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Transmission of hepatitis C virus in the dialysis setting and strategies for its prevention

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Abstract

Hepatitis C virus (HCV) infection is more common among hemodialysis patients than the general population and transmission of HCV in dialysis clinics has been reported. In the context of the increased morbidity and mortality associated with HCV infection in the end stage renal disease population, it is important that dialysis clinics have processes in place for ensuring recommended infection control practices, including Standard Precautions, through regular audits and training of the staff. This review will summarize the epidemiology of HCV infection and risk factors for HCV transmission among hemodialysis patients. In addition, the proper protocols are required to investigate suspected cases of HCV transmission in dialysis facilities and recommendations for prevention of HCV transmission in will be reviewed.

1 | BACKGROUND

Hepatitis C virus (HCV), a small RNA virus from the *Hepacivirus* genus in the *Flaviviridae* family, encodes its own error-prone RNA-dependent RNA polymerase,[1] thereby enabling rapid mutation immediately after infection[2] and, in most cases, successful evasion of host immune response.[3] Because acute hepatitis C is so often asymptomatic,[4] the early stages of disease are not well understood. It has been estimated that 15%-40% of acutely infected persons clear the infection, while the remainder have persistent infection and hepatic inflammation (ie, chronic hepatitis C [CHC]). Approximately 10%-20% of persons with CHC progress to cirrhosis over 20–30 years; of persons with cirrhosis, 1%-5% develop hepatocellular carcinoma and 3%-6% progress to hepatic decompensation per year. Mortality for CHC patients with hepatic decompensation is 15%-20% in the first year.[5]

Shortly after HCV was first identified as a cause of transfusion- associated hepatitis,[6] two urban hemodialysis clinics in the United States reported a 12% seroprevalence for HCV in 1990.[7] The Dialysis Outcomes and Practice Patterns Study (DOPPS) identified a mean hemodialysis facility prevalence of HCV infection of 13.5% (range2.6%-22.9%) on data collected randomly from selected facilities in Europe, Japan, and the United States during 1998–2001[8] and a 9.5% seroprevalence among hemodialysis patients in 12 nations from 1996–2011.[9]

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DISCLOSURES

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DOPPS data have also been used to compare mortality, hospitalization, and quality of life among HCV-positive and HCV-negative patients on hemodialysis. Compared to HCV-negative patients, HCV-positive patients enrolled in DOPPS between 1996 and 2015 had higher risk (case-mix adjusted hazard ratios [95% confidence interval]) of all-cause (1.12 [1.05–1.20]) and liver-related (5.90 [3.67–9.50]) mortality and all-cause (1.09 [1.04–1.13]) and liver-related (4.40[3.14–6.15]) hospitalization.[10] Quality of life scores were also significantly worse for HCV-positive hemodialysis patients compared to those who were HCV-negative (adjusted odds ratios [95% confidence intervals]) for depression (1.27 [1.16–1.40]), pruritus (1.27[1.18–1.36]), and anorexia (1.22 [1.12–1.32]).[10]

HCV not only affects the liver; it is a systemic disease with multiple extrahepatic effects of which the kidneys are a major target organ. In a large meta-analysis, it was estimated that 30% of CHC patients have mixed cryoglobulinemia with 4.9% having symptomatic disease, 10.1% have chronic kidney disease (CKD) including end-stage renal disease (ESRD), 15% have diabetes and 25% have depression.[11] All of these outcomes are significantly increased compared to HCV-negative controls. Mixed cryoglobulinemia is a known cause of membranoproliferative glomerulonephritis[12,13] and HCV-infected patients are at increased risk for proteinuria[14] and progression to ESRD.[15] The risk of progression to ESRD was twice as high among persons with CHC compared to persons without CHC in a community cohort from Taiwan (multivariable Hazard Ratio 2.33, 95% CI 1.40–3.89)[16] and a cohort of US veterans (adjusted Hazard Ratio 1.98, 95% CI 1.81–2.16).[17] In a cohort with CKD from Taiwan, patients with pre-existing CKD were 32% more likely to progress to ESRD if they were anti-HCV seropositive.[18] This disease pathway undoubtedly contributes to the higher HCV seroprevalence among hemodialysis patients.

It has been estimated that approximately 3.9–4.6 million people in the United States are infected with HCV.[19,20] Based on death certificates analysis, mortality from HCV has steadily increased in the United States—from 11 051 deaths in 2003 to 19 368 deaths in 2013—surpassing the declining mortality from all other nationally notifiable infectious conditions combined.[21] Death certificates have been shown to substantially underestimate actual deaths where hepatitis C is an underlying or contributing cause. In a well-defined cohort of patients with CHC who had liver disease recorded as an underlying or contributing cause of death, only 30% had HCV coded on the death certificate.[22] Similarly, while incidence and mortality for most types of cancers decreased or stabilized in the United States between 2008 and 2012, incidence from liver and intrahepatic bile duct cancer increased on average 2.2% per year during that time-frame. Deaths from liver cancer and HCV were highest in persons born between 1945 and 1965.[23]

HCV transmission occurs primarily through contact with blood products. Currently, the most significant risk factor for transmission in the community is injection drug use, the primary driver of the increase in hepatitis C infection in the United States since 2004.[24] Due to potential blood exposures in hemodialysis settings, hemodialysis patients are at risk for acquiring HCV from another patient in association with their dialysis treatment. Unfortunately, HCV infections and transmissions continue to occur in outpatient dialysis units.[25,26] Healthcare-associated HCV infections have also been reported in other healthcare settings and these are typically due to breaches in injection safety.[27]

2 | LABORATORY TESTING

With third-generation testing, antibodies to HCV (anti-HCV) can be detected as early as 10 weeks after exposure.[28] Initial screening at the initiation of dialysis with anti-HCV antibody testing and alanine aminotransferase (ALT) is recommended for all hemodialysis patients. For patients susceptible to hepatitis C, monitoring of ALT is recommended monthly, and repeat anti-HCV testing is recommended every 6 months.[29] A positive anti-HCV antibody test may indicate either current infection or resolved past infection. With anti-HCV testing, particularly in low-risk populations, there is a potential for false-positive results.[30] The Center for Disease Control and Prevention (CDC) updated guidelines for hepatitis C testing recommend that a positive anti-HCV antibody result should always be followed-up with testing for the presence of HCV RNA with an FDA-approved nucleic acid test (NAT) to determine if an individual is viremic with active HCV infection.[31] NATs can detect HCV RNA as early as 1 week after exposure and should be detectable in all infected cases by 2–3 weeks post-exposure. Currently available HCV NATs are highly sensitive, detecting as little as 5 IU/mL of HCV RNA, and highly specific (99%).[28] Effective treatment regimens are now available for HCV-infected hemodialysis patients identified as HCV RNA positive.[32] Decisions on the appropriate timing and choice of antiviral therapy must be individualized to each patient depending on comorbidities and transplant candidacy.

HCV is classified into seven genotypes numbered 1 through 7, differing from one another by approximately 30% of the full genome nucleotide sequence. HCV is further classified into 67 subtypes denoted by lower-case letters and differing by at least 15% of the full genome nucleotide sequence.[1] Genotypes 1, 2, and 3 are most common in the United States, with genotypes 4, 5, and 6 occurring at a rate of 1%-2% or less.[33,34] Worldwide, genotypes 1 and 3 are the most common at 44% and 25%, respectively, with considerable variation in prevalence and genotype populations among nations.[35] It has been recommended that genotype testing be used to guide the proper choice of direct acting antiviral agents for treatment of HCV, although newer pangenotypic agents may make genotype testing less important. Other necessary work-up is outlined in American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) guidelines.[36]

Molecular methods for the study of transmission linkages between patients exploit the genetic variation in the hypervariable region 1 (HVR1) of HCV.[37] Within an individual patient, HCV exists as a population of closely related but non-identical variants referred to as quasispecies. Quasispecies continually evolve within the host due to selective pressure from host immunity and viral RNA point mutations.[1] A novel technology, the Global Hepatitis Outbreak and Surveillance Technology (GHOST), developed at CDC, uses next generation sequencing of the HVR1 to compare genetically related HCV quasispecies between patient samples to evaluate their genetic relatedness. GHOST results help epidemiologists evaluate the likelihood of transmission linkages between patients and estimate the extent of possible transmission within a population.[38–40]

3 | EPIDEMIOLOGY OF HCV TRANSMISSION AMONG HD PATIENTS

The hemodialysis setting has unique features that facilitate transmission of HCV, such as high risk of blood contamination of surfaces, objects and devices, and a large number of patients treated simultaneously in a shared space. Newly-acquired HCV infections (ie, seroconversions) are not uncommon in HD facilities. DOPPS reported seroconversion rates between 1.1% and 3.6% per 100 patient-years in participating countries.[8] In the United States, data from national surveillance of dialysis-associated diseases in 2002 showed an incidence rate of 0.34%.[41] Data from 45 dialysis facilities across the United States from 1997 to 2004 showed an annual incidence rate of 0.96%.[42]

Although more recent data on incidence are not available, HCV outbreaks in HD facilities continue to be reported. Between 2008 and 2017, 21 outbreaks in US dialysis facilities, defined as two or more new HCV infections in the same clinic, with 102 outbreak-associated cases of HCV were reported to the CDC (Figure 1),[27] although there may be underreporting to CDC or local health departments.

For all outbreaks reported to CDC from 2008 to 2017, epidemiologic investigations were performed by local health departments with support from CDC. Investigations included interviews of dialysis facility staff, interviews of patients for HCV risk factors, review of patient charts, and review and observation of infection control practices at the facilities. A common finding from the investigations was that usually no single risk factor or single exposure was found to be associated with transmission of HCV. Newly infected patients were often found to have been treated in close proximity (both time and location) to a previously HCV infected patient in the clinic, either in an adjacent or nearby dialysis station during the same shift or sharing the same station during consecutive shifts.[43–48] In multiple investigations, transmission of HCV from a known CHC or previously HCV-infected patient in the same dialysis facility was confirmed by molecular testing showing closely related viruses.[43,44,46–48] For example, in one outbreak, a new HCV case was found to have been dialyzed in a station next to a previously-infected patient on the same shift and their viruses had high homology (99.66% of nucleotide identity). This finding, together with the absence of other HCV risk factors or common exposures outside of the dialysis setting, was strong evidence that the previously-infected patient was the source and dialysis-related healthcare transmission had occurred.[43]

Evidence from outbreaks suggests that transmission of HCV in dialysis facilities cannot be solely a function of machine contamination, but instead occurs through contamination of equipment, medications or other supplies, environmental surfaces, and/or healthcare worker hands as a result of poor infection control practices.[26,48,49] These observed transmission patterns demonstrate that use of dedicated machines or institution of isolation precautions for HCV-infected patients (without correction of underlying infection control breaches) would not effectively halt transmission.[50]

4 | FACTORS ASSOCIATED WITH HCV TRANSMISSION IN DIALYSIS FACILITIES

Multiple outbreak investigations which evaluated dialysis patient HCV risk factors and healthcare exposures, including dialysis treatment factors, identified dialysis facilities as the most likely setting where transmission occurred.[43–45,48] However, no single factor was identified as being associated with HCV transmission within a facility. In an epidemiologic study involving patients treated at 53 outpatient dialysis facilities in the United States, practices that were independently associated with facility HCV prevalence were failure to properly clean and disinfect priming receptacles between patients, handling blood specimens near medication preparation area and clean supplies, use of a mobile cart to deliver injection medications, and failure to clean and disinfect high-touch surfaces on dialysis machines between patients.[48] This study also found high patient-to-staff ratio and increased baseline facility HCV prevalence to be associated with HCV transmission. Outbreak investigations have reported similar infection control breaches, especially in cleaning and disinfection of equipment and environmental surfaces, adherence to hand hygiene and glove use, vascular access care, and medication preparation and administration.[43–45,47,51] Infection control breaches identified during investigation of HCV outbreaks from 2008 to 2017 are shown in Table 1. Cleaning and disinfection of equipment and environmental surfaces were the most common breaches identified; breaches in more than one infection control category were identified in 71% of outbreaks.

In three (14.3%) of the outbreaks, no specific infection control breaches were identified at the time of the investigations; however, these investigations were conducted several weeks or months after the outbreaks started and observation of practices in place at the time of transmission was not possible.

Other facility factors likely contribute to the failure of maintaining optimal infection control practices. Examples that have been determined to be significant include small or cluttered treatment areas that do not allow adequate space and separation between dialysis stations, quick turnovers between shifts and rushed treatment schedules that do not allow adequate time for cleaning and disinfection, high staff turnover, and staff lacking infection control training and supervision. All of these factors can contribute to non-adherence to proper infection control practices.[51]

In addition to infection control breaches and factors that can facilitate breaches, there are practices related to HCV screening and interpretation of results that can undermine early detection of potential HCV transmission in dialysis facilities. Many facilities screen less frequently than currently recommended by the CDC (every 6 months).[29] In addition, if HCV screening detects new HCV seroconversion, the results might not be shared with the patient, documented in patient medical record, or not acted upon by medical staff.[43,44,51] As a result, newly infected patients may not be referred for appropriate care in a timely manner and no actions were initiated to improve infection control practices and prevent further transmission. For example, a large outbreak in Pennsylvania with 18 acutely infected patients extending from 2008 to 2013, including a cluster of confirmed transmission among six patients during 2010–2012, is an example of these missed steps (patients were not

notified of the results and no action was taken after seroconversions were noted in the medical records).[43]

5 | RECOMMENDATIONS FOR PREVENTION OF HCV TRANSMISSION IN DIALYSIS FACILITIES

Infection control breaches are the major contributor to HCV transmission in dialysis facilities. HCV screening incorporated into a robust infection control program is the key to prevent transmission. CDC recommendations to prevent transmission of HCV have been available since 2001.[29] Details of HCV laboratory diagnostics are available elsewhere.[28] All dialysis patients should be screened for anti-HCV antibody upon admission to the facility. Any patient with a positive anti-HCV antibody result should be further tested for HCV RNA and referred for consideration of treatment if positive. Patients with negative anti-HCV antibody on admission should be screened every 6 months afterward for anti-HCV antibody and if positive, obtain reflex HCV RNA testing. For patients who had past HCV infection that has resolved spontaneously or with treatment (ie, achieved sustained viral response), facilities should consider routine screening using HCV RNA testing instead of anti-HCV. Patients with prior infection will remain anti-HCV antibody positive so that new infection could only be detected using HCV NAT testing. Any new HCV infections should be reported to local public health agencies and steps be taken to prevent further transmission of the virus (see below). Also, anti-HCV negative patients should have ALT monitored monthly and any unexplained increase in ALT should warrant HCV testing.[29]

To prevent transmission of HCV in dialysis facilities, in addition to screening, adherence to recommended infection control practices are needed. This includes the following recommendations:

1. Routinely evaluate infection control practices in each facility and ensure adherence to infection control standards through regular evaluation audits. The evaluation should be performed by staff with infection control knowledge and expertise. The evaluation should encompass all aspects of infection control practices, including: hand hygiene and glove use, injection medication preparation and administration, vascular access care, cleaning and disinfection. Audit tools are available and can be used to help assess infection control practices (https://www.cdc.gov/dialysis/prevention-tools/audit-tools.html). Facilities may also choose to report results to the National Healthcare Safety Network Dialysis Prevention Process Measures which can help track practice adherence over time (https://www.cdc.gov/nhsn/dialysis/process-measures/index.html).
2. Promptly address any gaps in infection control identified during routine audits. Feedback to staff can be offered at the time when gaps are found, during staff meetings or through training. Additional observations or audits may be warranted to ensure those gaps are mitigated.
3. Maintain a training program to ensure all dialysis staff are aware of current infection control guidelines and adhere to good infection control practices.

Infection control training should not only be offered when staff begin working at the facility, but should also be offered regularly and after infection control gaps are found.

4. Follow CDC recommendations for HCV screening of hemodialysis patients and management of patients who test positive and immediately report any case of new case of HCV infection to public health agencies. Any new HCV infections among hemodialysis patients should be investigated (see below).[26,29]

The above steps are not specific to preventing HCV transmission, but are part of a basic infection control program. In fact, each facility should establish an infection prevention program with essential components that include staffing, education and training, surveillance for infections/adverse events and monitoring of dialysis practices. A detailed description of such program is available.[52]

6 | RECOMMENDED PROCEDURES WHEN A NEW HCV INFECTION IS IDENTIFIED IN A DIALYSIS FACILITY

Any HCV seroconversion in a dialysis facility patient should be treated as a possible transmission at the facility and be investigated thoroughly. The algorithm in Figure 2 describes steps that should be taken when one or more newly acquired HCV infections are identified in a facility.

A new HCV infection may be identified through routine HCV screening. Less commonly, new HCV infections may be detected if patients develop signs or symptoms of acute hepatitis that prompt HCV testing. When a new HCV infection does occur, the facility should initiate the evaluation process by reviewing the patient's HCV testing results to confirm the seroconversion (ie, the patient had a previous negative anti-HCV test, and subsequently has a positive test). The seroconversion and need for reflex tests as well as the results of those tests should be explained to the patient. The facility should record the results in the medical record, notify the medical director to arrange the patient for further evaluation and referral to a hepatologist or other experienced provider for treatment.

We recommend that facilities report all new HCV infections and HCV seroconversions to the local or state health department.[29,53] Reporting to public health agencies helps facilitate HCV surveillance and facilitate support from public health experts in investigation of new infections.[26,54] The CMS End Stage Renal Disease Program Interpretive Guidance also requires facilities to report hepatitis sero-conversions and clusters of infections to the health department https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/downloads/SCletter09-01.pdf.

Patients with new HCV infection should be evaluated for traditional HCV risk factors (such as intravenous drug use) and other healthcare exposures (such as vascular access surgery, endoscopy) outside of the hemodialysis setting. A careful review of the patient's chart review should also be performed to understand the patient's history, previous HCV test results, and liver function test results in order to confirm seroconversion and identify risk

factors. Although transmission at the dialysis facility is a strong possibility, HCV acquisition from sources outside of the facility has been reported and should be considered.[55]

Anytime healthcare-related transmission of HCV is suspected, a thorough investigation is warranted; involvement of public health agencies can help facilitate these investigations and is strongly encouraged. The investigation may include three components:

1. Identify all HCV infected patients in the facility and look for potential links between the new HCV infections and CHC patients. The facility should review HCV testing results of all patients in the facility and have a list of all HCV-infected patients. This helps identify any other new HCV cases and previously-infected patients. The facility can then compare station/chair assignment, staff assignments of new HCV cases with known previously-infected patients to see if they fit any patterns described above: did the new HCV cases share the same station/ chair with previously-infected patients on consecutive shifts? Did they stay close to each other on the same shift? Did they share common staff? These factors are evaluated for the exposure period of new HCV cases.

   The possible HCV exposure window maybe estimated as 2 weeks prior to the last negative anti-HCV result through two weeks before the first positive anti-HCV result. Elevations in liver function tests, if noted and not clearly ascribed to other clinical comorbidities, may help to define the most likely time of exposure within that window as the 3 months to 2 weeks prior to their first elevation. Close proximity between a new HCV case and a previously-infected patient suggests a potential epidemiologic link. In some circumstances, more infection control observations and audits may be warranted for areas of the facility (stations/ chairs/pods) where epidemiologic links are identified.

2. Review and audit of infection control practices at the facility is indicated, including hand hygiene and glove use, injection medication preparation and administration, vascular access care, and cleaning and disinfection. This should be done regardless of the results of the investigation. The areas of concern as listed above should be targeted. CDC has audit tools available for this purpose. Any breaches identified should be corrected through on-site feedback and training and other strategies to improve infection control practices. Increased frequency of audits may be warranted during and after the outbreak to ensure all gaps in process have been thoroughly addressed and corrected.

3. Facilities should consider obtaining blood specimens (following special instructions) from the newly diagnosed HCV cases and previously-infected patients for molecular testing. Sequencing techniques can be used to evaluate relatedness between viruses from patients.[56] A close relatedness between new HCV cases and known HCV patients strengthens the evidence of HCV transmission at the facility. Examples of the use of HCV molecular testing in HCV outbreaks are available.[43,44,57] Potential outbreaks should be identified through epidemiologic investigation which can be enhanced with the use of molecular laboratory methodologies.

Given the nature of HCV infection with a long incubation period and a large proportion of infected individuals with asymptomatic infection, facilities with an HCV outbreak should increase the frequency of HCV screening of all HCV negative patients to identify any potential new HCV cases. Screening should be performed monthly or every 3 months until 6 months after the last new HCV case.[26,29] The facility should consider consulting with local or state health departments on the preferred approach. Since more frequent HCV testing is not routine practice, the facility should notify patients of the reason for increased testing. This allows for increased awareness and transparency for patients under evaluation. In case of multiple seroconversions or even a single documented transmission in the facility, patient notification is strongly recommended. A toolkit for patient notification is available on the CDC website https://www.cdc.gov/injectionsafety/pntoolkit/index.html.

7 | SUMMARY AND FUTURE DIRECTIONS

Preventing transmission of HCV among chronic hemodialysis patients requires consistent adherence to infection control and HCV screening recommendations in a patient care environment that stresses the importance of these protocols and guidelines. Together with new antiviral therapy for HCV, elimination of HCV in dialysis units may be possible, thereby reducing the considerable morbidity and mortality associated with this disease.[49] Any new HCV infection in a dialysis facility patient should be treated as a possible healthcare-associated HCV transmission at the facility and trigger a thorough investigation. The investigation should include an epidemiologic review of HCV risk factors, review of potential transmission opportunities and audits of infection control practices to identify and address lapses. All new HCV infections should be reported to the appropriate local and state public health department. Future studies may help to elucidate the impact of HCV treatment programs, role of separate patient rooms or other innovative prevention strategies on HCV transmission in dialysis centers. As new strategies become available, consistent adherence to recommended infection control practices will remain the key to prevention transmission of HCV and other infections among hemodialysis patients.

8 | DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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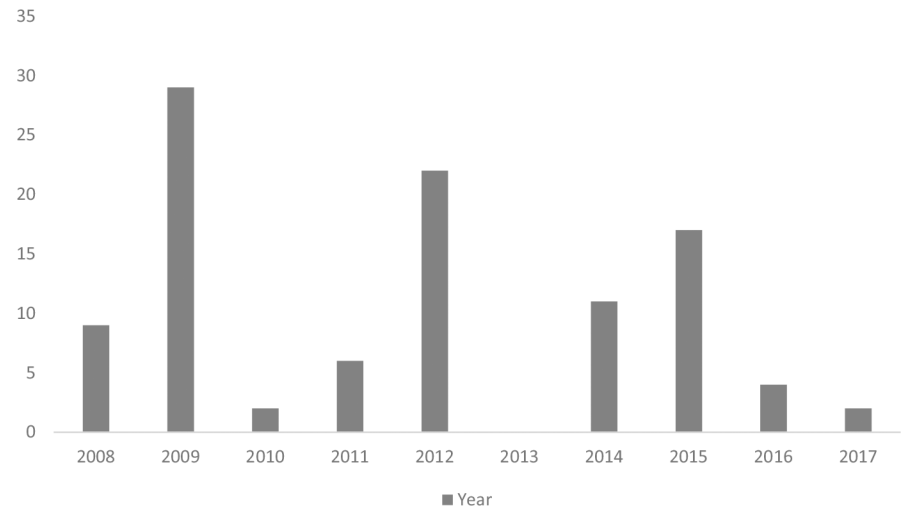

FIGURE 1.

Number of incident hepatitis C virus (HCV) infections from outbreaks in the United States dialysis facilities reported to the Centers for Disease Control and Prevention, 2008–2017

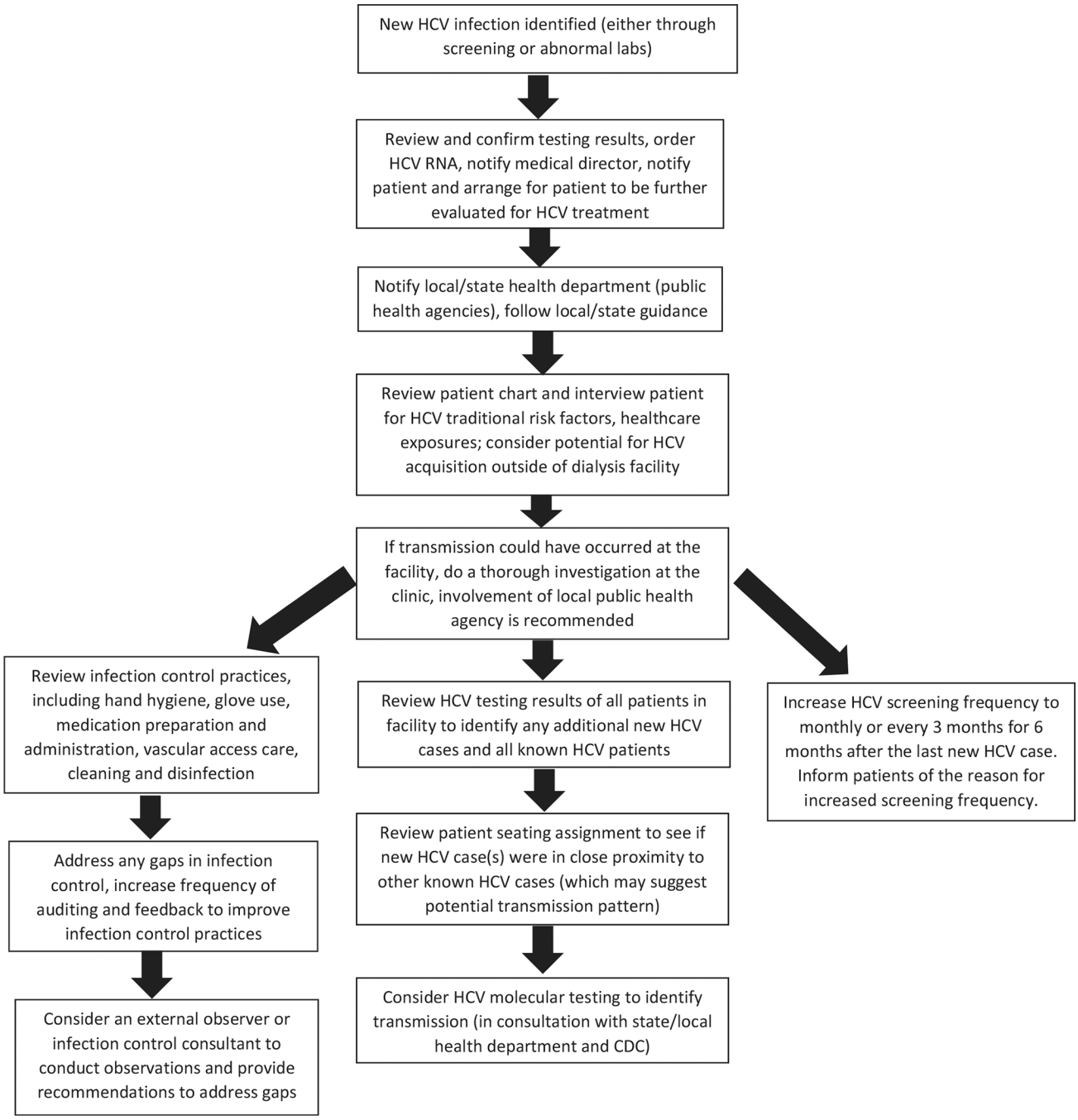

FIGURE 2.

Algorithm to investigate an outbreak of hepatitis C virus infection when one or more new hepatitis C virus (HCV) infections are identified in a dialysis facility

TABLE 1

Infection control breaches identified in hepatitis C outbreaks reported to the Centers for Disease Control and Prevention, 2008–2017 (N = 21)

Category of infection control practice	Number of outbreaks with breaches identified (%)	Examples of breaches observed
Multiple infection control breaches	15 (71.4)	Combinations of examples below
Environmental cleaning and disinfection	14 (66.7)	Cleaning and disinfection not done in a standard manner and thoroughness and vigorousness varied, cleaning when patients were still in chairs, a limited number of wipes were used, surfaces not kept visibly wet for the appropriate contacts time, moving the wipe from dirty areas back to cleaned areas, blood spills, and blood stains poorly cleaned[43–45,47,51]
Hand hygiene and glove use	8 (38.0)	Hand hygiene not performed and/or gloves not changed after contact with one patient and prior to contacting another patient, or between touching patients and environmental surfaces, inadequate duration and thoroughness of hand hygiene[43,44,47,51]
Injection medication preparation and administration	7 (33.3)	Using a mobile cart for medications and supplies in treatment area, medication preparation and storage performed in contaminated areas, poor disinfection of catheter hubs and vial tops, used sharps discarded in an empty cardboard box rather than a puncture-proof sharps container, poor labeling of multi-dose vials, and use of single-dose vials (such as erythropoietin) for multiple patients[43–45]
Separation of dirty and clean areas	7 (33.3)	Storing clean supplies on potentially contaminated surfaces, having lab work done close to medication preparation areas, use of a mobile cart for medications and supplies in treatment area, failure to separate clean and dirty sinks[44,45,47]
Vascular access care practices	5 (23.8)	Staff touching multiple objects prior to direct contact of the patient or patient's catheter during steps of the vascular access procedure without glove change and hand hygiene in between, and with incomplete antisepsis/disinfection of access sites and catheter hubs[43]
No infection control breaches identified at the time of investigation	3 (14.3)	