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Outbreak of Hepatitis B and Hepatitis C Virus Infections Associated with a Cardiology Clinic, West Virginia, 2012–2014

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Abstract

Objective—To stop transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in association with myocardial perfusion imaging (MPI) at a cardiology clinic.

Design—Outbreak investigation and quasispecies analysis of HCV hypervariable region 1 genome.

Setting—Outpatient cardiology clinic.

Patients—Patients undergoing MPI.

Methods—Case patients met definitions for HBV or HCV infection. Cases were identified through surveillance registry crossmatch against clinic records and serological screening. Observations of clinic practices were performed.

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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.

Conflicts of interest The authors report no conflicts of interest

Results—During 2012–2014, seven cases of hepatitis C and four cases of hepatitis B occurred in four distinct clusters among patients at a cardiology clinic. Among three case-patients with HCV infection who had MPI on 6/25/2014, two had 98.48% genetic identity of HCV RNA. Among four case-patients with HCV infection who had MPI on 3/13/2014, three had 96.96% molecular identity of HCV RNA. Two clusters of two patients each with HBV infection had MPI on 3/7/2012 and 12/4/2014. Clinic staff re-used saline vials for more than one patient. No infection control breaches were identified at the compounding pharmacy that supplied the clinic. Patients seen in clinic through 3/27/2015 were encouraged to seek testing for HBV, HCV and human immunodeficiency virus. The clinic switched to all single-dose medications and single-use intravenous flushes on 3/27/2015 and no further cases were identified.

Conclusions—This prolonged healthcare associated outbreak of hepatitis B and hepatitis C was most likely related to breaches in injection safety. Providers should follow injection safety guidelines in all practice settings.

Introduction:

Hepatitis B and hepatitis C infections are most commonly associated with injection drug use[1–6] and high-risk sexual activity.[6,7] However, persons age 55 years and older with acute hepatitis B or acute hepatitis C are more likely than uninfected controls to report dialysis or injections in healthcare settings during the incubation period.[8] Patient to patient transmission of hepatitis B and hepatitis C has been reported in association with inadequate infection control during surgical,[9] dental[10] and podiatric[11] procedures, blood glucose monitoring,[12] injections,[13,14] and hemodialysis.[15] Large outbreaks[16,17] have been reported among patients who received injections contaminated by a hepatitis C-infected healthcare worker diverting narcotic medications for personal use.

Healthcare associated outbreaks may require notification of hundreds of patients about potential exposure to bloodborne pathogens[18] and are a high priority for health departments. We present a prolonged healthcare associated outbreak of hepatitis B and hepatitis C that was recognized and reported by a primary care physician.

Methods:

On November 20, 2014, a physician reported a case of hepatitis C in an elderly woman with multiple underlying medical problems (“Patient 1”) who presented with acute transaminase elevation on October 10, 2014. The patient had no behavioral risk factors so healthcare exposure was suspected as the cause of her infection. Beginning in January 2015, we performed site visits for all settings where care had been provided during the incubation period, including “Clinic A” where the patient had undergone myocardial perfusion imaging (MPI).

Epidemiological Investigation

In February 2015, a retrospective search of the West Virginia hepatitis C registry for acute hepatitis C cases seen at Clinic A led to detection of Patient 2, who tested positive for HCV on April 30, 2014.

We crossmatched lists of Clinic A patients seen one week before and one week after Patients 1 and 2 against the hepatitis B, hepatitis C and HIV registries. Of nine total patients with hepatitis C identified in the registry crossmatch, six underwent MPI on June 25, 2014 (same day as Patient 1), and March 12 and 13, 2014 (same day as Patient 2 and the day before). The remaining three patients first tested hepatitis C positive prior to MPI and were eliminated from further investigation. We subsequently offered serological testing for HBV, HCV and HIV to all Clinic A patients who had MPI on June 25, and March 12 to 13, 2014. We forwarded anti-HCV positive patient specimens to CDC for additional testing.

During June 2015, "Patient 3" was identified through routine surveillance, with transaminase elevation and HBV infection in May 2015 and history of MPI at Clinic A in December 2014. A retrospective search of the registry for acute cases of hepatitis B seen at Clinic A identified "Patient 4." We crossmatched lists of clinic patients seen the same day and the day before patients 3 (12/3/2014 to 12/4/2014) and 4 (3/6/2012 to 3/7/2012) against the hepatitis B and hepatitis C registries. Two additional patients with hepatitis B were identified; one underwent stress-testing on the same day as Patient 3 (12/4/2014) and the other underwent stress-testing on the same day as patient 4 (3/7/2012). We subsequently offered serological testing for HBV, HCV and HIV to patients seen on December 3 and 4, 2014, and March 6 and 7, 2012.

Similarly, we offered HBV, HCV, and HIV testing to the Clinic A physician and technician.

We interviewed case patients[19] to identify behavioral risk factors and healthcare exposures. We reviewed medical records to verify dates of procedures and test results. We obtained time for each MPI procedure from Clinic A, based on the perfusion image date/time stamp.

Laboratory methods

HCV molecular testing of patient specimens was performed at CDC. Genetic relatedness among patient HCV isolates was determined by quasispecies and phylogenetic analysis of the HCV genome encompassing the hypervariable region 1 as previously described.[20,21] Hypervariable region 1 quasispecies sequences variants from patient specimens were compared to each other and to corresponding sequences of the same HCV genotype from randomly selected HCV-infected patients identified through the National Health and Nutrition Examination Survey, a representative sample of the noninstitutionalized civilian population of the United States.

Case definitions

A case of *acute hepatitis C* was defined as an individual who underwent MPI at Clinic A and subsequently developed illness consistent with the 2012 acute hepatitis C case definition.[22]

A case of *acute hepatitis B* was defined as a Clinic A patient who underwent MPI and subsequently developed illness consistent with the 2012 acute hepatitis B case definition.[22]

Patients were further categorized as: *known case* if the case had positive HBV (total hepatitis B core antibody, hepatitis B surface antigen, HBV DNA) or HCV (hepatitis C antibody, HCV RNA, or genotype) results in the West Virginia hepatitis B or hepatitis C registries

prior to MPI at Clinic A; *hepatitis C past or present infection* if the case was asymptomatic but was diagnosed with hepatitis C after MPI; *hepatitis B non-acute infection* if the case was asymptomatic but was diagnosed with hepatitis B after MPI; *not a case* if HBV or HCV test results were negative; and *unknown* if test results for HBV or HCV infection were unavailable.

Infection control interviews and observations

During site visits in January and March 2015, we interviewed clinic staff about infection control procedures, injection safety and staff vaccination. We observed initiation of intravenous access, preparation and administration of 99mTc sestamibi and administration of intravenous flushes.

Investigation of compounding pharmacy

In May 2015, we interviewed staff pharmacists and observed procedures at the compounding pharmacy where 99mTc sestamibi was prepared for use during MPI. We obtained names of patients who had tagged white blood cells (tWBC) prepared on the same day and the day before 99mTc sestamibi was prepared for hepatitis C case-patients. We crossmatched these names against the hepatitis B, hepatitis C and HIV registries.

Results:

Epidemiology

Based on serological testing and hepatitis B and hepatitis C registry matching, two clusters of hepatitis C and two clusters of hepatitis B were identified among patients who underwent MPI stress testing at Clinic A between 2012 and 2014 (Figures 1a–d). None of the newly identified patients reported behavioral risk factors on interview.

The Clinic A technician tested negative for HIV, HBV and HCV. The physician had detectable hepatitis B surface antibody, but was otherwise negative for HIV, HBV or HCV.

Laboratory Data

HCV RNA from two patients who underwent MPI stress testing on June 25, 2014 showed 98.48% nucleotide sequence identity (Figure 2). HCV RNA from 3 patients who underwent stress testing on March 13, 2014 showed 96.96% to 99.24% sequence identity.

Infection control and clinic practices

Prior to March 27, 2015, Clinic A received four doses of 99mTc Sestamibi daily, calibrated to 40 millicuries as of 10 AM, 12 PM, 2 PM, and 4 PM. Usually four patients were scheduled for MPI daily; however, the physician accepted walk-in patients and diluted the doses on a bench top in the hot lab to accommodate the extra patients, using a fresh vial of single-dose saline and a 3 cc syringe.

Figure 3 shows routine injection practices in the procedure room of the cardiology clinic. Briefly, the technician started the patient's heparin lock. The physician entered the procedure room carrying a 3 cc syringe of 99mTc Sestamibi enclosed in a metal casing (to minimize

radiation exposure) and the saline vial that had been used to dilute isotope in the hot lab. After injecting 99mTc Sestamibi into the patient's heparin lock, the physician reused his syringe to draw up a saline flush from the vial he was carrying and injected the flush in the heparin lock. The physician then returned to the hot lab, and discarded the needle, syringe and vial.

Infection Control Recommendations

On March 25, 2015, we recommended that Clinic A replace all saline vials with pre-packaged single-use saline flushes, order only patient-specific pre-calibrated doses of 99mTc Sestamibi, cease dilution of pharmacy-prepared doses on the benchtop, switch to needleless or retractable systems for injection, and ensure all staff that perform invasive procedures complete bloodborne pathogen and infection control trainings and obtain hepatitis B vaccine.

Compounding pharmacy

On average, the compounding pharmacy prepared Tc Sestamibi for 45–50 patients at 15 facilities daily and tWBC for 3–4 patients per week. Orders of 99mTc Sestamibi were prepared and packaged for delivery by 7:30 AM. Patient blood for tWBC arrived in a lead-lined container to a completely separate preparation room later in the day; all waste was discarded in that room and the only item to leave the room was the tWBC in the same lead-lined container used for delivery of the patient blood. There were two days on which tWBC were prepared and HCV clusters were detected; on March 13, 2014, 99mTc Sestamibi was prepared four hours before tWBC preparation, and on June 25, 2014, 99mTc Sestamibi was prepared three hours before tWBC preparation. None of four patients who had tWBC prepared on March 11–13, 2014 and June 23–25, 2014 were identified in the hepatitis B or hepatitis C registries. No breaches of infection control, environmental cleaning or aseptic technique were identified.

Patient notification

Beginning March 11, 2016, patients who had undergone MPI at the cardiology clinic between March 1, 2012 and March 27, 2015, were notified by mail of potential exposure to bloodborne pathogens, advising consideration of testing for HBV, HCV and HIV infections. Because of resulting media coverage, an elderly woman (Patient 5) self-reported a diagnosis of hepatitis C after undergoing MPI in July 2010 at Clinic A. Patient 5 had been monitored monthly by her physician who noted elevated transaminases in October 2010, prompting him to order diagnostic testing which returned positive for HCV. The patient denied any hepatitis C risk factors and her physician did not know why she became infected. In the ensuing weeks, three additional patients self-reported hepatitis C after undergoing MPI at Clinic A between July 2010 and June 2011. Therefore, on May 9, 2016, a media announcement was released expanding notification to all patients seen at Clinic A through March 27, 2015.

Discussion

This outbreak of hepatitis B and hepatitis C occurred as four distinct transmission clusters between March 2012 and December 2014 at an outpatient cardiology clinic (Figure 1a–d). After patient notification, four additional patients self-reported hepatitis C in temporal association with MPI suggesting possible viral hepatitis transmission in association with the clinic as far back as 2010. While we were unable to characterize the exact mode of viral hepatitis transmission, we recommended safe injection practices, including single-use flushes and needle-less injection equipment. After the clinic implemented these recommendations, no further cases were identified.

This outbreak illustrates both the importance and the challenge of recognizing an index case of acute hepatitis B or hepatitis C that might be associated with a healthcare associated outbreak. Clinicians in the United States are often the first to recognize viral hepatitis outbreaks related to healthcare exposure,[10,14,17,23] as occurred with Patient 1. Patient 1 had several medical encounters but no history of high-risk behaviors. Because Patient 1 had no reported symptoms of acute hepatitis C, a public health investigation would not have been conducted without physician notification. Outbreak recognition can also occur from review of surveillance case reports[24] as occurred with Patient 3. Recognition is challenging because less than one third of adults with acute HBV infection[25] and approximately one third of persons with acute HCV infection[26] have symptoms. In addition, surveillance data underestimate the occurrence of acute hepatitis B and hepatitis C[27] and surveillance case definitions are insensitive compared to physician diagnosis.[28] Finally, the prevalence of chronic hepatitis C in the United States is estimated at one percent[29]; therefore, the overwhelming majority of patients newly diagnosed with hepatitis C have chronic, non-acute infection and source of infection cannot be determined.

While outbreaks of hepatitis B[23] and hepatitis C[13,14, 24, 30–32] related to unsafe injection practices are infrequently recognized, unsafe injection practices have been described in a sizeable minority of health settings. In one survey, 43% of 370 physicians from eight states reported that healthcare personnel in their workplace reentered multidose vials with the same syringe for an additional dose for the same patient; yet only 26% of physicians reporting this practice indicated that multidose vials are never used for more than one patient in their workplace.[33] In an observational study of 31 clinics, almost 20% stored single use vials for use on another patient.[34] Unsafe injection practices resulted in notification of more than 66,768 patients related to 38 events in 24 states between 2011 and 2018.[35] More than half of the events involved exposures occurring in a non-hospital setting (n=21, 55%), and were identified on the basis of unsafe practices without documentation of disease transmission (n=20, 53%).[35]

We were unable to characterize the precise mechanism of transmission of hepatitis B and hepatitis C in Clinic A. While infection control breaches at a compounding pharmacy have previously resulted in HCV transmission,[36] we found no evidence of infection control breaches and no opportunities for contamination from processing of blood at the compounding pharmacy. Both the technician and physician at Clinic A tested negative for HBV, HCV and HIV infections. The technician and physician at Clinic A denied that a vial

entered with a used syringe from one patient could have been subsequently used for another patient; however, the most likely explanation for multiple transmission events (Figures 1a–d) is inadvertent re-use of a saline vial contaminated by syringe reuse (e.g., step 8, Figure 3). Both the technician and the physician routinely reused single-dose vials in the procedure room; inadvertent reuse of a contaminated vial for another patient might have occurred in either the procedure room or the hot lab, resulting in transmission of viral hepatitis. Injection safety breaches similar to those described in this report have been associated with clusters of hepatitis B[23] and hepatitis C.[13, 14, 24, 30–32] CDC has developed resources and recommendations for clinicians to ensure that safe injection practices are used in all healthcare settings.[37] Relevant recommendations include not entering medication vials with a used syringe and dedicating single-dose vials for one patient only.

We identified at least six limitations in our investigation. First, patient interviews were conducted six months or more after the procedure potentially resulting in recall bias; response to viral hepatitis risk factor questions were self-reported potentially resulting in information bias. Second, molecular testing was unavailable for some cases of hepatitis C and all cases of hepatitis B because the infection resolved or was successfully treated, the patient refused testing, or the patient was deceased. For example, it is unknown if the HCV infected cases from March 12, 2014 are related to those from March 13, 2014. Third, hepatitis C is frequently asymptomatic, so the date of infection cannot be determined for some cases who tested positive after the procedure. Fourth, the West Virginia hepatitis B and hepatitis C registries do not contain all hepatitis B and hepatitis C cases because some viral hepatitis cases may not have been reported, and registries were incomplete. This, taken with the fact that only 33% of adults with acute hepatitis C or acute hepatitis B infections have symptoms suggests that bloodborne pathogen infection associated with this clinic may be under recognized through registry crossmatch. Fifth, the times for stress tests were the only procedure times documented by Clinic A. There was no information on when intravenous access was started or when 99mTc Sestamibi or other medications were administered. Each patient spent around two hours in the clinic, so there was substantial overlap of patient care when multiple patients were scheduled the same day. Sixth, environmental cleaning and hand hygiene procedures were not reviewed at the clinic in detail; however, it is unlikely that either of these could explain clusters of three to six patients with hepatitis C. Our paper illustrates the strengths of multiple methods of case-finding, including registry crossmatch, patient call-back for serological testing, and media notification; detailed patient interviews[19]; and molecular analysis.[38] Ultimately, the outbreak was brought to a close after the clinic implemented good injection safety practices.

Adherence to good infection control practices in all health care environments is a fundamental responsibility of all health professionals. Providers practicing in outpatient settings can access CDC guidelines for infection prevention and infection prevention checklists on-line.[39] When systems promoting safe injection practices fail, patient safety depends on recognition and reporting of unsafe injection practices,[31, 36] physician reporting of index cases or clusters of acute viral hepatitis plausibly related to transmission in healthcare,[10, 14, 17, 23] and public health surveillance systems designed to detect the outlier case of acute hepatitis B or acute hepatitis C in a patient with no behavioral risk factors who has exposures in healthcare settings.[24]

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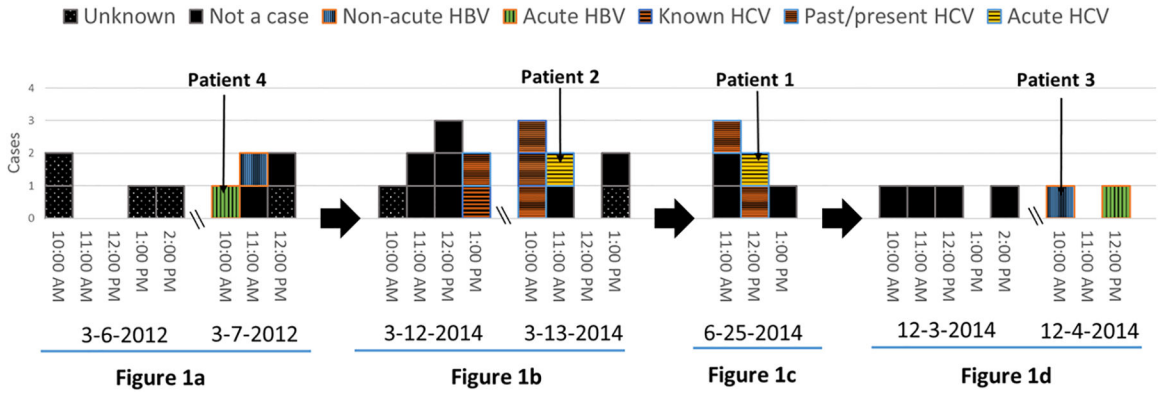

Figure 1. Hepatitis Status of Patients by Date and Time of MPI Stress Test, Clinic A, West Virginia, 2012–2014

Four clusters of viral hepatitis are organized chronologically according to date and time of MPI. Patients 1–4 are numbered sequentially based on the order in which they were identified during the investigation.

1a March 6 and 7, 2012 (N=9). Patient 4 ("acute hepatitis B") and a deceased HBV positive patient ("non-acute hepatitis B") were identified through the HBV registry crossmatch. Five patients could not be tested ("unknown"); four were deceased and one refused. Two patients were tested and were negative ("not a case"). No patients had evidence of HCV or HIV infection.

1b March 12–13, 2014 (N=15). Patient 2 was identified through registry crossmatch with acute hepatitis C and a positive HCV test from April 30, 2014. Four patients with past or present HCV were identified, including a cluster of three patients with past or present HCV 1a with consecutive procedure times between 10:19 and 10:59 AM on March 13, and 96.96% molecular identity. Patient 2 was also known to have HCV genotype 1a but had a resolved infection at the time of investigation. Two patients with hepatitis C seen at 1:05 PM ("past or present HCV") and 1:46 PM ("known case") on March 12 also had resolved infection. Two patients refused hepatitis testing ("unknown") and seven tested negative for HCV ("not a case"). None of these patients had positive results for HIV and two had evidence of past infection with HBV.

1c June 25, 2014 (N=6). Patient 1 presented with acute elevation of ALT to 888 IU/mL on October 10, 2014 and was diagnosed with hepatitis C. Three patients with consecutive MPI procedure times between 11:47 AM and 12:33 PM were HCV genotype 1a positive, including two with past or present hepatitis C and one patient with acute hepatitis C (Patient 1). HCV isolates from two patients, including Patient 1, showed 98.48% molecular identity. The patient with past or present HCV seen at 12:33 PM had a resolved infection. Three patients were negative for HCV ("not a case"). All patients had negative tests for HBV and HIV.

1d December 3–4, 2012 (N=8). Patient 3 was identified through surveillance with positive anti-HBc IgM, HBsAg and ALT of 345 IU/mL on May 30, 2015 but was classified as "non-acute" because of lack of symptoms clearly related to HBV infection. A deceased patient with acute hepatitis B was identified through registry crossmatch. One patient refused testing ("unknown") and three were negative for hepatitis B ("not a case"). HCV tests results were negative and HIV testing was not done.

Abbreviations: ALT, alanine aminotransferase; anti-HBc IgM, immunoglobulin M antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MPI, myocardial perfusion imaging

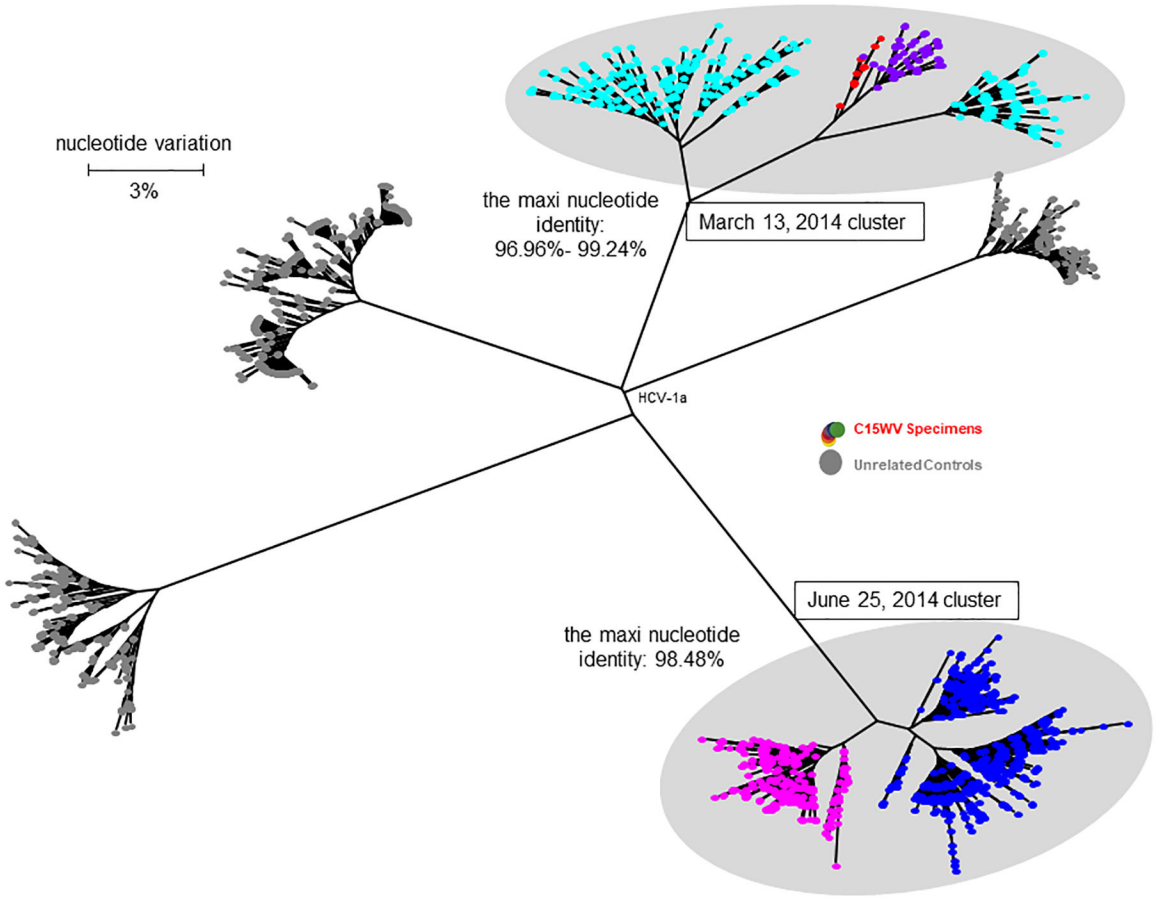

Figure 2. HCV E1-HVR1 Quasispecies Sequences, West Virginia, 2014

Quasispecies analysis demonstrating 98.48% molecular identity between two patients who underwent MPI on June 25, 2014, including Patient 1; and 96.96% molecular identity between three patients who underwent MPI on March 13, 2014. (E1-HVR1 region, 264 bp in length, only unique NGS454 sequences are shown)

Abbreviations: bp, base pairs; E1, envelope protein 1; HCV, hepatitis C virus; HVR1, hypervariable region 1; NGS454, The Next Generation Sequencing Platform of Roche 454.

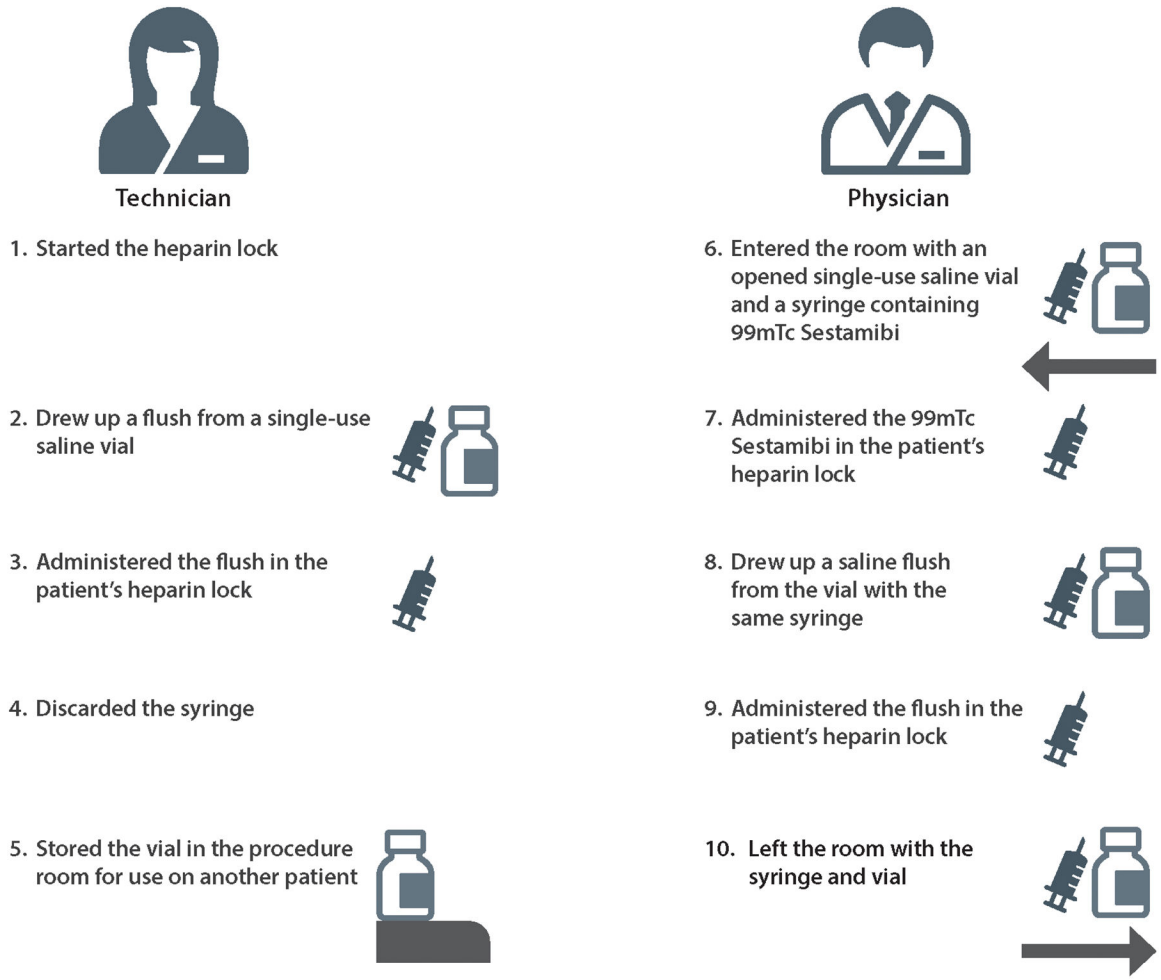

Figure 3. Technician and Physician Injection Practices in the Cardiology Clinic Procedure Room

With every patient seen in the cardiology clinic, the technician carried out steps 1 – 5 and the physician carried out steps 6 – 10. In step 6, the physician entered the procedure room with the single-dose vial that had been used for dilution of 99mTc Sestamibi in the hot lab, and a 3 cc syringe containing 99mTc Sestamibi enclosed in a metal casing to minimize radiation exposure. The physician carried out steps 7 – 9 and left the procedure room (step 10) carrying the syringe and vial back to the hot lab to be discarded.