds 5 years in many parts of the country.

The optimal approach to HCV treatment in kidney transplant candidates on dialysis is in constant flux. HCV-positive transplant recipients have lower all-cause and renal allograft survival than HCV-negative recipients, irrespective of donor HCV status. When HCV-infected organs were used exclusively in HCV-infected recipients, wait-list time was reduced. \(^6^7\) A retrospective study of 6830 HCV-positive recipients between 1995 and 2009 reported at least 1 year wait-time saved, 29% increased mortality, and 18% higher allograft loss compared to HCV-negative donor recipients. \(^6^8\) The patient and graft survival among HCV-positive recipients of HCV-positive donor kidneys is slightly lower than those of HCV-negative kidneys. Computerized mathematical risk and decision analysis models evaluated optimal treatment timing in the peri-transplantation period. \(^6^9\) A recent Monte Carlo micro-simulation of 100,000 HCV-positive transplant candidates examined the cost-effectiveness of pre- and post-transplantation treatment by liver histology (METAVIR fibrosis stages F0—F4) and local wait-list time over a lifetime horizon and showed that pre-kidney transplantation treatment yielded higher quality-adjusted life-years and that optimal treatment timing depended on fibrosis stage and access to HCV-positive donor kidneys, generally favoring delaying treatment when a near-term allograft was available. \(^7^0\)

### Table 1. Challenges interpreting hepatitis C virus (HCV) test results in hemodialysis (HD) patients

| Testing modality                        | Result                                                                 | Interpretation                                                                 |
|-----------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| ALT                                     | Only 12%—31% of HD patients with HCV-RNA and 4%—67% with HCV antibody have elevated serum ALT levels. | • Elevations are insensitive indicators of incidental HCV infection.  
• Baseline ALT levels are significantly lower among HD patients than in the general population.  
• ALT levels correlate weakly with liver histology changes in the general population and even less in the HD population.  
• Because ALT levels are poor markers of subclinical liver inflammation, depressed in HD patients at baseline, and may be affected by variable serum HCV-RNA levels, the sensitivity and positive predictive value for acute infection in patients receiving HD is low. |
| Anti-HCV positive, HCV-RNA negative     | This pattern usually reflects a previous infection that has been cleared, either by natural resolution or by HCV therapy. | • Individuals with this pattern remain at risk for HCV re-infection.  
• Detection of new infections or recurrent viremia may be delayed by biannual screening guidelines, and even further delayed by insurance provider denial of necessity for more frequent than annual testing. |
| Anti-HCV negative, HCV-RNA positive     | Causes of a nonreactive anti-HCV in the presence of HCV-RNA include:  
(i) an acute infection in the “window” period that has not had time to mount a detectable immune response; and  
(ii) immunosuppressed states, including those in patients requiring dialysis, which have depressed anti-HCV responses. | Findings that anti-HCV is unreactive in a small percentage of HCV-RNA—positive hemodialysis patients support that HCV-RNA testing provides more reliable screening in the HD population. |
Kidney transplantation wait-times are more than 3 to 5 years in many parts of the country, and 40% of HCV-infected kidneys are discarded.71-72 DAAs are safe and effective pre- and posttransplantation7 and have made it possible to use HCV-viremic kidneys in HCV-negative recipients. The use of HCV-positive renal allografts has varied among transplant centers. Half of the transplant centers in 2017 used HCV-infected kidneys, and fewer than half of HCV-positive recipients received HCV-infected kidneys.68,74 The THINKER, EXPANDER, and NECKER trials demonstrated in single centers that HCV-viremic kidneys could potentially be safely transplanted into uninfected recipients, and sustained viral response obtained with early treatment initiation.75-77 The Multicenter Study to Transplant Hepatitis C–infected Kidneys (MYTHIC) prospectively evaluated transplantation of 30 HCV-viremic kidneys into HCV-uninfected recipients at 7 U.S. transplant centers between May and October 2019, followed by early initiation of 8 weeks of DAA therapy, demonstrated safety and efficacy at 6 months.78 The growing momentum for HCV-viremic kidney use in HCV-negative recipients increased the competition for HCV-infected organs, diminished the wait-time advantage, and, with the lower DAA cost, has called into question prior recommendations to defer treatment and instead to treat pre–kidney transplantation and again post–kidney transplantation if an HCV-infected allograft becomes available. The HCV therapy timing for kidney transplant candidates should include DAA availability and cost and should be individualized by patient preference, available donor options (living, HCV-infected), local waiting times, recipient comorbidities, and degree of liver disease.

Limitations of DAA Treatment
The high cost and lack of DAA availability in some regions of the world limit treatment scale-up strategies necessary to achieve control in the HD population.79 Guidelines do not yet recommend treatment-as-prevention strategies to control HCV transmission in HD facilities. Nevertheless, antiviral resistance and reinfection are likely to become more prevalent with more extensive DAA use for treatment-as-cure and prevention among high-risk patients unable to take medications reliably.78

Micro-elimination of HCV in Dialysis Centers
As long as HCV-infected patients are being dialyzed in the same facility as uninfected patients, the risk of nosocomial transmission will remain (Figure 4). To achieve micro-elimination of HCV in HD clinics, we need to cure more patients than are contracting the disease in this setting. We need to find and to cure the HCV infections early, before the virus has a chance to spread to other patients.

Figure 2 outlines an algorithm for HCV micro-elimination for the HD population. The foundation for micro-elimination is universal DAA treatment of all infected patients, combined with frequent, regularly scheduled HCV-RNA viremia testing and ≤1 month before HD at a new facility. Quarterly testing during the early micro-elimination phase of HCV control has the advantage of early diagnosis and longitudinal tracking. Operational management strategies, likewise, are crucial for HCV control. Bedside and electronic health record technology, required in many HD facilities by governmental regulation, assist management process flow and can be used for optimization of safety in this complex, continuous data stream–driven environment. System programs aid bedside care with programmed reminders, alerts, and internal and external communication capabilities. Broadening engineered systems’ capability to securely store and transmit data to healthcare providers, HD facilities, and

Figure 3. Optimized hepatitis C testing algorithm for hepatitis C virus (HCV) micro-elimination in hemodialysis (HD) patients. DAA, direct-acting antiviral agent.
How to prevent HCV transmission in HD facilities

**Improve care at the bedside**
- Adhere to standard Infection control procedures and hygienic precautions
- Reduce clinical care complexity and urgency

**Avoid HCV treatment delay**
- Make DAA universally available
- Treat HCV-infected HD patients and transplant candidates immediately after diagnosis

**Prevent facilitation of HCV transmission**
- Use technology to optimize process and decrease the manual follow-up of testing, reporting, and treatment referrals
- Clean contaminated dialysis machines, surfaces, equipment, staff

**Eliminate diagnostic escape**
- Use high sensitivity and specificity biomarkers
- Test regularly
- Test frequently during early micro-elimination phase

Figure 4. Tips for achieving micro-elimination of hepatitis C virus (HCV) at hemodialysis (HD) facilities. CDC, Centers for Disease Control and Prevention.

Public health surveillance services would facilitate the process and create a mechanism for HCV-RNA data tracking, enabling assessment of longitudinal outcomes.80–82

The size of a HD facility’s HCV-infected reservoir affects the risk for inadvertent hand-borne transmission. High HD facility prevalence is a strong risk factor for seroconversion,9 and studies demonstrate clustering of seroconversions when infected and susceptible patients are dialedyzed proximally.3,34–38 Moderate-to-high HCV-prevalent facilities experience above-average annual HCV incidence and are expected to benefit from optimal prevention strategies. Physical segregation of viremic and susceptible patients with their equipment and staff until the patient has been treated and cure obtained optimally prevents HCV transmission. Sensitive, specific, frequent testing and patient segregation successfully have controlled HD facility HBV transmission. Even before universal HBV vaccine availability, HBV incidence and prevalence among the HD population declined dramatically (Figure 1).4–6

Alternatively, a communal HCV micro-elimination strategy is expected to provide adequate management for facilities, particularly those with lower HCV prevalence, that simultaneously implement treatment-for-cure strategies. Separation of HCV-infected and susceptible patients by physical distance and dialysis shift time in a communal unit that dialyzes HCV-infected and susceptible patients concurrently is expected to provide modest protection of nosocomial HCV transmission. This is supported by a recent analysis by the Dialysis Outcomes and Practice Patterns Study (DOPPS) that found, albeit not associated with significantly lower seroconversions, that the use of isolation machines without isolation of patient or staff showed a trend toward lower rates of HCV conversion.9 Use of DAA treatment-for-prevention can be considered on dialysis days for patients dialyzing concurrently with viremic patients.

Each HD alternative has advantages and disadvantages. Physical segregation in isolated HD units provided effective and efficient transient management of COVID-19—infected patients during the 2020 pandemic. A similar control strategy for higher HCV-prevalent facilities can be considered. Segregated HD, transiently provided until a patient obtains cure, is associated with higher HD and organizational management costs. Advantages include prevention of nosocomial transmission and its associated long-term medical costs,83,84 avoidance of extensive and widespread treatment-as-prevention DAA use, lower drug costs, and decreased risk for development of DAA resistance and drug side effects. Although the outcome of segregated HD on HCV micro-elimination efforts is unknown, recent initiatives and COVID-19 infection management have highlighted an isolation approach’s feasibility.85,86 One survey showed the lowest HCV infection incidence among HD units that used isolated rooms to treat HCV-infected patients.87 A 2016 Cochrane organization systematic review reported the absence of quality randomized controlled trials, quasi—randomized controlled trials, and cluster randomized controlled trials, and concluded that the question had not been adequately studied.86 That notwithstanding, isolated HD until treatment-for-cure has been obtained provides the safest approach for transmission prevention and is particularly advantageous for higher HCV-prevalent HD facilities. Universal treatment of HCV-infected HD patients with DAA, balanced with immediate renal allograft availability, and regular HCV-RNA testing are recommended.88

Patients benefit from treatment, and physicians have a duty to avoid the harm of nosocomial infection. The costs of DAA treatment and chronic HCV infection are
high. For that reason, cost-effective rationing strategies are being developed. In the United States, the medical costs of chronic HCV infection nearly doubled between 1997 and 2017\textsuperscript{89} and are proportionally higher among the highly-affected HD subpopulation. Patients with ESRD comprise 1\% of the U.S. Medicare population but require 7\% of the budget.\textsuperscript{89,90} Hepatitis C–infected HD patients’ extensive hepatic and extra-hepatic morbidities and 26\% higher mortality\textsuperscript{91} have additional long-term financial consequences.\textsuperscript{92–94} Cost-effectiveness analyses show that early diagnosis and treatment increases quality-adjusted life-years\textsuperscript{46,70,95} and reduces cost.\textsuperscript{93} Accordingly, micro-elimination of HCV from the HD population, which entails prevention of transmission and early diagnosis and treatment, is uniquely positioned for potential long-term cost-effectiveness.

**FUTURE DIRECTIONS**

The opportunity is at hand to improve HD patients’ health with a focus on modifiable determinants of HCV transmission. The current guidelines and system do not provide a path toward HCV micro-elimination or a HD environment safe from significant HCV transmission risk. Hepatitis C virus seroconversion continues within HD facilities. The World Health Organization goal to micro-eliminate HCV from the HD population by 2030 is not on target to be met. Inadvertent infection control breaches are inevitable, and a high HCV prevalence persists in the HD population. Hepatitis C virus guidelines can be constructed for early and accurate detection and proactive prevention for HCV transmission in HD facilities, and for universal transmission of HCV-infected HD patients with effective medications available for treatment-as-cure of the virus and treatment-as-prevention. The current HCV transmission prevention guidelines require reconsideration. The Institute of Medicine’s “To Err Is Human” report raised awareness that well-designed systems prevent errors. We need to take the next steps toward a hemodialysis process designed to “prevent errors by making it hard for good people to do the wrong thing.”\textsuperscript{96}

**DISCLOSURE**

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**REFERENCES**

1. World Health Organization. Eliminate hepatitis [news release]. 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed May 6, 2021.

2. Lazarus JV, Safreed-Harm on K, Thurzs MR, et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. *Semin Liver Dis*. 2018;38:181–192.

3. Jadoul M, Cornu C, van Ypersele de Strihou C. Incidence and risk factors for hepatitis C seroconversion in hemodialysis: a prospective study. The UCL Collaborative Group. *Kidney Int*. 1993;44:1322–1326.

4. Lanini S, Puro V, Lauria FN, et al. Patient to patient transmission of hepatitis B virus: a systematic review of reports on outbreaks between 1992 and 2007. *BMC Med*. 2009;7:15.

5. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599.

6. Holmberg SD, Suryaprasad A, Ward JW. Updated CDC recommendations for the management of hepatitis B virus–infected health-care providers and students. *Morbid Mortal Wkly Rep*. 2012;61:1–12.

7. Campo DS, Xia GL, Dimitrova Z, et al. Accurate genetic detection of hepatitis C virus transmissions in outbreak settings. *J Infect Dis*. 2016;213:957–965.

8. Centers for Disease Control and Prevention. Healthcare-associated hepatitis B and C outbreaks (≥2 cases) reported to the Centers for Disease Control and Prevention (CDC) 2008. Atlanta, GA: Centers for Disease Control and Prevention; 2020.

9. Jadoul M, Bieber BA, Martin P, et al. Prevalence, incidence, and risk factors for hepatitis C virus infection in hemodialysis patients. *Kidney Int*. 2019;95:939–947.

10. Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013;57:1333–1342.

11. Carvalho-Filho RJ, Feldner AC, Silva AE, et al. Management of hepatitis C in patients with chronic kidney disease. *World J Gastroenterol*. 2015;21:408–422.

12. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144:705–714.

13. Alter MJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. *JAMA*. 1990;264:2231–2235.

14. Cottrell EB, Chou R, Wasson N, et al. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;158:109–113.

15. Hagan H, Jordan AE, Neurer J, et al. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men. *AIDS (London, England)*. 2015;29:2335–2345.

16. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis*. 2018;66:1360–1365.

17. Shire NJ, Sherman KE. Epidemiology of hepatitis C virus: a battle on new frontiers. *Gastroenterol Clin N Am*. 2015;44:699–716.
18. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int. 1997;51:981-999.
19. Montella M, Crispo A, Grimaldi M, et al. An assessment of hepatitis C virus infection among health-care workers of the National Cancer Institute of Naples, Southern Italy. Eur J Public Health. 2005;15:467-469.
20. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep. 2001;50:1-43.
21. Egro FM, Nwaiwu CA, Smith S, et al. Seroconversion rates among health care workers exposed to hepatitis C virus-contaminated body fluids: the University of Pittsburgh 13-year experience. Am J Infect Control. 2017;45:1001-1005.
22. King KC, Strony R. Needlestick. Treasure Island, FL: StatPearls Publishing; 2020.
23. Tavoschi L, Mason L, Petriti U, et al. Hepatitis B and C among healthcare workers and patient groups at increased risk of iatrogenic transmission in the European Union/European Economic Area. J Hosp Infect. 2019;102:359-368.
24. Yazdanpanah Y, De Carli G, Migueres B, et al. Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: a European case-control study. Clin Infect Dis. 2005;41:1423-1430.
25. Hatzakis A, Wait S, Bruix J, et al. The state of hepatitis B and C. J Viral Hepatitis. 2011;18(suppl 1):1-16.
26. Sulkowski MS, Ray SC, Thomas DL. Needlestick transmission of hepatitis C. JAMA. 2002;287:2406-2413.
27. Fissell RB, Bragg-Gresham JL, Woods JD, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int. 2004;65:2335-2342.
28. Kumagai J, Komiyi Y, Tanaka J, et al. Hepatitis C virus infection in 2,744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. J Med Virol. 2005;76:498-502.
29. Finelli L, Miller JT, Tokars JI, et al. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial. 2005;18:52-61.
30. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75:A6.
31. Halfon P, Roubicek C, Gerolami V, et al. Use of phylogenetic analysis of hepatitis C virus (HCV) hypervariable region 1 sequences to trace an outbreak of HCV in an autodialysis unit. J Clin Microbiol. 2002;40:1541–1545.
32. Fabrizi F, Messa P. Transmission of hepatitis C virus in dialysis units: a systematic review of reports on outbreaks. Int J Artif Organs. 2015;38:471–480.
33. Centers for Disease Control and Prevention. CDC urging dialysis providers and facilities to assess and improve infection control practices to stop hepatitis C virus transmission in patients undergoing hemodialysis. Am J Transpl. 2016;16:1633–1634.
34. Nguyen DB, Gutowski J, Ghiselli M, et al. A large outbreak of hepatitis C virus infections in a hemodialysis clinic. Infect Control Hosp Epidemiol. 2016;37:125–133.
35. Rao AK, Luckman E, Wise ME, et al. Outbreak of hepatitis C virus infections at an outpatient hemodialysis facility: the importance of infection control competencies. Nephrol Nurs J. 2013;40(101-110):164. quiz 111.
36. Savel A, Simon F, I泽zet J, et al. A large nosocomial outbreak of hepatitis C virus infections at a hemodialysis center. Infect Control Hosp Epidemiol. 2005;26:752–760.
37. I泽zet J, Sandres-Sauné K, Kamar N, et al. Incidence of HCV infection in French hemodialysis units: a prospective study. J Med Virol. 2005;77:70–76.
38. Thompson ND, Novak RT, Datta D, et al. Hepatitis C virus transmission in hemodialysis units: importance of infection control practices and aseptic technique. Infect Control Hosp Epidemiol. 2009;30:900–903.
39. O’Shaughnessy MM, O’Regan JA, Murray FE, et al. Re-infection following sustained virological response with a different hepatitis C virus genotype: implications for infection control policy. Clin Kidney J. 2012;5:250–253.
40. Arrais TC, Van Dooren S, Vandamme AM, et al. Change in hepatitis C virus genotype in hemodialysis patients after end-of-treatment response to interferon monotherapy–relapse or re-infection? J Med Virol. 2008;80:80–86.
41. Hepatitis C virus transmission at an Outpatient Unit–New York, 2001–2008. MMWR Morb Mortal Wkly Rep. 2009;58: 189–194.
42. Nguyen DB, Bixler D, Patel PR. Transmission of hepatitis C virus in the dialysis setting and strategies for its prevention. Semin Dial. 2019;32:127–134.
43. Girou E, Chevaliez S, Chailine D, et al. Determinant roles of environmental contamination and noncompliance with standard precautions in the risk of hepatitis C virus transmission in a hemodialysis unit. Clin Infect Dis. 2008;47:627–633.
44. Shimokura G, Chai F, Weber DJ, et al. Patient-care practices associated with an increased prevalence of hepatitis C virus infection among chronic hemodialysis patients. Infect Control Hosp Epidemiol. 2011;32:415–424.
45. Krause G, Trepka MJ, Whisenhunt RS, et al. Nosocomial transmission of hepatitis C virus associated with the use of multidose saline vials. Infect Control Hosp Epidemiol. 2003;24:122–127.
46. Fox DS, McComb JS. Optimizing HCV treatment–moving beyond the cost conundrum. J Hepatol. 2016;65:222–225.
47. Bergman S, Accortt N, Turner A, et al. Hepatitis C infection is acquired pre-ESRD. Am J Kidney Dis. 2005;45:684–689.
48. Konerman MA, Lok AS. Diagnostic challenges of hepatitis C. JAMA. 2014;311:2536–2537.
49. Ghany MG, Marks KM, Morgan TR, et al. Hepatitis C guidance later in 150 prospectively tested persons who inject drugs. PLoS One. 2014;9, e97022.
50. Spengler U. Direct antiviral agents (DAAs)–a new age in the treatment of hepatitis C virus infection. Pharmacol Ther. 2018;183:118–126.
51. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019;393:1453–1464.
86. Bravo Zuñiga JI, Loza Munárriz C, López-Alcalde J. Isolation as a strategy for controlling the transmission of hepatitis C virus (HCV) infection in haemodialysis units. Cochrane Database Syst Rev. 2016:CD006420.

87. dos Santos JP, Loureiro A, Cendoroglo Neto M, et al. Impact of dialysis room and reuse strategies on the incidence of hepatitis C virus infection in haemodialysis units. Nephrol Dial Transplant. 1996;11:2017–2022.

88. Pagan J, Ladino M, Roth D. Treating hepatitis C virus in dialysis patients: how, when, and why? Semin Dial. 2019;32:152–158.

89. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73:A7–A8.

90. United States Renal Data System. 2018 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.

91. Fabrizi F, Dixit V, Messa P. Hepatitis C virus and mortality among patients on dialysis: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2019;43:244–254.

92. Jaime Caro J, Eddy DM, Kan H, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health J. 2014;17:174–182.

93. Vemer P, Corro Ramos I, van Voorn GA, et al. AdViSHE: A validation-assessment tool of health-economic models for decision makers and model users. PharmacoEconomics. 2016;34:349–361.

94. Levin HM, McEwan PJ. Cost-Effectiveness Analysis: Methods and Applications, vol. 4. Newbury Park, CA: Sage; 2000.

95. Maunoury F, Clément A, Nwankwo C, et al. Cost-effectiveness analysis of elbasvir-grazoprevir regimen for treating hepatitis C virus genotype 1 infection in stage 4-5 chronic kidney disease patients in France. PLoS One. 2018;13, e0194329.

96. Kohn LT, Corrigan JM, Donaldson MS, eds. to err is human. building a safer health system. Washington, DC: National Academies Press; 2000:600.