An Outbreak of Hepatitis C Virus Infections among Outpatients at a Hematology/Oncology Clinic

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Background: **Approximately 2.7 million persons in the United States have chronic hepatitis C virus (HCV) infection. Health care–associated HCV transmission can occur if aseptic technique is not followed. The authors suspected a health care–associated HCV outbreak after the report of 4 HCV infections among patients at the same hematology/oncology clinic.**

Objective: **To determine the extent and mechanism of HCV transmission among clinic patients.**

Design: **Epidemiologic analysis through a cohort study.**

Setting: **Hematology/oncology clinic in eastern Nebraska.**

Participants: **Patients who visited the clinic from March 2000 through December 2001.**

Measurements: **HCV infection status, relevant medical history, and clinic-associated exposures. Bivariate analysis and logistic regression were used to identify risk factors for HCV infection.**

Results: **Of 613 clinic patients contacted, 494 (81%) underwent HCV testing. The authors documented infection in 99 patients who lacked previous evidence of HCV infection; all had begun treatment at the clinic before July 2001. Hepatitis C virus genotype 3a was present in all 95 genotyped samples and presumably originated from a patient with chronic hepatitis C who began treatment in March 2000. Infection with HCV was statistically significantly associated with receipt of saline flushes ($P < 0.001$). Shared saline bags were probably contaminated when syringes used to draw blood from venous catheters were reused to withdraw saline solution. The clinic corrected this procedure in July 2001.**

Limitation: **The delay between outbreak and investigation (>1 year) may have contributed to an underestimate of cases.**

Conclusions: **This large health care–associated HCV outbreak was related to shared saline bags contaminated through syringe reuse. Effective infection-control programs are needed to ensure high standards of care in outpatient care facilities, such as hematology/oncology clinics.**

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Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease in the United States (1). It is transmitted primarily through percutaneous exposure to contaminated blood (2). Health care–associated HCV transmission has been attributed to breaches in aseptic technique (3–5). In September 2002, a gastroenterologist notified the Office of Epidemiology at the Nebraska Health and Human Services System in Lincoln, Nebraska, of a cluster of 4 HCV genotype 3a infections in patients who received care at a single outpatient clinic in eastern Nebraska. Because these patients reported no typical risk factors for HCV infection and genotype 3a accounts for less than 8% of HCV infections in the United States, we suspected health care–associated transmission (1).

The implicated facility was an independently owned and operated hematology/oncology clinic located inside a hospital complex. The clinic opened in January 1998, and approximately 500 patient visits occurred per month. The staff comprised an oncologist, a registered nurse, a certified nurse assistant, and a secretary. In October 2002, 1 month after the gastroenterologist's report, the clinic voluntarily closed. We compared clinic patient lists with Nebraska's HCV, HIV, and hepatitis B virus (HBV) registries and identified a patient with preexisting chronic HCV genotype 3a infection who enrolled at the clinic in March 2000. We found no evidence of HIV or HBV transmission. Preliminary interviews with clinic staff revealed that the nurse who had worked at the clinic since its opening was dismissed in July 2001 because of breaches in infection-control practices. We initiated an investigation to confirm the hypothesis of health care–associated transmission and to determine the extent of the outbreak and its mechanism of transmission.

METHODS

Case Finding and Laboratory Testing

Using clinic records, we identified all patients who visited the clinic from March 2000 through December 2001. We contacted all living patients and offered them free HCV testing. Structured in-person interviews were conducted in a private setting with participating patients to

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Editorial comment 940
Related article 903
Summary for Patients I-38

Web-Only
Appendix
Appendix Figure
Conversion of figures and tables into slides

assess their medical history, including previous hepatitis diagnosis and risk factors for HCV infection.

All specimens were tested for HCV antibodies by using enzyme immunoassay (EIA) (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois). Positive results on EIA were confirmed by using recombinant immunoblot assay (RIBA) (Chiron RIBA HCV 3.0 SIA, Chiron Corp., Emeryville, California) or HCV qualitative polymerase chain reaction (PCR) (Cobas Amplicor HCV Test v2.0, Roche Molecular Diagnostic Systems, Branchburg, New Jersey) (6). Because of concerns that immunosuppressed patients could have impaired antibody response, we also tested specimens from patients seen before July 2001 by using a transcription-mediated amplification (TMA) assay (Gen-Probe Inc., San Diego, California). A positive HCV test result was defined as a positive finding on TMA or a confirmed positive finding on EIA. Samples that were positive on PCR or TMA were genotyped by using gene sequencing of the 5' untranslated region (PE Applied Biosystems, Foster City, California).

Epidemiologic Investigation

We reviewed and abstracted the medical records and medication sheets of the tested patients using structured forms to identify clinic-associated risk factors for HCV transmission, such as number of clinic visits, presence of a central venous catheter, and percutaneous exposures. A case was defined as a positive HCV test result in a clinic patient treated from March 2000 through December 2001 who did not have evidence of preexisting HCV infection (that is, abnormal alanine aminotransferase [ALT] levels or positive HCV test results) before enrollment at the clinic. We considered the date of HCV infection onset to be the date when an ALT level greater than 3 times the upper limit of normal was first recorded (7).

We conducted a cohort analysis to evaluate the association between exposures at the clinic and HCV infection. To further evaluate the variables associated with HCV infection in the cohort analysis and to investigate potential confounding among these variables, we performed an analysis that focused on risk factor exposure during the period of probable transmission (Appendix, available at www.annals.org).

Review of Infection-Control Practices

The physician and nurse who worked at the clinic during the outbreak period were unavailable or unwilling to submit to interviews and HCV testing. We interviewed other health care workers and patients to corroborate staff adherence to infection-control standards.

Statistical Analysis

We made comparisons by using the *t*-test, the Fisher exact test, or the chi-square test, as appropriate (Epi Info, version 3.01, 2003, Centers for Disease Control and Prevention, Atlanta, Georgia). *P* values less than 0.05 were considered statistically significant.

Context

Hepatitis C virus (HCV) may be transmitted through health care–associated exposure involving poor aseptic technique.

Contribution

In an outpatient hematology/oncology clinic, 99 patients who did not have previously known HCV infection acquired the virus, apparently because a health care worker reused contaminated syringes and saline bags.

Cautions

Researchers may have missed some cases because the investigation occurred more than a year after the outbreak.

Implications

We need active, effective infection-control programs for outpatient care settings.

–The Editors

RESULTS

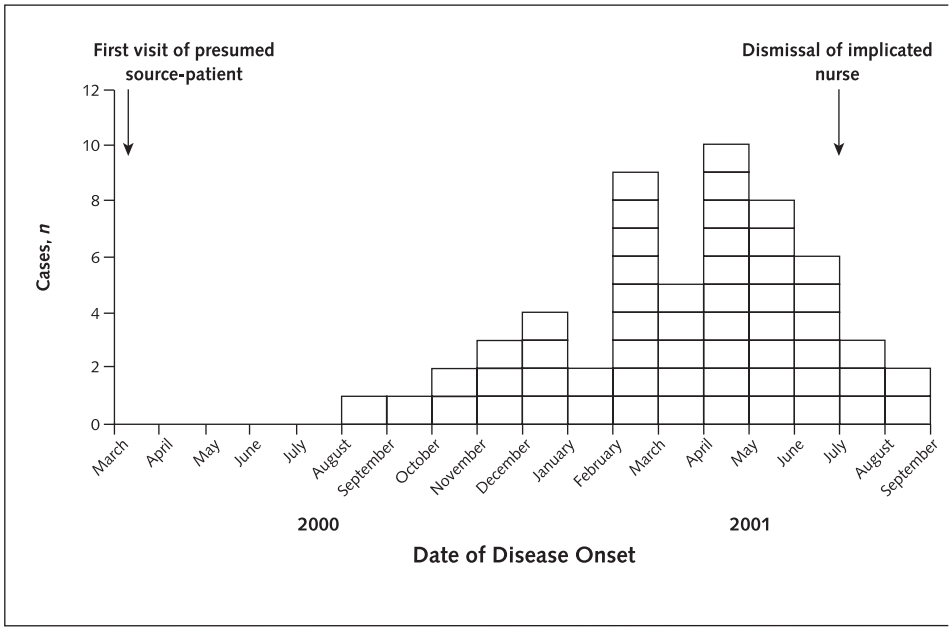
Case Finding and Laboratory Testing

A total of 842 patients attended the clinic from March 2000 through December 2001. We contacted the 613 (73%) living patients; 494 of these (81%) agreed to testing. Twenty-one tested patients whose medical charts could not be located were excluded from analysis. No cases were seen among the 103 tested patients who began treatment after the nurse's dismissal in July 2001. Therefore, we defined our study period as March 2000 to July 2001 and considered only exposures that occurred during this period.

Among the 370 eligible patients, 101 tested positive for HCV: 80 were EIA positive and PCR positive; 18 were EIA negative but TMA positive; and 3 were EIA positive, PCR negative, and RIBA positive. One patient with inconclusive HCV test results (positive EIA, negative PCR and TMA, and indeterminate RIBA results) was excluded from analysis. We also excluded 2 persons with evidence of preexisting HCV infection. One visited the clinic only once, in March 2001, and had elevated ALT levels before that visit. The other person was the presumed outbreak source-patient identified during our preliminary investigation. This patient enrolled at the clinic in March 2000 with preexisting chronic HCV genotype 3a infection (viral load $>$ 200 000 copies/mL); a central venous catheter was implanted at that time.

The resulting cohort of 367 patients seen at the clinic from March 2000 to July 2001 consisted of 99 HCV-positive patients who lacked evidence of preexisting HCV infection and met the case definition and 268 HCV-negative patients. The overall attack rate was 27% (99 of 367 patients). Genotype 3a was identified in 95 (96%) cases; in 4 cases, low levels or absence of HCV RNA precluded genotype determination.

Figure. **Number of cases of hepatitis C virus infection, by estimated onset date (*n* = 56) (Nebraska, March 2000–July 2001).**



Onset is considered to be the date of the first alanine aminotransferase level greater than 3 times the upper limit of normal.

Epidemiologic Investigation

Descriptive Epidemiology

Most infected patients were female (60%), and the median age was 66 years (range, 21 to 95 years). Ninety-five of the 99 patients (96%) had cancer as an underlying disease, and the median number of clinic visits was 21 (range, 3 to 78 visits). Signs and symptoms of acute HCV infection were uncommon: Four (4%) patients had clinical jaundice, and 16 (16%) reported nausea. We estimated an onset date of infection for 56 (57%) case-patients (**Figure**). Only 2 (2%) case-patients exhibited spontaneous viral clearance (that is, undetectable HCV RNA) at the time of the investigation.

Eighty-three (84%) infected patients had a central venous catheter in place while receiving care at the clinic. Twenty-six (26%) infected patients did not receive any intravenous drug at the clinic during the outbreak period, but did have catheters flushed with saline solution. All 99 patients who developed HCV infection visited the clinic the same day as a previously HCV-infected patient and had saline flushes on those days.

Analytic Epidemiology

Among the 367 patients in the cohort analysis, 140 (38%) received 1 or more saline flushes during the study period (**Table 1**). Of those, 99 (71%) became infected, compared with no infection among the 227 patients who did not receive a saline flush during that time (relative risk, undefined; $P < 0.001$). Bivariate analysis also indicated an association between HCV infection and 5 other variables: sex, underlying diagnosis, presence of central venous catheter, exposure to subcutaneous injections, and number of clinic visits.

In the multivariable analysis using the case-patients with estimated date of onset, only the number of saline flushes remained significantly associated with HCV infection in our model (adjusted odds ratio, 2.1 [95% CI, 1.3

Table 1. **Attack Rates of Hepatitis C Virus Infection, by Demographic and Selected Clinical Characteristics, among 367 Tested Patients at the Hematology/Oncology Clinic, March 2000–July 2001***

Characteristic	Attack Rate by Characteristic, % (*n*/*n*)		Relative Risk (95% CI)	*P* Value
	Present	Absent		
Men	34 (40/117)	24 (59/250)	1.45 (1.0–2.0)	0.04
Cancer	36 (95/267)	4 (4/100)	8.9 (3.4–23.6)	<0.001
Presence of a central venous catheter	72 (83/115)	6 (16/252)	11.4 (7.0–18.5)	<0.001
Receiving ≥1 saline flushes	71 (99/140)	0 (0/227)	Undefined	<0.001
Receiving ≥1 subcutaneous injections	71 (57/80)	15 (42/287)	4.9 (3.6–6.6)	<0.001

* NA = not available.

Table 2. **Unconditional Multivariable Analysis of Risk Factors for Hepatitis C Virus Infection Using the 56 Case-Patients with Estimated Dates of Onset and 56 Controls, March 2000–July 2001***

Characteristic	Case-Patients (*n* = 56)	Controls (*n*= 56)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Men, *n (%)*	27 (48)	19 (34)	1.8 (0.8–4.2)	2.7 (0.7–10.3)
Presence of central venous catheter, *n (%)*	47 (84)	13 (23)	17.3 (6.7–44.5)	2.8 (0.4–18.3)
Cancer as underlying diagnosis, *n (%)*	54 (96)	40 (71)	10.8 (2.3–49.7)	1.2 (0.1–14.3)
≥1 subcutaneous injection, *n (%)*	21 (38)	6 (11)	5 (1.7–15.6)	2.6 (0.2–30.4)
Mean saline flushes (range), *n*†	8.9 (2–30)	1.1 (0–12)	NA	2.1 (1.3–3.2)

* Each value was adjusted for other risk factors in the model and number of clinic visits. NA = not available.
† Number of saline flushes was analyzed as a continuous variable.

to 3.2]) (**Table 2**; methods described in Appendix, available at www.annals.org). Of note, the 10 case-patients with the earliest onset dates all received a saline flush on a day when the source-patient visited the clinic (**Appendix Figure**, available at www.annals.org).

Review of Infection-Control Practices

Our investigation revealed that the clinic had no active infection-control program. We also learned that, from its opening in January 1998 until July 2001, a single nurse was responsible for all catheter care, medication infusion, and blood specimen collection. Patients reported that this nurse reused disposable syringes to withdraw saline solution from 500-mL bags after withdrawing blood from central venous catheters. One patient recalled seeing blood in the saline bag in the beginning of 2001. The saline solution was used to flush the central and peripheral venous catheters of subsequent patients; assuming each flush required 10 to 20 mL of saline solution, each bag could have served 25 to 50 patients.

Three patients approached the hospital infection-control committee in February 2001 and reported the nurse's syringe reuse. Citing the clinic's independent ownership and operation, the hospital took the position that it was not responsible for overseeing the clinic's infection-control practices but forwarded these concerns to the clinic oncologist. In April 2001, as part of a process for the clinic to become certified as a cancer research center, outside reviewers identified infection-control violations (for example, use of shared saline bags and reuse of syringes) at the clinic and reported them to its oncologist (8). In July 2001, the oncologist dismissed the nurse implicated in these violations, and replacement nurses began prefilling single-use syringes with saline in a dedicated work area each morning. The infection-control breaches were never reported to state health authorities. In early 2004, the state of Nebraska revoked the oncologist's and nurse's professional licenses. Eighty-nine HCV-infected patients are involved in litigation against the oncologist, the nurse, and the hospital.

DISCUSSION

Our investigation describes one of the largest health care–associated outbreaks of HCV infection ever documented. The virus originated from a patient with chronic hepatitis C and spread to at least 99 patients at this outpatient hematology/oncology clinic as a result of disposable syringe reuse and contamination of shared saline bags. The high attack rate probably resulted from characteristics inherent to a hematology/oncology practice, such as repeat patient visits and frequent venous infusions. In addition, these immunosuppressed patients had a lower rate of spontaneous viral clearance than that seen in immunocompetent patients (14% to 26%), which resulted in longer periods of viremia (7). These factors together create opportunities for spread of bloodborne pathogens if aseptic technique is not strictly followed (9). Despite the high attack rate, the fact that our investigation started only after an alert gastroenterologist's report illustrates the difficulty in identifying HCV outbreaks and the need for improved HCV surveillance, such as targeted follow-up by public health authorities of infected persons perceived to be at low risk for HCV infection (for example, persons >60 years of age) (9, 10).

The primary limitation of our investigation was that it began more than 1 year after the exposures. This probably resulted in an underestimate of the number of cases, given high mortality rates among hematology/oncology patients. In addition, we could not entirely exclude the hypothesis of health care worker–to–patient transmission because the health care workers operating the clinic during the outbreak were not tested. However, the context of syringe reuse supports the hypothesis of patient-to-patient transmission. Finally, fingerprinting analysis of HCV isolates was not deemed necessary given the epidemiologic association among case-patients and the finding of a single uncommon genotype among all 95 genotyped cases.

Adherence to proper infection-control practices could have prevented this outbreak. Contamination of intravenous solutions as a result of syringe reuse has been described

as a mechanism of transmission in previous outbreaks (11–13). Therefore, infection-control recommendations state that sterile, disposable needles and syringes must be used for every injection (8, 14). Although administering saline from common bags to multiple patients might be a frequent practice in certain health care settings, alternative methods (for example, using prefilled single-use syringes or single-dose vials) should be encouraged given the risks for solution contamination. If multiple-dose vials are used, they should be restricted to a centralized medication area and health care workers should not reuse needles or syringes to access the vials.

Patients deserve effective infection control wherever they receive health care. Hospitals are obligated to implement infection-control programs to obtain and maintain accreditation (15). However, most patient encounters with the health care system in the United States now take place in outpatient care settings, which are rarely subject to such requirements (16). This trend underscores the need for strategies to implement and maintain infection-control programs in outpatient care settings, which should include rigorous training and oversight of health care workers, along with establishment of clear procedures and responsibilities for reporting and investigating outbreaks (9, 17, 18).

In summary, a licensed health care worker's routine reuse of syringes while administering saline flushes resulted in large-scale transmission of HCV. Delayed recognition, reporting, and correction of deficient practices contributed to the duration and magnitude of this outbreak. This report is a reminder that all suspected cases of health care–associated bloodborne infections deserve vigorous investigation because they might signal a widespread problem. Moreover, it is critical that outpatient care settings, such as hematology/oncology clinics, establish effective infection-control programs to ensure high standards of health care.

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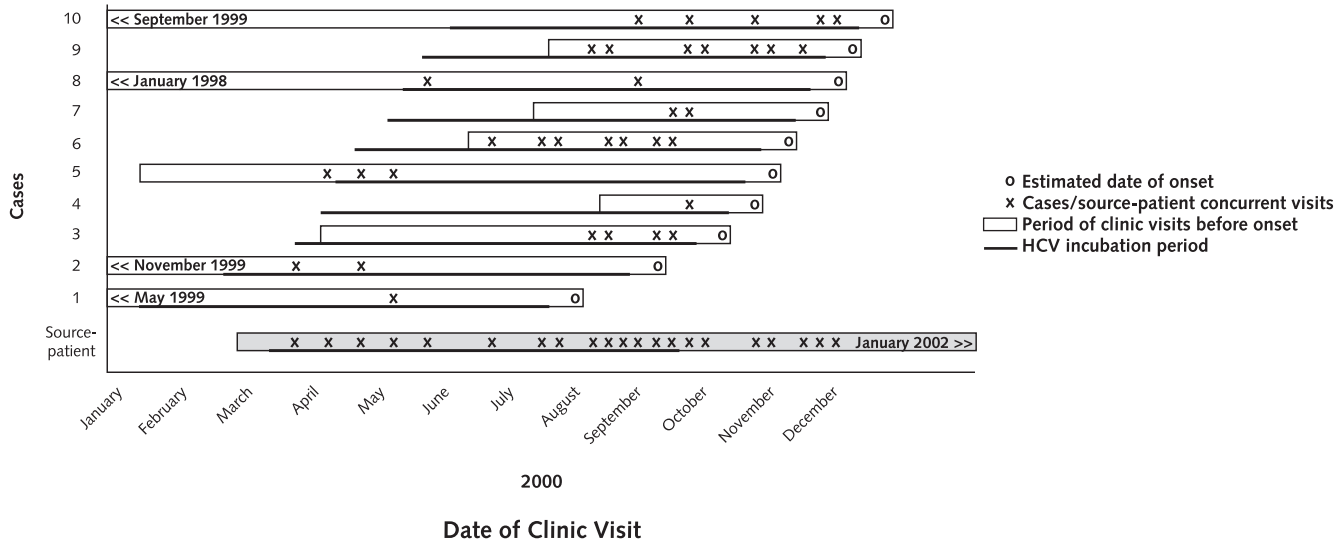
Collection and assembly of data: A. Macedo de Oliveira, K.L. White, D.P. Leschinsky, B.D. Beecham.

Appendix Figure. **Timeline of clinic visits for the 10 case-patients with the earliest dates of onset and for the source-patient (Nebraska, March 2000–July 2001).**



APPENDIX

The cohort analysis identified 6 variables associated with HCV infection: sex, underlying diagnosis, presence of central venous catheter, number of clinic visits, exposure to saline flushes, and exposure to subcutaneous injections. To further evaluate these variables, we performed an analysis focusing on risk factor exposure during the period of probable transmission. We selected case-patients ($n = 56$) for whom an onset date could be estimated and defined the period of probable infection as the interval from 6 months to 2 weeks before this date, which corresponds to the HCV incubation period (7). The onset date was assigned as the date when an ALT level greater than 3 times the upper limit of normal was first recorded. This proved to be a good estimate since no patients without HCV infection had ALT levels greater than 3 times the normal limit of normal. Case-patients for whom we could not estimate an onset date were excluded from this analysis. Among patients without infection, we selected 1 control per case-patient. Controls had to have visited the clinic on or during the 7 days preceding the onset date of the case and have been clinic patients for at least 6 months at that time. Case-patients and controls were not matched otherwise. In this analysis, to control for confounding among variables, we calculated adjusted odds ratios according to an unconditional multivariable logistic regression model.

We counted the number of saline flushes during the period of probable infection among case-patients and controls. The logistic regression model assessed the number of saline flushes as a discrete variable, in contrast to the dichotomous variable (no flush vs. $\geq$1 flushes) used in the cohort analysis. This allowed a more precise evaluation of the risk. We also included the other variables associated with HCV infection in the cohort analysis (that is, sex, underlying diagnosis, presence of central venous catheter, exposure to subcutaneous injections, and number of clinic visits) in the model. Only the number of saline flushes remained significantly associated with HCV infection (adjusted odds ratio, 2.1 [CI, 1.3 to 3.2]) (**Table 2**). The probability of HCV infection increased for each additional flush, nearing 100% after 8 flushes.