VOLUME 26, NUMBER 9 SEPTEMBER 2005

The Official Journal of The Society for Healthcare Epidemiology of America

PUBLISHED FOR THE SOCIETY BY SLACK INCORPORATED

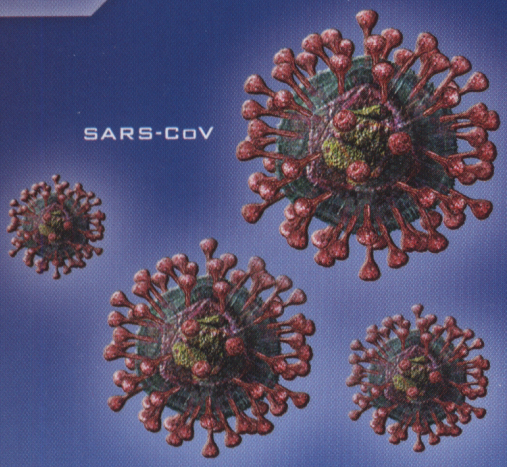
INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY™

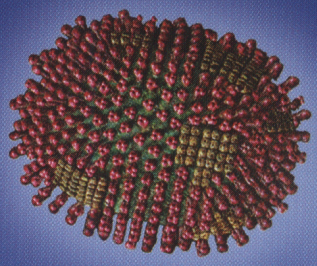
EDITORIAL

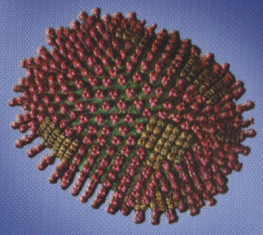
ORIGINAL ARTICLES

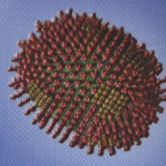
Continued inside.

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press









IT'S TIME FOR A CHANGE.

It's not just TB anymore. The challenges of infectious disease control are growing daily. Pathogens like SARS-CoV and avian influenza have altered the playing field because they have the potential to be transmitted via the airborne route.

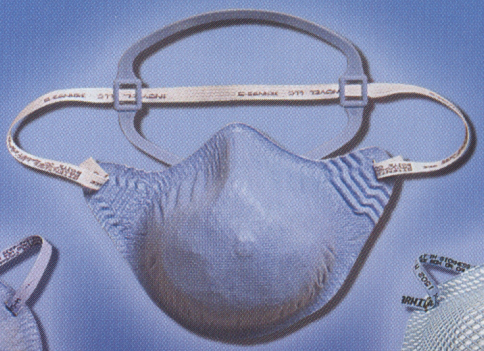
New challenges call for new solutions. And that's where Inovel comes in.

We're a new company, licensed by Moldex,® one of the largest manufacturers of safety and personal protection products in the industrial market and holder of over 40 patents and numerous proprietary technologies.

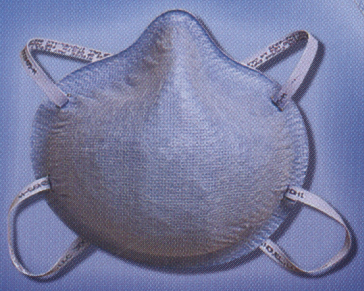
Beginning with a complete line of respirators, we're now manufacturing products using these patented technologies and innovative designs specifically for the healthcare market.

Different by design, our patented, new generation of respirators are more comfortable, and because they're more durable, they can be worn longer. And, they're easier to put on and fit. In fact, in recent fit tests at Hollywood Presbyterian Medical Center, Inovel respirators achieved a 96% pass rate.

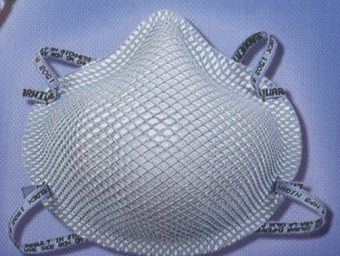
So don't delay, new additions to the list of airborne pathogens may be added at anytime. Call Inovel toll-free at 866.5.INOVEL (866-546-6835), ext. 500 today for free samples, or an informative product demo. Or visit our website at www.inovelmedical.com.



3100 SERIES N95 PARTICULATE RESPIRATOR & SURGICAL MASK



3000 SERIES N95 PARTICULATE RESPIRATOR & SURGICAL MASK



1500 N95 SERIES

10111 W. Jefferson Blvd., Culver City, CA 90232
Phone toll-free 866.5.INOVEL (866-546-6835), ext. 500
www.inovelmedical.com

INOVEL™
Different by design.™

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

Vol. 26 No. 9 September 2005

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY™

CONTENTS

Continued from cover

CONCISE COMMUNICATION

PUBLISHER: Infection Control and Hospital Epidemiology (ISSN-0195-9417, Canadian GST#129780466) is published exclusively by SLACK Incorporated 12 times a year. Address: 6900 Grove Road, Thorofare, NJ 08086. Telephone: (856) 848-1000.

SHEA: 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314; telephone, 703-299-0200; fax, 703-299-0204; e-mail address, info@shea-online.org.

SUBSCRIPTIONS: Requests should be addressed to the publisher. Subscription rates in the United States and possessions: Individual: One year-$149.00; Two years-$253.00; Three years-$335.00; *Institutional: One year-$279.00; Two years-$474.00; Three years-$628.00. Fellows: $54.50 per year with proof of training status. Canada: add 7% Goods & Services tax; Overseas: add $49.00 each year for* delivery by air service. Single copies of current issues may be obtained for $24.00.

INSTRUCTIONS TO AUTHORS: Authors may submit electronic versions of their manuscripts prepared in accordance with the 2004 revision of the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." An electronic version is available at www.icmje.org. Submit to RapidReview.com. All submissions must be accompanied by copyright form(s) signed by all authors.

REPRINTS: All requests to reprint or use material published herein should be addressed to John Kain, SLACK Incorporated, 6900 Grove Road, Thorofare, NJ 08086. For reprint orders and prices, contact Rebecca Fogarty at (856) 848-1000. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by SLACK Incorporated, provided that the base fee of $1.00 per copy, plus $.20 per page is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923; phone (978) 750-8400. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

CHANGE OF ADDRESS: Notice should be sent to the publisher 6 weeks in advance of effective date. Include old and new addresses with zip codes. The publisher cannot accept responsibility for undelivered copies. Periodicals postage paid at Thorofare, New Jersey 08086-9447 and at additional mailing offices. POSTMASTER: Send address changes to SLACK Incorporated, 6900 Grove Road, Thorofare, NJ 08086.

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY is listed in Index Medicus, Current Contents-Clinical Practice, Hospital Literature Index, Cumulative Index to Nursing & Allied Health Literature, Nursing Abstracts, Laboratory Performance Information Exchange System, and RNdex Top 100.

Vol. 26 No. 9 September 2005

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY™

EDITORIAL OFFICE
SLACK Incorporated
6900 Grove Road
Thorofare, NJ 08086
(856) 848-1000; (856) 848-6091 (FAX)
E-mail: iche@slackinc.com

EDITORIAL ADVISORY BOARD

CORPORATE
President
Peter Slack
Executive Vice President
Richard N. Roash
Vice President, Publishing Operations
John C. Carter
Vice President, U.S. Sales
Wayne McCourt
Vice President, International Sales
William Harley
Vice President, Finance
Darrell Blood
Vice President, Information Services
Jon Schafer
Creative Director
Linda Baker

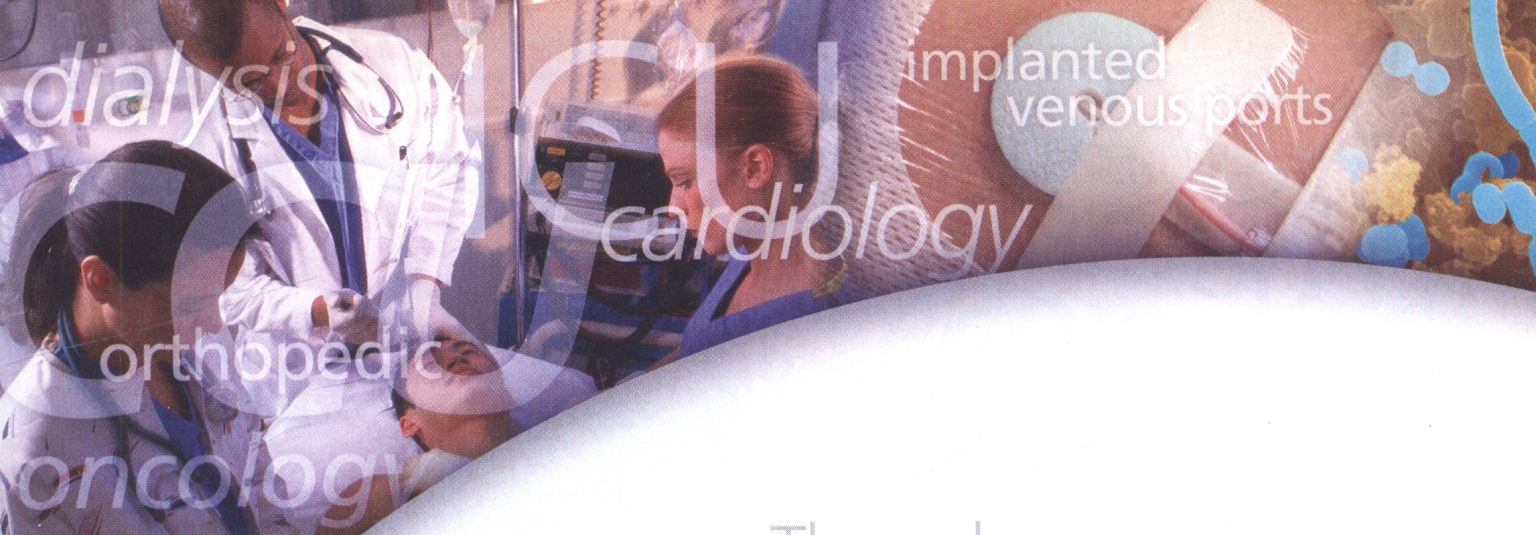
EDITORIAL
Editorial Director
Jennifer A. Kilpatrick, ELS
Executive Editor
Shirley P. Strunk, ELS
Associate Editor
Jaime Underwood

SALES
Director of Association Services
Kathy Huntley
Sales Director, Recruitment/Classified Division
Kristy Irwin
Advertising Sales Administrator
Monique McLaughlin
Advertising Sales Representative
Scotty Turner
Classified/Recruitment Sales
Elizabeth Roash
Director of Reprint Sales
John Kain

PRODUCTION
Production Director
Christine Malin
Circulation Director
Lester J. Robeson, CCCP

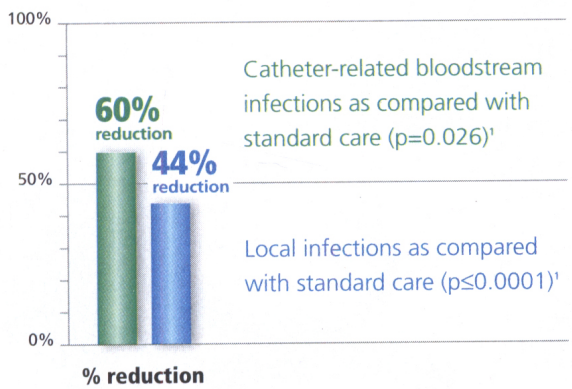
SLACK INCORPORATED
6900 Grove Road
Thorofare, NJ 08086-9447
(856) 848-1000

AMP



The only
percutaneous device dressing
proven to reduce the incidence of
CRBSI and local infections[1]

BIOPATCH Dressing is specifically designed to inhibit bacterial growth around all percutaneous devices, including catheters and orthopedic pins.



Powerful protection... Powerful proof.

- BIOPATCH Dressing provides protection against a broad spectrum of bacteria including resistant strains MRSA and VRE, as well as *Candida albicans*.
- In a controlled, randomized trial, use of BIOPATCH Dressing resulted in a reduction in the incidence of CRBSI and local infections as compared with standard care.[1]

BIOPATCH*
ANTIMICROBIAL DRESSING
with Chlorhexidine Gluconate

B.E.S.T. Practice *means* BIOPATCH DRESSING Every Single Time.†

For additional information or technical support, call ***1-877-384-4266*** *or visit our website at* ***www.biopatch.com.***

† Not for use on premature infants, patients with known sensitivity to CHG. Safety and effectiveness in children under 16 years of age has not been established.

1. Maki DG, Mermel L, Genthner D, Hua S, Chiacchierini RP. An evaluation of BIOPATCH Antimicrobial Dressing compared to routine standard of care in the prevention of catheter-related bloodstream infection. Johnson & Johnson Wound Management, a division of ETHICON, INC. 2005. Data on file.

Johnson & Johnson
Wound Management

P.O. Box 151, Somerville, NJ 08876-0151

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

Expert Test Services for Diagnosis of Invasive Fungal Infection

Beacon Diagnostics™ Laboratory

Beacon Diagnostics Laboratory is a fully CLIA-certified reference laboratory specializing in (1,3)-β-D-glucan analysis as an aid to diagnosing Invasive Fungal Infections (IFI).

The Fungitell™ Assay

The Fungitell assay detects (1,3)-β-D-Glucan, a fungal cell wall component that is shed into the tissues and bloodstream of patients suffering from invasive fungal infection.[1,2] Most medically important fungal pathogens contain (1,3)-β-D-Glucan and are thus detectable using the Fungitell assay.* Beacon Diagnostics Laboratory performs (1,3)-β-D-Glucan testing using the Fungitell assay.

Monitoring serum glucan for evidence of elevated and rising levels provides a convenient marker for IFI. Levels greater than or equal to 80 pg/mL, in at risk patients, are considered positive. Because a fungal infection is a dynamic process, repeat testing (typically 2-3 times per week) improves sensitivity.

*Fungi that do not synthesize (1,3)-β-D-Glucan, such as Zygomycetes, will not generate positive results with this assay.

1 Odabasi, et al. (2004) Clinical Infectious Diseases. 39:199-205.
2. Pazos, et al. (2005) Journal of Clinical Microbiology. 43:299-305

Submitting Samples

Sample submission forms can be obtained by calling (800) 568-0058 or by visiting our website at www.BeaconDiagnostics.com.

Turn-Around Time

All samples are analyzed and reported within 48 hours of receipt at our laboratory.

For More Information Please Contact Us at:

Telephone
(800) 568–0058 or (508) 540–3054

Email
info@beacondiagnostics.com

Website
www.beacondiagnostics.com

BeaconDiagnostics™ LABORATORY
A Division of Associates of Cape Cod

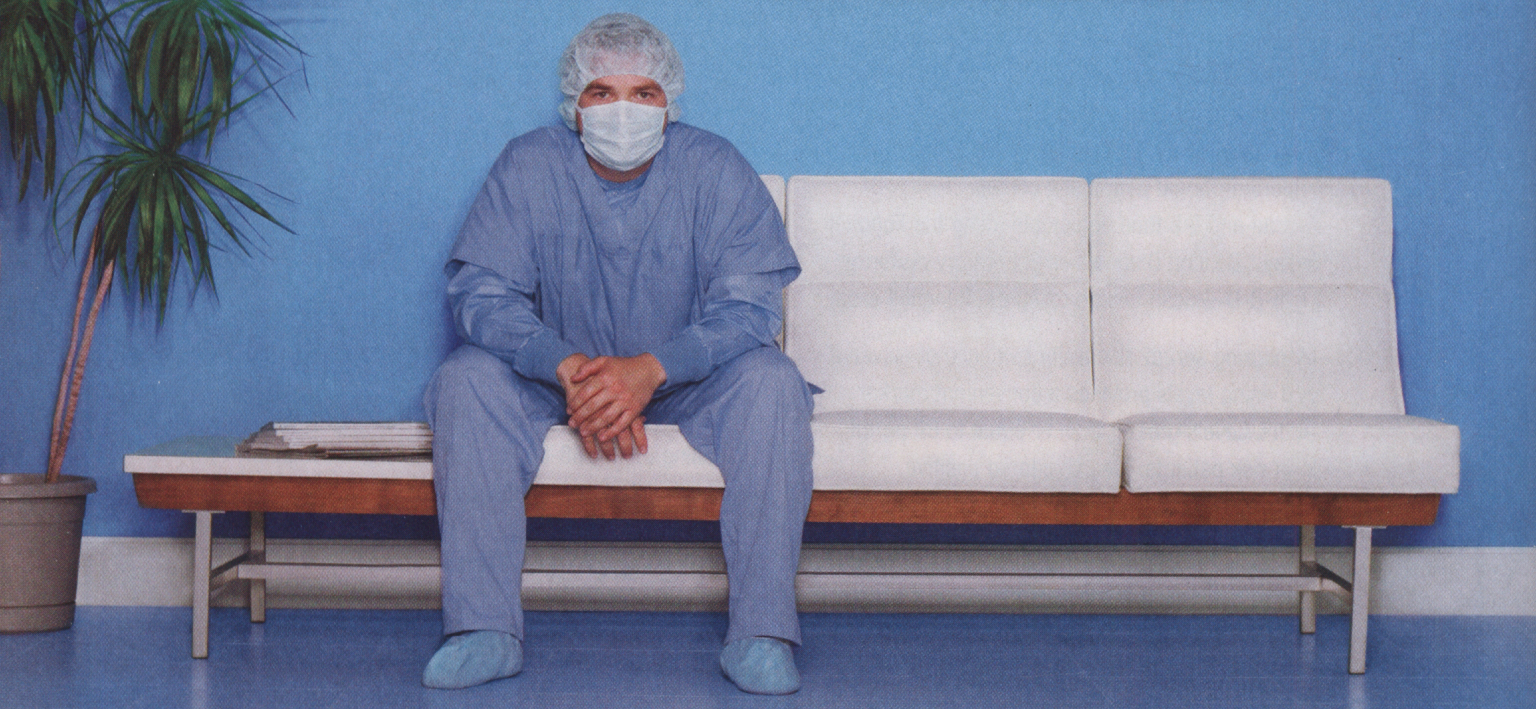
124 Bernard E. Saint Jean Drive, E. Falmouth, MA 02536 > Tel: (800) 568–0058 > Fax: (508) 540–9333

PN001465 Rev000

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

STERILIZATION ASSURANCE | SKIN PREP | STERILE FIELD AND SURFACE | WOUND MANAGEMENT | ENVIRONMENTAL CLEANING | CONSULTING SERVICES | PATIENT ASSESSMENT

Without the right infection prevention system, you may as well operate in the WAITING ROOM



Introducing 3M Infection Prevention Solutions.

Every step in the infection prevention process is critical, or your operating room could be as contaminated as the common areas. But who can keep up with all of the new products and research developments available today? We can.

At 3M, we are committed to helping health care facilities reduce the risk of nosocomial infections. So we not only provide you with innovative products – we equip you with a comprehensive *system* of products, services and technical support, as well as educational and in-service programs all customized for your hospital.

For more information, call the 3M Health Care Customer Helpline at **1-800-228-3957** or click on www.3M.com/healthcare. We're with you, step by step.

3M Infection Prevention Solutions. A vital step in Infection Prevention.

3M Medical
from the 3M Health Care family

3M

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

Editorial

Healthcare Behaviors and Risky Business: First, Do No Harm

David K. Henderson, MD

In an opinion piece entitled "Risky Business," which was published in *Infection Control and Hospital Epidemiology* in 1990, Susan Beekmann, Barbara Fahey, Julie Gerberding, and I wrote about the subject of occupational risk for blood-borne pathogen transmission in the healthcare setting.[1] In that piece, we presented a table suggesting a group of prevention strategies that we believed could help mitigate some of the risks associated with managing patients infected with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and other blood-borne pathogens in healthcare settings (Table).

In 1999, the Institute of Medicine of the National Academy of Sciences published an assessment of patient safety in U.S. healthcare institutions.[2] The Institute of Medicine report was entitled "To Err Is Human." This report underscored the frequency of adverse events in healthcare and emphasized the importance of getting healthcare workers to modify ingrained behaviors to improve patient safety and to mitigate risk in the healthcare setting.[2]

The first information about the acquired immunodeficiency syndrome (AIDS) was published in the Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report* on June 6, 1981.[3] Because of the striking similarities between the epidemiology of this new syndrome and that of HBV, concern arose almost immediately about the risks for occupational and nosocomial transmission.[4] As early as 1986, documented episodes of occupational infection were reported in the literature.[5] Despite an awareness—as early as 1949—of the occupational hazards associated with handling blood from, and managing patients infected with, HBV,[6] the healthcare profession had never seriously addressed issues related to workplace safety in a systematic way before the HIV epidemic. Interest in worker safety had just begun to develop concomitant with the marketing of the original HBV vaccine in the late 1970s, but this interest was truly galvanized by the HIV epidemic.

TABLE*
STRATEGIES TO PREVENT OCCUPATIONAL EXPOSURES AND INFECTIONS WITH BLOOD-BORNE PATHOGENS

Thoughtful, consistent use of standard/universal precautions
Retraining staff about occupational risks
Modifying procedures intrinsically associated with risk
Modifying medical or nursing school curricula
Development and use of technology to reduce exposure risk
Development of effective post-exposure chemoprophylaxis
Immunization

*Modified from reference 1.

The ensuing 25 years have seen a variety of interventions designed to facilitate both decreasing risks and "doing no harm" in the healthcare setting.

In some respects, as a profession, we have come to understand these risks far better than one might have ever imagined in the early 1980s. That's the good news. The bad news is that we continue to struggle on a daily basis with what must now be considered "routine" practice issues relating to the transmission of blood-borne pathogens in the healthcare setting. What must be considered simply "bad behaviors" continue to occur in our workplace on a far-too-frequent basis. As is so often the case in medicine, progress is incremental and not necessarily linear.

This issue of *Infection Control and Hospital Epidemiology* contains no fewer than seven articles addressing various aspects of patient and healthcare worker safety relating directly to the presence of blood-borne pathogens in the healthcare environment. Unfortunately—from both the risky business and the first, do no harm perspectives—much of the news in this issue is not good. Four of these articles describe epidemics of blood-borne pathogen infections among patients receiving healthcare in four different

Dr. Henderson is Deputy Director for Clinical Care, National Institutes of Health Clinical Center, Bethesda, Maryland.
Address reprint requests to David K. Henderson, MD, Building 10, Room 6-1480, 10 Center Drive, Bethesda, MD 20892. dkh@nih.gov

clinical settings. In each of these articles, the assumption is that healthcare providers facilitated infection transmission through the use of procedures that could well be categorized as risky business.

The first of these articles describes a large outbreak of HBV infections among patients receiving treatment at a private physician's office.[7] The epidemic was identified when two low-risk patients were detected as having acute HBV infection. These two patients had no identifiable risk factors for HBV infection, but did attend the same physician's practice. Despite using a variety of approaches to identify potential cases in the cluster, the investigators could evaluate fewer than 25% of the potentially exposed individuals. Their inability to evaluate three-fourths of the population at risk is a serious limitation for this study. Nonetheless, they found that 38 patients had serologic or clinical evidence of recent HBV infection, but were able to interview only 24 of the 38. The investigators conducted a cohort study to demonstrate that the receipt of injections in the physician's office was strongly associated with hepatitis (only the number of injections received was significant among the potential risk factors entered into their multiple logistic regression model). The investigators also found that most of the medications administered in this office were ordered in multidose vials, that these vials were used for multiple patients, and that these vials also were entered by at least one staff member without changing needles. For the epidemic to occur in the first place, work practices and infection control procedures in this clinic must have been inadequate.

The authors of this article make no comment on the physician's practice, except to state that he failed to report the case of acute HBV infection that he observed.[7] The medications most frequently administered in this practice were vitamin B12, atropine, and dexamethasone in injections that combined two of these agents or all three in one syringe.[7] These medicines accounted for 90% of the injections in this practice. The medical and clinical rationale for the administration of these injections is neither provided nor discussed, but must be considered, especially from the first, do no harm perspective.

In a second article, from Lyon, France, Savey et al. describe a large outbreak of HCV infections among 70 patients attending a private hemodialysis center in France.[8] Before the epidemic, the prevalence of HCV infection among patients attending the center was 10.2%. In 2001, 22 instances of HCV seroconversion (involving fully 36% of the susceptible patients attending the center) were identified. Patients became infected with four distinct genotypic variants of HCV in the epidemic, and the occurrence of infection with a distinct subtype was associated with distinct dialysis patterns (ie, the specific days of the week on which dialysis occurred). Two serious limitations of this study are (1) that the authors were able to evaluate the HCV infection statuses of only 10 of 35 healthcare workers who provided care in the center during the epidemic and (2) that the investigators were not able to observe the practices of healthcare workers directly, as the center had been closed as a direct result of the epidemic. Nonetheless, in their investigation, the authors found several breaches of expected infection control practice in this dialysis center. The authors speculate that a variety of factors likely contributed to the epidemic—disorganization of care, reduced space for care, understaffing, high rates of staff turnover, and inadequate training.

In a third article, Faustini et al. report a cluster of HCV infections associated with the transfusion of autologous, ozone-enriched blood in Rome, Italy.[9] In this study, the identification of three individuals newly diagnosed as having HCV and the realization that all three had received ozone-enriched autologous blood transfusions at the same hospital on the same day prompted an epidemiologic investigation. The rationale for ozone therapy is not discussed, but the authors do provide two references for the practice. Again, the rationale for this clinical practice is not discussed, but must be considered, especially from the first, do no harm perspective. This study has several limitations, as well. First, the authors really do not know how this unique treatment modality contributes to the risk for infection, they can only surmise. Second, the kinetics of infection implied in the article simply cannot explain what happened. The one specific day in which all three of the patients received ozone treatments was only two or three days before the diagnosis of hepatitis in one of the three—clearly leaving inadequate incubation time for this infection. On balance, however, as is the case for the two articles discussed above, the almost inevitable conclusion to be reached from this investigation is that the practice of ozone-enriched autologous transfusion was associated with risk for HCV infection, and that cross-contamination with HCV was somehow associated with this practice.

The concise communication by Germain et al. from France in this issue of *Infection Control and Hospital Epidemiology* describes a cluster of three HCV infections in a surgery practice.[10] These clustered infections were related to use of multidose vials by the anesthesia staff. The anesthetist reported it likely that several injections from two separate vials of fentanyl delivered to the first patient were prepared using the same syringe and needle. The second vial was reused on the other three clustered patients. In addition, the authors note that review of infection control procedures identified that injections were administered directly into peripheral venous catheters that did not have in-line anti-reflux valves.

Thus, these four articles underscore that—despite the emphasis on preventing transmission of blood-borne pathogens in the healthcare setting for the past two decades—the healthcare workers who were caring for the patients in these four centers used inadequate, and sometimes even slipshod, infection control procedures. This lack of attention to the appropriate details of infection prevention stands a substantial risk to do harm to patients and simply must be viewed as unnecessary risky business.

This issue of *Infection Control and Hospital Epidemiology* also contains two additional articles that raise "red flags" for those of us interested in trying to prevent the transmission of blood-borne pathogens in the healthcare

setting. The first of these articles, by Shah et al., provides a detailed analysis of the comparative rates of hospital-based and non–hospital-based healthcare workers' compensation claims for needlestick injuries in the state of Washington from 1996 through 2000.[11] This descriptive study contains several pieces of disquieting news. First, the investigators noted a steady increase in compensation claims for needlestick injuries occurring among healthcare workers working in non-hospital settings. Although they noted a small, but statistically insignificant, decrease in injuries among hospital-based healthcare workers, the investigators also noted that their data collection was incomplete. The fact that no decrease in injuries and occupational exposures could be detected in this 5-year period is discouraging.

In this study, disposal of used needles and recapping of needles were most frequently associated with needlestick exposures for non–hospital-based healthcare workers. In the context of our experience during the past 15 years in managing occupational exposures to blood-borne pathogens in the healthcare setting, this finding seems (to paraphrase the words of former New York Yankee catcher Yogi Berra) "like déjà vu all over again." Thus, despite the enormous investment in training of healthcare workers who have the potential for exposure to blood in the workplace, and despite substantial investment in, and development of, safer technologies, these injuries and exposures continue to occur at an alarming rate.

El-Far et al. evaluated the rate of antiretroviral resistance among isolates of HIV in source-patients for needlestick exposures in Sao Paulo, Brazil.[12] In this small study, the authors were able to evaluate the genotypic resistance patterns of HIV isolates from 18 patients whose blood or body fluids served as the source of occupational exposures and from 26 additional patients considered "potential sources for accidents." They found that 18 of 44 individuals had isolates with genotypic resistance to either nucleoside analogues, protease inhibitors, or both. These investigators suggest that this finding calls into question the use of recommended post-exposure prophylaxis regimens to which the isolates with genotypic resistance might not be susceptible. Although these data definitely do raise concern, no instances of transmission were documented in this admittedly very small study. One additional distressing finding from this study was the fact that two of the source-patients who had never had any exposure to antiretroviral agents had HIV isolates that had genotypic resistance to one or more antiretroviral agents.

I would caution that the clinical relevance of genotypic resistance to failure of post-exposure chemoprophylaxis is only loosely connected. On consideration of the mechanisms of action of the various classes of antiretroviral drugs, virtually none of them are intuitive candidates for prophylaxis. Even in 2005, I believe we have an extremely limited understanding of how these agents prevent infection. A fascinating article by Pope et al. demonstrated that the in vitro infectivity of HIV-pulsed dendritic cells for susceptible T cells was blocked by the addition of a nucleoside analogue.[13] Further, when Sperling et al. reanalyzed the genotypic resistance patterns from the mothers in the AIDS Clinical Trials Group Protocol 076 trials of zidovudine administered to attempt to prevent maternal–fetal transmission of HIV, no correlation could be found between zidovudine resistance and transmission.[14]

This issue of *Infection Control and Hospital Epidemiology* does contain a little good news. Landrum et al. describe the effective use of the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, PA) to evaluate source-patient infection status and compared their findings with enzyme-linked immunosorbent assay tests.[15] Although this test is not approved by the Food and Drug Administration for use with serum, it performed admirably in this study when compared with traditional test methodology. These investigators also found that the use of the rapid test reduced both costs and healthcare worker anxiety, although they acknowledge that the findings relating to decreases in healthcare worker anxiety could easily be subject to recall bias.

The healthcare workplace is far from risk free. The past two decades have seen a remarkable investment of effort and resources in an attempt to mitigate the risk for transmission of blood-borne pathogens in healthcare settings. This issue of *Infection Control and Hospital Epidemiology* demonstrates that we have a long way to go to reduce risks and to increase patient safety in the healthcare environment. Five of these articles emphasize that in the 15 years that have elapsed since our "Risky Business" article was published, we have not accomplished even the first of the seven strategies that we identified in that article. Several safer devices have found their way into the healthcare workplace in the past 15 years, and implementation of these devices has reduced risks for some types of occupational exposures. The use of needleless intravenous devices, for example, has clearly reduced occupational needlestick exposures, but may have had an adverse effect on bacteremia rates.[16,17] Healthcare worker safety must, of necessity, not adversely affect patient safety or patient care.

Whereas we have learned a great deal about the epidemiology of, and factors contributing occupational and nosocomial risk for, occupational exposures to blood, we have made little progress in developing strategies that make it possible to alter long-term habits and ingrained healthcare worker behaviors that are associated with risk for transmission of blood-borne pathogens to the healthcare workers themselves and their patients. Especially in instances in which staffing ratios are less favorable and workloads are increased, maintaining the consistent, sentient use of basic standard/universal precautions as well as the principles of aseptic technique have proved to be significant challenges for all of healthcare. Lack of adherence to these sensible guidelines contributes unnecessary risk in our workplace. This issue of *Infection Control and Hospital Epidemiology* demonstrates conclusively that blood-borne pathogen risks are bidirectional and that patient safety may be substantially compromised as a result of "corner-cutting" and "shortcuts" in healthcare.

The "wake-up" call that was provided by the Institute of Medicine's report on patient safety in U.S. healthcare underscores the necessity that the healthcare industry develop new strategies for ensuring compliance with appropriate aseptic techniques, basic infection control procedures, and standard/universal precautions. We simply must intensify our focus on both goals—increasing patient safety and decreasing occupational risks.

REFERENCES

1. Beekmann SE, Fahey BJ, Gerberding JL, Henderson DK. Risky business: using necessarily imprecise casualty counts to estimate occupational risks for HIV-1 infection. *Infect Control Hosp Epidemiol* 1990;11:371-379.
2. Committee on Quality of Health Care in America. *To Err Is Human: Building a Safer Health System.* Washington, DC: Institute of Medicine Press; 1999.
3. Centers for Disease Control. *Pneumocystis* pneumonia. *MMWR* 1981; 30:250-252.
4. Centers for Disease Control. Acquired immune deficiency syndrome: precautions for clinical and laboratory staffs. *MMWR* 1982;31:577-580.
5. Stricof RL, Morse DL. HTLV-III/LAV seroconversion following a deep intramuscular needlestick injury. *N Engl J Med* 1986;314:1115.
6. Leibowitz S, Greenwald L, Cohen I, et al. Serum hepatitis in a blood bank worker. *JAMA* 1949;140:1331-1333.
7. Samandari T, Malakmadze N, Balter S, et al. A large outbreak of hepatitis B virus infections associated with frequent injections at a physician's office. *Infect Control Hosp Epidemiol* 2005;26:745-750.
8. Savey S, Simon F, Izopet J, Lepoutre A, Fabry J, Desenclos J-C. A large nosocomial outbreak of hepatitis C virus infections at a hemodialysis center. *Infect Control Hosp Epidemiol* 2005;26:752-760.
9. Faustini A, Capobianchi MR, Martinelli M, Abbate I, Cappiello G, Perucci CA. A cluster of hepatitis C virus infections associated with ozone-enriched transfusion of autologous blood in Rome, Italy. *Infect Control Hosp Epidemiol* 2005;26:762-767.
10. Germain J-M, Carbonne A, Thiers V, et al. Patient-to-patient transmission of hepatitis C virus through the use of multidose vials during general anesthesia. *Infect Control Hosp Epidemiol* 2005;26:789-792.
11. Shah SM, Bonauto D, Silverstein B, Foley M. Workers' compensation claims for needlestick injuries among healthcare workers in Washington State, 1996–2000. *Infect Control Hosp Epidemiol* 2005;26:775-781.
12. El-Far F, Medeiros EAS, Gasparoto CT, Diaz RS. Antiretroviral drug resistance among patients with human immunodeficiency virus who act as sources or potential sources in occupational accidents involving healthcare workers. *Infect Control Hosp Epidemiol* 2005;26:782-788.
13. Pope M, Gezelter S, Gallo N, Hoffman L, Steinman RM. Low levels of HIV-1 infection in cutaneous dendritic cells promote extensive viral replication upon binding to memory CD4+ T cells. *J Exp Med* 1995;182:2045-2056.
14. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant: Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1996;335:1621-1629.
15. Landrum ML, Wilson CH, Perri LP, Hannibal SL, O'Connell RJ. Usefulness of a rapid human immunodeficiency virus–1 antibody test for the management of occupational exposure to blood and body fluid. *Infect Control Hosp Epidemiol* 2005;26:768-774.
16. Cookson ST, Ihrig M, O'Mara EM, et al. Increased bloodstream infection rates in surgical patients associated with variation from recommended use and care following implementation of a needleless device. *Infect Control Hosp Epidemiol* 1998;19:23-27.
17. Kellerman S, Shay DK, Howard J, et al. Bloodstream infections in home infusion patients: the influence of race and needleless intravascular access devices. *J Pediatr* 1996;129:711-717.

For persistent antiseptic activity, you're in the clear with Hibiclens.®

Clinical studies* have proven the efficacy and persistence of Hibiclens, demonstrating how it goes to work on germs and provides a cumulative effect that continues to kill germs long after your shift is over.

The most recent study observed agar plates that were inoculated with staph aureus. Hands were washed with Hibiclens, and then pressed onto the inoculated plates – palms down. The plates were then incubated and a whitish film of staph aureus grew in areas not affected by Hibiclens.

Hibiclens, armed with its 4% chlorhexidine gluconate (CHG) formulation immediately killed germs and displayed a cumulative effect that didn't know when to quit. In fact, this demonstration showed the antiseptic still killing on the fifth day of use and 6 hours after the final daily handwash.**

Immediately kill and keep killing germs with Hibiclens. For more information, call 1-800-843-8497.

*Regent Medical Study #030917-150
The persistence of Hibiclens provides extra protection. Recommended antiseptic procedures of your institution should be followed when using Hibiclens.

**The darker color in the hand print shows the cumulative effect of Hibiclens on staph aureus, the fifth day of use, 6 hours after the final daily handwash.

Regent Medical®

HIBICLENS®

First & last wash of the day!

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

As your knowledge grows, your influence multiplies.

Earn the degree you need to help protect people from the spread of infectious disease. Walden University offers rigorous academic programs taught by public health experts from around the world, and our online format lets you share and learn best practices with a tight-knit community of professors and professionals just like you. The need is great for highly skilled epidemiologists. To learn about enrolling, call or go online.

MASTER'S AND PH.D. DEGREES ONLINE

Ph.D. in Public Health - Epidemiology

Master of Public Health

M.S. in Public Health

Walden University is accredited by The Higher Learning Commission and a member of the North Central Association, www.ncahlc.org; 312-263-0456.

Walden University's Master of Public Health program is in applicant status for accreditation by the Council on Education for Public Health (CEPH). CEPH is a professional accrediting agency recognized by the U.S. Department of Education.

WALDEN UNIVERSITY

A higher degree. A higher purpose.

866-492-5336

www.WaldenU.edu/iche

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

A LARGE OUTBREAK OF HEPATITIS B VIRUS INFECTIONS ASSOCIATED WITH FREQUENT INJECTIONS AT A PHYSICIAN'S OFFICE

Taraz Samandari, MD, PhD; Naile Malakmadze, MD; Sharon Balter, MD; Joseph F. Perz, DrPH; Marina Khristova, PhD; Leah Swetnam, MD; Katherine Bornschlegel, MPH; Michael S. Phillips, MD; Iqbal A. Poshni, PhD; Preeti Nautiyal, MD; Omana V. Nainan, PhD; Beth P. Bell, MD; Ian T. Williams, PhD

ABSTRACT

OBJECTIVES: To determine whether hepatitis B virus (HBV) transmission occurred among patients visiting a physician's office and to evaluate potential transmission mechanisms.

DESIGN: Serologic survey, retrospective cohort study, and observation of infection control practices.

SETTING: Private medical office.

PATIENTS: Those visiting the office between March 1 and December 26, 2001.

RESULTS: We identified 38 patients with acute HBV infection occurring between February 2000 and February 2002. The cohort study, limited to the 10 months before outbreak detection, included 91 patients with serologic test results and available charts representing 18 case-patients and 73 susceptible patients. Overall, 67 patients (74%) received at least one injection during the observation period. Case-patients received a median of 14 injections (range, 2–25) versus 2 injections (range, 0–17) for susceptible patients ($P < .001$). Acute infections occurred among 18 (27%) of 67 who received at least one injection versus none of 24 who received no injections (RR, 13.6; CI_{95}, 2.4–undefined). Risk of infection increased 5.2-fold (CI_{95}, 0.6–47.3) for those with 3 to 6 injections and 20.0-fold (CI_{95}, 2.8–143.5) for those with more than 6 injections. Typically, injections consisted of doses of atropine, dexamethasone, vitamin B12, or a combination of these mixed in one syringe. HBV DNA genetic sequences of 24 patients with acute infection and 4 patients with chronic infection were identical in the 1,500-bp region examined. Medical staff were seronegative for HBV infection markers. The same surface was used for storing multidose vials, preparing injections, and dismantling used injection equipment.

CONCLUSION: Administration of unnecessary injections combined with failure to separate clean from contaminated areas and follow safe injection practices likely resulted in patient-to-patient HBV transmission in a private physician's office (*Infect Control Hosp Epidemiol* 2005;26:745-750).

An estimated 1.25 million Americans are chronically infected with hepatitis B virus (HBV), resulting in approximately 5,000 deaths annually.[1,2] In 2001, there were approximately 78,000 new HBV infections, with 8,156 cases of acute hepatitis B reported to the Centers for Disease Control and Prevention (CDC).[3] The most commonly reported risk factors for infection among case-patients with acute hepatitis B are injection drug use or multiple sexual partners.[4] Both chronically and acutely infected individuals can potentially serve as reservoirs of HBV infection.

Patient-to-patient transmission of HBV in healthcare settings is rarely reported and has been primarily recognized in the context of outbreaks.[5] When identified, most of these outbreaks have been associated with breaks in standard infection control practices by healthcare workers, resulting in the contamination of equipment or medications. Vehicles implicated in outbreaks involving patient-to-patient transmission include multidose vials,[6-8] finger-stick devices,[9,10] acupuncture needles,[11] and jet injection guns.[12]

In December 2001, two women, 79 and 92 years old, were diagnosed as having symptomatic acute hepatitis B. They had no identified risk factors for infection, but both patients had attended the same physician's office in New York City. We conducted an investigation to determine whether these patients acquired hepatitis B at this office, whether additional cases were associated with the office, and the potential mechanisms of HBV transmission among the infected patients.

Drs. Samandari, Perz, Khristova, Nainan, Bell, and Williams are from the National Center for Infectious Diseases, Division of Viral Hepatitis; Dr. Malakmadze is from the Global Immunization Division, National Immunization Program; Drs. Samandari, Malakmadze, and Phillips are from the Epidemic Intelligence Service, Epidemiology Program Office; and Dr. Swetnam is from the Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia. Drs. Balter, Phillips, Poshni, and Nautiyal and Ms. Bornschlegel are from the New York City Department of Health and Mental Hygiene, New York, New York.

Address reprint requests to Dr. Ian Williams, Division of Viral Hepatitis, MS G-37, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333. iwilliams@cdc.gov

The authors thank Michael P. Mullen, MD, who reported the outbreak; Gregory Armstrong, MD, for assisting with the mathematical model; Paul Swenson, PhD, for testing the HBsAg subtypes; Wendi Kuhnert, PhD, for managing laboratory samples; and Marcelle Layton, MD, for her guidance through the investigation and for the preparation of the manuscript. They also thank Paula E. Del Rosso, RN; Robin R. Hennessy; Alan Dunn, MD; Kathy Legaspi, RN; Stephanie Sharps, MD; Sirenda Vong, MD MSc; Don Weiss, MD, MPH; Dan Cimini, RN, MPH; and Karen Schlanger, MPH, for participating in the investigation.

METHODS

Identification and Interviews of Case-Patients

We reviewed laboratory reports received by the New York City Department of Health (DOH) of positive test results for serologic markers of acute HBV infection between January 2000 and December 2001. These reports were cross-matched with the names of the patients attending the physician's office. Letters recommending testing for serologic markers of HBV infection were sent to patients with available office charts, a telephone outreach campaign to notify all patients was conducted, a press release was issued, and local physicians were notified.

Patients with acute HBV infection were interviewed using a standardized questionnaire that collected information about demographics, symptoms, and potential risk factors for infection both inside and outside the physician's office. Potential risk factors outside the office could have included injection drug use or high-risk sexual behavior. Possible risk factors associated with the physician's office could have included receipt of fingersticks or injections.

Laboratory Methods

Serologic testing for HBV infection was performed at the New York City DOH laboratory and included total antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and hepatitis B surface antigen (HBsAg) (Abbott Laboratories, Abbott Park, IL). If the total anti-HBc was positive, testing for IgM anti-HBc was performed (Abbott Laboratories). Samples from some patients were sent by their physicians to commercial laboratories for testing and the results were provided to the investigators.

Samples from HBsAg-positive patients tested by the DOH laboratory were analyzed for the HBsAg subtype by enzyme immunoassay at the Seattle King County Public Health Laboratory, Department of Health.[13] Samples from HBsAg-positive or IgM anti-HBc–positive patients were tested at the Molecular Epidemiology Laboratory, Division of Viral Hepatitis, CDC, for HBV DNA by nested polymerase chain reaction (PCR) using commercially available reagents and previously published techniques.[14] A 1,500-bp region of the HBV genome spanning part of the HBV polymerase gene, pre-S1, pre-S2, and most of the S region was amplified as three fragments. Primers used for the first round of PCR of fragment 1, fragment 2, and fragment 3 were as follows: sense 2317 5'-AGACCACCAAATGCCCCTATC, anti-sense 2933 5'-TCGGGAAAGAATCCCAGAGGAT; sense 2767 5'-GGAAGGCTGGTATTCTAT, anti-sense 457 5'-AGGACAAACGGGCAACATACCT; and sense 179 5'-CTAGGACCCCTGCTCGTGTT, anti-sense 704 5'-CGAACCACTGAACAAATGGCACT, respectively. Primers used for the PCR of fragment 1, fragment 2, and fragment 3 were as follows: sense 2418 5'-GCGTCGCAGAAGATCTCAATCT, anti-sense 2894 5'-CCCATGCTGTAGCTCTTGTTCCC; sense 2820 5'-CTACACGTAGCGCCTCATTTTG, anti-sense 267 5'-CCTCCCCCTAGAAAATTGAGAG; and sense 248 5'-CTAGACTCGTGGTGGACTTCTCT, anti-sense 662 5'-AACGGACTGAGGCCCACTCCCATA, respectively.

Serologic Definitions

Patients whose serum was positive for IgM anti-HBc were classified as having acute HBV infection. If the date of onset could be determined, it was presumed that the patient was likely viremic for a period of 12 weeks after elevation of liver-associated serum enzymes.[15]

Patients whose serum was positive for HBsAg and total anti-HBc but negative for IgM anti-HBc were classified as having chronic HBV infection. Patients whose serum was positive for anti-HBs and negative for other markers were considered to have immunity consistent with a history of vaccination. Patients who were negative for total anti-HBc, HBsAg, and anti-HBs were classified as susceptible.

Cohort Study

To identify factors associated with HBV infection, a retrospective cohort study was conducted among patients visiting the same physician's office during the study period from March 1 to December 26, 2001. Case-patients who were diagnosed as having acute infection prior to September 1, 2001, were excluded because they could have been exposed prior to the study period. Additionally, patients were excluded if their charts were missing from the physician's office, if they had evidence of prior infection or immunization, or if they had incomplete serologic test results. The dates of visits, percutaneous exposures, and demographics were abstracted from patient charts.

Office Inspection and Environmental Assessment

The physician and his staff were tested for serologic markers of HBV infection and interviewed regarding their duties, procedures, and practices. Two medical technicians were observed preparing and administering mock injections.

Statistical Analysis

Comparisons of age, number of injections, and number of visits were made using a nonparametric test (Kruskal–Wallis one-way analysis of variance; Epi-Info software, version 6.04b, CDC, Atlanta, GA). Relative risks (RRs) and 95% confidence intervals (CI_{95}) were calculated for associations of acute infection with various exposures. Continuous variables relating to the quantities of injectable medications were dichotomized using levels corresponding to the median. When a 0 cell occurred on univariate analysis, 0.5 was added to each cell, RRs were calculated using Woolf's estimate, and the Fisher exact confidence intervals were determined.[16] A logistic regression model was used to evaluate infection status in relation to selected variables using SAS software (version 8.01; SAS Institute, Inc., Cary, NC). The independent variables were entered manually and assessed for colinearity, after which both stepwise forward and backward elimination were performed. To characterize the risk of infection per injection, infection status was also modeled using maximum likelihood methods.[17] *P* values of less than .05 were considered statistically significant.

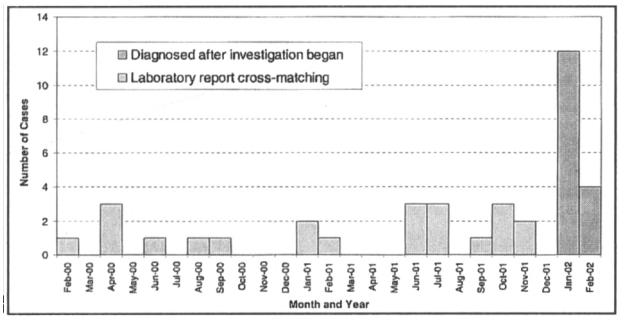


FIGURE 1. Cases of acute hepatitis B virus infection among patients visiting a physician's office from January 2000 to February 2001, by date of positive serologic test result (n = 38). Solid bars (February 2000 to November 2001) represent cases of acute hepatitis B virus infection identified through cross-matching the names of the patients visiting the physician's practice with the laboratory reports. Hatched bars (January and February 2002) represent patients for whom serologic data became available after the outbreak investigation was initiated.

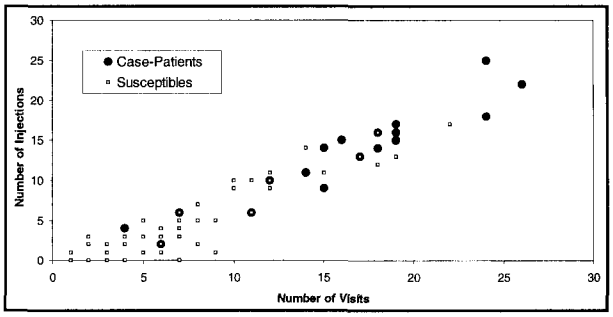


FIGURE 2. Number of injections received by case-patients (n = 18) with acute hepatitis B virus infection and susceptible patients (n = 73), by number of visits to the physician's office from March 1 to December 26, 2001. For susceptible patients, each square may represent more than one individual.

RESULTS

Identification of Patients With HBV Infection

Letters were sent to 1,042 patients. When information from the cross-match of patient names with reports of positive results on serologic tests received by the New York City DOH, chart reviews, and serologic testing as a part of the investigation were combined, serologic results were available for 222 patients. Four patients were identified as chronically infected, 28 patients had resolved infection, and 2 patients had serologies consistent with prior immunization. Thirty-eight patients had evidence of acute HBV infection, with onsets between February 2000 and February 2002, 4 of whom reported jaundice (Fig. 1). The mean age of patients with acute HBV infection was 71 years (range, 46 to 92 years) and 60% were women.

Among 24 patients with acute HBV infection who were interviewed, no exposures common to all patients were identified except attendance at this office. During the 6-month period prior to the onset of HBV infection, one case-patient reported injection drug use. None of the patients reported any other percutaneous exposures or high-risk sexual activity. No common exposures to other healthcare providers were identified.

Serotyping and Molecular Results

Thirteen of 17 serum samples from HBsAg-positive patients had identifiable subtypes; all were subtype adw2. HBV was sequenced from the serum of 28 HBsAg-positive patient samples; all 28 sequences, including sequences from the 4 patients identified as chronically infected, were identical in all 3 regions examined. The sequences all belonged to HBV genotype A.

Cohort Study

A total of 275 patients visited the physician's office between March 1 and December 26, 2001. We obtained complete serologic information for 139 (51%) of these patients. Patients with known serologic status made significantly more visits to the physician's office during the study period than did those with unknown serologic status (8.8 vs 5.3 visits, respectively; $P < .01$); however, their mean ages did not differ significantly (59 and 60 years, respectively; $P = .87$). Forty-eight patients (35%) were excluded because of evidence of HBV infection prior to September 1, 2001 (n = 40) or because their charts could not be found for abstraction (n = 8). Thus, the cohort analysis included 91 patients (18 case-patients and 73 susceptible patients). Their average age was 56 years (range, 21 to 92 years), 55 (60%) were women, and they had an average of 7.8 visits (range, 1 to 26 visits) to the office during the study period.

The median age of case-patients was 74 years (range, 47 to 92 years) and that of susceptible patients was 50 years (range, 21 to 87 years) ($P < .01$). The median number of office visits of the case-patients was 17 (range, 4 to 26 visits) and of the susceptible patients was 4 (range, 1 to 22 visits) ($P < .01$). Overall, 67 patients (74%) were injected with at least one medication during the period of observation, including all case-patients. Case-patients received a median of 14 injections (range, 2 to 25 injections), whereas susceptible patients received a median of 2 injections (range, 0 to 17 injections) during this period ($P < .001$; Fig. 2). Acute infections occurred in 27% of those receiving at least 1 injection compared with 0% of those receiving no injections (estimated RR, 13.6; CI_{95}, 2.4 to undefined; Table). Compared with those who received 0 to 2 injections, those who received 3 to 5 injections had a 5.2-fold (CI_{95}, 0.6 to 47.3) higher risk of becoming infected and those who received more than 6 injections had a 20.0-fold (CI_{95}, 2.8 to 143.5) higher risk of becoming infected.

Among the 91 patients included in the cohort study, injections were administered during 488 (69%) of 710 office visits during the observation period. Typically, patients received doses of atropine, dexamethasone, or vitamin B12 in injections that combined two or three of these medications. Indications for these medications were not available from patient charts. Seventy-five percent of all injections contained 2 medications and 19% contained 3 medications. Receiving injectable substances other than atropine, dexamethasone, and vitamin B12 was not significantly associated with infection. Such substances, which represented

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE
RISK OF ACQUIRING HEPATITIS B VIRUS INFECTION AMONG A COHORT OF PATIENTS TREATED AT THE PHYSICIAN'S OFFICE BETWEEN MARCH 1 AND DECEMBER 26, 2001

	Exposed Patients		Unexposed Patients			
Characteristic	No. of Cases (%)	Total	No. of Cases (%)	Total	RR	CI_{95}
Total cohort (n = 91)						
Age > 55 y	15 (32)	47	3 (7)	44	4.7	1.5–15.1
Female	10 (18)	55	8 (22)	36	0.8	0.4–1.9
Patient of the physician for > 5 y*,†	10 (34)	29	2 (7)	28	4.8	1.2–20.1
> 5 visits to office†	17 (35)	48	1 (2)	43	15.2	2.1–109.7
≥ 1 injection	18 (27)	67	0 (0)	24	13.6	2.4–undefined
> 3 injections†	17 (40)	42	1 (2)	49	19.8	2.8–142.8
> 2 injections during 1 visit	4 (44)	9	14 (17)	82	2.6	1.1–6.2
Finger-stick glucometer	1 (14)	7	17 (20)	84	0.7	0.1–4.6
Phlebotomy (≥ 1 time)	17 (21)	81	1 (10)	10	2.1	0.3–14.1
Received injection on same day as a potential source-patient‡	17 (33)	51	1 (3)	40	13.3	1.9–96.0
Subset of cohort receiving ≥ 1 injection						
> 7.5 mL of injectable medications†	16 (48)	33	2 (6)	34	8.2	2.0–33.1
> 10 injectable medications†	15 (44)	34	3 (9)	33	4.8	1.5–15.2
Atropine ≥ 1 time	18 (28)	64	0 (0)	3	2.3	0.2–undefined
Atropine > 3 times†	16 (47)	34	2 (6)	33	7.7	1.9–31.2
Dexamethasone ≥ 1 time	17 (29)	58	1 (11)	9	2.6	0.4–17.5
Dexamethasone > 3 times†	13 (48)	27	5 (13)	40	3.8	1.6–9.6
Vitamin B12 ≥ 1 time	18 (29)	63	0 (0)	4	2.9	0.3–undefined
Vitamin B12 > 4 times†	14 (48)	29	4 (11)	38	4.6	1.7–12.5
Any medication other than atropine, dexamethasone, or vitamin B12 ≥ 1 time	12 (38)	32	6 (17)	35	2.2	0.9–5.1

RR = relative risk; CI_{95} = 95% confidence interval.
*Information was available for 57 of the 91 patients in the cohort study.
†The cutoff shown was at the median.
‡Dates of visits when injections were administered were available for three chronically infected patients and five case-patients whose likely period of viremia was known.

less than 10% of the total number of injections administered, included vitamin B1, vitamin B6, penicillin G, calcium, diphenhydramine, influenza vaccine, liver extract, and a tuberculin test.

To examine the role that potential source-patients may have had in transmitting HBV infection, we determined the incidence of infection according to whether the patient had ever received an injection on the same day as a patient who was identified as likely to have circulating HBV (ie, chronically infected patients or acutely infected patients whose likely viremic period could be determined) during the observation period of March 1 to December 26, 2001. Acute infections occurred among 17 (33%) of 51 patients who received an injection on the same day as a potential source-patient versus 1 (3%) of 40 patients lacking this exposure (RR, 13.3; CI_{95}, 1.9 to 96; Table).

Multivariate analysis was conducted using the following independent variables: age, gender, number of injections received, type of medication, cumulative volumes of medications administered, and whether an injection was received on the same day as one administered to a patient known to be chronically infected or acutely infected with known onset of acute infection. Only the number of injections remained significantly associated in the final regression model (odds ratio, 1.33; CI_{95}, 1.18 to 1.50). There was no association with a specific medication or medication combination when the number of injections was controlled for in the model. The maximum likelihood estimation model indicated that a patient's average risk of infection increased by 5% (CI_{95}, 3% to 7%) with each additional injection received in the office during the study period (Fig. 3).

Office Inspection and Environmental Assessment

The office staff who administered injections included the physician, a medical assistant, an office assistant, and two medical technicians. Procedures performed at the office that involved percutaneous exposures were finger-stick glucose checks, phlebotomy, and injection of medications or vaccinations. All staff members gave injections, although most were administered by the medical technicians. All

five medical staff in the physician's office were negative for markers of HBV infection and one staff member had serologies consistent with hepatitis B vaccination.

This office purchased all injectable medications as multidose vials. Injections were prepared from multidose vials stored on a table in a small medication room. Typically, a single injection consisted of aliquots of two or three different medications that were drawn from these vials after wiping the tops with an alcohol swab. During a mock preparation of an injection, we observed that one technician did not change needles between entering multidose vials. For the three most commonly used medications (atropine, dexamethasone, and vitamin B12), each vial yielded an average of 20 to 40 doses. The multidose vials, which did not require refrigeration, were stored on this table for 1 to 3 weeks. After an injection was administered, the syringe and needle were not disposed of intact in the patient room but were returned to the medication room and dismantled on the same table surface used to store and prepare injectable medications. The used needle was disposed of in a sharps container also located on this table.

Control Measures

The physician complied with the order of the New York City DOH to cease administering injections on December 26, 2001. In February 2002, the New York City DOH communicated by letter with all physicians in the city concerning the critical importance of adhering to guidelines for the control of infection and blood-borne pathogens, properly handling needles and multidose vials, vaccinating healthcare workers against HBV, and promptly notifying the health department of reportable diseases. The physician retired from medical practice and permanently closed his office in April 2002.

DISCUSSION

We have described a large outbreak of HBV infections among patients visiting a physician's office, including 38 cases documented during a 2-year period. The risk of infection was strongly associated with the receipt of injections at this office. Practices that increased the risk for blood contamination of injection equipment were observed. Frequent administration of injectable medications, for which no indications were given in patient medical charts, served to amplify the outbreak.

Our investigation indicated that HBV was most likely transmitted from patient to patient via contaminated injections of medications drawn from multidose vials. All medications for injection were drawn from multidose vials that were typically stored for several weeks in the same area where used syringes and needles were dismantled. Microscopic droplets of blood could have contaminated the tops of these vials during disassembly of needles and syringes.[18] HBV can be present on environmental surfaces in the absence of any visible blood and still cause transmission. In addition, HBV remains viable for at least 7 days on environmental surfaces at room temperature.[19] Thus, medications

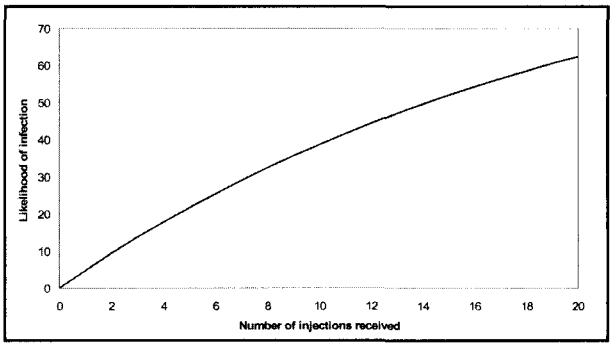


FIGURE 3. Likelihood of acute hepatitis B virus infection as a function of the number of injections received at the physician's office between March 1 and December 26, 2001. The likelihood of infection per injection was modeled using the following equation: case = $1 - e^{(-\beta * \text{number of injections})}$, where the outcome variable "case" was coded "1" for case and "0" for susceptible, and β, an estimator of the risk of infection from each injection, was estimated from actual case-patient data by maximum likelihood methods.

in the multidose vials could have become contaminated with HBV when a needle was subsequently inserted into the vial. Although the physician's staff reported wiping the tops of vials with alcohol swabs before inserting needles, this may not have been done consistently or may not have been adequate to remove or inactivate all traces of HBV. The practice of filling a syringe with several medications without changing needles may have further contributed to cross-contamination of multidose vials with HBV. Additionally, numerous opportunities existed for susceptible patients to become infected because most patients had multiple visits to this office to receive injections.

In our investigation, the genetic sequence of HBV was identical in all samples examined, including 4 chronically infected patients and 24 acutely infected patients, suggesting that this outbreak started with a single patient infected with HBV. Most infected patients continued to visit the office and receive injections on a regular and frequent basis. Any of these patients could have served as a source of infection for other patients in the practice during the approximate 3-month period that they were viremic during their acute infection or for an indefinite period if chronic infection developed. Therefore, the number of potential source-patients likely increased over time, serving to expose an expanding number of patients in the practice.

The chief limitations of this investigation stem from the incomplete ascertainment of serologic status among patients attending the practice and deficiencies in record-keeping practices by the office. Serologic test results were available for approximately half of the patients eligible for the retrospective cohort study. However, patients without serologic test results were found to have had significantly fewer visits to the office and thus received fewer injections than patients for whom serologic test results were available. It follows that patients without serologic test results were likely to be at a lower risk of infection compared with the patients included in the analysis. As a result, the magnitude of the association with injections likely would have

been larger if these patients' serologic statuses had been ascertained, suggesting that our risk estimates were biased conservatively. The deficiencies in recordkeeping at the office also hindered our investigation; several patient charts could not be located, a complete set of invoices was unavailable to verify that syringes and needles were not reused, and there were no records indicating which staff member administered injections or what time of day a patient visited the office.

The physician had not reported the cases of acute hepatitis he diagnosed among his patients to the health department as required by state and local law. The New York City DOH receives more than 3,000 reports of HBV and hepatitis C virus infections each month. Although both physicians and laboratories are required by law to report these cases to the New York City DOH, nearly all of these reports are received from laboratories and most represent chronic infections or repeat testing of previously reported cases. Most laboratory reports lack the demographic, clinical, and epidemiologic information necessary to identify clusters of acute hepatitis cases. Therefore, clinician reporting of isolated cases and suspected clusters of acute hepatitis continues to play an important role in outbreak detection and control.

To prevent transmission of blood-borne pathogens in healthcare settings, providers need to understand and practice in accordance with basic infection control principles including appropriate use of multidose vials and separation of clean and contaminated areas. Since 1992, the state of New York has required that all healthcare professionals receive training in infection control and barrier precautions every 4 years. Records indicate that this physician received such training, suggesting that this type of educational measure may be insufficient by itself. Ensuring that appropriately educated providers apply infection control principles correctly and consistently is difficult and may be particularly challenging in outpatient settings that often lack a formal structure for monitoring and oversight.

We have described an outbreak of HBV infections among patients in a medical practice that is believed to have resulted from administration of unnecessary injections combined with failure to separate clean from contaminated areas and follow safe injection practices. Better characterization of the frequency and characteristics of blood-borne pathogen transmission in outpatient settings is warranted, and improved methods to ensure appropriate infection control practices in outpatient settings are needed.

REFERENCES

1. McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health* 1999;89:14-18.
2. Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization: an economic analysis of current recommendations. *JAMA* 1995;274:1201-1208.
3. Centers for Disease Control and Prevention. *Disease Burden From Viral Hepatitis A, B and C in the United States*. Atlanta, GA: Centers for Disease Control and Prevention; 2004. Available at www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/disease_burden2004.pdf. Accessed August 16, 2005.
4. Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States 1982-1998: implications for vaccination programs. *J Infect Dis* 2002;185:713-719.
5. Williams IT, Perz JF, Bell BP. Viral hepatitis transmission in ambulatory healthcare settings. *Clin Infect Dis* 2004;38:1592-1598.
6. Hutin YJ, Goldstein ST, Varma JK, et al. An outbreak of hospital-acquired hepatitis B virus infection among patients receiving chronic hemodialysis. *Infect Control Hosp Epidemiol* 1999;20:731-735.
7. Alter MJ, Ahtone J, Maynard JE. Hepatitis B virus transmission associated with a multiple-dose vial in a hemodialysis unit. *Ann Intern Med* 1983;99:330-333.
8. Carl M, Francis DP, Maynard JE. A common-source outbreak of hepatitis B in a hemodialysis unit. *Dialysis & Transplantation* 1983;12:222-229.
9. Polish LB, Shapiro CN, Bauer F, et al. Nosocomial transmission of hepatitis B virus associated with the use of a spring-loaded fingerstick device. *N Engl J Med* 1992;326:721-725.
10. Quale JM, Landman D, Wallace B, Atwood E, Ditore V, Fruchter G. Déjà vu: nosocomial hepatitis B virus transmission and fingerstick monitoring. *Am J Med* 1998;105:296-301.
11. Kent GP, Brondum J, Keenlyside RA, LaFazia LM, Scott HD. A large outbreak of acupuncture-associated hepatitis B. *Am J Epidemiol* 1988;127:591-598.
12. Canter J, Mackey K, Good LS, et al. An outbreak of hepatitis B associated with jet injections in a weight reduction clinic. *Arch Intern Med* 1990;150:1923-1927.
13. Swenson PD, Riess JT, Krueger LE. Determination of HBsAg subtypes in different high risk populations using monoclonal antibodies. *J Virol Methods* 1991;33:27-38.
14. Garfein RS, Bower WA, Loney AM, et al. Factors associated with fulminant liver failure during an outbreak among injection drug users with acute hepatitis B. *Hepatology* 2004;40:865-873.
15. Hoofnagle JH, Di Bisceglie AM. Serologic diagnosis of acute and chronic viral hepatitis. *Semin Liver Dis* 1991;11:73-83.
16. Fleiss JL. *Statistical Methods for Rates and Proportions*, ed. 2. New York: John Wiley & Sons; 1981:64-67.
17. Kleinbaum DG. *Logistic Regression: A Self-Learning Text*. New York: Springer-Verlag; 1994.
18. Dankert J, Uitentuis J, Houwen B, Tegzess AM, van der Hem GK. Hepatitis B surface antigen in environmental samples from hemodialysis units. *J Infect Dis* 1976;134:123-127.
19. Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of hepatitis B virus after drying and storage for one week. *Lancet* 1981;1:550-551.

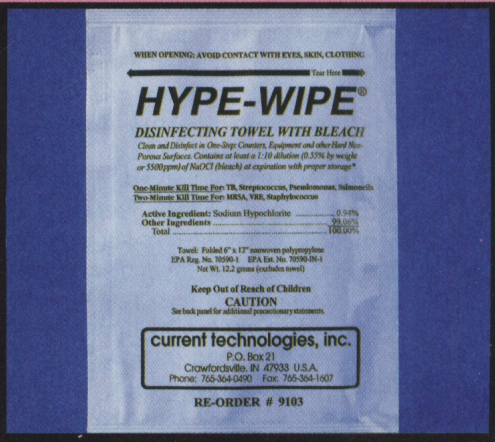
NEW! KILLS C. DIFF.

OUR BLEACH DISINFECTANTS ARE THE BEST AVAILABLE!

- Kill a broad range of microorganisms
- In the *Shortest* contact times!

CALL FOR FREE SAMPLES

Choose Between Towelettes or Spray Bottles



BLEACH-RITE® Disinfecting Spray

- Available in 16 oz., 32 oz. and 64 oz. bottles
- Ships with spill-proof cap and trigger sprayer

HYPE-WIPE® Towelettes

- Full Size (6" X 12" towel in a pocket-sized pouch) is sufficient to wipe down 40 sq. feet.
- Mini (3" X 3" towel) is great for glucometers, coagulation devices plus small spills

Kill Claims / Contact Times

- *BLEACH-RITE*® Disinfecting Spray:
  - 30-second kill time for TB, VRE, Streptococcus and C. difficile (vegetative cells)
  - One-minute for Coronavirus (SARS), HIV, MRSA, Hepatitis-A, Herpes Simplex, Poliovirus, Rotavirus, Pseudomonas, Salmonella, Staphylococcus
- *HYPE-WIPE*® Bleach Towelettes:
  - One-minute kill time for TB, Streptococcus, Salmonella, Pseudomonas and C. difficile (vegetative cells)
  - Two minutes for MRSA, VRE, Staphylococcus

TECHNICAL INFORMATION

- EPA registered as a one-step cleaner / disinfectant.
- Pre-mixed, formulated at .525%, the 1:10 (5250 ppm) dilution of bleach recommended by NCCLS, OSHA, CDC.
- Safe for use on hard, non-porous surfaces including plastics, glass, ceramics, tile, linoleum, enamel, stainless steel. Will corrode aluminum.
- Stabilized for an eighteen-month shelf life.

For use in Lab, Med / Surg, Physician Offices, Research and Industrial Settings:

- For cleaning / disinfecting pipettes, probes, blood pressure cuffs, slide prep area, centrifuges, diagnostic equipment including glucometer and coagulation devices.
- For use on non-critical surfaces and items in clinical / research / industrial labs and hospital areas including ER, OR, radiology, nursing stations, wards, clinics, dialysis and outpatient.
- For use in blood banks, physician and dental offices, phlebotomy trays, ambulances, nursing homes, veterinarian facilities, wastewater facilities, and restrooms.

Solutions To Your Everyday Infection Control Problems

Product list on reverse side. Call for samples and pricing. Order through distributors or direct.

CURRENT TECHNOLOGIES, INC.
P.O. Box 21
Crawfordsville, IN USA 47933
Phone: 1-800-456-4022 or 1-765-364-0490
FAX: 1-765-364-1607
E-mail: currtech@qserve.net

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

A LARGE NOSOCOMIAL OUTBREAK OF HEPATITIS C VIRUS INFECTIONS AT A HEMODIALYSIS CENTER

Anne Savey, MD; Fernando Simon, MD; Jacques Izopet, MD, PhD; Agnès Lepoutre, MD; Jacques Fabry, MD; Jean-Claude Desenclos, MD, PhD

ABSTRACT

OBJECTIVE: To identify modes of HCV transmission during an outbreak of HCV infection in a hemodialysis unit.

DESIGN: An epidemiologic study, virologic analysis, assessment of infection control practices and procedures, and technical examination of products and dialysis machines.

SETTING: A private hemodialysis unit treating approximately 70 patients.

PATIENTS: Detection of HCV RNA by PCR was performed among patients receiving dialysis in 2001. Case-patients were patients who had a first positive result for HCV RNA between January 2001 and January 2002 and either acute hepatitis, a seroconversion for HCV antibodies, or a previous negative result. Three control-patients were randomly selected per case-patient.

RESULTS: Of the 61 patients treated in the unit in 2001 and not infected with HCV, 22 (36.1%) became case-patients with onset from May 2001 to January 2002 for an incidence density rate of 70 per 100 patient-years. Phylogenic analysis identified four distinct HCV groups and an index case-patient for each with a similar virus among patients already known to be infected. No multidose medication vials or material was shared between patients. Connection to a dialysis machine by a nurse who had connected an HCV-infected patient "just before" or "one patient before" increased the risk of HCV infection, whereas using the same dialysis machine after a patient infected with HCV did not. Understaffing, lack of training, and breaches in infection control were documented. Direct observation of practices revealed frequent flooding of blood into the double filter on the arterial pressure tubing set.

CONCLUSIONS: During this outbreak, HCV transmission was mainly patient to patient via healthcare workers' hands. However, transmission via dialysis machines because of possible contamination of internal components could not be excluded (*Infect Control Hosp Epidemiol* 2005;26:752-760).

The prevalence of hepatitis C (HCV) infection among patients receiving dialysis varies from 3% to 71% between countries[1,2] and between centers within a given country.[3-7] A large European study revealed a mean prevalence of 17.7% (HCV antibodies) with a north–south gradient and a mean annual incidence of 1.7%.[8] In France, a study[9] of 1,323 patients receiving dialysis in 25 centers found that 18.6% had HCV antibodies (range, 0% to 44%), of whom 70% were HCV RNA positive. Other, monocentric studies conducted in France reported similar findings (HCV infection ranging from 15% to 37%).[10-15]

The risk of HCV transmission to patients receiving hemodialysis by blood transfusion has been considerably reduced since screening of the blood of donors was introduced in 1992 and the use of erythropoietin transfusion to treat anemia has decreased.[16,17] However, transmission of HCV in dialysis units has not disappeared. In several outbreak reports, the use of phylogenic analysis suggested that HCV transmission could be related to breaches in standard precautions leading to contamination of hands and the environment (ie, the reuse of dialyzers and dialysis equipment, the internal contamination of dialysis machines, and the use or sharing of multidose vials or other articles and devices among patients).[1,8,18]

On December 20, 2001, a private hemodialysis unit in southern France notified the Regional Infection Control Coordinating Center for South-East France of nine HCV seroconversions found after routine HCV screening between September and December 2001. Systematic testing for HCV RNA by polymerase chain reaction (PCR) was then done for all patients who received dialysis in the unit. A multidisciplinary outbreak investigation team was formed to identify the modes of transmission and implement appropriate control measures. On January 17, 2002, 13 additional new HCV infections were identified among patients who received dialysis in the hemodialysis unit. The unit was

Drs. Savey and Fabry are from C. Clin Sud-Est, Centre Hospitalier Lyon Sud, Lyon, France. Drs. Simon, Lepoutre, and Desenclos are from the Département Maladies Infectieuses, Institut de Veille Sanitaire, St. Maurice, France. Dr. Izopet is from the Laboratory of Virology, Centre Hospitalier Universitaire Purpan, Toulouse, France. Dr. Simon is also from the European Program on Intervention Epidemiology Training, Stockholm, Sweden.

Address reprint requests to Dr. Anne Savey, C. Clin Sud-Est, Centre Hospitalier Lyon Sud, pavillon 1M, F-69 495 Pierre-Benite cedex, France. anne.savey@chu-lyon.fr

The authors thank the following individuals who actively contributed to the investigation: J. Blanco; M. Bourdiol-Razes; B. Canaud; S. Coudrais; A. Cournoyer; A. Ficheux; V. Garcia; L. Gazagne; N. Gourdoux; B. Lantz; I. Martin; F. Stec; B. Tran; and D. Verjat.

subsequently closed on January 22, 2002, by the Ministry of Health and the patients were transferred to another unit within the institution.

METHODS

Setting

The hemodialysis unit is operated by a private institution that owns two other units in two other cities in southern France. The three units use the same products, materials, dialysis machines, and procedures. The hemodialysis unit in which the outbreak occurred had been enlarged from 8 to 12 dialysis stations in armchairs in April 2001. Since then, the hemodialysis unit has regularly treated approximately 70 patients who receive dialysis in three shifts per day (morning, afternoon, and evening) three times a week (Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday). Patients receive dialysis on the same days and shifts and, whenever possible, in the same station. No isolation procedure (dedicated staff, area, or dialysis machine) is used for patients infected with HCV. All dialysis machines are of the same brand and type (Fresenius 4008 H, Fresenius Medical Care, Lexington, MA) and all dialyzer membranes and tubing sets are disposable and never reused.

HCV infection is monitored through serum alanine aminotransferase (ALT) testing monthly and systematic, third-generation, enzyme-linked immunosorbent assay (EIA) every 6 months (March and September). There was no precise written protocol for HCV testing in case of an ALT increase. In early 2001, prior to the beginning of the outbreak, the prevalence of HCV infection was 10.2% (5 of 49) in the hemodialysis unit and 15.8% (23 of 146) and 16.7% (8 of 48) in the two other units run by the institution, respectively. The mean seroconversion rate for the three units was 3 to 4 per 100 patient-years between 1997 and 2001. In 2001, one seroconversion and no seroconversions had occurred in the two other units, respectively.

Epidemiologic Investigation

Definitions. A case-patient was defined as an incident HCV infection in a patient who received dialysis in the hemodialysis unit in 2001 with a first positive HCV RNA identification between January 1, 2001, and January 30, 2002, and (1) an increase of ALT of at least twice the patient's mean value in 2001 (referred to as acute hepatitis below), (2) seroconversion for HCV antibodies, or (3) a previous HCV RNA–negative result during the same period. The date of onset of acute hepatitis was defined as the first increase of ALT of at least twice the patient's mean value in 2001. A patient receiving dialysis in the hemodialysis unit during 2001 was defined as chronically infected with HCV if he or she was known to be positive for HCV antibodies on January 1, 2001, or prior to admission to the hemodialysis unit if admitted after January 1, 2001.

For each case-patient, we defined a presumed infection period (during which HCV infection was most likely acquired) that ranged from a minimum of 14 days before the episode of acute hepatitis or 5 days before the first positive HCV RNA identification if earlier to a maximum of 92 days before the episode of acute hepatitis (or admission date in the hemodialysis unit if after) or 5 days before the last negative HCV RNA identification if later.[14] Case-patients were considered potentially infectious 49 days before the increase of ALT or 5 days before the last negative HCV RNA test result if later. Patients chronically infected with HCV were considered infectious from January 1, 2001, or the date of admission to the hemodialysis unit in 2001.

Case-Finding and Data Collection. Active case-finding using HCV RNA PCR was performed among patients receiving dialysis in the unit in 2001. Data on age, gender, primary cause of renal failure, medical and dialysis history, blood transfusions, recent surgical or invasive medical procedures, insulin therapy and other treatments, travel abroad, tattoos, piercings, and intravenous drug use were collected for case-patients from the medical records. For each hemodialysis session, date, connecting hours, type of vascular access, connecting nurses, and dialysis machine identification number were obtained from the hemodialysis unit database. All healthcare workers who worked in the hemodialysis unit during early 2002 (n = 29) or at any time during 2001 (n = 35) were invited to visit the referent occupational health physician of the hemodialysis unit. During this visit, they were informed of the outbreak and testing for ALT, HCV antibodies, and HCV RNA was recommended.

Case–Control Study. To assess the role of hemodialysis machines and nurses' care activities in the transmission of HCV, we conducted an incidence density case–control study[19,20] among patients receiving dialysis in the hemodialysis unit in 2001. For each case-patient, three control-patients were chosen from among patients with no HCV infection (ie, those who were not chronically infected with HCV on January 1, 2001, or on the date of admission if later and those who had a negative HCV RNA PCR result 3 weeks after the last day of the infection period of the matched case-patient or later) at the time of onset of acute HCV infection in the case-patient. Accordingly, a potential control-patient could serve as a control-patient several times but for different infection periods. Because of the high incidence of HCV infection within the unit, a patient with no HCV infection at the time of inclusion as a control-patient could later become a case-patient.[19,20]

To assess the role of dialysis machines and nurses in HCV transmission, we defined two sets of exposure variables to HCV during the presumed infection period: being connected to the same dialysis machine used by a patient infected with HCV and being connected by a nurse who had connected a patient infected with HCV. The latter included the following exposures during the presumed infection period: being connected three or more times by a nurse who had connected an HCV-infected patient just before and being connected three or more times by a nurse who had connected an HCV-infected patient one patient before. The cutoff of three times was determined after observation of the distribution of the number of connections for these two variables to have a level of exposure among control-patients of approximately 20% to 25%. A case-patient or a control-patient was considered

exposed to HCV if the patient to whom he or she had been exposed in the hemodialysis unit, via the dialysis machine or the connecting nurse, was infectious during the presumed infection period of the matched case-patient, as defined above. The other exposures and individual risk factors that were also tested were age, gender, type of nephropathy, being connected by a nurse in training, and the nurse-to-patient ratio during the dialysis session.

Statistical Analysis. We described cases of HCV infection by time, place, and patient characteristics and calculated attack rates and incidence densities by patient-years of dialysis during 2001. Because of the incidence density design, we did a matched analysis[19] of the case–control study using univariate and multiple conditional logistic regression with Stata software (version 6.0; StataCorp, College Station, TX). All variables were introduced in the multivariate model, as well as interaction terms, and were excluded in the modeling procedure according to the likelihood ratio and Wald test statistics, and we checked for the fit of the final model.[21] To assess whether specific modes of transmission may have occurred for specific genotypes, we ran a secondary univariate analysis by specific genotypes in which the exposure of interest had to match the HCV genotype analyzed.

Virologic Investigation

A virologic investigation was performed for all patients receiving dialysis in the unit in January 2002 and on archived sera of patients discharged in 2001. HCV RNA was detected by PCR using the Cobas Amplicor HCV (version 2; Roche Molecular Diagnostics, Alameda, CA) technique.[22] After amplification by PCR, genotyping was done by direct sequencing of the NS5B region.[23] A phylogenic analysis was undertaken after amplification and two-strand direct sequencing was performed on a nested PCR product in the E2 gene encompassing the HVR-1 region[15] to determine the consensus sequence. Sequences were aligned and compared with reference sequences (GenBank, National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD) and sequences from local HCV strains. Tree topology was inferred by neighbor-joining with the Kimura two-parameter distance matrix (Phylogeny Interference Package, version 3.56; Department of Genetics, University of Washington, Seattle, WA) with a transition–transversion ratio of 2.0 and drawn with TreeView software (version 1.4; Division of Environmental and Evolutionary Biology, University of Glasgow, Glasgow, United Kingdom). Robustness of grouping was assessed by bootstrap resampling (1,000 replications) (CLUSTAL W software, European Molecular Biology Laboratory, Heidelberg, Germany).

Assessment of Infection Control Practices and Procedures

We first inspected the hemodialysis unit after the transfer of staff and patients to another unit to assess its organization, equipment, and day-by-day staff planning during 2001. The French Ministry of Health recommends one nurse for every four patients and two nurses for every eight patients in a dialysis center for a total nurse-to-patient ratio of 0.375. We calculated the number of days with a nurse-to-patient ratio less than 0.375 for different intervals in 2001 to assess the level of understaffing during 2001. We also analyzed staff turnover, the prior experience of the staff with dialysis, the level of technical training for dialysis of newly recruited nurses compared with what is considered the gold standard (1 week of theoretical and 4 weeks of practical training before full inclusion in the planning), and the educational program for infection control and prevention.

We then directly observed (audited) the staff in the unit of transfer in January 2002. Five investigators observed 46 dialysis sessions during 3 consecutive days that included all shifts (morning, afternoon, and evening) and all patients and staff of the hemodialysis unit. Standardized forms were used to collect information on patient care (connection to and disconnection from the dialysis circuit, monitoring, administration of injections and perfusions, incidents, and observance of standard precautions), cleaning and disinfection of the dialysis machines between sessions and at the beginning and end of the day, and cleaning and disinfection of other materials and environmental surfaces. An evaluation of the disinfecting products used in the unit and the procedures for cleaning the dialysis machines was performed by two experts. They also disassembled the 14 dialysis machines, examined them for blood contamination of internal components or dysfunctions, and reviewed their maintenance records.

RESULTS

Description of the Outbreak

Twenty-two cases were identified by HCV RNA testing among the 61 patients who received dialysis in the hemodialysis unit in 2001 and were known to be HCV negative for an attack rate of 36.1% and an incidence density of 70 per 100 patient-years of dialysis. Twenty-one case-patients had an increase of ALT of at least twice their mean value in 2001 and one case-patient had an increase that did not reach this threshold (this case-patient had a previous negative result for HCV RNA in 2001). At the time of the investigation, only 10 (45.5%) of the 22 case-patients had HCV antibodies by EIA. Acute hepatitis occurred between May 2001 and January 2002 (Fig. 1) with presumed infection periods ranging from March 23 to December 25, 2001. Five (10.2%) of the 49 patients cared for in the hemodialysis unit at the beginning of 2001 were known to be chronically infected with HCV. One of these five patients left the unit, whereas another entered the unit during 2001.

The mean age of the case-patients was 69.7 years (range, 28 to 82 years), and the male-to-female ratio was 2.1. Six case-patients had a central venous catheter and 16 had an arteriovenous fistula. At the onset of acute hepatitis, the duration of dialysis in the unit ranged from 20 to 835 days (mean, 421 days). Medical exposures with potential risk of HCV infection in 2001 were found for 11 case-patients (insulin therapy for 2, blood transfusions for 2 but not during the presumed period of infection, invasive procedures for 3 [1

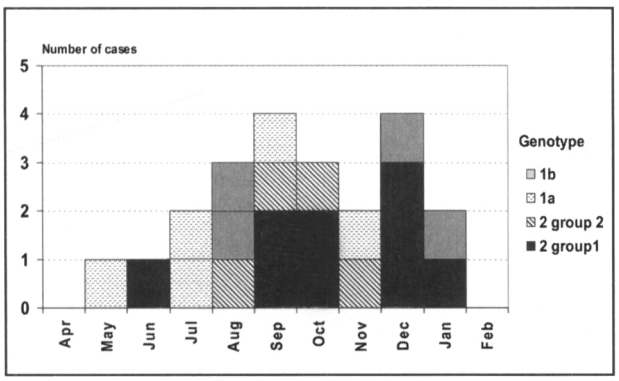


FIGURE 1. Cases (n = 22) of hepatitis C virus infection among patients receiving hemodialysis in a dialysis unit in France by month of onset of acute hepatitis C and by genotype (May 2001 to January 2002).

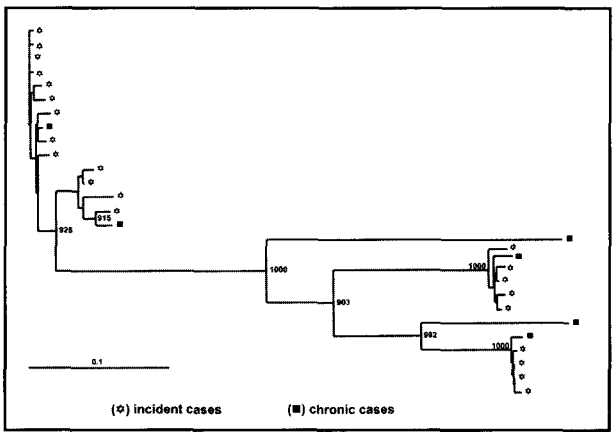


FIGURE 2. Phylogenic analysis of the HVR-1 region of hepatitis C virus (HCV) from incident and chronic cases (for clarity, reference sequences and local HCV strains are not indicated).

colonoscopy, 1 angioplasty, and 1 parathyroidectomy], hospitalizations outside the unit for 3, and dialysis in another European country for 1). We found no evidence of multidose medication vials or materials being shared among patients in the unit. Common exposures could be documented for only a few of the 22 case-patients. Of healthcare workers present in the hemodialysis unit in January 2002, 26 were tested for ALT, HCV antibodies, and RNA and all were negative. Only 10 of those who had worked (n = 35) in the unit in 2001 could be contacted and tested; all of them had negative results.

Virologic Analysis

Of the six patients chronically infected in 2001, two were infected with HCV genotype 1b, one with HCV genotype 1a, two with HCV genotype 2, and one with HCV genotype 3a. The strains from the 22 incident cases belonged to genotypes 1b (4 cases), 1a (5 cases), and 2 (13 cases). The phylogenic analysis of the HVR-1 region revealed four distinct groups with a sequence homology: 1a (five incident and one prevalent cases), 1b (four incident and one prevalent cases), one group of genotype 2 (nine incident and one prevalent cases), and another group of genotype 2 (four incident and one prevalent cases). The mean pairwise nucleotide genetic distances were 0.0040 for cluster 1a, 0.0000 for cluster 1b, and 0.0092 and 0.0043 for the two genotype 2 clusters, respectively. Bootstrap values of 92% to 100% were obtained for each cluster.

Therefore, for each genotype cluster of incident cases, a patient with a similar virus (index case-patient) was found among patients of the hemodialysis unit known to be chronically infected (Fig. 2). All patients with genotype 2 received dialysis on Tuesdays, Thursdays, and Saturdays; all patients with genotype 1a or 1b received dialysis on Mondays, Wednesdays, and Fridays. No transmission occurred from one day to another (Table 1). Transmissions from index case-patients occurred during the same shift (genotype 1a), the following shift (one of the genotype 2 groups), or both (genotype 1b and the second genotype 2 group).

Environmental and Medical Practices Investigation

Organization of the Unit. The total surface of the hemodialysis unit met legal requirements; however, the three rooms dedicated to patient dialysis (with four stations each) were exiguous. The inspection of the hemodialysis unit revealed a lack of individualized space for injection and infusion preparations and for cleaning and decontaminating materials and a lack of a water source in the medical office and in the "isolation station" dedicated to emergency, hospitalized, or severely ill patients. We also found that distances between patients and dialysis machines were less than the legal requirement (1.5 m) and that only mild soap was used for hand antisepsis.

Staff Planning and Training. Overall, 57.3% of the work days in 2001 (180 of 314) had a nurse-to-patient ratio less than the national standard of 0.375: for 131, the ratio was between 0.375 and 0.33; and for 49, the ratio was between 0.25 to 0.33. The number of days with a nurse-to-patient ratio less than 0.375 increased gradually during 2001 as the hemodialysis unit was enlarged from 8 to 12 dialysis stations: from January 1 to May 12 with 8 dialysis stations, the ratio was less than 0.375 for 12% of the days; from May 14 to June 30 with 10 stations, it was less than 0.375 for 19% of the days; and from July 2 to September 1 with 11 stations and also from September 3 to December 31 with 12 stations, it was less than 0.375 for 100% of the days.

We also documented a high turnover of healthcare workers: of the 10 nurses present in January 2001, only 3 were still working in the hemodialysis unit in December. The staff of the hemodialysis unit was then completed with nurses from the two other sites of the institution (10 such nurses worked in the hemodialysis unit at different periods from April to December) and with untrained temporary healthcare workers (2 nurses and 20 nurses' aides for short periods from April to December). The training of newly recruited nurses was insufficient, with their full integration occurring too early. The absence of systematic technical

TABLE 1
DISTRIBUTION OF THE 22 NEW CASES AND 4 PREVALENT CASES OF HEPATITIS C VIRUS IN AN OUTBREAK IN A HEMODIALYSIS UNIT IN FRANCE IN 2001

Days of Dialysis Session	Shift	Genotype (No. of Prevalent Cases)			
		1a	1b	2, Group 1	2, Group 2
Monday, Wednesday, and Friday	Morning	5 (1)	3 (1)	-	-
	Afternoon	-	1	-	-
	Evening	-	-	-	-
Tuesday, Thursday, and Saturday	Morning	-	-	(1)	-
	Afternoon	-	-	4	3 (1)
	Evening	-	-	5	1

training for recruited or temporary nurses' aides was noticed. On-site training of newly recruited nurses was done by a senior nurse included in the planning but not dedicated to training activities. In addition, the hemodialysis unit had no chief nurse from April to September 2001 and no technical agent for floor disinfection during the day (done only at night). There was no infection control and prevention team or educational program in the hemodialysis unit.

Observation and Audit of Practices. The observation of dialysis sessions revealed numerous opportunities for blood contact between patients via either the activities of healthcare workers or dialysis machines. Insufficient adherence with standard precautions (eg, lack of glove use and the sharing of small equipment such as clamps and scissors among patients) was detected. There were problems related to healthcare organization such as exiguous rooms, cluttered carts commonly used during the connection and disconnection of patients that are difficult to disinfect, and the presence of blood-contaminated items (eg, biohazard containers close to cleaning supplies and lack of a patient-free period between shifts for the disinfection of floors, surfaces, and equipment). There was a lack of knowledge of or adherence to procedures such as basic hand hygiene (eg, handwashing with mild soap instead of antiseptic scrub or hydroalcoholic solutions). The quality of antisepsis for connections or injections was substandard. Healthcare workers made numerous passages from one patient to another or to a dialysis machine or a keyboard with contaminated gloves or without handwashing, particularly during busy periods or emergencies. There was a lack of routine decontamination of surrounding surfaces and equipment, including when blood spilled.

In addition, we observed ten instances of accidental flooding of patient blood into the external filters of the arterial pressure tubing set. Although all lines and filters are disposable and never reused, the Luer-Lock and the internal pressure sensor located inside the dialysis machine are not accessible for routine disinfection. For three patients, the flooding of blood reached the second filter or even farther.

Technical Evaluation of Disinfection Products and Dialysis Machines. Freka-Nol (Fresenius Medical Care), which was used for routine surface disinfection (ie, of dialysis machines, chairs, and tables) and for blood spills, was not virucidal and contained more than 30% alcohol, which is not recommended by the French Society for Hygiene. Internal disinfection of the dialysis machines between sessions was done using Oxagal (Hemodia, Labège, France) then Puristeril 340 (Fresenius Medical Care) until December 2001, and using heat plus Diasteril (Fresenius Medical Care) thereafter. These three products are supposed to have virucidal activity, but only the latter provided a test proving efficacy against non-enveloped virus under conditions of use. We did not find any problem in the disinfection programming and control of disinfection cycles of dialysis machines in reference to manufacturer recommendations and maintenance records. Disassembly of the 14 dialysis machines did not reveal any dysfunction. Visual examination of the internal circuits of the dialysis machines in relation to the patient circuits (including venous and arterial blood pressure sensors) did not reveal traces of blood.

Case–Control Study

We included the 22 case-patients and 62 control-patients in the case–control analysis. Case-patients and control-patients had had 2,207 dialysis sessions during the study period. On univariate matched analysis, being connected to a dialysis machine during the infection period three or more times by a nurse who had connected an HCV-patient before was significantly associated with an increased risk of HCV infection. The odds ratio (OR) was 18.2 (95% confidence interval [CI_{95}], 5 to 65) for connecting the patient "just after" and 10.0 (CI_{95}, 3.3 to 30) for connecting the patient "one patient after" a patient infected with HCV. Case-patients and control-patients did not differ significantly regarding age, gender, cause of renal failure, and, during the infection period of matched case-patients, being connected to the same dialysis machine after a patient infected with HCV, being connected by a nurse in training, and the mean nurse-to-patient ratio (Table 2). Variables in Table 2 were included in the conditional multiple regression model. In the final model in which the variable being connected to the same dialysis machine after a patient infected with HCV was forced, only being connected three or more times by a nurse who had connected an HCV-infected patient just before or one patient before significantly increased the risk of HCV infection (Table 3).

TABLE 2
CHARACTERISTICS OF THE CASE-PATIENTS AND CONTROL-PATIENTS OF A HEPATITIS C VIRUS OUTBREAK IN A HEMODIALYSIS UNIT IN FRANCE IN 2001

Characteristic	Case-Patients (n = 22)	Control-Patients (n = 62)	OR (CI_{95})	P
Mean age, y	70	69.4		.91
Female	7 (31.8%)	40 (64.5%)		
Male	15 (68.2%)	22 (35.5%)	1.2 (0.4–3.2)	
Nephropathy				
Vascular	9 (40.9%)	13 (20.9%)	2.9 (0.9–9.3)	
Diabetic	5 (22.7%)	11 (17.7%)	1.9 (0.5–7.2)	
Other	8 (36.4%)	34 (54.8%)	Reference	
Unknown	0 (0.0%)	4 (6.4%)	-	
Connection to the same dialysis machine used by an HCV-infected patient (exposed)	12 (54.5%)	25 (40.3%)	1.8 (0.7–4.7)	
Connection by a nurse who had connected an HCV-infected patient just before (exposed)				
< 3 times	3 (13.6%)	46 (74.2%)	Reference	
⩾ 3 times	19 (86.4%)	16 (25.8%)	18.2 (5–65.1)	
Connection by a nurse who had connected an HCV-infected patient one patient before (exposed)	20 (90.9%)	36 (58.1%)		
< 3 times	6 (27.3%)	49 (79.0%)	Reference	
⩾ 3 times	16 (72.7%)	13 (21.0%)	10.0 (3.3–30)	
Connection by a nurse in training (exposed)	11 (50.0%)	40 (64.5%)	0.6 (0.2–1.5)	
Mean nurse-to-patient ratio	4.5	4.4		.62

OR = odds ratio; CI_{95} = 95% confidence interval; HCV = hepatitis C virus.

Univariate analysis of case–control data by specific genotype gave similar results for genotypes 1a, 1b, and one of the two genotype 2 groups. However, for the HCV genotype 2 group, in addition to being connected by a nurse who had connected an HCV-positive patient of genotype 2, we found an almost fivefold increased risk that was not statistically significant for patients connected to the same dialysis machine just after a patient infected with HCV genotype 2 (OR, 4.6; CI_{95}, 0.8 to 24.9; $P = .07$).

DISCUSSION

Our investigation found that 22 patients acquired HCV infection in a single hemodialysis unit during a 9-month period. This is the largest outbreak of hepatitis C ever reported among patients receiving dialysis. We found no common risk factor or exposure that could explain the occurrence of the cases. Transmission occurred between patients receiving dialysis on the same day during either the same shift (genotype 1a; Table 1), suggesting horizontal transmission via healthcare workers; the shift after (genotype 2, group 1), which could be consistent with vertical transmission possibly via dialysis machines; or both (genotypes 1b and 2, group 2). The analysis of structures, equipment, staff planning, and healthcare practices showed numerous breaches in infection control. Their accumulation supports the hypothesis of transmission via the contaminated hands of healthcare workers, gloves, or small pieces of medical equipment. The case–control study also strongly suggested that HCV was mostly transmitted via healthcare workers during the successive connections of patients.

Our investigation was retrospective and had some limitations. Because of its closure, we could not directly observe the staff in the hemodialysis unit under day-to-day working conditions in 2001. The audit of practices was done in another unit, which could have contributed to the underassessment of some risk factors. In addition, we had to rely on staff interview and medical chart review, which also could have reduced the identification of specific conditions that enhanced HCV transmission. Because there were two other units with the same procedures, a systematic comparison of practices among the three units might have been helpful. However, our limited resources would not allow this, and a retrospective comparison could have been subject to recall biases.

We used an incidence density case–control study design,[19,20] which allows an appropriate estimate of the relative risk when the outcome is frequent. In this design, case-patients and control-patients are matched on the date of case onset and a control-patient may become a case-patient later.[20] Our shorter period of infection as

TABLE 3
RESULTS OF CONDITIONAL MULTIPLE LOGISTIC REGRESSION ANALYSIS IN THE CASE–CONTROL STUDY OF AN OUTBREAK OF HEPATITIS C VIRUS IN A HEMODIALYSIS UNIT IN FRANCE IN 2001

Risk Factor	OR	CI_{95}	P*
Connection by a nurse who had connected an HCV-infected patient just before	10.99	2.55–47.43	.001
Connection by a nurse who had connected an HCV-infected patient one patient before	4.96	1.33–18.44	.017
Connection to the same dialysis machine used by an HCV-infected patient	2.82	0.61–13.12	.18

OR = odds ratio; CI_{95} = 95% confidence interval; HCV = hepatitis C virus.
*Likelihood ratio test of the model: $P < .0001$; fit of the model: $P = .86$.

compared with that documented in the literature could be viewed as a problem. However, if it is used for case-patients and control-patients, there is no bias. Furthermore, it reduces the random misclassification of exposure that arises when this period increases too much toward the maximum, which reduces the odds of observing an effect.[14,24]

The reorganization of the hemodialysis unit in 2001, which increased the number of dialysis stations from 8 to 12 and led to the disorganization of care, reduced space, understaffing, high staff turnover, and lack of training of new staff, probably contributed to HCV transmission. This is consistent with a study indicating that highly trained staff were associated with a lower prevalence of HCV.[25] In the hemodialysis unit, the high staff turnover probably contributed to reduced compliance with standard precautions and basic hygiene. New workers enrolled in this context were not prepared to adequately face many of the situations that create opportunities for blood contact from patient to patient in a busy dialysis unit. In addition, as previously described, unsatisfactory environmental cleaning (maladapted procedures and non-virucidal products) and a small distance between patients[26] may have also contributed to HCV transmission.

The hemodialysis unit belongs to a private institution that has two other units with the same equipment, products, and procedures. However, no increase in HCV infection was observed in those units. A high baseline prevalence of HCV contributes to transmission to patients.[7] However, the baseline prevalence of HCV in the hemodialysis unit (10.2%) was similar to that in the two other units (14.6% and 15.7%). These rates were also normal for France.[9]

The hemodialysis unit monitored HCV infection through monthly ALT and biannual EIA HCV antibody testing. The ALT level of hemodialysis patients is frequently lower than that of other patients and is a poor predictor of HCV-induced liver disease.[27] In our investigation, we compared ALT levels with patients' baseline levels and not with the laboratory threshold level.[9] Our findings also corroborate previous studies indicating that patients receiving dialysis may have a delayed or disturbed HCV antibody response.[4,9,16,28-31] The EIA done in September 2001 detected only 9 case-patients, whereas systematic RNA detection by PCR identified 22 case-patients, 12 of whom were negative for HCV antibodies by EIA. RNA detection by PCR allowed timely assessment of the magnitude of the outbreak and implementation of control measures.

Routine screening for HCV infection among patients receiving dialysis varies widely from one center to another,[32-38] and European recommendations consider only antibody testing.[39] Our experience with this outbreak indicates that this strategy may not be optimal and that guidelines for monitoring HCV infection among patients receiving dialysis need updating. It appears reasonable to recommend screening ALT monthly plus HCV antibody testing by EIA every 6 months and in cases of elevated serum ALT (ie, twice the baseline level of the patient). If unexplained ALT elevations persist in patients whose test results are repeatedly negative for HCV antibodies, testing for HCV RNA should be considered.[24] Each new patient who enters a dialysis unit should also be evaluated once for ALT level , HCV antibodies using EIA, and HCV RNA using PCR.

HCV transmission via blood transfusion[4,8,29,35,40-42] has been controlled in France since 1992.[17] Many clusters of HCV infections or outbreaks in dialysis units have been investigated using state-of-the-art molecular methods.[11,15,16,31,43-49] This approach allows for documentation of the importance of the residual nosocomial spread of HCV. In our study, the phylogenic analysis demonstrated that transmission of HCV occurred in the hemodialysis unit for each of four distinct genotype groups, with a source-patient who received dialysis in the unit in 2001 and was chronically infected with a homologous virus. Despite a high prevalence during the outbreak and contrary to what has been reported in other studies,[47,50] no HCV infection was detected among the healthcare workers in the hemodialysis unit in 2001 who had been tested.

The hemodialysis unit had spontaneously adopted double filters (which were changed for each patient) on both arterial and venous lines as internal transducers in the dialysis machine.[14,24] The audit of practices documented a high frequency of flooding of blood in the filters of the arterial pressure tubing set protecting the internal sensor (although the positive pressure at that level is theoretically less favorable for wetting the filters with blood). Two successive episodes of flooding of blood in the arterial double filters could have contributed to the transmission of HCV via dialysis machines. This abnormal frequency can be explained by the fact that new healthcare workers were less experienced with circuit assembly and surveillance and had less training on preventing the blood from flowing back.

They were not sensitized to react when the filters became wet (there was no written procedure to immediately send the dialysis machine to technical control and disinfection). The case–control study pointed to horizontal transmission for the four HCV genotypes involved in the outbreak. However, vertical transmission via dialysis machines may have also been involved for one of the genotype 2 groups.

This large outbreak resulted mainly from patient-to-patient transmission via the hands of healthcare workers during care in the unit. However, vertical transmission via a dialysis machine previously used by a patient infected with HCV cannot be completely excluded. Corrective measures were therefore established before reopening the hemodialysis unit. The staff was reinforced. An infection control team was created. Continuous education and training on technical dialysis procedures was instituted. Infection control policies were established. Strict observance of hand hygiene was instituted with the introduction of hydroalcoholic solutions. Standard precautions and environmental disinfection were monitored. The choice of products and procedures (skin antisepsis and material disinfection) was improved. Level of safety and quality regarding the hazard of wetting arterial and venous filters was optimized. Data collection on dialysis sessions and control procedures was improved. Room space was optimized to increase the distance between patients and to allow for the reorganization of care and circuits.

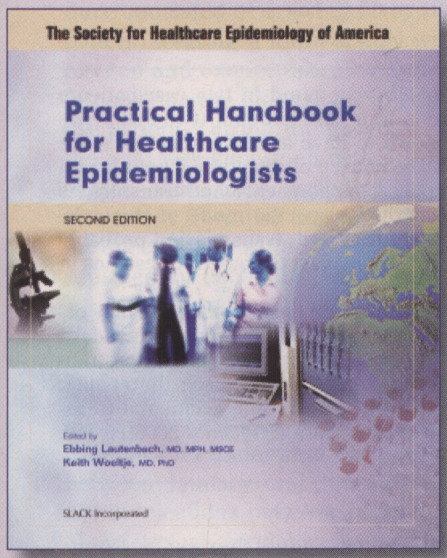
Isolation of HCV-infected patients is controversial[6,36,40,51-56] and is not recommended by guidelines such as those of the Centers for Disease Control and Prevention.[24] For the control of this outbreak, isolation of HCV-infected patients was not required. However, the hemodialysis unit managers preferred to separate HCV-positive and HCV-negative patients, but not to dedicate dialysis machines. The hemodialysis unit reopened 2 months after closure and no seroconversions had been observed as of the end of 2004. The decision to close the hemodialysis unit was made by the Ministry of Health following intense media coverage. Although effective implementation of control measures would have been possible without closing the hemodialysis unit, closure facilitated reorganization of the unit into a more secure and serene climate for patients, healthcare workers, and public health professionals. However, such a decision should also take into account the potential harm and inconvenience to patients.

REFERENCES

1. Wreghitt TG. Blood-borne virus infections in dialysis units: a review. *Rev Med Virol* 1999;9:101-109.
2. Finelli L, Miller J, Tokars J, Alter M, Arduino M. National surveillance of dialysis-associated diseases in the United States, 2002. *Semin Dial* 2005;18:52-61.
3. Schneeberger PM, Keur I, van Loon AM, et al. The prevalence and incidence of hepatitis C virus infections among dialysis patients in the Netherlands: a nationwide prospective study. *J Infect Dis* 2000;182:1291-1299.
4. Hinrichsen H, Leimenstoll G, Stegen G, Schrader H, Folsch UR, Schmidt WE. Prevalence and risk factors of hepatitis C virus infection in haemodialysis patients: a multicentre study in 2,796 patients. *Gut* 2002;51:429-433.
5. Jadoul M, Cornu C, van Ypersele de Strihou C. Universal precautions prevent hepatitis C virus transmission: a 54 month follow-up of the Belgian Multicenter Study. The Universitaires Cliniques St-Luc (UCL) Collaborative Group. *Kidney Int* 1998;53:1022-1025.
6. dos Santos JP, Loureiro A, Cendoroglo Neto M, Pereira BJ. 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.
7. Petrosillo N, Gilli P, Serraino D, et al. Prevalence of infected patients and understaffing have a role in hepatitis C virus transmission in dialysis. *Am J Kidney Dis* 2001;37:1004-1010.
8. Jadoul M. Epidemiology and mechanisms of transmission of the hepatitis C virus in haemodialysis. *Nephrol Dial Transplant* 2000;15(suppl 8):39-41.
9. Salama G, Rostaing L, Sandres K, Izopet J. Hepatitis C virus infection in French hemodialysis units: a multicenter study. *J Med Virol* 2000;61:44-51.
10. de Lamballerie X, Olmer M, Bouchouareb D, Zandotti C, De Micco P. Nosocomial transmission of hepatitis C virus in haemodialysis patients. *J Med Virol* 1996;49:296-302.
11. Le Pogam S, Le Chapois D, Christen R, Dubois F, Barin F, Goudeau A. Hepatitis C in a hemodialysis unit: molecular evidence for nosocomial transmission. *J Clin Microbiol* 1998;36:3040-3043.
12. Olmer M, Bouchouareb D, Zandotti C, de Micco P, de Lamballerie X. Transmission of the hepatitis C virus in an hemodialysis unit: evidence for nosocomial infection. *Clin Nephrol* 1997;47:263-270.
13. Simon N, Courouce AM, Lemarrec N, Trepo C, Ducamp S. A twelve year natural history of hepatitis C virus infection in hemodialyzed patients. *Kidney Int* 1994;46:504-511.
14. Delarocque-Astagneau E, Baffoy N, Thiers V, et al. Outbreak of hepatitis C virus infection in a hemodialysis unit: potential transmission by the hemodialysis machine? *Infect Control Hosp Epidemiol* 2002;23:328-334.
15. Izopet J, Pasquier C, Sandres K, Puel J, Rostaing L. Molecular evidence for nosocomial transmission of hepatitis C virus in a French hemodialysis unit. *J Med Virol* 1999;58:139-144.
16. Grethe S, Gemsa F, Monazahian M, Bohme I, Uy A, Thomssen R. Molecular epidemiology of an outbreak of HCV in a hemodialysis unit: direct sequencing of HCV-HVR1 as an appropriate tool for phylogenetic analysis. *J Med Virol* 2000;60:152-158.
17. Trepo C, Pradat P. Hepatitis C virus infection in Western Europe. *J Hepatol* 1999;31(suppl 1):80-83.
18. Hardy N, Chiao J, Arora N, Mars R, Jenkins S. Hepatitis C virus in the hemodialysis setting: detecting viral RNA from blood port caps by reverse transcription-polymerase chain reaction. *Clin Nephrol* 2000;54:143-146.
19. Rodrigues L, Kirkwood BR. Case-control designs in the study of common diseases: updates on the demise of the rare disease assumption and the choice of sampling scheme for controls. *Int J Epidemiol* 1990;19:205-213.
20. Rothman K. *Epidemiology: An Introduction*. Oxford: Oxford University Press; 2002:73-93.
21. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York: John Wiley & Sons; 1989.
22. Doglio A, Laffont C, Caroli-Bosc FX, Rochet P, Lefebvre J. Second generation of the automated Cobas Amplicor HCV assay improves sensitivity of hepatitis C virus RNA detection and yields results that are more clinically relevant. *J Clin Microbiol* 1999;37:1567-1569.
23. Sandres-Saune K, Deny P, Pasquier C, Thibaut V, Duverlie G, Izopet J. Determining hepatitis C genotype by analyzing the sequence of the NS5b region. *J Virol Methods* 2003;109:187-193.
24. Anonymous. Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR Recomm Rep* 2001;50(RR-5):1-43.
25. Fissell R, Bragg-Gresham J, Woods J, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004;65:2335-2342.
26. Zampieron A, Jayasekera H, Elseviers M, et al. European study on epidemiology and the management of HCV in the haemodialysis population: Part 1. Centre policy. *EDTNA ERCA J* 2004;30:84-90.
27. Natov S, Pereira J. Routine serologic testing for hepatitis C virus infection should be instituted among dialysis patients. *Semin Dial* 2000;13:393-398.
28. Almroth G, Ekermo B, Mansson A, Svensson G, Widell A. Detection and prevention of hepatitis C in dialysis patients and renal transplant recipients: a long-term follow up (1989–January 1997). *J Intern Med* 2002;215:119-128.
29. Pujol FH, Ponce JG, Lema MG, et al. High incidence of hepatitis C virus infection in hemodialysis patients in units with high prevalence. *J Clin Microbiol* 1996;34:1633-1636.
30. Fabrizi F, Martin P, Dixit V, et al. Acquisition of hepatitis C virus in hemodialysis patients: a prospective study by branched DNA signal

amplification assay. *Am J Kidney Dis* 1998;31:647-654.
31. Irish DN, Blake C, Christophers J, et al. Identification of hepatitis C virus seroconversion resulting from nosocomial transmission on a haemodialysis unit: implications for infection control and laboratory screening. *J Med Virol* 1999;59:135-140.
32. Dalekos G, Boumba D, Katopodis K, et al. Absence of HCV viraemia in anti-HCV-negative haemodialysis patients. *Nephrol Dial Transplant* 1998;13:1804-1806.
33. Schneeberger PM, Toonen N, Keur I, van Hamersvelt HW. Infection control of hepatitis C in Dutch dialysis centres. *Nephrol Dial Transplant* 1998;13:3037-3040.
34. Saab S, Brezina M, Gitnick G, Martin P, Yee HF Jr. Hepatitis C screening strategies in hemodialysis patients. *Am J Kidney Dis* 2001;38:91-97.
35. Jadoul M. Transmission routes of HCV infection in dialysis. *Nephrol Dial Transplant* 1996;11(suppl 4):36-38.
36. Zuckerman M. Surveillance and control of blood-borne virus infections in haemodialysis units. *J Hosp Infect* 2002;50:1-5.
37. Fabrizi F, Martin P, Dixit V, et al. Detection of de novo hepatitis C virus infection by polymerase chain reaction in hemodialysis patients. *Am J Nephrol* 1999;19:383-388.
38. Tokars JI, Frank M, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2000. *Semin Dial* 2002;15:162-171.
39. European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section VI. Haemodialysis-associated infection. *Nephrol Dial Transplant* 2002;17(suppl 7):72-87.
40. 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.
41. Zeuzem S, Scheuermann EH, Waschk D, et al. Phylogenetic analysis of hepatitis C virus isolates from hemodialysis patients. *Kidney Int* 1996;49:896-902.
42. Keur I, Schneeberger PM, van der Graaf Y, Vos J, van Dijk WC, van Doorn LJ. Risk factors for HCV infection in two haemodialysis units in The Netherlands. *Neth J Med* 1997;50:97-101.
43. Allander T, Medin C, Jacobson SH, Grillner L, Persson MA. Hepatitis C transmission in a hemodialysis unit: molecular evidence for spread of virus among patients not sharing equipment. *J Med Virol* 1994;43:415-419.
44. Iwasaki Y, Esumi M, Hosokawa N, Yanai M, Kawano K. Occasional infection of hepatitis C virus occurring in haemodialysis units identified by serial monitoring of the virus infection. *J Hosp Infect* 2000;45:54-61.
45. Kokubo S, Horii T, Yonekawa O, Ozawa N, Mukaide M. A phylogenetic-tree analysis elucidating nosocomial transmission of hepatitis C virus in a haemodialysis unit. *J Viral Hepat* 2002;9:450-454.
46. Abacioglu YH, Bacaksiz F, Bahar IH, Simmonds P. Molecular evidence of nosocomial transmission of hepatitis C virus in a haemodialysis unit. *Eur J Clin Microbiol Infect Dis* 2000;19:182-186.
47. Norder H, Bergstrom A, Uhnoo I, et al. Confirmation of nosocomial transmission of hepatitis C virus by phylogenetic analysis of the NS5-B region. *J Clin Microbiol* 1998;36:3066-3069.
48. Katsoulidou A, Paraskevis D, Kalapothaki V, et al. Molecular epidemiology of a hepatitis C virus outbreak in a haemodialysis unit: Multicentre Haemodialysis Cohort Study on Viral Hepatitis. *Nephrol Dial Transplant* 1999;14:1188-1194.
49. Gonzalez-Candelas F, Bracho MA, Moya A. Molecular epidemiology and forensic genetics: application to a hepatitis C virus transmission event at a hemodialysis unit. *J Infect Dis* 2003;187:352-358.
50. Petrarulo F, Maggi P, Sacchetti A, Pallotta G, Dagostino F, Basile C. HCV infection occupational hazard at dialysis units and virus spread, among relatives of dialyzed patients. *Nephron* 1992;61:302-303.
51. Gilli P, Soffritti S, De Paoli Vitali E, Bedani PL. Prevention of hepatitis C virus in dialysis units. *Nephron* 1995;70:301-306.
52. Saxena AK, Panhotra BR, Sundaram DS, et al. Impact of dedicated space, dialysis equipment, and nursing staff on the transmission of hepatitis C virus in a hemodialysis unit of the Middle East. *Am J Infect Control* 2003;31:26-33.
53. Zamir D, Storch S, Zonder HB, Zamir C, Weiner P. Hepatitis C virus seroconversion and genotype prevalence in patients and staff on chronic hemodialysis. *J Clin Gastroenterol* 1999;28:23-28.
54. Djordjevic V, Stojanovic K, Stojanovic M, Stefanovic V. Prevention of nosocomial transmission of hepatitis C infection in a hemodialysis unit: a prospective study. *Int J Artif Organs* 2000;23:181-188.
55. Harmankaya O, Cetin B, Obek A, Seber E. Low prevalence of hepatitis C virus infection in hemodialysis units: effect of isolation? *Ren Fail* 2002;24:639-644.
56. Valtuille R, Moretto H, Lef L, Rendo P, Fernandez JL. Decline of high hepatitis C virus prevalence in a hemodialysis unit with no isolation measures during a 6-year follow-up. *Clin Nephrol* 2002;57:371-375.

Take the Lead in Infection Control



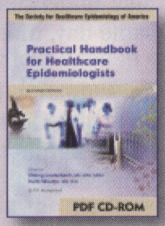
Practical Handbook for Healthcare Epidemiologists, Second Edition
Ebbing Lautenbach MD, MPH, MSCE,
University of Pennsylvania, Philadelphia, PA
and Keith Woeltje MD, PhD,
Washington University School of Medicine, St. Louis, MO
400 pp., Hard Cover, 2004,
ISBN 1-55642-677-1
Order#16771, **$94.95**

If you work in today's healthcare epidemiology programs **you will need** the latest edition of *Practical Handbook for Healthcare Epidemiologists*. Situations that are encountered daily can be challenging, and now the answers needed are available in one solid resource.

Extensively updated and revised, this **best selling** handbook is concise and user-friendly, and will provide practical information regarding many aspects of establishing and managing a healthcare epidemiology program.

The Society for Healthcare Epidemiology of America (SHEA) has recruited over 50 recognized leaders in the field to share their expertise. They discuss overarching goals, as well as successful strategies for handling specific situations and problems. There is also extensive information on infection control in the outpatient setting and measures to take after exposure to infectious agents. ***This is the most complete hands-on source about healthcare epidemiology and infection prevention and control.***

Buy Both the Book and PDF CD-ROM – Save 25%!



Practical Handbook for Healthcare Epidemiologists, Second Edition PDF CD-ROM
CD-ROM, 2004,
ISBN 1-55642-699-2
Order#16992, **$94.95**

All the text, all the images–in a user-friendly PDF CD-ROM.

QUANTITY	TITLE	ORDER #	PRICE
	Practical Handbook for Healthcare Epidemiologists, 2E	16671	$94.95
	Practical Handbook for Healthcare Epidemiologists, 2E PDF CD-ROM	16992	$94.95
	Special: Book and PDF CD-ROM	**16771 & 16992**	$142.42
		Subtotal	$
		Handling Charge	( )
		CA & NJ Sales Tax*	$5.00
		TOTAL	$

Please add applicable state and local taxes.

Are the shipping and billing addresses the same? ❑ Yes ❑ No

Name _____

Address _____

_____

City _____ **State** _____ **Zip** _____

Phone _____ **Fax** _____

Email _____

❑ Check enclosed *(Payable to SLACK Inc)*

❑ Purchase Order or Bill Me *(Please attach this order form to purchase order)*

❑ Charge my: ❑ VISA ❑ MasterCard ❑

Account # _____ Security Code* _____ Exp. Date _____

Signature _____

Prices subject to change. Shipping charges may apply. Shipping and handling charges are non-refundable.
Credit card orders will not be processed without the security code.

Call to order: 800-257-8290 or 856-848-1000

Visit our Website at: www.slackbooks.com/epidemiology

SLACK Incorporated
Professional Book Division
6900 Grove Road
Thorofare, New Jersey
08086-9864

FAX: 856-853-5991

Send e-mail to:
orders@slackinc.com

CODE: 1A1178

A CLUSTER OF HEPATITIS C VIRUS INFECTIONS ASSOCIATED WITH OZONE-ENRICHED TRANSFUSION OF AUTOLOGOUS BLOOD IN ROME, ITALY

Annunziata Faustini, MD, DrPH; Maria R. Capobianchi, BS; Mauro Martinelli, MD; Isabella Abbate, BS; Giuseppina Cappiello, BS, MD; Carlo A. Perucci, MD, DrPH

ABSTRACT

OBJECTIVE: To describe an outbreak of hepatitis C virus (HCV).

DESIGN: Retrospective cohort study.

SETTING: Outpatient department of a hospital in Rome, Italy.

PATIENTS: All 42 patients exposed to ozone therapy by autohemotherapy or intramuscular injection from January to June 2001.

METHODS: Epidemiologic investigation, serologic analysis, and virus genotyping.

RESULTS: Thirty-one (74%) of the patients agreed to participate in the study. Three (9.7%) had symptoms of HCV infection. This incidence rate was higher than the rate of 1.4 per 100,000 per year in the regional population. Six patients were positive for HCV antibodies and HCV RNA for a prevalence rate of 19.4%, which was much higher than the estimate of 0.9% in the population. Virus genotype 1b was found in two case-patients (one symptomatic) and 2c in four case-patients (two symptomatic), one of whom was known to have an HCV infection since 1986 and could have been the source of infection. The infected patients were all being exposed to ozone-enriched transfusions of autologous blood. Although the specific mode of transmission between patients was not detected, transmission probably occurred during one of the three busiest therapeutic sessions in the 6-month period.

CONCLUSIONS: Transmission of HCV infection may occur during medical procedures with limited bleeding. Standard precautions must be applied in any healthcare setting; restricting the number of individuals treated during each therapeutic session could be an effective way of avoiding accidental transmission of infection (*Infect Control Hosp Epidemiol* 2005;26:762-767).

Transmission of hepatitis C virus (HCV) was well documented in the 1990s in settings where invasive procedures are used, such as dialysis units,[1-3] hematology wards,[4] pediatric oncology services,[5] endoscopy units,[6,7] and hospitals during pharmaceutical research.[8] The mechanism of transmission between patients was not well established in many of these cases, although possibilities include the improper use of syringes[9] and repeated blood sampling.[8] A recent study[10] reported that medical procedures with limited bleeding may allow for the transmission of HCV infection in healthcare settings, as has already been documented for hepatitis B virus (HBV). Only two reports involve alternative medical procedures in HCV transmission.[11,12] In both cases, the procedure was the ozone-enriched transfusion of autologous blood and the hypothesized mechanism of transmission was the reuse of the glass syringe used to collect the oxygen–ozone mixture from the ozone apparatus.

We report the results of an epidemiologic and molecular investigation of a cluster of hepatitis C infections among patients who underwent ozone therapy in Rome, Italy.

In May 2001, three cases of HCV were reported to the regional epidemiologic surveillance center. The first patient, a 63-year-old man, was referred to the hospital with jaundice on March 24; the second, a 38-year-old woman, presented with symptoms on April 29; and the third, a 59-year-old man, was admitted to the hospital with jaundice on May 8. He had had negative test results for HCV in February 2001. All three patients presented with jaundice and an elevated level of alanine aminotransferase (ALT) (range, 53 to 337 IU/L). They were positive for HCV antibodies and negative for both HBV (anti-HBs and anti-HBc) and hepatitis A virus antibodies. Test results for HCV RNA were positive in all three cases. The patients had undergone ozone-enriched blood transfusions on the same day, March 21, at the same hospital in Rome.

We started an epidemiologic investigation to define the extent of the cluster (including asymptomatic infection), the genotype of the virus strains involved in this outbreak, and the factors associated with HCV infection.

Drs. Faustini and Perucci are from the Department of Epidemiology, Local Health Authority RM-E; Ms. Capobianchi, Ms. Abbate, and Ms. Cappiello are from the National Institute of Infectious Diseases "Lazzaro Spallanzani"; and Dr. Martinelli is from the General Hospital "Villa San Pietro," Rome, Italy. Ms. Abbate is also from the Hospital "Sandro Pertini," Rome, Italy.

Address reprint requests to A. Faustini, MD, DrPH, Department of Epidemiology, LHA RME, via Santa Costanza n. 53, 00198 Rome, Italy. faustini@asplazio.it

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

METHODS

Ozone Therapy

Ozone therapy, through intramuscular injection or transfusion of autologous blood, has been prescribed to patients with ischemic arteriopathy, diabetes mellitus, hormonal disorders, chronic hepatitis, chronic renal insufficiency, autoimmune diseases, and joint disorders such as arthritis or a prolapsed disk.[13,14] The therapy at this particular hospital consisted of cycles of one to nine transfusions of autologous blood given once a week or cycles of one to nine intramuscular injections of ozone. This therapy was given in the outpatient department of the hospital in daily sessions during which up to 11 patients were treated, although not always in the same room. The procedure consisted of drawing 50 to 100 mL of blood from the patient, treating it immediately with a gaseous mixture of oxygen and ozone (taken by syringe from a gas tank and infused into the blood), and injecting it promptly back into the patient. During the gaseous enrichment of the blood, the vein was kept open with a saline solution. Disposable devices were used, including the syringe with which gas was taken from the tank and the sterile connecting tube for injecting the saline solution. They were supposed to be replaced for each new patient.

Epidemiologic Investigation

Different exposure groups were chosen: patients who underwent ozone-enriched autohemotherapy or ozone intramuscular therapy in the hospital on March 21, 2001; patients who underwent ozone-enriched autohemotherapy between January and June 2001; and patients who had ozone injections between January and June 2001. A group of patients who underwent other invasive procedures were nonrandomly selected from those who had undergone surgical or orthopedic interventions or phlebotomy at the same hospital between May and November 2001.

The groups were chosen according to different hypotheses regarding the transmission of HCV infection. The first hypothesis was that exposure of the second and third case-patients to the first case-patient occurred on March 21 because that was the only time during the 6-month period when all three symptomatic case-patients were together. A second hypothesis assumed that the transmission of infection could have occurred in more than one session from a common source or from different sources, and thus asymptomatic case-patients could have played a role. Analyzing intramuscular injections separately from autotransfusions could answer the question about the role of the instruments and practices used in ozone therapy as possible vehicles of infection. We compared ozone therapy with other invasive procedures to determine whether there was an increased risk associated with it.

The patients from these groups who agreed to participate in the study were interviewed and tested for HCV antibodies. HCV RNA and genotypes were analyzed for those patients who were positive for HCV antibodies. The study started in June 2001 when questionnaires and tests were administered to the three symptomatic case-patients; in the period from September 2001 to February 2002, data were collected for the other exposed subjects.

Data on age, gender, chronic diseases (diabetes, renal insufficiency, hemophilia, and thalassemia), invasive therapeutic procedures, previous diagnoses of hepatitis, clinical indications and number of ozone therapy sessions, and risk factors for HCV infection were collected using a questionnaire and the patients' medical records. We gathered information about other invasive procedures, transplants, intravenous drug use, and sexual partners positive for HCV antibodies. We considered the risk period for infection to be the 6 months prior to onset of hepatitis or, for asymptomatic patients, the time elapsed from January to the date of blood sampling. Incident cases of hepatitis were defined as patients who presented with jaundice and elevated ALT levels who were also positive for HCV antibodies and negative for hepatitis A and B. Prevalent cases included all of the patients positive for HCV antibodies.

Laboratory Investigation

A third-generation immunoenzymatic assay (Axsym HCV, version 3.0; Abbott Laboratories, Abbott Park, IL) was used for HCV antibody testing. A commercially available quantitative polymerase chain reaction (PCR) assay (Amplicor HCV Monitor 2.0, Roche Diagnostics, Monza, Italy) was used to measure HCV RNA and a line probe assay (InnoLipa HCV II, Bayer Diagnostics, Milan, Italy) was used to genotype HCV.

To perform a phylogenic analysis of HCV, RNA was extracted from plasma samples using the QIAamp Viral RNA kit (QIAGEN, Hilden, Germany). Retrotranscription was performed by random hexamer method for 1 hour at 42°C, followed by 15 minutes at 65°C with M-MuLV Reverse Transcriptase (Roche). For NS5B amplification, a semi-nested PCR was used.[15] HVR-1 region amplification was performed by using genotype-specific primers: for genotype 1b, we performed a nested PCR as described by Enomoto et al.[16]; and for genotype 2, we used the method described by Sandres et al.[17] All PCRs were performed with a high-fidelity polymerase with proofreading activity (Platinum Pfx DNA Polymerase, Life Technologies, Milan, Italy).

Direct sequencing of PCR products was performed on ABI Prism 310, with the BigDye Terminator cycle sequencing kit, following the manufacturer's instructions (Applied Biosystems, Warrington, United Kingdom). Nucleotide sequences were aligned by using the CLUSTAL W program (version 1.4; European Molecular Biology Laboratory, Heidelberg, Germany). HVR-1 sequences were compared with sequences referenced in the literature by BLAST (Basic Local Alignment Search Tool, National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD), and, on the basis of the similarity score, the four patients with genotype 2a/2c were assigned to genotype 2c. To evaluate the degree of genetic segregation among NS5B and HVR-1 nucleotidic sequences, a pairwise matrix of evo-

TABLE
CLINICAL CHARACTERISTICS AND HEPATITIS C VIRUS TEST RESULTS OF PATIENTS TREATED WITH OZONE THERAPY ON MARCH 21, 2001, IN A HOSPITAL OUTPATIENT DEPARTMENT IN ROME, ITALY

Patient No.	Order of Treatment*	Age (y)	Gender	Previous HCV Immunologic Status	Type of Ozone Therapy	Date of Symptom Onset	Result of Test for HCV Antibodies	Virus Genotype†
1	1st	58	Female	Unknown	Intramuscular injection		Negative	
2	2nd	51	Male	Unknown	Intramuscular injection		Negative	
3	3rd, 4th, or 5th	70	Female	Negative in 1998	Autohemotherapy		Negative	
4	3rd, 4th, or 5th	69	Male	Unknown	Autohemotherapy		Positive	2a/2c
5	3rd, 4th, or 5th	65	Male	Unknown	Autohemotherapy		Positive	1b
6	6th or 7th	63	Male	Unknown	Autohemotherapy	March 24	Positive	1b
7	6th or 7th	73	Male	Positive in 1986	Autohemotherapy		Positive	2a/2c
8	8th or 9th	36	Female	Unknown	Autohemotherapy	April 29	Positive	2a/2c
9	8th or 9th	59	Male	Negative in 2001	Autohemotherapy	May 8	Positive	2a/2c

HCV = hepatitis C virus.
*Treatment order is approximate due to the possible difference between order of registration and order of treatment.
†As determined by reverse hybridation assay.

lutionary distances was generated using Kimura's two-parameter model of evolution.

Phylogenic trees were constructed using the neighbor-joining method. Bootstrap analysis was used to place approximate confidence limits on individual branches. The numbers at the nodes indicate the frequency with which the node occurred in 1,000 bootstrap replicates; values greater than 95% are shown. All of the algorithms used were included in the Mega package.[18]

Statistical Analysis

HCV incidence was calculated as the number of cases among all ozone-treated patients from January to June 2001 in each exposure group. Infection prevalence was calculated as the percentage of patients positive for HCV antibodies in the total and in the different exposure groups. The 95% confidence intervals (CI_{95}) were calculated according to binomial distribution.

RESULTS

Patients Treated With Ozone Therapy in the 6-Month Period From January to June 2001

Among a total of 42 patients who underwent ozone therapy in the hospital between January and June 2001, 31 (74%) agreed to participate in the study: 19 (70.4%) of the 27 who were treated with intramuscular injections and 12 (80%) of the 15 who were treated with autohemotherapy. The average age of ozone-treated patients was 55.1 years and 54.8% were male; those who underwent autohemotherapy were older (mean age, 63.6 years) and more likely to be male (66.7%).

There were 27 ozone treatment sessions during the therapeutic cycle between January and June 2001, during which a total of 69 blood transfusions and 72 injections were performed. Among patients treated by intramuscular injection, one reported a previous diagnosis of HBV and two had a previous negative test result for HCV antibodies; none of these patients tested positive for HCV antibodies during this study.

Among patients who had undergone a transfusion of ozone-enriched autologous blood, six were positive for HCV antibodies, three of whom presented symptoms between March 24 and May 8, and were diagnosed as having acute hepatitis. A different set of three patients had had previous tests for HCV: one reported acute hepatitis in 1986 that was later confirmed to be HCV genotype 2a/2c, another patient was tested for HCV in 1998 and reported a negative result, and the third patient developed acute, symptomatic HCV but had had a negative HCV test result in February. This is the only patient for whom a seroconversion was reported.

The incidence rate of HCV was 9.7% (3 of 31; CI_{95}, 2.0% to 25.8%) in the entire group who underwent ozone therapy and 25.0% (3 of 12; CI_{95}, 6.5% to 67.2%) among patients who underwent autologous blood transfusions. The average population incidence of HCV was 1.4 per 100,000 inhabitants per year during the period from 1996 to 2000 among the 5,200,000 inhabitants in the region. The prevalence of infection was 19.4% (6 of 31; CI_{95}, 7.5% to 37.5%) among patients exposed to ozone therapy and 50% (6 of 12; CI_{95}, 21.1% to 78.9%) among those who had only transfusions, compared with an estimated prevalence of 0.9% in the regional population.

Patients Treated With Ozone Therapy on March 21

Ten patients received ozone therapy in the outpatient department on March 21, 2001: eight underwent infusions of autologous blood and, in a separate room, two received intramuscular injections of ozone. One patient who received a blood transfusion did not agree to participate and

another did not agree to participate until 2004. The mean age of the nine participating patients treated on March 21 was 60.4 years (range, 36 to 73 years). All of the six patients who tested positive for HCV antibodies were in this group. The other three patients were diagnosed as being HCV negative and did not report previous diagnoses of hepatitis or jaundice (Table). Of the nine patients, two had diabetes mellitus. The first symptomatic case-patient with hepatitis had undergone an intestinal endoscopy and a cycle of intramuscular therapy in January 2001, the second symptomatic case-patient had had a surgical treatment in March, and the third had had a cardiac catheterization in February, each at a different hospital. The two symptomatic patients (who were treated eighth and ninth) were relatives and lived in the same town, although not in the same house. None of the nine patients had undergone dialysis or blood transfusion during the previous 6 months, were intravenous drug injectors, had tattoos or piercings, or had sexual partners with a previous diagnosis of HCV.

Patients Who Had Undergone Other Invasive Procedures

Among patients exposed to other invasive procedures who participated in the investigation, 22 had been hospitalized for surgical or orthopedic interventions and others had undergone phlebotomy in the outpatient department. Their mean age was 51.1 years and 56% were male. All of these patients were negative for HCV antibodies.

Virus Genotypes and Phylogenic Analysis

The HCV RNA test results were positive for all six patients positive for HCV antibodies; the virus genotype was 1b for two patients and 2a/2c for the other four (Table). The phylogenic analysis of HCV for the six patients is shown in the figure. Because direct sequencing of HVR-1 PCR amplicons was performed, the data refer to the predominant variants present in each patient at the time of analysis. HCV genotypes from the four patients who were previously determined to have genotype 2a/2c by reverse hybridization were recognized to be 2c on the basis of sequence analysis. Sequences from patients 7, 8, and 9 were grouped in a separate subcluster within the genotype 2a/2c cluster, with a bootstrap value equal to 100 for both NS5B and HVR-1 sequences; a nonsignificant bootstrap value of 42 was found for the fourth patient. The two patients with genotype 1b did not show any distinct segregation pattern within the cluster, including all genotype 1 sequences.

The Dynamics of Infection

The four patients infected with HCV genotype 2c shared therapeutic sessions on March 21, March 28, and April 4. Some of them also shared other sessions during the therapeutic cycle: patients 4 and 7, both asymptomatic, shared a session on March 14; and patients 4 and 8 shared a session on March 7. Patients 7, 8, and 9 shared two more sessions on April 11 and 18.

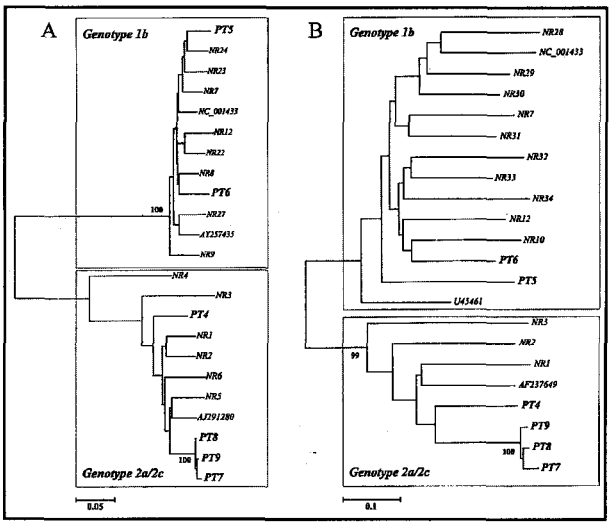


FIGURE. Phylogenic trees constructed with (A) NS5B and (B) HVR-1 sequences from six patients exposed to ozone-enriched transfusion of autologous blood in a hospital in Rome, Italy, in 2001. The patients involved in the outbreak are indicated as PT and are numbered as in the table. Reference genotypes 2c and 1b sequences from GenBank (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD) are indicated with their accession numbers. Nonrelated (NR) patient sequences obtained in our laboratory, including patients with genotypes 1b, 2a (NR4 and NR3), and 2c (NR 1, NR2, NR 5, and NR6), are also included. Genetic distance is indicated by a horizontal bar. The numbers at the nodes indicate the frequency with which the node occurred in 1,000 bootstrap replicates; values greater than 95% are indicated.

Although the precise order of treatment on March 21 was not reported, we could infer from the registry that those who received intramuscular injections were treated at the beginning of the session. The three patients infected with genotype 2c could have been treated one after another at the end of the session held on March 21 (Table), the first being the carrier, positive since 1986. These three patients shared five sessions from March 21 to April 18. The average number of ozone-enriched autologous transfusions was the same (4.8) for both HCV-positive and HCV-negative patients. The ozone therapy was administered by the same two healthcare workers, a physician and a trained nurse, during the entire therapeutic cycle. More patients (10 per day on average) were treated in the three treatment sessions occurring between March 21 and April 4 than in the other sessions during the entire 6-month period (4.5 per day on average).

DISCUSSION

The incidence and prevalence of HCV infection were much higher among patients exposed to ozone-enriched blood transfusion (25% and 50%, respectively) than in the general population of the region (1.4 per 100,000 and 0.9%, respectively). Incidence and prevalence were also higher in our study group than in the general population older than 59 years (1.6 per 100,000 and 1.7%, respectively). These data, together with the absence of cases among patients exposed to the most common mechanisms of transmission such as intravenous drug use and transfusion, suggest that

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

the HCV infections we reported were associated with autohemotherapy.

Our initial hypothesis was that the first patient had been infected before March 21; he could have been infected from an asymptomatic carrier during one of the previous six sessions of autohemotherapy that he had undergone since January 2001, and he could have transmitted the HCV infection to the other symptomatic patients on March 21. In favor of this hypothesis is that the time elapsed between March 21 and the onset of symptoms for the first case-patient was too short to be considered the incubation period. Two other factors supporting this hypothesis are the order of patients in the outpatient clinic and the fact that the three symptomatic case-patients shared only the session on March 21 during the entire period from January to June.

This hypothesis was not confirmed because the viruses of the three case-patients belonged to different genotypes (1b for the first case and 2c for the others). Nor was confirmed the hypothesis that the first case-patient, symptomatic on March 24, was exposed during a previous ozone session because the two patients infected with HCV genotype 1b did not show significant sequence correlation. It is likely that the first case-patient acquired the infection from a source not connected with the hospital cluster.

The possible transmission of infection between patients infected by HCV genotype 2c is further supported because this genotype is less common in Italy than genotype 1b, which accounts for up to 65% of HCV infections.[19,20] According to phylogenic analysis, patient 4 was not clearly assigned to a defined cluster within the genotype 2 sequences, whereas the other three cases (patients 7, 8, and 9) showed a distinct cluster with a high degree of sequence correlation.

We are confident that the results of phylogenic analysis clearly point to a cluster of three similar virus strains. Direct sequencing of PCR amplicons was performed for both NS5B and HVR-1, and the last one is considered a valid tool to detect genetic correlation of HCV strains in previous studies of nosocomial transmission of HCV.[21-23] In addition, this approach is less prone than the clonal approach to spurious clustering or unclustering due to the high and inconstant mutation rate of this region.[24] The source was probably the patient who had been infected since 1986, and transmission most likely occurred during one of the five sessions between March 21 and April 18. The treatment sequence strongly suggests the March 21 session because the asymptomatic patient was treated sixth or seventh and the two symptomatic case-patients were treated eighth and ninth.

We did not find the mechanism or vehicle by which the infection was transmitted. A contamination of the syringe with which ozone gas was taken or the sterile connecting tube of saline infusion is only a hypothesis, although the most plausible given the available data. We did not find any association between infection and number of transfusions, but more patients (10 per day on average) were treated in three of the five sessions in which transmission of HCV infection may have occurred than in the other sessions during the entire 6-month period (4.5 per day on average). This could be a factor in facilitating an accidental lapse from the usual precautionary procedures. A previous study[1] described transmission of HCV infection between patients treated in a dialysis unit. A single strain of the virus had apparently been transmitted to five patients who were treated in the same room on repeated occasions but who did not share hemodialysis machines. The authors concluded that the spread of the virus may occur frequently in environments where parenteral routes are accessible despite rigorous preventive measures. Another study[10] detected a specific mode of transmission of HCV infection in the shared use of a spring-loaded device for routine blood glucose monitoring of patients.

The results of molecular tests in this study support a more complicated explanation than we first hypothesized. In fact, we detected six HCV-infected patients among those treated with autohemotherapy, but only three were infected by the same virus. The other three prevalent case-patients, one who was symptomatic, were not related or associated with the other three HCV-infected patients.

We have reported a cluster of three cases of HCV genotype 2c associated with ozone-enriched autohemotherapy. The infection was probably due to a common source and occurred at one of the five sessions attended by the patients together, possibly one of the three that had more patients than usual.

The infection could have been due to an accidental reuse of the syringe with which ozone gas was taken or the sterile connecting tube of saline infusion. This study supports the hypothesis that transmission of HCV infection may occur during medical procedures with limited bleeding.

REFERENCES

1. Allander T, Medin C, Jacobson SH, Grillner L, Persson MA. Hepatitis C transmission in a hemodialysis unit: molecular evidence for spread of virus among patients not sharing equipment. *J Med Virol* 1994;43:415-419.
2. Stuyver L, Claeys H, Wyseur A, et al. Hepatitis C virus in a hemodialysis unit: molecular evidence for nosocomial transmission. *Kidney Int* 1996;49:889-895.
3. Izopet J, Pasquier C, Sandres K, Puel J, Rostaing L. Molecular evidence for nosocomial transmission of hepatitis C virus in a French hemodialysis unit. *J Med Virol* 1999;58:139-144.
4. Allander T, Gruber A, Naghavi M, et al. Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward. *Lancet* 1995;345:603-607.
5. Widell A, Christensson B, Wiebe T, et al. Epidemiologic and molecular investigation of outbreaks of hepatitis C virus infection on a pediatric oncology service. *Ann Intern Med* 1999;130:130-134.
6. Bronowicki JP, Venard V, Botté C, et al. Patient-to-patient transmission of hepatitis C virus during colonoscopy. *N Engl J Med* 1997;337:237-240.
7. Andrieu J, Barny S, Colardelle P, et al. Prevalence and risk factors of hepatitis C virus infection in a hospitalized population in a gastroenterology unit: role of endoscopic biopsies [in French]. *Gastroenterol Clin Biol* 1995;19:340-345.
8. Schvarcz R, Johansson B, Nystrom B, Sonnenborg A. Nosocomial transmission of hepatitis C virus. *Infection* 1997;25:74-77.
9. Lutz CT, Bell CE, Wedner HJ, Krogstad DJ. Allergy testing of multiple patients should no longer be performed with a common syringe. *N Engl J Med* 1984;310:1335-1337.
10. Desenclos J-C, Bourdiol-Razes M, Rolin B, et al. Hepatitis C in a

ward for cystic fibrosis and diabetic patients: possible transmission by spring-loaded finger-stick devices for self-monitoring of capillary blood glucose. *Infect Control Hosp Epidemiol* 2001;22:701-707.
11. Gabriel C, Blauhut B, Greul R, Schneeweis B, Roggendorf M. Transmission of hepatitis C by ozone enrichment of autologous blood. *Lancet* 1996;347:541.
12. Daschner FD. Hepatitis C and human immunodeficiency virus infection following ozone autohaemotherapy. *Eur J Clin Microbiol Infect Dis* 1997;16:620.
13. Bocci V. Biological and clinical effects of ozone: has ozone therapy a future in medicine? *Br J Biomed Sci* 1999;56:270-279.
14. Bocci V. Autohaemotherapy after treatment of blood with ozone: a reappraisal. *J Int Med Res* 1994;22:131-144.
15. Norder H, Bergstrom A, Uhnoo I, et al. Confirmation of nosocomial transmission of hepatitis C virus by phylogenetic analysis of the NS5-B region. *J Clin Microbiol* 1998;36:3066-3069.
16. Enomoto N, Kurosaki M, Tanaka Y, Marumo F, Sato C. Fluctuation of hepatitis C virus quasispecies in persistent infection and interferon treatment revealed by single-strand conformation polymorphism analysis. *J Gen Virol* 1994;75:1361-1369.
17. Sandres K, Dubois M, Pasquier C, et al. Genetic heterogeneity of hypervariable region 1 of the hepatitis C virus (HCV) genome and sensitivity of HCV to alpha interferon therapy. *J Virol* 2000;74:661-668.
18. Kumar S, Tamura K, Jakobsen IB, Nei M. MEGA3: integrated software for molecular evolutionary genetics analysis and sequence alignment. *Briefings in Bioinformatics* 2004;5:150-163.
19. Campello C, Poli A, Dal MG, Besozzi-Valentini F. Seroprevalence, viremia and genotype distribution of hepatitis C virus: a community-based population study in northern Italy. *Infection* 2002;30:7-12.
20. De Socio GV, Francisci D, Mecozzi F, et al. Hepatitis C virus genotypes in the liver and serum of patients with chronic hepatitis C. *Clin Microbiol Infect* 1996;2:20-24.
21. Abacioglu YH, Bacaksiz F, Bahar IH, Simmonds P. Molecular evidence of nosocomial transmission of hepatitis C virus in a haemodialysis unit. *Eur J Clin Microbiol Infect Dis* 2000;19:182-186.
22. 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.
23. Bruguera M, Saiz J, Franco S, et al. Outbreak of nosocomial hepatitis C virus infection resolved by genetic analysis of HCV RNA. *J Clin Microbiol* 2002;40:4363-4366.
24. Mizuno M, Higuchi T, Kanmatsuse K, Esumi M. Genetic and serological evidence for multiple instances of unrecognized transmission of hepatitis C virus in hemodialysis units. *J Clin Microbiol* 1998;36:2926-2931.

USEFULNESS OF A RAPID HUMAN IMMUNODEFICIENCY VIRUS-1 ANTIBODY TEST FOR THE MANAGEMENT OF OCCUPATIONAL EXPOSURE TO BLOOD AND BODY FLUID

Michael L. Landrum, MD; Clarissa H. Wilson, RN, BSN, MSA; Luci P. Perri, RN, MSN, MPH, CIC; Sandra L. Hannibal, BS, MT (ASCP); Robert J. O'Connell, MD

ABSTRACT

OBJECTIVE: To describe the usefulness of the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, PA) in cases of occupational exposure regarding its use with source-patient sera, effects on post-exposure prophylaxis (PEP) use, potential cost savings, and effects on healthcare worker (HCW) stress reaction symptoms.

DESIGN: Before-and-after analysis.

SETTING: A 269-bed, tertiary-care medical center with adjacent clinics.

PARTICIPANTS: All source-patients and HCWs experiencing an occupational exposure during the study period.

METHODS: Use of the OraQuick test with patient sera was validated prior to its use for occupational exposures. Exposures from January 1 through July 10, 2003 (enzyme immunoassay [EIA] group) and July 11 through December 31, 2003 (OraQuick group) were retrospectively reviewed and the use and cost of PEP was compared for each group. Randomly selected HCWs from both groups completed a survey to assess their stress reaction symptoms.

RESULTS: After exclusion, there were 71 exposures in the EIA group and 79 in the OraQuick group. OraQuick results were 100% concordant with the reference standard of EIA and Western blot using patient sera. The mean number of doses ingested per course of PEP was significantly higher for HCWs in the EIA group (3.8; range, 0 to 6) compared with the OraQuick group (1.2; range, 0 to 3; $P = .016$). Cost analysis revealed a mean savings of $6.62 with the OraQuick test per occupational exposure. Although the survey failed to detect an overall reduction in HCW stress reaction symptoms using OraQuick for source-patient testing, 11 HCWs in the EIA group had repetitive thoughts of the exposure compared with 5 in the OraQuick group ($P = .049$).

CONCLUSION: Because of the reduction in ingested doses of unnecessary PEP and reduced cost of occupational exposure management with their use, rapid HIV-antibody tests should be the preferred method for source-patient testing following an occupational exposure (*Infect Control Hosp Epidemiol* 2005;26:768-774).

Needlestick and mucocutaneous occupational exposures are extremely common clinical occurrences. However, despite the estimated millions of occupational exposures that have occurred since the beginning of the human immunodeficiency virus (HIV) epidemic in the United States, only 57 definitive cases of HIV seroconversion attributed to an occupational exposure have been reported in healthcare workers (HCWs), with an additional 139 cases considered possible.[1,2] Despite the small risk of seroconversion, occupational exposures remain problematic to the U.S. healthcare system for many reasons, including the costs of evaluating occupational exposures, the direct and indirect costs of post-exposure prophylaxis, and the anxiety and stress experienced by HCWs.[3-5] Many of these costs could be mitigated by rapidly and correctly determining the HIV serostatus of source-patients.

The most recent Centers for Disease Control and Prevention guidelines for management of occupational exposures state that rapid HIV-antibody tests should be considered when the results of enzyme immunoassay (EIA) testing on the source-patient might be delayed.[4] Currently, there are four[6-9] available Food and Drug Administration (FDA)-approved rapid HIV tests that lend themselves to use in the post-exposure setting. Our occupational exposure management program uses the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, PA), which detects antibody to gp41 present in oral mucosal transudate, whole blood, serum, or plasma,[6,10] with a sensitivity and a specificity of 96.0% to 100% and 99.8% to 100%, respectively.[6,10-12] Although it is not FDA approved for use with patient serum, others have shown excellent performance with this use.[10,12] Use of the OraQuick test with patient serum would

Drs. Landrum and O'Connell are from the Department of Infectious Diseases; Ms. Wilson, Ms. Perri, and Dr. O'Connell are from the Department of Infection Control; and Ms. Hannibal is from the Immunology Laboratory, Department of Pathology, Wilford Hall Medical Center, Lackland Air Force Base, San Antonio, Texas.

Address reprint requests to Michael L. Landrum, MD, 759 MDOS/MMII, Wilford Hall Medical Center, 2200 Bergquist Drive, Ste. 1, Lackland Air Force Base, San Antonio, TX 78236. michael.landrum@lackland.af.mil

The views expressed herein are the private opinions of the authors and are not to be considered as official or reflecting the views of the U.S. Air Force, the U.S. Department of Defense, or the U.S. Department of Health and Human Services.

The authors thank Lt. Fairlight Reese for her assistance with performing the validation of the OraQuick testing.

Presented in part at the 42nd Annual Meeting of the Infectious Diseases Society of America; October 1, 2004; Boston, MA.

TABLE 1
COSTS OF LABORATORY TESTS AND COMPONENTS OF THE STANDARD OCCUPATIONAL EXPOSURE PANELS

			HCW Panel	
Test	Cost ($)	Source-Patient Panel	Less Severe Occupational Exposure	More Severe Occupational Exposure
OraQuick*	8.03	X	X	X
HIV EIA*	12.33	X	X	X
HBsAg	10.83	X	X	X
HBsAb	14.45			X
HCV Ab	14.86	X	X	X
ALT	1.65	X	X	X
AST	1.65			X
Bilirubin	1.65			X
Creatinine	1.65			X
BUN	1.65			X
CBC	5.84			X
β-HCG	6.71			X

HCW = healthcare worker; HIV = human immunodeficiency virus; EIA = enzyme immunosorbent assay; HBsAg = hepatitis B virus surface antigen; HBsAb = hepatitis B virus surface antibody; HCV Ab = hepatitis C virus antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell count; β-HCG = human chorionic gonadotropin.
*The HIV EIA was included for analysis from January 1 to July 11, 2003; the OraQuick test (OraSure Technologies, Bethlehem, PA) was included for analysis from July 11 to December 31, 2003.

be ideal in the occupational exposure setting because other laboratory testing following an occupational exposure requires patient serum and serum is easily transportable to a central laboratory, thus simplifying quality assurance and reducing training requirements.

Other investigators have shown that the use of rapid HIV-antibody tests reduces the cost of occupational exposure management and prescriptions for post-exposure prophylaxis.[13-16] However, these studies used tests that are no longer available[13,15,16] or are not FDA approved.[14] Furthermore, these studies assumed that rapid HIV testing resulted in reduced occupational exposure–related stress reaction symptoms in HCWs.[13,15,16] Therefore, we sought to describe the accuracy of OraQuick compared with standard EIA for source-patient testing in the occupational exposure setting using sera and the effects on post-exposure prophylaxis use, cost, and occupational exposure–related stress reaction symptoms in HCWs.

METHODS

OraQuick Testing

OraQuick testing was performed according to the instructions in the package insert,[6] with the exception of its use with serum. Validation was performed in accordance with published standards and guidelines[17-20] using EIA (HIV AB HIV-1/HIV-2 [rDNA], Abbott Laboratories, Abbott Park, IL) with confirmation of positive results by Western blot (Calypte, Cambridge Bio-tech HIV-1 Western Blot, Calypte Biomedical Corp., Pleasanton, CA) as the reference standard. Clinical serum samples (n = 35) with varying patterns of reactivity to EIA and Western blot were tested with OraQuick and EIA and Western blot. In addition, confirmatory EIA was performed on each sample of source-patient serum tested with OraQuick from July 11 to December 31, 2003.

Occupational Exposure Procedure

A protocol based on the guidelines[4] of the Centers for Disease Control and Prevention was followed for all reported occupational exposures. This protocol included immediate consultation with employee health personnel for the management of blood-borne pathogen exposures. HCWs were educated and voluntary informed consent was obtained for HIV testing. Depending on the results of a severity assessment, laboratory panels were obtained from each source-patient and HCW (Table 1), and post-exposure prophylaxis recommendations were given. During the study period, the recommended post-exposure prophylaxis regimen consisted of zidovudine and lamivudine (dispensed as one tablet, Combivir, GlaxoSmithKline, Research Triangle Park, NC), with or without nelfinavir depending on exposure type and severity.[4] Employee health personnel recorded these data along with demographics, type of occupational exposure, and the interval from the time the occupational exposure occurred until the serostatus of the source-patient was known.

Following each occupational exposure, employee health personnel contacted each HCW to ensure that the necessary follow-up testing was performed and to track the use of post-exposure prophylaxis and the number of ingested doses. Data regarding the initiation, number of doses dispensed and ingested, interval, and reasons for stoppage of post-exposure prophylaxis were collected.

Use of Post-Exposure Prophylaxis

We performed a retrospective before-and-after analysis of all reported occupational exposures from January 1 through December 31, 2003. From January 1 to July 10, 2003, EIA was used for source-patient testing (EIA group), and from July 11 to December 31, 2003, the OraQuick test

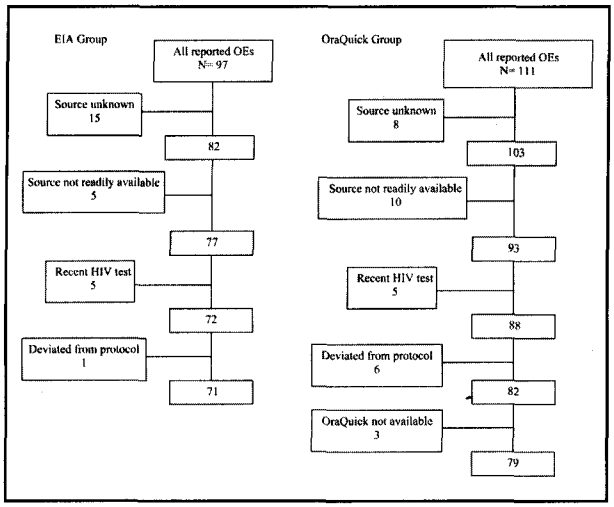


FIGURE. Derivation of occupational exposures. The enzyme immunoassay (EIA) group was from January 1 to July 10, 2003, and the OraQuick (OraSure Technologies, Bethlehem, PA) group was from July 11 to December 31, 2003. HIV = human immunodeficiency virus; OEs = occupational exposures.

was used (OraQuick group). All occupational exposures during this time were reviewed. Exposures were excluded from analysis for the following reasons: the source-patient was unknown or unavailable, the source-patient had a recent HIV test, or deviation from the institutional occupational exposure protocol occurred (such as sending source-patient serum for testing prior to reporting an occupational exposure or performing EIA testing when OraQuick was available).

Cost Analysis

A cost analysis of the two groups was performed using the institutional laboratory and post-exposure prophylaxis costs. Cost of laboratory tests included direct and indirect costs (Table 1). The acquisition cost of one tablet of zidovudine–lamivudine was $6.08, and the cost of one tablet of nelfinavir was $6.85. The mean occupational exposure cost was calculated using the formula A + (B*C) + [(D*E) + (F*G)], where A is the cost of source-patient evaluation, B is the proportion of occupational exposures for which post-exposure prophylaxis was dispensed, C is the cost of dispensed doses of post-exposure prophylaxis, D is the proportion of occupational exposures for which a more severe HCW laboratory panel was obtained, E is the cost of a more severe HCW laboratory panel, F is the proportion of occupational exposures for which a less severe HCW laboratory panel was obtained, and G is the cost of a less severe HCW laboratory panel.

Survey of HCW Anxiety

One of the authors (MLL) retrospectively administered a telephone survey based on previously reported stress reaction symptoms of HCWs following occupational exposures to HCWs randomly selected from each group.[3] The questions were as follows: "Were you worried about becoming infected with HIV when you left work on the day your exposure occurred?" "Did you have repeated thoughts of the exposure or attempt to avoid thoughts of the exposure? If yes, for how long?" "Did you have difficulty falling asleep or staying asleep after your exposure?" "Did you feel concerned about your future after your exposure? If yes, for how long?" and "Did you have difficulty concentrating after your exposure? If yes, for how long?"

Statistical Analysis

Statistical analysis of the two groups was performed with SPSS software (version 11.5.1; SPSS, Inc., Chicago, IL). For validation of the use of OraQuick with serum, concordance with EIA and Western blot was determined using Cohen's kappa test for dichotomous data, and sensitivity and specificity were calculated with binomial 95% confidence intervals (CI_{95}). Continuous variables were analyzed with the two-sided Mann–Whitney *U* test or Student's *t* test for independent samples, and categorical variables were analyzed with the two-sided Fisher's exact test or Pearson's chi-square test. HCWs were selected for the survey using random numbers generated by Microsoft Excel 2000 software (Microsoft Corp., Redmond, WA). A sample size of 36 participants for the survey (18 from each group) provided 80% power to detect a 50% reduction in "yes" responses for each individual question between the OraQuick and EIA groups.

Data were collected and analyzed for quality assurance purposes, and the Wilford Hall Medical Center Institutional Review Board approved the publication.

RESULTS

OraQuick Testing

Of the 35 validation serum samples, 23 were negative by EIA and Western blot and 12 were repeatedly reactive by EIA and confirmed by Western blot. OraQuick testing was universally concordant with the reference method (κ = 1.000). Therefore, with the use of patient sera, both sensitivity and specificity were 100% (CI_{95}, 77.9% to 100% and 87.8% to 100%, respectively).

During both the EIA and the OraQuick periods, all source-patients tested negative for HIV. From July 11 to December 31, 2003, following implementation of OraQuick for source-patient testing, OraQuick was used in 79 occupational exposures and there was 100% concordance (κ = 1.000) between OraQuick using patient sera and EIA. Therefore, during the study period, the specificity of OraQuick with patient sera was 100% (CI_{95}, 96.3% to 100%). In addition, the mean interval between the report of an occupational exposure and the report of a source-patient's HIV test result was significantly longer for the EIA group (3,254 minutes; range, 716 to 9,208 minutes) compared with the OraQuick group (117 minutes; range, 40 to 501 minutes; $P < .001$).

Use of Post-Exposure Prophylaxis

There were 97 reported occupational exposures in the EIA group and 111 in the OraQuick group. After exclu-

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE 2
CHARACTERISTICS OF OCCUPATIONAL EXPOSURES ANALYZED BY ENZYME IMMUNOASSAY AND ORAQUICK* TESTING

Characteristic	EIA Source-Patient Testing† (N = 71)	OraQuick Source-Patient Testing† (N = 79)	P
Female HCW	39 (55%)	36 (46%)	.327‡
Exposure location			.076§
Inpatient unit	47 (66%)	62 (78%)	
Outpatient unit	13 (18%)	14 (18%)	
Laboratory	4 (6%)	2 (3%)	
Unknown	7 (10%)	1 (1%)	
HCW mean age, y (range)	30.6 (18–51)	31 (19–63)	.759‖
HCW job category			.188§
Technician	31 (44%)	34 (43%)	
Physician	21 (30%)	30 (38%)	
Nurse	13 (18%)	15 (19%)	
Volunteer	1 (1%)	0	
Housekeeper	1 (1%)	0	
Unknown	4 (6%)	0	
Incident type			.525§
Percutaneous	49 (69%)	60 (76%)	
Mucosal	13 (18%)	13 (16%)	
Cutaneous	9 (13%)	6 (8%)	
Post-exposure prophylaxis recommended	5 (7%)	6 (8%)	1.000‡

EIA = enzyme immunosorbent assay; HCW = healthcare worker.
*OraSure Technologies, Bethlehem, PA.
†Number of occupational exposures.
‡Fisher's exact test (two-sided).
§Pearson's chi-square test (two-sided).
‖Student's *t* test for independent samples (two-sided).

sion, there were 71 and 79 exposures in the EIA and the OraQuick groups, respectively (Figure). There were no significant differences regarding HCW gender, exposure location, HCW age, HCW job category, or incident type between the two groups (Table 2). Post-exposure prophylaxis was recommended for similar numbers of incidents in the two groups: five times in the EIA group and six times in the OraQuick group (6.9% vs 7.6%, respectively; $P = 1.000$). However, due to one individual's misinterpretation of our procedures during the OraQuick test period, the more severe HCW laboratory panel was obtained seven times in the EIA group compared with 20 times in the OraQuick group (9.8% vs 25%; $P = .019$).

The comparison data regarding post-exposure prophylaxis are provided in Table 3. No post-exposure prophylaxis course included nelfinavir. The mean number of doses of zidovudine–lamivudine dispensed in the EIA group per post-exposure prophylaxis course was 12.7 (range, 0 to 72) compared with 5.0 in the OraQuick group (range, 0 to 6; $P = .500$). However, the mean number of ingested doses per post-exposure prophylaxis course was significantly higher for the EIA group (3.8 doses; range, 0 to 6) compared with the OraQuick group (1.2 doses; range, 0 to 3; $P = .016$). No HCW discontinued post-exposure prophylaxis due to adverse drug effects in either group. In all cases, post-exposure prophylaxis was discontinued when a negative result for EIA or OraQuick testing was obtained for a source-patient. The results were not significantly altered when occupational exposures that had been excluded for deviations from the protocol were included or when OraQuick was unavailable in an intent-to-treat analysis (data not shown).

Cost Analysis

The cost of source-patient evaluation was $4.30 less for the OraQuick group compared with the EIA group, regardless of occupational exposure severity (Table 4). However, the cost of evaluation and management of a HCW varied depending on whether the occupational exposure was less severe or more severe.[4]

For a less severe occupational exposure, there was no difference in the cost of HCW evaluation and management between the EIA and the OraQuick groups because no post-exposure prophylaxis was recommended and HCW laboratory testing was minimal. Therefore, for less severe occupational exposures, $4.30 was saved per exposure using the OraQuick test.

For a more severe occupational exposure, HCW evaluation and management in the EIA group cost $150.49 compared with $103.67 in the OraQuick group,

TABLE 3
CHARACTERISTICS OF POST-EXPOSURE PROPHYLAXIS FOR THE TWO GROUPS

Characteristic	EIA Source-Patient Testing (N = 71)	OraQuick* Source-Patient Testing (N = 79)	P
HCW begins post-exposure prophylaxis†	9 (13%)	6 (8%)	.415‡
Mean no. of zidovudine–lamivudine doses dispensed (range)	12.7 (0–72)	5.0 (0–6)	.500§
Mean no. of zidovudine–lamivudine doses ingested (range)	3.8 (0–6)	1.2 (0–3)	.016§

EIA = enzyme immunosorbent assay; HCW = healthcare worker.
*OraSure Technologies, Bethlehem, PA.
†Number of HCWs from each group starting post-exposure prophylaxis.
‡Fisher's exact test (two-sided).
§Mann–Whitney *U* test (two-sided).

TABLE 4
COST-ANALYSIS (IN U.S. DOLLARS) USING ORAQUICK* FOR SOURCE-PATIENT TESTING COMPARED WITH ENZYME IMMUNOASSAY AND WESTERN BLOT

	EIA Source-Patient Testing (N = 71)	Actual OraQuick Source-Patient Testing (N = 79)	Actual Savings†	Idealized OraQuick Source-Patient Testing	Idealized Savings‡
Less severe occupational exposure					
HCW	39.67	39.67	-	39.67	-
Laboratory	39.67	39.67	-	39.67	-
Post-exposure prophylaxis	0.00	0.00	-	0.00	-
Source-patient	39.67	35.37	4.30	35.37	4.30
Total cost	79.34	75.04	4.30	75.04	4.30
More severe occupational exposure					
HCW	150.49	103.67	46.82	39.67	110.82
Laboratory	73.27	73.27	-	39.67	33.60
Post-exposure prophylaxis	77.22	30.40	46.82	0.00	77.22
Source-patient	39.67	35.37	4.30	35.37	4.30
Total cost	190.16	139.04	51.12	75.04	115.12
Mean cost of occupational exposure§	92.47	85.85	6.62	75.04	17.43

EIA = enzyme immunosorbent assay; HCW = healthcare worker.
*OraSure Technologies, Bethlehem, PA.
†Actual difference in cost between EIA and OraQuick groups.
‡Difference in cost between EIA group and idealized cost using OraQuick for source-patient testing.
§Weighted mean using the following formula: mean occupational exposure cost = A + (B*C) + [(D*E) + (F*G)], where A is the cost of source-patient evaluation; B is the proportion of occupational exposures for which post-exposure prophylaxis was dispensed; C is the cost of dispensed doses of post-exposure prophylaxis; D is the proportion of occupational exposures for which a more severe HCW laboratory panel was obtained; E is the cost of a more severe HCW laboratory panel; F is the proportion of occupational exposures for which a less severe HCW laboratory panel was obtained; and G is the cost of a less severe HCW laboratory panel.

for a difference of $46.82. When the cost for source-patient evaluation was added, the total cost for a more severe occupational exposure in the EIA and the OraQuick groups was $190.16 and $139.04, respectively. An idealized analysis in which all unnecessary post-exposure prophylaxis and laboratory testing was eliminated for more severe occupational exposures revealed that the savings resulting from the use of OraQuick would be $115.12 per occupational exposure.

Overall, on comparison of the mean occupational exposure costs, the use of OraQuick for source-patient testing saved at least $6.62 per occupational exposure, which would translate to an annual cost savings of $1,059.46 at our institution. However, with further reductions in unnecessary post-exposure prophylaxis and laboratory testing, the expected savings would be $17.43 per occupational exposure, or $2,789.25 annually.

Survey of HCW Anxiety

The survey was completed by all 18 initial contacts from the EIA group and 19 of 22 contacts from the OraQuick group (Table 5). There were 24 (27%) "yes" responses in the EIA group compared with 16 (17%) in the OraQuick group ($P = .106$). Eleven (61%) of the HCWs in the EIA group responded "yes" to the second question compared with 5 (26%) in the OraQuick group ($P = .049$). The median duration of repeated thoughts of the exposure was 1.25 days (range, 0 to 11 days; interquar-

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE 5
RESULTS OF A SURVEY* REGARDING HEALTHCARE WORKER ANXIETY

HCW Answer†	EIA Source-Patient Testing (N = 18)	OraQuick‡ Source-Patient Testing (N = 19)	P§
Worried about becoming infected with HIV	5 (28%)	4 (21%)	.714
Repeated thoughts of the exposure	11 (61%)	5 (26%)	.049
Difficulty sleeping	1 (6%)	1 (5%)	1.000
Concerned for your future	5 (28%)	3 (16%)	.447
Difficulty concentrating	2 (11%)	3 (16%)	1.000
Total	24 (27%)	16 (17%)	.106

HCW = healthcare worker; EIA = enzyme immunosorbent assay; HIV = human immunodeficiency virus.
*For complete questions, see METHODS, Survey of HCW Anxiety.
†Number of "yes" responses of a potential 90 responses in the EIA group and 95 responses in the OraQuick group.
‡OraSure Technologies, Bethlehem, PA.
§Fisher's exact test (two-sided).

tile range, 3.00) in the EIA group compared with 0 days (range, 0 to 210 days; interquartile range, 2.00; $P = .168$) for the OraQuick group.

DISCUSSION

Following validation with patient sera, we examined the impact of the OraQuick Rapid HIV-1 Antibody Test on occupational exposure management in our institution regarding the use of post-exposure prophylaxis, cost savings, and HCW stress reaction symptoms related to the exposure. We found that OraQuick performed well using patient sera, significantly reduced the number of ingested doses of unnecessary post-exposure prophylaxis, resulted in cost savings, and resulted in a trend toward reduction in the stress reaction symptoms of HCWs following an occupational exposure.

Recommended regimens for post-exposure prophylaxis vary depending on two variables: HIV status of the source-patient and exposure type, categorized as less or more severe.[4] In our institution, the HIV prevalence among source-patients is low (0.2%; Robert J. O'Connell, MD, unpublished data, January 10, 2005), and most occupational exposures involve a source-patient whose HIV status is unknown at the time of the exposure. Therefore, post-exposure prophylaxis is generally not recommended unless the exposure type is more severe or HIV risk factors are present in the source-patient.[4] Prior to using OraQuick at our institution, a more severe exposure often resulted in the HCW's receiving at least 3 days of unnecessary post-exposure prophylaxis until the EIA results of the source-patient were known. In all occupational exposures during the study period, post-exposure prophylaxis was determined to be unnecessary because the source-patients were found to be HIV negative.

Previous investigators have estimated the achievable reduction in post-exposure prophylaxis using a rapid HIV-antibody test.[13,15,16] Unfortunately, HCWs may still be prescribed post-exposure prophylaxis while awaiting the results of the source-patient's rapid HIV-antibody test, especially if results are unexpectedly delayed. In addition, prescribing practices for post-exposure prophylaxis vary considerably among institutions, from a two- or three-drug regimen for only high-risk exposures in some hospitals (as in our institution) to an expanded three-drug regimen for all exposures.[13,15,21] For these reasons, the reductions in post-exposure prophylaxis and cost may be vastly different between institutions. Our analysis shows, however, that even in a setting where a two-drug post-exposure prophylaxis regimen is recommended for less than 10% of occupational exposures, use of a rapid HIV-antibody test such as OraQuick still results in a significant reduction in the number of ingested doses of post-exposure prophylaxis. This difference accounts for even occupational exposures for which post-exposure prophylaxis was prescribed due to delays in obtaining OraQuick results. By reducing unnecessary post-exposure prophylaxis, the risk of potentially common and serious adverse effects[2,4,21] is undoubtedly reduced.

The current study confirmed the results of previous investigations that found that the use of a rapid HIV-antibody test reduced the cost of occupational exposure management.[13,15] Kallenborn et al.[13] reported a savings of approximately $300 per exposure using a rapid HIV-antibody test, and Machado et al.[15] reported a savings of nearly $30 per exposure. We found a more modest actual cost reduction of $6.62 per exposure and an idealized cost reduction of $17.43, both smaller than previous reports. Although the cost of medication acquisition in the previous reports accounts for some of this difference, it is most notable that these studies used an expanded three-drug regimen following all occupational exposures, regardless of risk of HIV transmission. Furthermore, Kallenborn et al. included an average of one lost workday per exposed HCW due to post-exposure prophylaxis–related toxicity in the cost analysis. Given that no HCW reported stopping post-exposure prophylaxis due to toxicity in our study, it seems unlikely that any missed a day of work due to adverse effects. In addition, the more severe HCW laboratory panel was obtained significantly more frequently during the OraQuick period, further diminishing the savings. These differences included, we still found that the use of OraQuick for source-patient testing resulted in reduced

costs compared with occupational exposure management using EIA.

Yet another potential advantage in using a rapid HIV-antibody test for screening source-patients is a reduction in stress and anxiety experienced by HCWs. Armstrong et al.[3] described a series of 22 HCWs who all worried about becoming infected with HIV; many had intrusive thoughts of the actual exposure, difficulty concentrating and sleeping, and emotional numbing. Interestingly, our survey revealed an overall trend of a reduction in these symptoms with the use of the OraQuick test, but there were limitations to our survey. Perhaps most important was the limitation of recall bias. The interval between the occupational exposure and the survey was several months longer for the EIA group than for the OraQuick group because all surveys were retrospectively administered 2 months following the end of the OraQuick test period. Recall bias may have then reduced the observed difference between the two groups, thus making the current data an underestimation of the actual difference.

We found that the OraQuick Rapid HIV-1 Antibody Test performed well using patient sera for screening source-patients in occupational exposures, significantly reduced ingested doses of unnecessary post-exposure prophylaxis, reduced the cost of occupational exposure management, and significantly reduced repetitive thoughts of the exposure. There appear to be few, if any, disadvantages to using rapid HIV-antibody testing in this setting. Given these advantages, rapid HIV-antibody tests should no longer be considered an alternative to EIA tests but rather should be the preferred approach used to screen source-patients following occupational exposures.

REFERENCES

1. Centers for Disease Control and Prevention. *Surveillance of Healthcare Personnel With HIV/AIDS, as of December 2002*. Atlanta, GA: Centers for Disease Control and Prevention; 2003. Available at www.cdc.gov/ncidod/hip/Blood/hivpersonnel.htm. Accessed April 27, 2005.
2. Gerberding JL. Occupational exposure to HIV in health care settings. *N Engl J Med* 2003;348:826-833.
3. Armstrong K, Gorden R, Santorella G. Occupational exposure of health care workers (HCWs) to human immunodeficiency virus (HIV): stress reactions and counseling interventions. *Soc Work Health Care* 1995;21:61-80.
4. Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR* 2001;50:1-52.
5. Gerberding JL, Henderson DK. Management of occupational exposures to bloodborne pathogens: hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. *Clin Infect Dis* 1992;14:1179-1185.
6. OraSure Technologies, Inc. *OraQuick Rapid HIV-1 Antibody Test* [package insert]. Bethlehem, PA: OraSure Technologies, Inc.; 2004:1-18.
7. Bio-Rad Laboratories. *Multispot HIV-1/HIV-2 Rapid Test*. Redmond, WA: Bio-Rad Laboratories; 2005:1-21.
8. Medmira Laboratories, Inc. *Reveal G2 Rapid HIV-1 Antibody Test*. Halifax, Nova Scotia, Canada: Medmira Laboratories, Inc.; 2004:1-13.
9. Trinity Biotech, PLC. *Uni-Gold Recombigen*. Wicklow, Ireland: Trinity Biotech, PLC; 2004:1-28.
10. O'Connell RJ, Merritt TM, Malia JA, et al. Performance of the OraQuick rapid antibody test for diagnosis of human immunodeficiency virus type 1 infection in patients with various levels of exposure to highly active antiretroviral therapy. *J Clin Microbiol* 2003;41:2153-2155.
11. Branson BM. Point-of-care tests for HIV antibodies. *J Lab Med* 2003;27:288-295.
12. Branson BM, Uniyal A, Kerndt P, Fridlund C, Granade T. Performance of newer rapid tests for HIV antibody with whole blood and plasma. Presented at the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA.
13. Kallenborn JC, Price TG, Carrico R, Davidson AB. Emergency department management of occupational exposures: cost analysis of rapid HIV test. *Infect Control Hosp Epidemiol* 2001;22:289-293.
14. Van den Berk GE, Frissen PH, Regez RM, Rietra PJ. Evaluation of the rapid immunoassay Determine HIV 1/2 for detection of antibodies to human immunodeficiency virus types 1 and 2. *J Clin Microbiol* 2003;41:3868-3869.
15. Machado AA, Martinez R, Haikal AA, Rodrigues Da Silva MCV. Advantages of the rapid HIV-1 test in occupational accidents with potentially contaminated material among health workers. *Rev Inst Med Trop Sao Paulo* 2001;43:199-201.
16. Salgado CD, Flanagan HL, Haverstick DM, Farr BM. Low rate of false-positive results with use of a rapid HIV test. *Infect Control Hosp Epidemiol* 2002;23:335-337.
17. U.S. Department of Health and Human Services. Medicare, Medicaid, and CLIA programs: regulations implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Final rule. *Federal Register* 1992;57:7002-7186.
18. College of American Pathology. *College of American Pathology General Checklist 42020*. Northfield, IL: College of American Pathology; 2003.
19. National Committee for Clinical Laboratory Standards. *Statistical Quality Control for Quantitative Measurements: Principles and Definitions*. Approved guideline, ed. 2. Wayne, PA: National Committee for Clinical Laboratory Standards; 1999.
20. Joint Commission on Accreditation of Healthcare Organizations. *2003 Hospital Accreditation Standards*. Oakbrook, IL: Joint Commission Resources; 2003. WT.1.40, QC.1.70, QC.1.80.
21. Wang SA, Panlilio AL, Doi PA, White AD, Stek M Jr, Saah A. Experience of healthcare workers taking postexposure prophylaxis after occupational HIV exposures: findings of the HIV postexposure prophylaxis registry. *Infect Control Hosp Epidemiol* 2000;21:780-785.

WORKERS' COMPENSATION CLAIMS FOR NEEDLESTICK INJURIES AMONG HEALTHCARE WORKERS IN WASHINGTON STATE, 1996–2000

Syed M. Shah, MD; David Bonauto, MD; Barbara Silverstein, PhD; Michael Foley, PhC

ABSTRACT

OBJECTIVES: To characterize accepted workers' compensation claims for needlestick injuries filed by healthcare workers (HCWs) in non-hospital compared with hospital settings in Washington State.

DESIGN: Descriptive study of all accepted workers' compensation claims filed between 1996 and 2000 for needlestick injuries.

PARTICIPANTS: All Washington State HCWs eligible to file a state fund workers' compensation claim and those who filed a workers' compensation claim for a needlestick injury.

RESULTS: There were 3,303 accepted state fund HCW needlestick injury claims. The incidence of needlestick injury claims per 10,000 full-time–equivalent HCWs in hospitals was 158.6; in dental offices, 104.7; in physicians' offices, 87.0; and in skilled nursing facilities, 80.8. The most common mechanisms of needlestick injury by work location were as follows: for hospitals, suturing and other surgical procedures (16.7%), administering an injection (12.7%), and drawing blood (10%); for dentists' offices, recapping (21.3%) and cleaning trays and instruments (18.2%); for physicians' offices, disposal (22.2%) and administering an injection (10.2%); and for skilled nursing facilities, disposal (23.7%) and administering an injection (14.9%). Nurses accounted for the largest (29%) proportion of HCWs involved, followed by dental assistants (17%) and laboratory technicians and phlebotomists (12%) in non-hospital settings. Rates of needlestick injury claims increased for non-hospital settings by 7.5% annually (95% confidence interval [CI_{95}], 4.89% to 10.22%; $P < .0001$). Rates decreased for hospital settings by 5.8% annually, but the decline was not statistically significant (CI_{95}, -12.50% to 1.34%; $P < .1088$). HCWs were exposed to hepatitis B, hepatitis C, and human immunodeficiency viruses in non-hospital settings.

CONCLUSION: There was a difference in the incidence rate and mechanisms of needlestick injuries on review of workers' compensation claim records for HCWs in non-hospital and hospital settings (*Infect Control Hosp Epidemiol* 2005;26:775-781).

Needlestick injuries in hospital settings have been the focus of many studies and major surveillance projects, and programs at the national level provide updated data from hospitals on a regular basis.[1,2] Healthcare workers (HCWs) in non-hospital settings are at risk for such injuries, yet few studies have been conducted to document the burden of the problem.[3-5]

In this study, we used databases for workers' compensation claims in Washington State to estimate the number and pattern of work-related needlestick injuries among HCWs in non-hospital compared with hospital settings. These databases have been used successfully in several studies examining injury hazards and industries at risk.[6-8]

METHODS

Description of the Workers' Compensation System in Washington State

In Washington State, employers are required to obtain workers' compensation insurance through the Department of Labor and Industries (L&I) State Fund unless they are able to self-insure, are self-employed, or are part of the federal government. The L&I State Fund covers approximately two-thirds of the workers in Washington State (the remainder work chiefly for the 400 largest employers in Washington State and are covered by their self-insured employers).

There are two major workers' compensation data systems: the L&I Industrial Insurance System (LINIIS) and the Medical Information Payment System (MIPS). Data included in the LINIIS are worker information (eg, age and gender), injury or illness information (injury by nature, type, source, and body part using American National Standard Institute [ANSI] Z-16.2 codes), a text description of the injury, the medical record and treatment information, employer industry codes (Standard Industrial Classification [SIC] code), occupation codes (Standard Occupational Code [SOC] 2000 version), and International Classification

The authors are from the Safety & Health Assessment & Research for Prevention (SHARP) Program, Washington State Department of Labor and Industries, Olympia, Washington.

Address reprint requests to Syed M. Shah, MD, Department of Community Health and Epidemiology, University of Saskatchewan, Health Sciences Building, 107 Wiggins Road, Saskatoon, SK S7N 5E5, Canada. syed.shah@usask.ca

Supported by Cooperative Agreement 1 U01 OH07292-01 from the National Institute for Occupational Safety and Health and the Washington State Department of Labor and Industries.

The authors thank the staff at SHARP for their insightful review and recommendations for this report. They also thank Richard Ordos from Washington State Department of Health for his help regarding hospital FTEs in Washington State, and John Kalat, Randy Clark, Scott McGeary, Steve Whittaker, and Hieu Pham for their help with this report.

of Diseases, 9th revision, codes for the allowed diagnosis of the claim. The MIPS captures all financial information associated with a workers' compensation claim. MIPS captures information on all hospital, physician, and pharmacy bills, wage replacement costs, days of lost time from work, costs from permanent and total disability awards, and costs from associated pensions.

All L&I State Fund claims are entered into LINIIS; however, only those self-insured claims resulting in 4 or more days of lost time (compensable claims) are fully coded in LINIIS. This study does not include most large hospitals because they are self-insured and our LINIIS database does not provide enough detail about their medical-only claims to allow us to extract their needlestick claims.

Identification of Workers' Compensation Claims From Healthcare Employers

All establishments primarily engaged in furnishing medical, surgical, and other health services to individuals are coded in the SIC system as SIC 80, "Health Services." However, large university teaching hospitals are coded under SIC major group 82, "Educational Services."

From LINIIS we obtained all accepted workers' compensation claim data for HCWs (employees working in SIC 80, Health Services, and the two major L&I State Fund teaching hospitals, classified under SIC 82, Educational Services) with a date of injury between January 1, 1996, and December 31, 2000. Accepted claims can be categorized as compensable or noncompensable. To qualify as a compensable claim, the injury must have resulted in 4 or more lost working days, had permanent partial disability, or resulted in death.

Definition and Characterization of Needlestick Injury Claims

Of all the accepted claims of HCWs, we extracted needlestick injury claims. We defined a needlestick claim if the ANSI[9] source code was "2202-needle" or the associated source code was "22021-needle broken in use," "22025-needle mishandled," "22029-needle-other," "22022-needle slipped," or "22020-needle-unsound," or if a text word search of the workers' compensation accident form for specific injury sources found the words "needle" or "stick" and "needlestick."

To further characterize the mechanism of needlestick injury, the principal investigator studied the 5- to 10-line injury event description in all accepted claims for needlestick injuries and classified the injury event into various categories. A total of 68 claims were excluded due to not being a needlestick injury. All medical records relevant to the claim are stored in an imaging system for review. The principal investigator reviewed these records to determine the infection status of source-patients for these needlesticks.

We used the two occupational class codes to define job category, an L&I occupation class code modified from SOC 1980 and a second code based on SOC 2000. We classified an additional 177 needlestick injury L&I State Fund claims in which the occupational class codes were originally missing. We were able to define the job category in most (99.5%) of these needlestick injury cases. We estimated the total direct cost for the accepted needlestick injury cases from data available from the provider medical bills in MIPS.

Employers in Washington State are required to pay workers' compensation insurance premiums based on the number of hours worked by their employees. On a quarterly basis, each employer reports the number of paid work hours for employees.

The number of full-time–equivalent employees (FTEs) was calculated with the assumption that each FTE works 2,000 hours per year (40 hours per week for 50 weeks per year). We obtained data regarding FTEs for the two major L&I State Fund teaching hospitals from the Washington State Department of Health hospital employee data.[10]

Statistical Analysis

Our detailed analysis focused on needlestick injury claims accepted by the L&I State Fund. Descriptive analyses included the frequency of claims by location (non-hospital and hospital settings) and job category. We calculated rates of accepted needlestick injury claims during the study years. Payroll data reported to the workers' compensation system were used to extract the number of hours worked. Number of hours was aggregated to the SIC level and reported for each year. The incidence rates of the claims were calculated by year and expressed as the number of claims per 10,000 FTEs. Testing for the trend of incidence rates over time was performed. We used a Poisson regression model to test for evidence of a trend in the rates of claims as a function of calendar year. The GENMOD procedure, with a Poisson distribution, was used to evaluate trends over time (using SAS software, version 8.2; SAS Institute, Inc., Cary, NC). We used the following regression model: $\text{Ln}(\lambda\text{year}) = \beta 0 + \beta 1\ (\text{year}) + \epsilon$. The λyear is the injury rate for each year and the natural log transformation ensures that the model-based predictions of rates are constrained to be greater than or equal to 0. We estimated the annual percent decrease in injury rate by exponentiating the coefficients from the fitted model. For example, the estimated coefficient of the accepted claim rate for needlestick injuries in non-hospital settings was 0.0725 with a standard error of 0.0127. The $\epsilon^{(0.0725)\text{-}1*100}$ translates into an annual increase of 7.5% in the rate of accepted claims during the study period.

RESULTS

A total of 74,758 workers' compensation claims in the health services industry (SIC 80) and 11,337 claims in educational services (SIC 82) were filed for work-related injuries or illnesses from January 1, 1996, to December 31, 2000. There were a total of 3,303 accepted L&I State Fund needlestick injury claims by HCWs. Only one of the accepted claims was compensable (4 or more days of lost time from work).

In non-hospital settings, the overall rate of injury was 71.3 per 10,000 FTEs per year, increasing from 59.4 claims

per 10,000 FTEs in 1996 to 79 claims per 10,000 FTEs in 2000. Trend analysis showed an annual average increase of 7.52% (95% confidence interval [CI_{95}], 4.89% to 10.22%; $P < .0001$). In hospital settings, the overall rate of injury was 156.9 per 10,000 FTEs, decreasing from 161.2 claims per 10,000 FTEs in 1996 to 120.6 per 10,000 FTEs in 2000. Trend analysis showed an annual average decrease of 5.83% (CI_{95}, -12.50% to 1.34%; $P < .1088$). The figure further illustrates injury rates in non-hospital and hospital settings.

Table 1 provides the distribution of workers' compensation claims for needlestick injuries among HCWs in Washington State as compared with hospital data available from the National Surveillance System for Health Care Workers (NaSH)[5] and the Exposure Prevention Information Network (EPINet).[6] In both hospital and non-hospital settings, nurses accounted for the largest proportion of injured HCWs. Dental assistants were the second most common occupational group to have a needlestick injury in non-hospital settings.

In non-hospital settings, disposal-related activities such as putting items into biohazard containers or an item protruding from a disposal container (eg, another needle from inside the container popping out or a butterfly needle coiling back) resulted in most (18%) of the needlestick injuries, followed by recapping (11%), administering injections (8.8%), and drawing blood (6.9%). HCWs in non-hospital settings sustained another significant proportion (14.1%) of injuries while cleaning trays and instruments and by unexpected movements of patients. In hospital settings, suturing and surgical procedures (16.7%), administering injections (12.7%), and

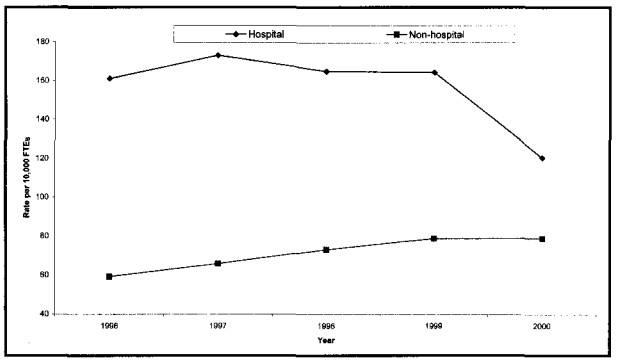


FIGURE. Labor and Industries State Fund claims for needlestick injury, Washington State, 1996 to 2000. FTEs = full-time–equivalent employees.

TABLE 1
NEEDLESTICK INJURIES BY JOB CLASSIFICATION AND WORK LOCATION IN WASHINGTON STATE COMPARED WITH DATA FROM THE EXPOSURE PREVENTION INFORMATION NETWORK (EPINET)* AND THE NATIONAL SURVEILLANCE SYSTEM FOR HEALTH CARE WORKERS (NASH)†

	Washington State		National Hospitals	
Job Category	**Non-Hospital Settings (%)**	**Hospital Settings (%)**	**EPINet, %**	**NaSH, %**
Physician	210 (8)	199 (26)	15	30
Nurse (RN or LPN)	724 (29)	343 (45)	44	44
Laboratory technician or phlebotomist	307 (12)	52 (7)	8	13
Technologist (non-laboratory)	86 (3)	32 (4)	5	
Housekeeper or laundry worker	35 (1)	38 (5)	4	3
Nursing aide (CAN or HHA)	194 (8)	14 (2)	3	
Surgery or other attendant	313 (12)	30 (4)	10	
Therapist (respiratory or other)	9 (0)	5 (1)	2	
Dental assistant	439 (17)	10 (1)		1
Dental hygienist	113 (4)			
Dentist	54 (2)	6 (1)	< 1	
Medical or nurse student	0 (0)	7 (1)	1	3
Support staff (clerical or administrative)	21 (1)	10 (1)		1
Other	13 (1)	17 (2)	8	4
Paramedic			< 1	
Occupation not reported	18 (1)	4 (1)		
Security			< 1	
Other student			1	
Research				1
Total	2,536 (100)	767 (100)	99.9‡	100

*Data from 13 teaching and 45 non-teaching hospitals, 2001.
†1995 to 1999.
‡Rounding error.

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE 2
CIRCUMSTANCES OF NEEDLESTICK INJURIES AMONG HEALTHCARE WORKERS IN WASHINGTON STATE COMPARED WITH DATA FROM THE EXPOSURE PREVENTION INFORMATION NETWORK (EPINET) AND THE NATIONAL SURVEILLANCE SYSTEM FOR HEALTH CARE WORKERS (NASH)

		National Hospitals		Washington Non-Hospital Settings				
When Injury Occurred	Washington Hospital Settings (%)	EPINet (%)	NaSH, %	Total (%)	Physicians' Offices (%)	Dentists' Offices (%)	Nursing Care Facilities (%)	Other* (%)
During use of item		564 (30.1)	27					
Administering an injection	97 (12.7)			223 (8.8)	121 (10.2)	13 (2.2)	73 (14.9)	16 (5.9)
Checking blood sugar with lancet	2 (0.3)			29 (1.1)	2 (0.2)	2 (0.3)	23 (4.7)	2 (0.7)
Administering local anesthesia	14 (1.8)			85 (3.4)	36 (3.0)	48 (8.1)	0 (0.0)	1 (0.4)
Blood draw	77 (10.0)			175 (6.9)	109 (9.2)	4 (0.7)	14 (2.9)	48 (17.7)
Suturing	84 (11.0)			91 (3.6)	88 (7.4)	2 (0.3)	0 (0.0)	1 (0.4)
Surgery	44 (5.7)			91 (3.6)	76 (6.4)	10 (1.7)	2 (0.4)	3 (1.1)
Stuck by colleague	19 (2.5)			51 (2.0)	27 (2.3)	20 (3.4)	3 (0.6)	1 (0.4)
Movement or restraint of the patient	36 (4.7)	10 (0.5)		173 (6.8)	79 (6.7)	18 (3.0)	41 (8.4)	35 (12.9)
Between steps of a multistep procedure		257 (13.7)						
Disassembling device	10 (1.3)	79 (4.2)		134 (5.3)	22 (1.9)	86 (14.5)	20 (4.1)	6 (2.2)
Preparing instrument for reuse	25 (3.3)	36 (1.9)		68 (2.7)	26 (2.2)	22 (3.7)	14 (2.9)	6 (2.2)
Recapping device	66 (8.6)	68 (3.6)	5	282 (11.1)	86 (7.3)	126 (21.3)	50 (10.2)	20 (7.4)
Withdrawing from resistant material	9 (1.2)	67 (3.6)		22 (0.9)	11 (0.9)	1 (0.2)	4 (0.8)	6 (2.2)
Other (after use, before disposal)		314 (16.8)						
Putting on gauze or a bandage or untying tourniquets	5 (0.7)			37 (1.5)	20 (1.7)	3 (0.5)	6 (1.2)	8 (2.9)
Handling or transferring specimens			5					
Cap fell off while disengaging or unscrewing	7 (0.9)			61 (2.4)	8 (0.7)	42 (7.1)	7 (1.4)	4 (1.5)
Collision with HCW with a sharp item	39 (5.1)		8	76 (3.0)	35 (3.0)	18 (3.0)	19 (3.9)	4 (1.5)
Handling or passing the device during or after use			10					
IV catheter–related cause			8					
Cleaning up trays, tables, or procedure areas	22 (2.9)		11	186 (7.3)	61 (5.2)	108 (18.2)	10 (2.0)	7 (2.6)
Disposal related or improper disposal			22					
En route to disposal	1 (0.1)			16 (0.6)	8 (0.7)	1 (0.2)	5 (1.0)	2 (0.7)
Item left on disposal container	8 (1.0)	12 (0.6)		21 (0.8)	9 (0.8)	0 (0.0)	11 (2.3)	1 (0.4)
Putting item into disposal container	71 (9.3)	122 (6.5)		407 (16.0)	215 (18.2)	32 (5.4)	91 (18.6)	69 (25.4)
Item protruding from disposal container	4 (0.5)	53 (2.8)		48 (1.9)	29 (2.4)	3 (0.5)	9 (1.8)	7 (2.6)
Item pierced the side of the disposal container	6 (0.8)	5 (0.3)		5 (0.2)	4 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Item pierced inappropriate disposal container		39 (2.1)						
Device left on floor, bed, or table or in gauze	77 (10.0)	116 (6.2)		134 (5.3)	44 (3.7)	9 (1.5)	71 (14.5)	10 (3.7)
Other	44 (5.7)	130 (6.9)	4	121 (4.8)	66 (5.6)	25 (4.2)	15 (3.1)	15 (5.5)
Total	767 (100.0)	1,872 (99.8)	100	2,536 (100.0)	1,182 (100.0)	593 (100.0)	489 (100.0)	272 (100.0)

HCW = healthcare worker; IV = intravenous.
*Other locations included blood banks, blood donor stations, medical laboratories, specialty outpatient facilities, dental laboratories, and kidney dialysis centers.

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE 3
INCIDENCE RATES OF WASHINGTON LABOR AND INDUSTRIES STATE FUND CLAIMS FOR NEEDLESTICK INJURIES IN THE HEALTH SERVICES INDUSTRY (STANDARD INDUSTRIAL CLASSIFICATION [SIC] 80), 1996–2000*

SIC	Description	Hours	No. of Claims	Average Annual Rate per 10,000 FTEs (CI_{95})
8062	General medical and surgical hospitals	15,639,238	124	158.6 (103.4–216.2)
8021	Offices and clinics of dentists	113,292,720	593	104.7 (70.5–136.7)
8011	Offices and clinics of doctors of medicine	261,037,511	1,135	87.0 (75.9–97.4)
8071	Medical laboratories	41,080,058	166	80.8 (70.0–92.3)
8051	Skilled nursing care facilities	132,830,673	368	55.4 (45.8–66.0)
8099	Health and allied services	12,030,267	26	43.2 (14.8–70.2)
8082	Home healthcare services	34,434,300	64	37.2 (17.7–58.4)
8059	Nursing and personal care facilities, NEC	30,658,977	57	37.2 (17.7–75.8)
8063	Psychiatric hospitals	25,302,129	40	31.6 (24.1–39.4)
8049	Offices and clinics of health practitioners	35,653,413	47	26.4 (9.2–43.2)
8093	Speciality outpatient facilities	38,951,834	47	24.1 (8.3–39.6)

FTEs = full-time–equivalent employees; CI_{95} = 95% confidence interval; NEC = not elsewhere classified.
*Restricted to SICs with more than 25 needlestick injuries during the study period.

drawing blood (10%) were major circumstances leading to a needlestick injury (Table 2).

The infection status of the source-patient was not available in the claim record for 2,913 (88.2%) of the cases. Of the 390 remaining cases, 157 source-patients were screened and had negative results for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV). HCWs in non-hospital settings were exposed to HBV (n = 13), HCV (n = 60), HIV (n = 11), both HCV and HBV (n = 8), and both HCV and HIV (n = 2). Exposures in hospital settings were to HBV (n = 2), HCV (n = 38), HIV (n = 13), both HCV and HBV (n = 2), and both HCV and HIV (n = 4).

The seroconversion status of most (n = 66) of the HCWs exposed to a known case of HCV was not known (follow-up test results were not available), 31 were negative on screening, 18 seroconverted to HCV (presence of antibodies to HCV), and 4 had HCV prior to the needlestick injury. Thirteen HCV seroconverters were in non-hospital settings (physicians' offices, 9; dentists' offices, 1; and nursing care facilities, 3). Available data did not show any seroconversion among those who were exposed to a source-patient with HIV or HBV.

The number of accepted claims and the corresponding claims rate in each of the health services industry groups (SIC 80) are presented in Table 3. The rate of accepted claims for needlestick injury was the highest for general medical and surgical hospitals (158.6 per 10,000 FTEs), followed by offices and clinics of dentists (104.7 per 10,000 FTEs) and offices and clinics of doctors of medicine (87 per 10,000 FTEs).

We also estimated the direct workers' compensation costs of needlestick injuries. A total cost of $970,603 (U.S. dollars) was incurred due to needlestick injuries during the 5-year period. The direct cost per claim was $311 on average in non-hospital settings. The average cost of claims with a known status (HCV, HBV, or HIV) of a source-patient was $827. The direct cost per claim was $324 on average in hospital settings, and it increased to $640 when restricted to claims with a known source.

DISCUSSION

This study represents one of the first efforts to document needlestick injuries to HCWs using statewide workers' compensation data. Assessment of such injuries at work sites and among individuals in various job categories in non-hospital settings is important to devise control strategies for caregivers.

We noted a decline in needlestick injury rates (not significant statistically) among HCWs in the hospital settings. Perry et al. noted a similar decrease in needlestick injury rates in both teaching and non-teaching hospitals between 1999 and 2001.[2] However, we noted a steady but significant ($P < .0001$) increase in the incidence rates of claims for needlestick injuries among HCWs in non-hospital settings in Washington State. HCWs in physicians' offices, dentists' offices, and other non-hospital settings face the risk of being exposed to and acquiring bloodborne pathogens through needlestick injuries. Because most hospitals were self-insured and thereby excluded from this report, the data were not representative of all hospital facilities across the state.

In our study, nurses ranked first among all healthcare occupations, accounting for the largest number of needlestick injuries, in hospital as well as non-hospital settings. These results are in agreement with those from two large datasets, the Centers for Disease Control and Prevention's NaSH[1] and the University of Virginia's International Healthcare Worker Safety Center, EPINet.[2] The other leading job category in hospital settings was physicians, in contrast to non-hospital settings, where dental assistants ranked second. Support staff members who do not use sharp items in their duties, but share the

common environment, were also exposed to needlestick injuries.

We studied the circumstances regarding needlestick injury and our basis of classification was the statement submitted by the injured worker on the workers' compensation claim form describing the circumstances surrounding the injury event. For example, if "while drawing blood, unexpected patient movement caused me to prick left index finger" was the statement of injury, we would classify this under the category of patient movement, not blood drawing.

Disposal of used needles and recapping of needles were two of the most important hazardous activities associated with needlestick injuries in non-hospital settings. A far greater number of needlestick injuries related to these two activities occurred in non-hospital settings as compared with hospital settings (Table 2). This has great implications for prevention of needlestick injuries in these work environments. Jagger et al.[11] noted that the majority of needlestick injuries occurred while the devices were being prepared for disposal or during or after disposal, and that one-third of all injuries were related to the recapping of devices. It has been argued that there may be little difference in injury rates between HCWs recapping or not recapping needles and that it would cease to be an issue if satisfactory disposal systems were always present at the point of use.[12,13] Hatcher[14] reported the results of "a sharps container quality project" where a multidisciplinary committee reviewed sharps containers, piloted one, found problems, and then selected and piloted another and so on until the desired sharps container was identified. This project resulted in a two-thirds reduction in the needlestick injury rate, with a cost savings of $62,000 per year to the center as a result of prevented needlestick injuries. The report of the Council on Scientific Affairs[15] noted that the introduction of safer needle devices, especially in combination with a comprehensive educational and training process, has resulted in a significant decline in the incidence of needlestick injuries.

The average cost of a needlestick injury was low in our study as compared with costs reported from other studies.[16] When we examined direct cost estimates of needlestick with available medical records on the status of the source-patient, the mean cost was higher in non-hospital settings as well as in hospital settings. This subset of data contains claims with records of exposures to HIV and HCV and simply reflects the additional cost associated with laboratory tests and prophylactic medication. Costs obtained from workers' compensation data may be different from true direct and indirect costs of needlestick injuries. A single indicator such as direct cost does not capture all dimensions of the injury burden. Burden also includes indirect costs (often borne by the worker and the worker's family as well as the employer and the community) such as lost productivity, increased absenteeism, higher employee turnover, and recruitment of replacement workers. Needlestick injuries also involve psychological morbidity. Fisman et al.[17] estimated the cost of such intangible factors as workers' anxiety and distress among HCWs who reported sharps-related injuries. The crude median amount that subjects were willing to pay to avert injury was $850 (U.S. dollars). When adjusted for patient risk status (HIV and HCV), the amount increased to $1,270. They suggested incorporating these costs into the economic analysis of sharps injury prevention.

Studies have shown significant underreporting of needlestick injuries. Some of the reasons for underreporting include lack of awareness of the need to report the injury, the perception that it is not worth reporting, and that the process of reporting is inconvenient and time consuming.[18,19] The problem is further compounded when workers apply for workers' compensation coverage and the definition of an occupational disease may restrict whether the affected worker qualifies for benefits.[20] The case definition of a needlestick injury is sensitive to the ANSI Z-16.2 coding for type, source, and nature of injury claims. Some of the needlestick injury incidents may not have been identified due to coding inconsistencies, leading to an underestimation of the number of incidents.

Nevertheless, this study suggests different risks for needlestick injury in non-hospital settings such as physicians' offices, nursing homes, and other nursing care facilities relative to hospital settings. Increased attention should be paid to the risk of needlestick injury faced by workers in the non-hospital setting. Training workers in the non-hospital setting in the proper disposal of used needles and prohibiting unsafe work practices according to National Institute for Occupational Safety and Health guidelines can help to prevent such injuries among HCWs.

REFERENCES

1. Centers for Disease Control and Prevention. The National Surveillance System for Health Care Workers (NaSH). *Summary Report for Data Collected From June 1995 Through July 1999*. Atlanta, GA: Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion; 2001. Available at www.cdc.gov/ncidod/hip/NASH/report.htm. Accessed May 4, 2004.
2. Perry J, Parker G, Jagger J. EPINet report: 2001 percutaneous injury rates. *Advances in Exposure Prevention* 2003;6:32-36.
3. Gillen M, McNary J, Lewis J, et al. Sharps-related injuries in California healthcare facilities: pilot study results from the Sharps Injury Surveillance Registry. *Infect Control Hosp Epidemiol* 2003;24:113-121.
4. Beltrami EM, McArthur MA, McGeer A, et al. The nature and frequency of blood contacts among home healthcare workers. *Infect Control Hosp Epidemiol* 2000;21:765-770.
5. Thurn J, Willenbring K, Crossley K. Needlestick injuries and needle disposal in Minnesota physicians' offices. *Am J Med* 1989;86:575-579.
6. Shah SM, Bonauto D, Silverstein B, Foley M, Kalat J. Injuries and illnesses from framing in residential construction, Washington State, 1993-1999. *J Occup Environ Med* 2003;45:1171-1182.
7. Silverstein B, Welp E, Nelson N, Kalat J. Claims incidence of work-related disorders of the upper extremities: Washington State, 1987 through 1995. *Am J Public Health* 1998;88:1827-1833.
8. Kaufman JD, Cohen MA, Sama SR, Shields JW, Kalat J. Occupational skin diseases in Washington State, 1989 through 1993: using workers' compensation data to identify cutaneous hazards. *Am J Public Health* 1998;88:1047-1051.
9. Pollack ES, Keimig D. *Counting Illnesses and Injuries in the Workplace: Proposals for a Better System*. Washington, DC: National Academy of Sciences; 1987.
10. Washington State Department of Health, Center for Health Statistics. *Trend Review*. Available at www.doh.wa.gov/EHSPHL/hospdata/

Summary/TrendReview.xls. Accessed December 15, 2002.
11. Jagger J, Hunt EH, Brand-Elnaggar J, Pearson RD. Rates of needlestick injury caused by various devices in a university hospital. *N Engl J Med* 1988;319:284-288.
12. Choudhury RP, Cleator SJ. Preventing needlestick injuries. *BMJ* 1991;302:1602.
13. Anonymous. Needlesticks: preaching to the seroconverted? *Lancet* 1992;340:640-641.
14. Hatcher IB. Reducing sharps injuries among healthcare workers: a sharps container quality improvement project. *Jt Comm J Qual Improv* 2002;28:410-414.
15. Tan L, Hawk JC, Sterling ML. Report of the Council on Scientific Affairs: preventing needlestick injuries in health care settings. *Arch Intern Med* 2001;161:929-936.
16. Jagger J, Hunt E, Pearson R. Estimated cost of needlestick injuries for six major needled devices. *Infect Control Hosp Epidemiol* 1990;11:584-588.
17. Fisman DN, Mittleman MA, Sorock GS, Harris AD. Willingness to pay to avoid sharps-related injuries: a study in injured health care workers. *Am J Infect Control* 2002;30:283-287.
18. Tandberg D, Stewart KK, Doezema D. Under-reporting of contaminated needlestick injuries in emergency health care workers. *Ann Emerg Med* 1991;20:66-70.
19. Hamory BH. Under-reporting of needlestick injuries in a university hospital. *Am J Infect Control* 1983;11:174-177.
20. Tereskerz PM, Jagger J. Occupationally acquired HIV: the vulnerability of health care workers under workers' compensation laws. *Am J Public Health* 1997;87:1558-1562.

ANTIRETROVIRAL DRUG RESISTANCE AMONG PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS WHO ACT AS SOURCES OR POTENTIAL SOURCES IN OCCUPATIONAL ACCIDENTS INVOLVING HEALTHCARE WORKERS

Fabiane El-Far, MD; Eduardo Alexandrino Servolo Medeiros, MD, PhD; Carlos Teodoro Gasparoto; Ricardo Sobhie Diaz, MD, PhD

ABSTRACT

OBJECTIVE: To determine human immunodeficiency virus (HIV) type 1 genotypic antiretroviral drug resistance profiles of patients presenting a risk or potential risk for occupational exposure of healthcare workers.

DESIGN: Observational survey involving HIV-infected patients. Blood samples collected from source-patients and potential source-patients underwent HIV-1 genotypic antiretroviral resistance testing and determination of CD4 counts and viral load. Affected healthcare workers were monitored for 6 months after exposure.

SETTING: The survey was conducted in a tertiary-care hospital located in Sao Paulo, Brazil. Sao Paulo is considered the epicenter of the HIV–acquired immunodeficiency (AIDS) virus epidemic in Brazil.

PARTICIPANTS: Source-patients, potential source-patients, and affected healthcare workers.

RESULTS: A total of 371 occupational exposures to biological materials were reported, 46 (12.3%) of which were from HIV-seropositive source-patients. Samples from 18 source-patients and 26 patients considered "potential sources for accidents" were analyzed. Of these 44 samples, 18 (41%) presented resistance-related mutations in reverse transcriptase, protease, or both. Of these 18 samples, 16 (89%) had resistance to drugs included in the prophylactic schedule recommended by the Brazilian Ministry of Health.

CONCLUSIONS: Use of the Centers for Disease Control and Prevention–Brazilian post-exposure prophylaxis regimen will result in the administration of antiretroviral agents to which the source HIV-1 isolate will often be resistant. Therefore, it would be advisable to carefully investigate the history of use of antiretroviral agents by source-patients and adjust the prophylactic therapy based on those data and, subsequently, the results of resistance testing (*Infect Control Hosp Epidemiol* 2005;26:782-788).

Each year, 380,000 cases of occupational exposure to human immunodeficiency virus (HIV) involving needlestick injuries are reported in the United States. Of these, 61% are caused by hollow-bore needles.[1] Guidelines for the prevention of occupational accidents during the manipulation of HIV-contaminated materials were first published by the Centers for Disease Control and Prevention (CDC) in 1982.[2] However, there was no recommendation for the use of antiretroviral agents such as zidovudine for post-exposure prophylaxis until 1990.[3] In 1997, it was demonstrated that zidovudine could lower the probability of the establishment of HIV infection in 81% of cases involving occupational accidents (95% confidence interval [CI_{95}], 43% to 94%).[4] Subsequently, more potent antiretroviral regimens came into use. In 1998, regimens including zidovudine and lamivudine in combination with protease inhibitors such as indinavir and nelfinavir were recommended.[5] Studies using animal models suggest that prompt initiation of antiretroviral prophylaxis results in a more efficacious preventive effect.[6]

In December 2001, the CDC reported that, to date, there were 57 confirmed and 138 possible cases of occupational transmission of HIV worldwide.[7] This is cause for worldwide concern. Significant factors contributing to treatment failure in general include adverse events and an intrinsic lack of efficacy of prophylactic antiretroviral therapy. Failure of prophylactic treatment after occupational exposure has been reported in 21 cases. Zidovudine was the only drug administered in 16 of these cases, a combination of zidovudine and dideoxyinosine was used in 2 cases, and zidovudine combined with two other drugs was used in 3 cases.[8] Specific failure of zidovudine as post-exposure prophylaxis occurred in at least 11 cases of occupational exposure of healthcare personnel between 1990 and 1997.[9]

The Brazilian Ministry of Health and the CDC both

Dr. El-Far is from the Instituto de Infectologia Emilio Ribas, Sao Paulo, Brazil. Drs. El-Far and Medeiros are from Infection Control Hospital Epidemiology; and Mr. Gasparoto and Dr. Diaz are from the Laboratório de Retrovirologia, Paulista School of Medicine, Infectious Disease Division, Federal University of Sao Paulo, Sao Paulo, Brazil.

Address reprint requests to Dr. Ricardo S. Diaz, Laboratório de Retrovirologia, Infectious Disease Division, Federal University of Sao Paulo, Rua Pedro de Toledo, 781 - 16° Andar. Vila Clementino, Sao Paulo, SP – Brazil, CEP: 04039-032. rsdiaz@usp.br

Supported in part by research grants from FAPESP (grant no. 1996-5709-0) and Pronex (grant no. 41.96.0943.00).

The authors thank the nurses of the hospital for their painstaking work and all of the patients who agreed to participate in this study.

encourage the use of an antiretroviral regimen consisting of two nucleoside reverse transcriptase inhibitors, zidovudine and lamivudine, for low-risk accidents and a regimen consisting of two nucleoside reverse transcriptase inhibitors plus a protease inhibitor (indinavir or nelfinavir) in high-risk cases. To date, there is no consensus on the ideal prophylaxis for occupational exposure when the source-patient demonstrates resistance to antiretroviral agents. In such cases, an alternative regimen is suggested. In most cases, the alternative regimen is based on the antiretroviral history of the source-patient or on previous antiretroviral resistance testing of the subject.[10]

We describe the antiretroviral resistance profiles of HIV-infected patients who became source-patients or potential source-patients for HIV occupational exposure.

METHODS

Study Design and Participants

An observational survey was conducted involving HIV-infected patients treated at the Federal University of Sao Paulo (UNIFESP) University Hospital in Sao Paulo, Brazil, between April 2000 and April 2001. The city of Sao Paulo is considered the epicenter of the HIV–acquired immunodeficiency virus (AIDS) epidemic in Brazil, accounting for 22% of all cases nationwide.[11] Two groups were studied: patients who represented a potential source of occupational HIV exposure for healthcare workers and patients who were actual sources of such exposure. Potential source-patients were patients who required venous or arterial intervention procedures but had not been involved in any healthcare worker's occupational accident at the time of this study. Source-patients were defined as those whose blood or infected body fluids came into contact with healthcare workers through occupational exposure, thereby requiring that the healthcare workers receive antiretroviral prophylaxis. All patients who were treated between April 2000 and April 2001 and who met these criteria were included in the study.

The UNIFESP Institutional Review Board approved the study, and all individuals gave written informed consent prior to their inclusion. The antiretroviral histories of patients were collected through interviews and data were cross-checked against hospital records.

Inclusion criteria were HIV positivity or AIDS, age of at least 18 years, admittance to the (UNIFESP) University Hospital, and considered to be a potential source of occupational exposure from biological materials or having been a source of healthcare worker occupational exposure for which antiretroviral prophylaxis was indicated.

Exclusion criteria were refusal to give informed consent, unconfirmed HIV positivity, age younger than 18 years, and HIV in addition to hepatitis B virus (HBV) or hepatitis C virus (HCV).

Methods

Sample and Data Collection. Two 5-mL blood samples were drawn from each source-patient and potential source-patient. Blood samples were analyzed in the UNIFESP Retrovirology Laboratory. Sample analysis included CD4/CD8 cell counts, HIV viral load determination, and evaluation of HIV-1 antiretroviral genotypic resistance. After blood samples had been drawn, each patient completed a questionnaire that included questions about the date of seroconversion, previous and current exposure to antiretroviral agents, and the motivation for seeking treatment. All data collected during patient interviews were cross-checked against medical charts.

Prophylaxis and DNA Testing. Healthcare workers who had suffered HIV occupational exposure received prophylactic treatment according to the recommendations of the Brazilian Ministry of Health AIDS Program.[11] These recommendations adhere to the 2001 guidelines for antiretroviral therapy set forth by the CDC.[7] Healthcare workers were monitored for 6 months. Finally, the results of genotyping based on DNA sequences of HIV obtained from source-patients were compared with those from the healthcare workers receiving the antiretroviral regimen, either previously or at the time of inclusion in the study. These results were also compared with those of patients receiving the same antiretroviral regimen.

CD4 Cell Counts. CD4+ and CD8+ T cells were counted using TriTest and TrueCount kits (Becton Dickinson Immunocytometry Systems, San Jose, CA), according to manufacturer guidelines.

Viral RNA Quantification. Viral RNA was quantified using the NucliSens Kit (bioMérieux, Lyon, France) for plasmatic RNA. The amplification relies on the simultaneous activity of RNAse H, AMV-reverse transcriptase, and T7 RNA polymerase at 41°C. Transcribed RNA is detected by electrochemiluminescence. The procedure was performed according to manufacturer instructions.

Antiretroviral Genotypic Resistance. Proviral HIV-1 DNA was purified using the QIAamp blood kit (Qiagen, Santa Clarita, CA), according to the manufacturer's instructions. In the first round of polymerase chain reaction (PCR), a 1.2-kb *pol* fragment was amplified.[8] The first-round product was used as the target of a second PCR, which yielded a 0.8-kb DNA fragment corresponding to the HIV-1 reverse transcriptase, in agreement with results from previous studies.[12] Amplification of the HIV-1 protease gene was achieved when the first-round product that had been used for reverse transcriptase amplification was used in a second PCR, yielding a 0.65-kb DNA fragment, as has also been previously described.[13] The PCR products were sequenced using an automated DNA sequencer (Bayer Diagnostics, Visible Genetics, Toronto, Ontario, Canada). Sequence analysis was performed using the OpenGene DNA sequencing system and GeneObjects software (Visible Genetics). Results were further analyzed using the beta-test database available on the Stanford University web site (www.hivdb.stanford.edu). In this study, high levels of antiretroviral drug resistance are referred to as complete resistance and intermediate levels of resistance are referred to as partial resistance.

TABLE 1
CHARACTERISTICS OF THE 19 SOURCE-PATIENTS AND THE RELATED OCCUPATIONAL HUMAN IMMUNODEFICIENCY VIRUS EXPOSURES

Characteristic	
Gender	
Male	7
Female	12
Median age, y (range)	29 (19–44)
Occupation	
Nurse	31.5%
Resident physician	31.5%
Attending physician	26.3%
Other	10.7%
Accident location	
Clinical infirmary	36.8%
Surgical ward	21%
Surgical center	31.5%
Other	10.7%
Hours to first dose of PEP after the accident*	
< 2	42%
2–48	47.3%
> 48	10.5%
Source of injury	
Needle	68.4%
Other	31.6%
Fluid involved	
Blood	73.6%
Other fluid mixed with blood	26.4%
Cause of accident	
Self-inflicted	68.4%
Result of patient movement	10.5%
Other	21.1%

PEP = post-exposure prophylaxis.
*Healthcare workers begin PEP (under direct observation) immediately on notification that an accident has occurred.

TABLE 2
DEMOGRAPHIC, VIROLOGIC, AND ANTIRETROVIRAL USE AND RESISTANCE DATA OF THE SOURCE-PATIENTS AND THE POTENTIAL SOURCE-PATIENTS

Characteristic	
Gender	
Male	24
Female	20
Median age, y (range)	35.8 (21–62)
Median time since receiving confirmation of HIV seropositivity, mo (range)	38 (1–144)
Median CD4 cell count, cells/mL (range)	132.5 (5–1,150)
Median viral load, copies/mL (range)	547,664 (< 80–6,000,000)
Patients previously exposed to ARV agents	28 (63%)
Median duration of previous ARV use, mo (range)	4 (1–48)
Patients without previous exposure to ARV agents	16 (36%)
ARV use of the 28 patients previously exposed	
ZDV	23
3TC	16
IDV	11
NFV	14
Patients with ARV drug resistance	18 (41%)
Patients with ZDV resistance	11
Patients with 3TC resistance	7
Patients with IDV resistance	2
Patients with NFV resistance	5
Patients with resistance to ZDV, 3TC, IDV, or NFV	16

HIV = human immunodeficiency virus; ARV = antiretroviral; ZDV = zidovudine; 3TC = lamivudine; IDV = indinavir; NFV = nelfinavir.

RESULTS

Occupational Accidents Involving Source-Patients

In 1992, the UNIFESP University Hospital Epidemiology Committee initiated a program to address occupational accidents involving biological materials; 2,800 cases have been reported to date. The committee is composed of one infectious diseases physician and four nurses working exclusively in this program 24 hours a day, 7 days a week. When an accident is reported, the local guidelines require that the prophylactic antiretroviral agents be immediately offered to the affected healthcare workers.

Between April 2000 and April 2001, 371 occupational accidents involving healthcare workers' contact with biological materials were reported to the committee. Of these, 46 (12.3%) involved HIV-1–positive source-patients. Twenty-seven of these 46 source-patients were excluded because they did not meet the inclusion criteria: 6 because they were co-infected with hepatitis (3 with HCV and 3 with HBV); 6 because they were younger than 18 years; 6 because they were involved in accidents that did not break the skin; 4 because they died before blood was drawn; and 5 because they refused to participate in the study or were unable to provide informed consent. Therefore, 19 source-patients were included in the analysis. Table 1 contains characteristics of the source-patients and the related occupational HIV exposures.

Because all occupational accidents involved percutaneous or mucosal contact with blood, healthcare workers involved in these accidents were given the antiretroviral regimen proposed by the Brazilian Ministry of Health, which is a 28-day course of zidovudine–lamivudine combined with either indinavir or nelfinavir. They were

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

TABLE 3
ANTIRETROVIRAL USE AND RESISTANCE DATA OF THE SOURCE-PATIENTS AND THE POTENTIAL SOURCE-PATIENTS WITH ANTIRETROVIRAL RESISTANCE

HIV Infection (mo)	ARV Agents Previously Used	RT Mutations	PG Mutations	Interpretation
36	ZDV, 3TC, ddI, IDV, NFV	M41L, L210E, T215H, P225E, F227M, M230R, L234K	L63P, V77I, L90V, I93L	PR: ZDV, DLV, NFV, SQV
36	ZDV, ddI, NVP	M41L, E44D, D67N, Y181C, L210W, T215Y	L63P, V77I, I93L	CR: ZDV, DLV, NVP; PR: d4T, ABC
1	None	L210C, T215I, K219I, P225A, F227I, M230R	L63P, A71T	PR: ZDV
1	ZDV, 3TC, NVP	K219E		PR: ZDV
2	ZDV, ddI, d4T, NFV	M41V, D67E, L74, L75, F77I, A98G, L100E, K101T, K103S, V108I	L63P	CR: EFV, DLV, NVP; PR: ZDV, 3TC
60	ZDV, d4T, 3TC, ddI, ABV, EFV, IDV, NFV, RTV	M41Q, E44R, A62P, D67Q, T69S, K70T	L24I, M46I, I84V	CR: ZDV, APV, NFV; PR: ddC, IDV, RTV, SQV
96	ZDV, 3TC, ddI, NVP, NFV	Y181T, M184V, G190W, L210R	K20R, M36I	CR: 3TC, EFV, NVP; PR: DLV
3	ZDV, 3TC, NVP, NFV	V179H, M184I, Y188I, G190C, T215V, K219I	L63H, V82I	CR: EFV, NVP, 3TC; PR: ABC, DLV
48*	ZDV, 3TC, d4T, EFV, IDV	Y181R, M184R, Y188P, G190R, T215F, K219D	No	CR: EFV, DLV, NVP; PR: ABC, 3TC, ZDV
60*	ZDV, 3TC, IDV	M41E, E44G, Y115, F116I, V118G, Q151R	No	PR: ZDV
24*	ZDV, ddC, 3TC, ddI, d4T, NVP, IDV, RTV	M41E, E44G, A62I, D67P, Y181C, M184V, K219E, F227A	M36I, I47T	CR: 3TC, DLV, NVP; RP: ZDV, ddI, ddC, ABC
12*	ZDV, ddI, d4T, NVP, NFV	K103R, Y115I, V118S, Q151S, V179N, M184I, Y188F, G190C, L210S, T215I, K219R	L10I, L63S, I93L	CR: ABC, 3TC, EFV, NVP; PR: ZDV, ddI, ddC, DLV
12*	ZDV, ddI, NFV	M41L	M46I, L63A, L90M	CR: NVF; PR: APV, IDV, RTV, SQV
108*	ZDV, 3TC, NVP, SQV, RTV	G190W, L210V, T215Y, K219Q	No	CR: ZDV; PR: EFV, NVP, d4T, ABC
144*	None	No	M36I, L63A, G73C, V77L, V82E, N88F, L90C, I93G	CR: NFV; PR: IDV, RTV, SQV
120	?	Y181L, M184N, L210T, T215R, K219R, P225E, M230W, L234S, P2362, G333E	K20R, I24Y, D30M, V32D, M36K, M46N, I47L, L63P	CR: DLV; PR: 3TC, NVP, APV, NFV

HIV = human immunodeficiency virus; ARV = antiretroviral; RT = reverse transcriptase; PG = protease gene; PR = partial ARV drug resistance; CR = complete ARV drug resistance; ZDV = zidovudine; 3TC = lamivudine; ddI = didanosine; d4T = stavudine; ddC = zalcitabine; ABV = abacavir; EFV = efavirenz; NVP = nevirapine; DLV = delavirdine; NFV = nelfinavir; IDV = indinavir; SQV = saquinavir; RTV = ritonavir; APV = amprenavir..
*Source-patients.

monitored for 6 months and no HIV seroconversion was detected.

Evaluation of Samples Obtained From Source-Patients and Potential Source-Patients

During the study, blood samples were collected from 27 sequential HIV-positive inpatients at the UNIFESP University Hospital. These samples were used for genotypic analysis of HIV DNA. This analysis was performed for exclusive use in this study. Results were neither offered to the patient nor used to determine therapeutic strategies.

A total of 46 samples were collected for genotypic analysis, 19 from source-patients and 27 from potential source-patients. In 18 of the 19 samples from source-patients and 26 of the 27 samples from potential source-patients, the quantity of HIV-1 PCR product was sufficient for genotypic analysis, resulting in a total of 44 analyzed samples. Table 2 contains demographics and information about antiretroviral exposure for these patients. Of the 44 patients analyzed, 18 (41%) were infected with HIV strains that were shown to have resistance related to mutations in the reverse transcriptase or in the protease gene, leading to partial or complete anti-

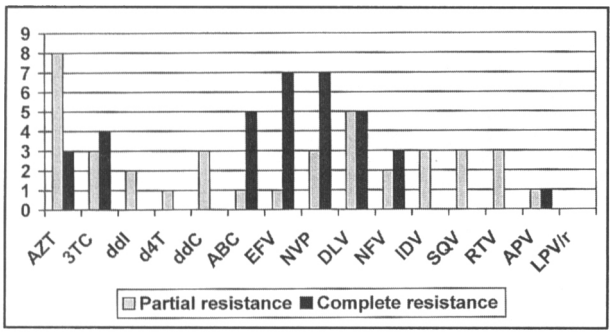


FIGURE. Number of patients with reverse transcriptase and protease gene mutations leading to partial or complete resistance to antiretroviral agents. AZT = zidovudine; 3TC = lamivudine; ddI = didanosine; d4T = stavudine; ddC = zalcitabine; ABC = abacavir; EFV = efavirenz; NVP = nevirapine; DLV = delavirdine; NFV = nelfinavir; IDV = indinavir; SQV = saquinavir; RTV = ritonavir; APV = amprenavir; and LPV/r = lopinavir/ritonavir.

retroviral drug resistance. Of these 18 patients, 16 had been previously exposed to antiretroviral agents and 2 had not (Table 2).

Resistance to zidovudine was detected in 11 (25%) of the 44 patients analyzed; 5 of the 11 were source-patients involved in occupational accidents for which the affected healthcare workers were given zidovudine as prophylaxis (Table 3). Resistance to lamivudine was found in 7 (16%) of the patients; 3 of the 7 were source-patients involved in occupational accidents for which lamivudine was administered. Resistance to the zidovudine–lamivudine combination was detected in 4 (9%) of the patients; 2 of the 4 were source-patients in accidents for which the affected healthcare workers received this combination. Resistance to the protease inhibitor nelfinavir was found in 5 (11.3%) and resistance to the protease inhibitor indinavir was found in 3 (6.8%) of the patients. Of these patients, 3 resistant to nelfinavir and 2 resistant to indinavir were also source-patients for accidents in which those drugs were used as prophylaxis (Figure). Overall, of the 18 patients who showed some level of resistance, 16 (89%) presented resistance to a drug included in the prophylactic schedule recommended by the Brazilian Ministry of Health to prevent HIV acquisition. Therefore, among these 44 cases, the recommended regimen would, theoretically, be less than completely effective in 36%.

Of these 18 patients showing antiretroviral drug resistance, 2 had no prior exposure to antiretroviral therapy. Nevertheless, partial resistance to zidovudine was detected in 1 of these 2 patients, and the other presented complete resistance to nelfinavir and partial resistance to indinavir, ritonavir, and saquinavir. The latter was also a source-patient for an accident in which nelfinavir, zidovudine, and lamivudine were used prophylactically. Of the 23 patients who had been previously exposed to zidovudine or were taking zidovudine at the time of the accident, 7 (30%) had resistance to zidovudine. Of the 16 patients who had been previously exposed to lamivudine or were taking lamivudine at the time of the accident, 4 (25%) had resistance to lamivudine. Of 11 patients previously exposed to indinavir, 1 (9%) had resistance to indinavir. Finally, of 14 patients previously exposed to nelfinavir, 3 (21%) had resistance to nelfinavir.

DISCUSSION

Between April 2000 and April 2001, there were 46 accidents reported involving HIV-positive source-patients at the UNIFESP University Hospital. Of these, 19 met the criteria for inclusion in this study. Of the 44 source-patients and potential source-patients for whom HIV-1 PCR results were obtained, 28 had previously been exposed to antiretroviral agents (median length of exposure, 4 months). The HIV from 30% of the patients exposed to zidovudine showed some level of resistance to this drug. Such resistance was found in the HIV of 25% of those exposed to lamivudine, 21% of those exposed to nelfinavir, and 9% of those exposed to indinavir. The same standard 28-day post-exposure prophylaxis regimen with zidovudine and lamivudine plus indinavir or nelfinavir was prescribed to all 18 of the healthcare workers involved in accidents. Of the source-patient HIV analyzed, resistance to zidovudine, lamivudine, nelfinavir, or indinavir was detected in 16 cases and resistance to the zidovudine–lamivudine combination was found in 4 cases. Therefore, for 16 (36.4%) of the patients, the drug schedule proposed by the Brazilian guidelines would likely be inappropriate.

Occupational accidents involving biological materials should be considered a medical emergency, in which the initial treatment should be given within 2 hours after the accident. Some potential risk factors for failure of prophylaxis have been identified: involvement of specific types of devices (hollow-bore needles) or devices visibly contaminated with patient blood; deep injury; symptomatic HIV infection in the source-patient; delayed initiation of antiretroviral prophylaxis; insufficient antiretroviral adherence; antiretroviral side effects; and antiretroviral drug resistance.[7,14] Resistance to antiretroviral agents is more commonly found among patients with clinical progression of HIV, increased quantitative plasma HIV RNA, or low CD4 cell counts.[15] We identified several risk factors for HIV transmission or presence of resistant viruses in our study. Among the patient samples evaluated, the median CD4 count and viral load were 132.5 cells/mL and 548,000 copies/mL, respectively. Blood was the most frequent fluid encountered. In 69% of the cases, the accidents involved needlesticks with hollow-bore needles. Most of the source-patients analyzed had previously been treated with more than one antiretroviral agent.

Since 1987, hospitals and other healthcare institutions have used prophylaxis for HIV occupational exposure empirically, first with zidovudine monotherapy and later employing regimens involving two or three different antiretroviral agents. Although empiric, the use of more than one antiretroviral drug class acting on HIV at distinct times during its replication cycle seemed a logical proposal for the safe prevention of viral replication and to decrease the risk of infection among healthcare workers. Because the number of patients with HIV re-

ceiving antiretroviral therapy and, consequently, survival time have increased since the introduction of protease inhibitors in 1998,[5] a new medical challenge has arisen—antiretroviral drug resistance. In this context, ideally, prophylaxis should be adjusted keeping antiretroviral drug resistance in mind. Specific failure of post-exposure prophylaxis with zidovudine given to healthcare workers occurred in at least 11 cases between 1990 and 1997. In 8 of these cases, the source-patient had previously received zidovudine as antiretroviral treatment. Of these 8 patients, 3 were investigated for antiretroviral agent sensitivity and 2 were shown to have a lower susceptibility to zidovudine. Therefore, one of the possible explanations for nosocomial HIV transmission to healthcare workers may be the presence of a virus with low antiretroviral susceptibility. Beltrami et al. recently described 5 healthcare workers who were infected with HIV despite prophylactic treatment with multiple drugs.[16]

Therefore, it is possible that a patient previously exposed to, or currently receiving, antiretroviral therapy may have developed antiretroviral drug resistance, especially if the patient has taken the drug sporadically or has a high viral load. Track et al. analyzed 15 source-patients and found that 10 of them had mutated codons that lower antiretroviral susceptibly; however, as in our study, none of the healthcare workers underwent HIV seroconversion.[17] On the other hand, Beltrami et al. recently described a case in which occupational transmission of an antiretroviral-resistant HIV strain occurred.[14] Through viral DNA analysis, the authors demonstrated that the viral strain in the source-patient was the same as that present in the infected healthcare worker. This case highlights the importance of using caution when prescribing prophylactic antiretroviral agents after occupational accidents.

Resistant strains can be effectively transmitted. For instance, in a group of patients studied between 2000 and 2001 in San Francisco, California, Grant et al. demonstrated that 13.2% had primary resistance to non-nucleoside reverse transcriptase inhibitors and 7% had primary resistance to protease inhibitors.[18]

Occupational HIV exposure needs to be treated as quickly and aggressively as possible, especially when there is a suspicion of antiretroviral drug resistance. Consulting a specialist is helpful but should not delay the initiation of prophylaxis. The results of the current study indicate that it is important to collect information about HIV-1 viral load and antiretroviral exposure from the source-patient to estimate the possibility of resistance and to determine the antiretroviral agents to which the HIV from the source-patient may be resistant. It is possible that expanded regimens that include new antiretroviral agents could be effective in cases in which it is not possible to determine whether the source-patient is at risk for antiretroviral drug resistance. One measure that might help avoid errors in prophylaxis prescription is individualized prophylactic prescription when source-patient antiretroviral drug resistance is suspected.

It would be advantageous to know in advance the general antiretroviral resistance patterns within a given population, as well as the primary antiretroviral drug resistance level in the area surrounding the accident location. As seen in our study, two patients who had not been previously exposed to antiretroviral therapy had some level of hypothetical loss of susceptibility to antiretroviral agents. It would be more appropriate to make decisions regarding which antiretroviral agents should be administered to an affected healthcare worker based on source-patient data regarding previous antiretroviral drug resistance. As seen in our study, antiretroviral speculation based on epidemiologic data is not 100% reliable. Because action should be taken within the first few hours after the accident and DNA genotyping could take days or even weeks, waiting for the results of resistance testing is not recommended.

In this study, we showed that use of the CDC–Brazilian post-exposure prophylaxis regimen will result in the administration of antiretroviral agents to which the source HIV-1 isolate will often be resistant. This may imply that there is a risk of failure of antiretroviral prophylaxis. There have been no controlled trials showing that the use of a regimen to which a virus is resistant will result in a higher risk of HIV-1 transmission to healthcare workers involved in occupational accidents. However, it would be advisable to carefully investigate the history of use of antiretroviral agents by source-patients and adjust the prophylactic therapy based on the clinical history of source-patients. In such cases, results of HIV resistance testing may aid in making decisions related to the later adjustment of the prophylactic regimen.

REFERENCES

1. Stark P. *Occupational Safety: Selected Cost and Benefit Implications of Needle Stick Prevention Devices for Hospitals.* Washington, DC: General Accounting Office; 2000. Publication no. Gao-01-60R.
2. Centers for Disease Control. Acquired immunodeficiency syndrome (AIDS): precautions for health-care workers and allied professionals. *MMWR* 1982;32:450-451.
3. Centers for Disease Control. Public Health Service statement on management of occupational exposure to human immunodeficiency virus, including zidovudine post exposure uses. *MMWR* 1990;39(RR-1):1-14.
4. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after occupational exposure. *N Engl J Med* 1997;337:1485-1490.
5. Centers for Disease Control and Prevention. Public Health Service guidelines for the management of health care workers' exposure to HIV and recommendations for post exposure prophylaxis. *MMWR* 1998;47(RR-7):1-28.
6. Bottiger D, Johansson N-G, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre and post exposure administration of BEA-005. *AIDS* 1997;11:57-62.
7. Centers for Disease Control and Prevention. Updated US Public Health Service guidelines for the management of occupational exposure to HBV, HCV and HIV and recommendations for post exposure prophylaxis. *MMWR* 2001;50(RR-11):1-42.
8. Kozal MJ, Shah N, Shen N, et al. Extensive polymorphisms observed in HIV-1 clade B protease gene using high-density oligonucleotide arrays. *Nat Med* 1996;2:753-759.
9. Jochimsen EM. Failures of zidovudine post-exposure prophylaxis. *Am J Med* 1997;102(suppl 5B):52-55.
10. Gerberding JL. Occupational exposure to HIV in health care settings. *N Engl J Med* 2003;348:826-833.
11. Committee Group Members of the Brazilian Government. *Ministério da Saúde: Recommendations for the Treatment of HIV Infection in Adults and Adolescents in Brazil—2001.* Committee Group Members

of the Brazilian Government; 2001. Available at www.aids.gov.br.
12. Frenkel LM, Wagner LE II, Aiwood SM, Cummins TJ, Dewhurst S. Specific, sensitive and rapid assay for human immunodeficiency virus type 1 pol mutations associated with resistance to zidovudine and didanosine. *J Clin Microbiol* 1995;33:342-347.
13. Pieniazek D, Peralta JM, Ferreira JA, et al. Identification of mixed HIV-1/HIV-2 infections in Brazil by polymerase chain reaction. *AIDS* 1991;5:1293-1299.
14. Beltrami EM, Luo CC, de la Torre N, Cardo DM. Transmission of drug resistant HIV after an occupational exposure despite post exposure prophylaxis with a combination drug regimen. *Infect Control Hosp Epidemiol* 2002;23:345-348.
15. Yeni PG, Hammer SM, Carpenter CC, et al. ARV treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society—USA Panel. *JAMA* 2002;288:222-235.
16. Beltrami EM, Cheingsong R, Respess R, Cardo DM. ARV drug resistance in HIV-infected source patients for occupational exposures to healthcare workers. Presented at the 4th Decennial International Conference on Nosocomial and Healthcare Associated Infections and the 10th Annual Meeting of the Society for Healthcare Epidemiology of America; March 5-9, 2000; Atlanta, GA.
17. Track PC, Bremer JW, Harris AA, Landay AL, Kesseler HA, Kuritzes DR. Genotypic analysis of HIV-1 isolates to identify ARV resistance mutations from source patients involved in health care worker occupational exposure. *JAMA* 1999;281:1085-1086.
18. Grant RM, Hecht FM, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA* 2002;288:181-188.

Concise Communication

Patient-to-Patient Transmission of Hepatitis C Virus Through the Use of Multidose Vials During General Anesthesia

Jeanne-Marie Germain, MD; Anne Carbonne, MD; Valérie Thiers, PhD; Hélène Gros, MD; Sylvie Chastan, MD; Elisabeth Bouvet, MD; Pascal Astagneau, MD, PhD

ABSTRACT

A cluster of four patients with hepatitis C virus (HCV) infection was identified in a surgery clinic. Molecular characterization revealed close homology between viruses. This cluster was related to unsafe injection practices through multidose vials and reused materials. Among 796 patients potentially exposed to and screened for HCV, no other cluster was identified (*Infect Control Hosp Epidemiol* 2005;26:789-792).

Hepatitis C virus (HCV) can be transmitted in healthcare settings from healthcare workers to patients[1,2] or from patient to patient.[3-9] However, the vehicle of transmission is not always determined. Several cases of HCV contamination have resulted from shared medical devices such as hemodialysis machines,[3] digestive endoscopy,[4] mechanical ventilation for operated on patients,[5] and injection materials or products.[6-9] We report an outbreak of patient-to-patient transmission of HCV through the use of multidose vials of anesthetic products and the reuse of injection materials.

In November 2001, acute HCV infection (asthenia, nausea, conjunctival icterus, elevated liver enzymes, and positivity of HCV enzyme-linked immunosorbent assay antibodies and HCV RNA) was diagnosed in a 35-year-old woman during a visit to a gastroenterology outpatient clinic of a tertiary-care reference hospital. The case-patient had no risk factors for acquiring HCV infection, such as a history of blood transfusion or intravenous drug use. She underwent surgery for synovial cysts of the wrist and foot in a surgical clinic within the 9 weeks prior to the HCV diagnosis. The case was reported to the health authorities and the regional center for nosocomial infection, which promptly launched an epidemiologic investigation.

METHODS

The case occurred in a 50-bed private surgical clinic in Western France. Approximately 5,000 to 6,000 surgical procedures and digestive endoscopies under general anesthesia are performed annually in this clinic.

The first part of the investigation included serologic screening and review of medical records of all patients who underwent surgery on the same day in the same operating room as the first positive patient. All healthcare personnel working in the operating room (the surgeon, the anesthetist, and two nurses) were tested for HCV. Assessment of the medical practices of the healthcare workers was performed by a hospital epidemiologist, who interviewed the nursing and medical staff according to the usual guidelines for standard precautions.[10]

In a second step, given that three other HCV-positive patients were identified in the same operative session, a large information and screening campaign was launched for exposed patients. All patients who had been operated on under general anesthesia performed by the anesthetist in the clinic during the previous 5 years were informed. Only sessions with at least one patient receiving more than one injection of anesthetic were traced. Each exposed patient received a letter that informed him or her about the potential risk of viral contamination during surgery and recommended serum testing for HCV, hepatitis B virus (HBV), and human immunodeficiency virus (HIV). The case definition was an HCV-positive patient operated on after another positive patient during the same operative session on the same day. Information was also shared with the population that could have been operated on in the clinic during the at-risk period by way of the media. A toll-free telephone number was set up at the clinic for patients to call.

All patients implicated in the index outbreak were tested for HCV RNA by reverse transcription polymerase chain reaction (Roche AMPLICOR HCV test Roche, Basel, Switzerland). HCV genotyping was accomplished by reverse hybridization assay (INNO-LiPA HCV-II, Innogenetics, Ghent, Belgium). Phylogenic analysis of NS5B and E2/HVR1 sequences (nucleotide positions 7915 to 8303 and 1325 to 1785, respectively) was performed to investigate any possible epidemiologic link among HCV RNA–positive patients. Parts of HCV genomes were amplified and directly sequenced in both directions in all HCV RNA–positive patients as previously described.[3] All of the studied sequences were compared with each other and with a control panel of genotype 1b, which consisted of type 1b isolates from unrelated patients with hepatitis C from the same geographic area plus 1b isolates extracted from the GenBank database (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD). The pairwise matrix was generated with the DNADIST program in the PHYLIP software package (version 3.572; Department of Genetics, University of Washington, Seattle, WA). Phylogenic tree analysis was done by the neighbor-joining method using Kimura's two-parameter correction, as implemented in the PHY-

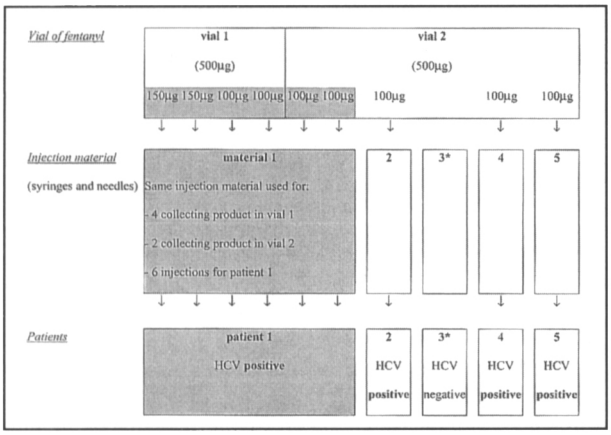


FIGURE 1. Use of a fentanyl vial between patients undergoing surgery in the same operating room on the same day. *The third patient did not receive a fentanyl injection. HCV = hepatitis C virus.

LIP package. The tree was drawn with TreeView software (version 1.4; Division of Environmental and Evolutionary Biology, University of Glasgow, Glasgow, United Kingdom). To further confirm the reliability of the phylogenic tree, bootstrapping was accomplished (1,000 replicates). The numbers at the nodes indicated the frequency with which the node occurred in 100 bootstrap replicates.

RESULTS

The index case-patient was operated on second (patient 2) on the same day and in the same room as four other patients. Of them, all except one (patient 3) were found to be HCV positive (Fig. 1). All HCV-positive patients were operated on by the same surgical staff. Patient 1 was a 44-year-old man who underwent surgery for osteosynthesis of the shoulder (Table). No prior test for HCV was revealed by his medical history, although a high level of liver enzymes associated with chronic alcohol consumption had been reported within the past year. The hepatic biopsy performed 7 months after surgery revealed lesions compatible with chronic hepatitis. He had never received a blood transfusion or used intravenous drugs; however, he reported a tattoo 3 years earlier. Patients 4 and 5 were operated on for warts and a skin graft, respectively. Patients 4 and 5 had positive test results for HCV antibodies and RNA, respectively, 15 and 14 weeks after surgery. They had no risk factors for HCV infection (eg, history of blood transfusion, intravenous drug use, tattoos, or piercings) other than the current surgery. Patient 3 had negative test results for HCV 15 weeks after surgery. The anesthetist, the surgeon, and the two nurses who participated in the surgery had negative test results for HCV.

All HCV-positive patients belonged to genotype 1b. The NS5B sequences derived from all HCV RNA–positive patients were compared. Nucleotide divergence between the newly HCV-infected patients (patients 2, 4, and 5) was 0.31% or less; for the one patient known to be HCV positive (patient 1), it was 1.5% or less. By comparison, the nucleotide divergences between the newly infected patients and the nearest sequences from the panel sequence (French HCV sequences: CNR-41, CNR-44, and control 2) were 5.4% to 8.5%. The analysis provided strong evidence that the three isolates from recently infected patients (patients 2, 4, and 5) and the putative source (patient 1) were closely related (mean pairwise nucleotide genetic distance, 0.014; bootstrap value, 98%; Fig. 2). In addition, the same clustering was identified in a second sample of patients 1 and 5 taken 3 to 4 months later, excluding the

TABLE
CHARACTERISTICS OF THE PATIENTS OPERATED ON IN THE SAME OPERATING ROOM ON THE SAME DAY AS THE INDEX CASE-PATIENT

Characteristic	Patient 1	Patient 2 (Index Case-Patient)	Patient 3	Patient 4	Patient 5
Age, y	44	35	29	26	78
Gender	Male	Female	Female	Female	Female
Risk factors for hepatitis C infection					
Blood transfusion	No	No	No	No	No
Intravenous drug use	No	No	No	No	No
Tattoo	Yes	No	No	No	No
Procedure	Osteosynthesis of the shoulder	Synovial cysts of the wrist and the foot	Incarnated nail	Wart	Skin graft
General anesthesia					
Propofol (200 mg/vial)	200 mg	200 mg	200 mg	200 mg	200 mg
Fentanyl (500 µg/vial)	700 µg	200 µg	–	100 µg	100 µg
Atracurium (50 mg/vial)	40 mg	–	–	–	–
Local anesthesia with lidocain	No	No	Yes	No	No

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

possibility of laboratory contaminations. Sequence analysis of the HCV E1-E2 fragment was possible in only two of the four HCV RNA–positive patients (patients 1b and 5b in Fig. 2). Pairwise analysis revealed the two sequences to be 98% homologous. Phylogenic comparisons revealed that the two sequences (patients 1 and 5) were clustered together, segregated from other genotype 1b sequences (data not shown).

All HCV-positive patients received general anesthesia consisting of intravenous fentanyl and propofol injections, whereas the HCV-negative patient received only propofol. The anesthetist reported as usual practices that several injections were probably delivered to patient 1 using the same syringe and needle from two different vials containing fentanyl, as described in Figure 1. The first vial dose of 500 µg was emptied with 4 repeated drawings. Two 100-µg doses were drawn from the second vial. The second vial was reused for patients 2, 4, and 5. In addition, injections were performed directly in peripheral venous catheters that did not have anti-reflux valves. No other medical device in contact with patient blood was shared among the patients.

Among patients operated on between 1997 and 2001, 1,201 were considered to have been exposed to the risk in the previous 5 years. Of them, 1,086 (90.4%) were informed by the mailing, 68 (5.7%) had no identified postal address, and 47 (3.9%) were dead at the time of the screening. Overall, 796 (66.3%) returned their serologic results for at least one virus. The response rate decreased from 81% for patients operated on in 2001 to 60% for patients operated on in 1997. The toll-free telephone number received more than 598 calls. Overall, 7 patients were found to be positive for HCV. No patient was HIV positive or had markers of acute or chronic hepatitis B. All HCV-positive patients were operated on at different times during the period (August 1997, January and November 1998, September 1999, May 2000, and January and November 2001). For each of them, all other patients who had surgery on the same day in the same room had negative test results. Among them, only two patients knew their serologic status for HCV before the investigation.

Several measures were promptly recommended: (1) stop reusing syringes and needles, (2) do not share vials of medications between patients, and (3) stop using multidose vials of fentanyl and replace them with single-dose vials.

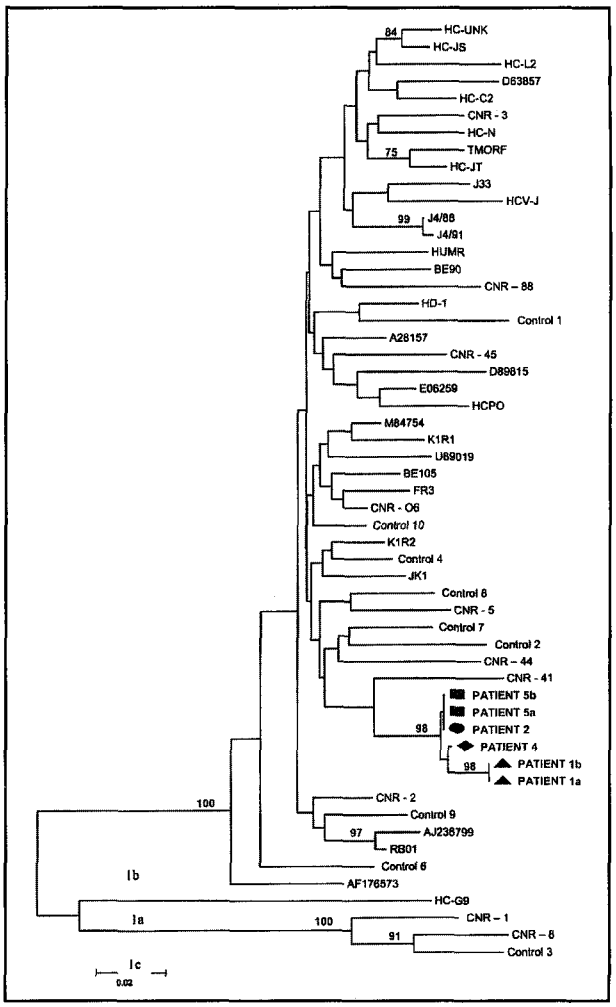


FIGURE 2. Phylogenic analysis and comparison of the four viruses.

DISCUSSION

We have reported a cluster of HCV infections with a well-documented mechanism of transmission related to anesthesia practices. The contamination could be explained by different cumulative factors including repeated drawings and injections of materials from a common vial, sharing of the same anesthetic vial among different patients, possible blood reflux in the catheter line, and presence of an infected source-patient at the onset of the surgery.

Multidose vials have been reported as a potential vehicle of nosocomial HCV,[6-9] HBV,[6,8] or HIV transmission in healthcare settings. However, the mechanism of vial contamination was not clearly established in these studies. In 1997, the French Society for Anesthesiology and Intensive Care reminded healthcare workers of the standard guidelines for hygiene practices, including recommendations for not sharing any injection materials during anesthesia.[11] The issue of whether products such as fentanyl should be delivered from several single-dose vials or multidose vials remains unresolved regarding both medical practices and economic considerations.

We did not identify any other cluster of patients who were positive for blood-borne virus in the previous 5 years. We could assume that it was unlikely that other clusters were not identified by the screening. Although not all of the exposed patients responded to the screening, the look-back investigation retrieved a large sample of individuals. In addition, special effort was made to screen all patients who had surgery on the same day as an HCV-positive patient detected by the screening. This result could be explained when considering the probabil-

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

ity of virus transmission during surgery, which depends on several factors. First, the probability of having an HCV-infected patient was likely to be low (approximately 1%), assuming that the patients operated on in the clinic were similar to the general adult population in France. Second, only viremic patients could transmit HCV via healthcare procedures. Third, transmission could occur only for those patients following positive patients. Finally, most surgical procedures performed in the clinic were short in duration and did not require multiple injections and drawings of fentanyl.

Most of the patients had viral screening in the 3 years preceding the implementation of control measures. Although this study provided a great opportunity to promote hygiene practices during surgery and anesthesia, the amount of time, money, and human resources spent retrieving exposed patients suggested that such an information campaign should not be extended for a longer period.

Drs. Germain, Carbonne, Gros, Bouvet, and Astagneau are from the Regional Coordinating Center for Nosocomial Infections Control; and Dr. Thiers is from the National Reference Center for Viral Hepatitis B & C, Pasteur Institute, Paris, France. Dr. Chastan is from the Departmental Direction of Sanitary and Social Affairs of Eure, Evreux, France. Dr. Astagneau is also from the Department of Public Health, Pierre et Marie Curie University, Paris, France.

Address reprint requests to Dr. Anne Carbonne, C. CLIN Paris-Nord, Institut Biomédical des Cordeliers (Esc. J), 15, rue de l'Ecole de Médecine, 75006 Paris, France. acarbonn@bhdc.jussieu.fr

REFERENCES

1. Esteban JI, Gomez J, Martell M, et al. Transmission of hepatitis C virus by a cardiac surgeon. *N Engl J Med* 1996;334:555-560.
2. Ross RS, Viazov S, Gross T, Hofmann F, Seipp HM, Roggendorf M. Transmission of hepatitis C virus from a patient to an anesthesiology assistant to five patients. *N Engl J Med* 2000;343:1851-1854.
3. Delarocque-Astagneau E, Baffoy N, Thiers V, et al. Outbreak of hepatitis C virus infection in a hemodialysis unit: potential transmission by the hemodialysis machine? *Infect Control Hosp Epidemiol* 2002;23:328-334.
4. Bronowicki JP, Venard V, Botte C, et al. Patient-to-patient transmission of hepatitis C virus during colonoscopy. *N Engl J Med* 1997;337:237-240.
5. Chant K, Kociuba K, Munro R, et al. Investigation of possible patient-to-patient transmission of hepatitis C in a hospital. *N S W Public Health Bull* 1994;5:47-51.
6. 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.
7. Tallis GF, Ryan GM, Lambert SB, et al. Evidence of patient-to-patient transmission of hepatitis C virus through contaminated intravenous anaesthetic ampoules. *J Viral Hepat* 2003;10:234-239.
8. Comstock RD, Mallonee S, Fox JL, et al. A large nosocomial outbreak of hepatitis C and hepatitis B among patients receiving pain remediation treatments. *Infect Control Hosp Epidemiol* 2004;25:576-583.
9. Widell A, Christensson B, Wiebe T, et al. Epidemiologic and molecular investigation of outbreaks of hepatitis C virus infection on a pediatric oncology service. *Ann Intern Med* 1999;130:130-134.
10. Centers for Disease Control and Prevention. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in healthcare settings. *MMWR* 1988;37:377-378.
11. French Society for Anesthesiology and Intensive Care. *Recommendations About Hygiene in Anesthesia* [in French]. Paris: French Society for Anesthesiology and Intensive Care; 1997. Available at www.sfar.org.

https://doi.org/10.1017/S0899823X00198770 Published online by Cambridge University Press

THINK innovation

THE EFFICACY OF CHLORAPREP® IN TWO NEW APPLICATORS

ChloraPrep's new 10.5mL applicator features patented new tinting technology that adds color to the solution as it passes through the sponge. The patented ampulized applicator eliminates the risk of contamination, protects the CHG molecule from degradation, and ensures a 2-year shelf life.

The new ChloraPrep® Swabstick provides significant improvement in performance over traditional swabsticks. It features a non-linting polyester polyurethane foam tip and a reinforced handle for friction application.

ChloraPrep, an FDA-approved patient preoperative skin prep, is the only 2% chlorhexidine / 70% alcohol-based antiseptic available which meets the CDC guidelines.[1]

CDC guidelines for cutaneous antisepsis are based on a collection of clinical evidence indicating a significant reduction in infection when a 2% chlorhexidine-based antiseptic is used. A meta-analysis of independent clinical studies consistently demonstrates reduction rates of 50%.[2]

Visit chloraprep.com for directions on use of all ChloraPrep® products.

chloraprep.com

ChloraPrep® 10.5mL with Tint

NEW

ChloraPrep® Swabstick

TOUCHING MORE LIVES

1. Centers for Disease Control and Prevention. Guidelines for the Prevention of Intravascular Catheter-Related Infections. MMWR Recomm Rep. 2002; 51 (RR-10). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5110a1.htm. Accessed on 1/26/05.

2. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: A Meta-Analysis. *Ann Intern Med.* 2002; 136:792-801.

THINK ChloraPrep®
Antiseptic Skin Prep
2% CHG & 70% IPA

REDUCE THE RISK.