Managing Occupational Risks for Hepatitis C Transmission in the Health Care Setting

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INTRODUCTION

Hepatitis C infection is a significant problem for medicine and society, both in the United States and throughout the world. The past 15 years have seen the characterization of hepatitis C virus (HCV) as the major cause of non-A, non-B hepatitis, development of effective screening tests for HCV antibody to improve the safety of the blood supply, delineation of the community and nosocomial epidemiology of HCV infection, development of a clear understanding about the prevalence and the factors that influence the prevalence of HCV infection in society, development of a substantial body of information about the natural history of HCV infection, host immunological responses to exposure and in-

fection, and immunopathogenesis of syndromes associated with acute and chronic infection, and substantial progress in the development of therapeutic interventions to modify or cure HCV infection.

As our understanding of the epidemiology, routes of transmission, and prevalence of HCV infection in society have developed, we have also come to understand that this blood-borne virus represents a substantial risk to health care workers from occupational exposure to blood and other body fluids containing the virus in the workplace.

The purpose of this article is to review the information obtained in the past decade about the epidemiology, nosocomial epidemiology, natural history, immunopathogenesis, and occupational risks associated with managing HCV in the health care workplace. In addition, the article delineates approaches to preventing occupational and iatrogenic exposure and infection with this blood-borne flavivirus.

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EPIDEMIOLOGY AND ROUTES OF TRANSMISSION

In the Community

HCV has become a major cause of blood-borne viral infection in the United States and in the world and is a major cause of chronic liver disease worldwide. Alter and coworkers from the Centers for Disease Control and Prevention assert that hepatitis C infection is the most common chronic blood-borne infection in the United States (14). These investigators determined the seroprevalence of HCV infection among participants in the National Health and Nutrition Examination Survey, conducted in the United States from 1988 to 1994 (232), to be 1.8% and estimated that between 3.1 million and 4.8 million people in the United States are HCV infected (15). Armstrong and coworkers used the same data to model HCV infection in the United States over time to estimate the seroprevalence of HCV infection in various groups of the U.S. population. The seroprevalence, stratified by decade of birth, ranged in this study from 1.1% to 4.1% (19). HCV infection was also found to be inversely associated with socioeconomic status in these studies.

Among blood donors in the United States, the prevalence of HCV infection (as determined by screening tests for anti-HCV antibodies) is approximately 0.5% for first-time donors and 0.003% for returning donors (42). Note that the prevalence among blood donors is significantly lower than for the population at large, suggesting efficacy of donor self-deferral practices in U.S. blood banks (42).

Hepatitis C is primarily a blood-borne or parenterally transmitted infection. Vehicles and routes of parenteral transmission include contaminated blood and blood products, needle sharing, contaminated instruments (e.g., in hemodialysis, reuse of contaminated medical devices, tattooing devices, acupuncture needles, razors, and manicure devices), and occupational and nosocomial exposures (e.g., needle stick injuries) (discussed below).

The epidemiology of HCV infection in the community in the Western world has changed dramatically over the past two decades, primarily as a result of the identification of non-A, non-B hepatitis as the major cause of transfusion-associated hepatitis (109), identification of the hepatitis C virus as the major cause of non-A, non-B hepatitis (67), cloning and specific identification of the HCV genome as the agent responsible for the overwhelming majority of cases of posttransfusion hepatitis (64–66), the development of screening tests for blood and blood products for transfusion to eliminate hepatitis C virus from the blood supply (13, 169, 184), and the development of PCR technology that can accurately detect the hepatitis C virus genome in the circulation of infected individuals (122, 374), which permits genotyping and sequencing of the genome to identify discrete strains of virus (315, 323).

Prior to these events, injection drug use and transfusion were the most common routes of transmission for HCV infection in the West. In the 1980s, the risk for hepatitis C infection associated with transfusion was nearly 20% per unit transfused (89). By the year 2002, as a result of both self-deferral and aggressive screening of the blood supply, the risk has dropped to less than 0.03% per unit transfused (172).

HCV infection was far and away the major cause of post-

transfusion hepatitis in the 1980s and 1990s, accounting for more than 85% of cases of posttransfusion hepatitis (11). The risk for infection following transfusion of a unit of blood contaminated with HCV is greater than 90% (356). Whereas needle sharing has consistently been among the most important risk factors for HCV transmission, once the blood supply could be effectively screened for hepatitis C virus, the most important behavioral risk factor for the transmission of HCV in developed countries of the West unquestionably became needle sharing and equipment sharing in the process of injection drug use, accounting for up to 60% of infections (14). Other routes of transmission are less clear. Alter and colleagues argue that sexual transmission accounts for as much as 20% of HCV infections overall; however, many authorities believe that sexual transmission is relatively uncommon (12, 167, 219, 235, 321, 336, 363).

Investigators have detected HCV nucleic acid in semen (113, 202), menstrual blood, and other body fluids. One piece of evidence that indirectly supports sexual transmission comes from studies of family contacts of HCV-infected individuals. In the overwhelming majority of such studies, only sexual partners of the infected individuals appear to be at substantially increased risk for infection, and in some of the studies, this risk increases with the length of time of potential exposure (4, 167, 168, 250, 340). Conversely, I note that common risk factors for infection that may have produced infection in both sexual partners were not excluded in the majority of these studies. Further evidence for sexual transmission comes from genotyping and genetic sequencing of strains from sexual partners. These studies demonstrate a very high degree of relatedness of the HCV genomes in a fraction, but certainly not in all, of the strains identified from sexual partners (3, 62, 225, 340).

Despite these pieces of information, the evidence for sexual transmission is often indirect, and a variety of other known risk factors for transmission (e.g., needle sharing) often cannot be excluded. Furthermore, studies of sexual partners of individuals who acquired HCV infection as a result of receiving contaminated blood or blood products often demonstrate extremely low rates of transmission to spouses or steady sexual partners (39, 129).

Data concerning other routes of transmission are even more speculative. Routes of infection that have been incriminated in some studies include intranasal cocaine use (12, 72), body piercing (12), tattooing (63, 135, 179, 329), acupuncture (166, 308, 311, 327), shaving in community barbershops (217, 350), manicuring and other procedures in commercial beauty shops (217), and even iatrogenic transmission in hospitals, as well as physicians' and dentists' offices. According to Alter, despite anecdotal cases (discussed below) documenting iatrogenic and nosocomial transmission, case-control studies have as yet failed to demonstrate health care procedures as a clear risk for HCV infection in the developed world (14).

Only a relatively small fraction of HCV infections are symptomatic. Most infected individuals remain asymptomatic and, presumably, undiagnosed. Based on available data, the majority of individuals who acquire HCV infection (perhaps as many as 70 to 85%) develop chronic infection and are therefore at risk for the sequelae of this infection. One published estimate suggests that HCV is responsible for 8,000 to 10,000 deaths annually in the United States (15). Hepatitis C is already the

most commonly implicated precipitating factor (responsible for more than 30% of cases) for liver transplantation in the United States (42).

In the Hospital

Patient-to-provider transmission. Since hepatitis C is a blood-borne infection and is transmitted efficiently by transfusion and by needle sharing, it stands to reason that an occupational risk for transmission of HCV in the health care setting might exist, including transmission from infected patients to staff, from patient to patient, and from infected providers to patients. Evidence that direct, percutaneous exposure to blood represents the primary route of transmission for HCV from patients to providers comes from case reports of occupational infection in the literature (46, 210, 223, 230, 237, 238, 282, 297, 300, 325, 330, 349, 351). So-called "inapparent parenteral inoculation" (60) and "inapparent parenteral transmission" likely account for the largest fraction of the remaining cases. Two case reports document transmission of HCV as a result of a splashes of blood from infected patients onto health care workers' mucous membranes (284, 293).

Whereas blood is the major reservoir for occupational infection, other body substances may present some (albeit likely substantially reduced) risks for HCV infection, particularly if the health care worker is exposed by the parenteral route or inadvertently receives a large inoculum. HCV RNA has been detected in several other body fluids from infected patients, including saliva (202, 372), menstrual fluid (313), semen (113, 199, 202), urine (202), spinal fluid (189), and ascites (202). Although HCV has been transmitted by a punch (2) and after human bites (92, 110), the most common circumstance resulting in occupational infection is percutaneous exposure, and the most frequent type of exposure resulting in HCV transmission is a needle stick with a hollow-bore, injection-style needle contaminated with blood from an infected patient. Transmission of HCV resulting from exposures to body fluids other than blood has not yet been documented, presumably because viral titers in these fluids are substantially lower than in blood. HCV environmental contamination has been suggested to play a role in some settings (i.e., specifically in the hemodialysis environment) (1, 8, 78, 198, 366) (see discussion below); however, transmission of a specific strain of HCV as a result of environmental contamination has not, to my knowledge, been documented.

Patient-to-patient transmission. Whereas a risk for occupational transmission from infected patients to health care workers providing care for them has been identified for several years, we have only recently begun to appreciate the risks for nosocomial and iatrogenic infection in certain patient populations. Transmission of HCV in the hemodialysis setting deserves special emphasis. The prevalence of HCV infection among hemodialysis populations varies from 4% to more than 70% in some countries (366). In the United States, in a survey of dialysis centers conducted in 2000, antibody directed against HCV was found in 1.7% of hemodialysis center staff and in 8.4% of patients at these centers (346). Although chronic, end-stage renal failure patients do receive transfusions of blood and blood products, an increasing number of instances of nosocomial, patient-to-patient spread of infection as well as

outbreaks of infection not linked to transfusion have been reported (1, 9, 56, 78, 88, 99, 100, 131, 136, 159, 160, 170, 198, 213, 238, 248, 316, 326, 333).

Spread in these units has been suggested (but not definitively proved) to be due to environmental contamination (1, 7, 8, 78, 198, 366), contaminated dialysis machines (21, 78, 198), inadequate infection control procedures in the dialysis unit (1, 56, 78, 88, 159, 198, 345), dialyzing infected and noninfected patients in the same area (56, 88, 160, 248, 333), and understaffing of the dialysis unit (248). Numerous cases of patient-to-patient HCV transmission have been linked to breaks in infection control technique (discussed in more detail below). Several instances of patient-to-patient HCV transmission have been reported from Europe in the recent past (40, 81, 186, 200, 211, 247, 292, 299, 312, 365). In addition, patient-to-patient transmission in health care settings, primarily related to faulty injection practices, appears to be a reasonably important mode of HCV transmission in developing countries (23, 117, 134, 156, 173, 216, 227, 273, 371).

In addition to clusters of HCV infections in the hemodialysis setting, cases and outbreaks of hepatitis C infection have been linked to a variety of medical procedures and interventions, including the use of spring-loaded finger stick devices (81, 247), gynecological and gynecologic endocrinologic procedures (200, 211, 263, 287), contamination of multidose vials (182, 186, 211, 312, 348, 365), contaminated intravenous administration devices (299), orthopedic procedures (286), cardiothoracic surgery (41, 90, 97), anesthesiologist's and anesthesia assistant's interventions (71, 143, 285), endoscopy (228), colonoscopy (40), administration of contaminated immunoglobulin preparations (61, 93, 171, 191, 192, 288, 317), organ transplantation (367), and outbreaks that were clearly nosocomial yet for which no etiology could be determined (178, 188, 290). Some, if not most, of these instances of HCV transmission most likely represent cross-contamination, due, at least in part, to inadequate infection control procedures or inadequate disinfection of devices or objects (40, 81, 143, 186, 200, 211, 228, 247, 292, 299, 312, 348, 365); others appear to be direct, provider-to-patient transmission (discussed in detail below).

Provider-to-patient transmission. To date, iatrogenic transmission of HCV from HCV-infected providers to their patients has been uncommon. Nonetheless, the last several years have seen reports of individual cases of provider-to-patient HCV transmission as well as both small and large clusters of HCV infections. The first suggestion of iatrogenic infection was reported from England in 1995 (261). At the time of the initial publication, infection from a surgeon to his patients was strongly suspected but not definitively proven. A patient who developed acute hepatitis C infection following cardiovascular surgery (without other risk factors) was found to have been operated on by a health care worker who was positive for antibody to HCV. During the time that this case was being investigated, the first report of documented iatrogenic transmission in surgery was reported from Spain (97). In a look-back study, these investigators identified 6 of 222 patients who had been operated on by an HCV-infected surgeon who acquired HCV infection. In five of the six cases, the HCV strain isolated from the patient was closely related to the strain carried by the surgeon (97). All of the patients who became

infected with the surgeon's strain had undergone valve replacement surgery (97).

As a result of completion of the detailed evaluation of the initial English case discussed above (261), Duckworth and colleagues reported that 1 out of 278 patients identified in a look-back study of patients who had had surgical procedures performed by an HCV-infected junior surgeon developed HCV infection with a strain identical to the surgeon's. The patient who developed HCV infection had undergone coronary artery bypass surgery, during which the infected surgeon was the first assistant (90). In the fall of 1999, a third case of surgeon-to-patient transmission was reported (263). Other than the fact that the surgeon involved was an English gynecologist and the patient who became infected had undergone a gynecological procedure, few details of this third case are available (263, 264). An extensive look-back study (including patients from as far back as 1978) was conducted on patients who had had procedures performed by this surgeon. More than 4,500 patients from 11 different hospitals in England and Wales in which this surgeon had performed procedures were tested. Eight of these 4,500 individuals were discovered to have HCV infection caused by the same strain of HCV as the surgeon's (264, 265). Although these cases occurred some time ago, the specific details of these investigations are still unavailable in the medical literature. Most of the information gleaned about these events was published in the lay press.

More recently, Ross and coworkers reported the results of a look-back study of the surgical patients of an HCV-infected orthopedic surgeon (286). These investigators evaluated 207 of the 229 patients who had undergone orthopedic operations in which an HCV-infected orthopedic surgeon had actively participated. Three of the 207 were found to be HCV infected (as determined by a positive HCV antibody test), and one of the three was found to harbor an HCV isolate that was nearly identical to the orthopedist's. The patient had undergone a total hip arthroplasty with trochanteric osteotomy (286).

The same investigators also conducted a look-back study of individuals who had been patients of an HCV-infected German obstetrician-gynecologist for the preceding 7 years. The obstetrician-gynecologist had been shown to transmit HCV infections to a patient on whom he had performed a caesarian section (287). The investigators were able to screen nearly 80% of the physician's 2,907 patients and did not identify any additional cases of transmission (287). Cody and coworkers recently documented transmission of HCV infection from an anesthesiologist who had acute HCV infection to a patient for whom the physician had provided anesthesia services during a thoracotomy. None of 348 patients for whom this physician had provided anesthesia services were infected.

Two additional look-back studies involving the potential for health care worker-to-patient transmission of hepatitis C are in progress in the United Kingdom (264, 265). In the first of these studies, in which approximately 1,900 patients were potentially exposed to an HCV-infected surgeon, three infections were directly linked to the infected provider (41, 265). In the second study, nearly 750 patients of an HCV-infected provider were contacted. In that investigation, only one infection has thus far been linked directly to the infected provider (265). Finally, the Public Health Laboratory Service in the United Kingdom recently reported initiating an additional look-back study in

southern England and sent letters to 228 patients of an HCV-infected practitioner offering follow-up testing, again after an index case was identified as being linked to the practitioner following an exposure-prone procedure (type unspecified).

The United Kingdom experience is distinctive in that the rate of HCV transmission from providers to patients seems to be higher in the United Kingdom look-back studies than in the other studies published to date. Summarizing the experience from the investigations and look-back studies in the United Kingdom (and excluding index cases for these investigations), 9 of 7,656 (0.12%) patients evaluated became infected with HCV strains identical to their practitioners'. The transmission rate in the United Kingdom studies, if one includes the index cases, is 0.18%. Experience in the other published look-back studies is substantially different. In four such studies, again excluding the index cases, no additional cases were found to have acquired iatrogenic HCV infection among more than 3,000 individuals tested. The transmission rate in these four studies, if one includes the index cases, is similar to that in the United Kingdom studies (0.13%). At least to date, the data available preclude any assessment of factors associated with risk for transmission in the health care setting. Nonetheless, the fact that two gynecologists, three cardiac or thoracic surgeons, and an orthopedic surgeon were involved in these instances of provider-to-patient transmission suggests that factors similar to those identified for hepatitis B transmission (149) are likely operative. The large studies and the recently reported experiences from the United Kingdom clearly interject a substantial dose of concern about the potential for iatrogenic spread of this blood-borne pathogen.

Ross and colleagues reported a cluster of cases of HCV infection linked to an anesthesia assistant (285). In this unusual case, the anesthesia assistant acquired acute HCV infection as a result of an occupational exposure to a patient in the operating room (presumably as a result of contaminating an open wound on his right-hand third finger). The assistant may have represented an increased risk for transmission because he was working while developing acute HCV infection. In the course of 3 weeks, during which his finger lesion was purportedly still weeping, he infected five patients (285). Interestingly, the assistant did not wear gloves, and the authors argued that this cluster would likely have been prevented entirely by the use of universal standard precautions (285).

In one highly unusual case, a child acquired HCV infection from his mother as a result of her providing health care (54). The child was a hemophiliac and required frequent clotting factor concentrate infusions. The child's mother provided this care; however, she did not wear gloves. The mother, who was chronically infected with HCV, recalled several instances in which she stuck her own finger with the needle for the infusion, with blood visible several times. She could not recall if she continued to use the same needle for the infusion, but it seems likely that she did (54). Sequence analysis demonstrated that the mother's and child's HCV isolates were identical.

A cluster of cases of iatrogenic HCV infection have also been identified that were linked to a health care worker's injecting drugs intended for patients into himself and then reusing the needle to inject his patients. In this outbreak, an anesthesiologist infected 171 patients with a hepatitis C strain that was identical to the strain he carried (35, 36).

Clearly, without meticulous attention to infection control and disinfection and sterilization procedures, the risk for transmission of blood-borne pathogens in the health care setting is magnified. In some countries where HCV infection is endemic in the general population, hospitalization and invasive procedures do appear to be significant risk factors for HCV infection in some epidemiological studies (87, 218, 327, 328).

NATURAL HISTORY

To be able to manage any disease state effectively, a practitioner must first have a clear understanding of the etiology, pathogenesis, and natural history of the condition. Whereas we learned about the etiology of hepatitis C in 1989 (65), and, in the past 12 to 13 years, a great deal of progress has been made in attempting to understand the pathogenesis and immunopathogenesis of infection caused by this flavivirus, the natural history of the disease caused by the hepatitis C virus still remains a matter of some controversy.

To understanding the natural history of the disease produced by this interesting pathogen, one needs several key pieces of data (302). To characterize the natural history of any disease, the investigator must first be able to determine the precise time of onset of the disease. Additionally, the investigator must have a clear appreciation for the signs, symptoms, and morbidity that the disease produces; a dependable marker or markers for the disease; accurate measures of disease progression; and reliable measures of disease status in order to chart the course of a chronic disease. Furthermore, one must be able to follow the disease in its isolated state, uninfluenced by comorbidities, therapeutic interventions, and other external factors in order to identify morbidity and mortality events directly associated with the disease (302).

The controversy regarding the natural history of hepatitis C infection arises from the fact that many, if not most, of the conditions outlined above cannot be met. The fact that 13 years after identification of the etiologic agent the natural history of the disease remains remarkably clouded relates directly to the complexity of hepatitis C infection. More than three-fourths of hepatitis C infections do not cause jaundice and are asymptomatic or at least so mild clinically that they are not detectable as significant clinical illnesses (353). The significance of asymptomatic HCV viremia in the absence of transaminase elevation is still not fully understood (69, 266, 305). Acute, symptomatic hepatitis C infection is a relatively uncommon presentation (unlike hepatitis B virus infection). More than 70 to 85% of individuals who are detected as being infected through the use of antibody screening progress to develop chronic infection. What remains unclear, however, is what fraction of patients exposed to and subsequently infected with the hepatitis C virus ultimately progress to serious liver disease, cirrhosis, and/or hepatocellular carcinoma. Further muddying this circumstance is the fact that recent information suggests that a population of patients may be exposed to the hepatitis C virus, clear the infection through natural or cellular immune mechanisms, never develop productive hepatitis C infection, and never make an antibody response against the virus (332). These individuals would be missed entirely by either anti-HCV antibody detection or PCR for HCV RNA. Interestingly, such individuals often do have immunological

memory, as manifested by robust, persistent T-cell cytotoxicity responses directed against HCV-associated epitopes.

We now appreciate that the scope of the natural history of hepatitis C infection encompasses a spectrum of virus-host interactions that range from immediate viral clearance without stimulating humoral immunity; acute subclinical infection that resolves spontaneously; subacute or acute infection that resolves spontaneously or leads to chronic viremia without defined histologic or biochemical evidence of hepatic disease; persistent but stable hepatitis without progression; and progressive disease that leads to acute or chronic liver failure, cirrhosis (which may range from relatively stable over time to rapidly progressive), and hepatocellular carcinoma. What remains elusive, even 13 years after the discovery of the hepatitis C virus, is the frequency of these various outcomes and the factors that influence them.

Some factors have been associated with either favorable or untoward outcomes of HCV infection; however, these findings are not always consistently identified from study to study. One recent study, for example, found that the following factors were associated with virus clearance: nonblack race, not coinfecting with human immunodeficiency virus (HIV), age less than 45 years, and the presence of ongoing infection with hepatitis B virus (337). Factors found in other studies that were not validated in the study of Thomas and coworkers cited above include the extent of weekly alcohol use and the frequency of injection drug use (337).

Conversely, when factors associated with the worst outcome, end-stage liver disease, were assessed in the same study, the following factors were identified as associated with this adverse outcome: age greater than 38 years, increasing time from first use of injected drugs, more frequent use of injecting drugs, consumption of more than 260 g of ethanol per week, and male gender. No association was found with HIV coinfection, black race, chronic carriage of hepatitis B virus, and HCV viral load or viral burden, as determined by quantitative PCR (337). Other investigators have suggested that alcohol consumption may be the or, at least, a primary determinant of fibrosis and cirrhosis as an outcome of HCV infection (254, 296, 352).

Other factors that have been associated with adverse outcomes of hepatitis C infection in some studies include the patients' major histocompatibility complex (MHC) class II alleles (20, 24, 76, 103, 215, 344); the viral HCV genotype in many (91, 157, 190, 239, 256, 257, 271, 314) but not all (283, 301, 368) studies; viral burden in some (130) but not all (102, 157, 337) studies; smoking (245, 296, 357); and coinfection with other blood-borne pathogens (2, 33, 111, 120, 269, 282, 319).

Several studies have identified HIV coinfection as predisposing to a more rapid progression of hepatitis C infection (summarized in reference 204). Several studies have suggested that the course of hepatitis C infection is accelerated and that the disease may produce more severe hepatic damage in HIV-coinfected patients (10, 30, 196, 204, 254, 319, 324, 337-340). These studies also demonstrate that patients infected with both viruses generally have higher circulating HCV viral burdens than do patients who are not HIV infected. Some of the health care workers who have become infected with both viruses following occupational exposures have had unusual courses, in-

cluding rapid progression of illness and delayed seroconversion (55, 282).

IMMUNITY AND IMMUNOPATHOGENESIS

The role that the host immune system plays, both in the defense against HCV infection and in the pathogenesis of HCV-associated disease states, has been a subject of intense interest and controversy over the past several years. This issue has been reviewed in detail (and, interestingly, from several various perspectives) in the past 5 years (83, 95, 118, 233, 279). The relative importance of the natural, humoral, and cellular limbs of the immune system has been the focus of much investigation during the past decade. Suffice it to say, as discussed above, that both direct and indirect evidence suggests that a variety of factors, some related to genetics, some related to host defense, some related to environmental factors, and some related to the virus, have been shown to influence outcome in this often persistent flavivirus infection.

A substantial body of evidence points to immune participation in the pathogenesis of HCV-associated illness. Both autoimmunity (274) (including a suggestion of autoimmune hepatitis) (233) and essential mixed cryoglobulinemia (243) are features frequently associated with HCV infection. Similarly, investigators have documented that cellular immunity plays a significant role in the pathology of HCV infection. Direct cell-mediated ($CD8^+$) cytotoxicity likely represents an important mechanism for the killing of HCV-infected hepatic cells (233). In addition, some investigators have postulated that $CD4^+$ cells may also contribute to the pathogenesis of infection (180). In fact, a host of presumably immunologically mediated extrahepatic manifestations have been documented as being associated with hepatitis C infection, including porphyria cutanea tarda, lichen planus, vitiligo, cryoglobulinemia, membranoproliferative glomerulonephritis, lymphoproliferative disorders (including non-Hodgkin's lymphoma), a Sjogren-like syndrome, ischemic retinopathy, systemic vasculitis, and autoimmune thrombocytopenia (summarized in references 96, 220, 229, 243, 251, 375, and 379).

With respect to the beneficial aspects of the host immunological responses, clearance of HCV infection is accomplished through balanced coordination of aggressive, effective, persistent cellular and humoral immune responses (176). Diminished effectiveness of cell-mediated cytotoxicity (165), inadequate $CD4^+$ helper T-cell responses (126), and decreased efficacy of B cells, which have been demonstrated in animal models of other viral infections (253, 341, 342), have all been associated with long-term viral persistence. A brief discussion of the relative contributions of humoral and cellular immunity to host defense follows.

Humoral Immunity

In the 15% of individuals who, when infected, spontaneously clear hepatitis C infection, recovery is frequently associated with (but not necessarily causally related to) the development of specific antibodies directed against HCV. The fact that HCV infection persists in the face of the antibody response indicates that, in the chronically infected patients, antibody is insufficient to clear the infection. Individuals who develop

chronic infection also develop HCV-specific humoral responses, though these responses are not adequate to clear infection. With respect to HCV infection, humoral immunity can assist in the direct neutralization of cell-free virions but can only play an extremely limited role in eradicating HCV inside cells.

Immunocompetent patients who acquire HCV infection commonly produce a variety of antibodies directed against both structural and nonstructural regions of the virus. The anti-envelope portion of the antibody response decreases gradually over time. In chronic infection, the host's humoral immunological response places substantial pressure on the virus, resulting in the emergence of generations of quasispecies (104–107). Some investigators have suggested that a brisk antibody response directed against the hypervariable region of the HCV envelope protein may be an important component of viral clearance mechanisms affecting recovery (208, 376–378). Ray and coworkers found that quasispecies complexity was increased and that selective pressure was decreased in five patients who had chronic infection manifested by persistent viremia (275).

Farci and coworkers provided convincing evidence that the ultimate outcome of hepatitis C infection (especially as regards viral clearance and recovery versus viral persistence) may be determined early in the course of primary infection by the rate at which diverse viral forms emerge (106). The emergence of increasing (as opposed to decreasing) numbers of quasispecies, presumably permitting the virus to escape host immunity, both humoral and cellular, predicts chronic infection (106). In this study, acute infection that progressed to chronicity was directly associated with the development of increasing viral diversity within the first 4 months of infection (106). The authors argue that monitoring viral diversity during the early evolution of infection may permit accurate prediction of outcome (106).

Not all studies have corroborated the finding that the immunological pressure may produce "escape" quasispecies. Working with a chimpanzee model of HCV infection, Bassett and coworkers found that viral clearance was not associated with an anti-envelope antibody response (25). In fact, in this animal model, antibody directed against the major variable envelope protein was identified only in animals that had persistent viremia. Taken together, these results suggest that, at least in the chimpanzee model, factors other than immunological pressure resulting in escape quasispecies may contribute to the maintenance of chronic infection. Other studies in patients (albeit with relatively small populations) (48, 207, 209, 212) concluded that the evolution of HCV quasispecies is not simply a matter of immunological pressure.

Cellular Immunity

Current evidence suggests that both $CD4^+$ and $CD8^+$ T lymphocytes play significant roles in host defense against hepatitis C infection. Studies in animal models and limited human studies of hepatitis C infection demonstrate that brisk T-helper and T-cytotoxic responses are both associated with resolution of HCV infection (59, 74, 83–85, 94, 126, 278–281, 360). Both helper and cytotoxicity responses are robust when infection resolves spontaneously; furthermore, these cellular responses appear to correspond in time with the resolution of infection

(195), although one recent primate study did not demonstrate a clear correlation between cellular responses and viral clearance (343). As noted above, when the host possesses certain HLA genes, spontaneous resolution of infection occurs more commonly (20, 24, 76, 103, 215, 344). Keeping in mind that spontaneous resolution is the exception rather than the rule for HCV infection, science needs to understand why these responses fail in the majority of instances. Some investigators have suggested that individuals who develop chronic viremia or infection produce modest, if any, CD4⁺ T-cell responses (126, 139, 332). Whether persistent infection produces or is a direct result of abnormal attenuation of T-cell responses is unclear at this time (231), though one argument that the virus is responsible for downregulation of the CD4⁺ responses comes from the fact that these responses develop (or redevelop) following interferon therapy (75).

Similarly, CD8⁺, suppressor, and cytotoxic responses in acute HCV infection are also incompletely characterized. Reasonably brisk cytotoxic responses have been documented among patients who develop chronic HCV infection (193, 335). Possible explanations for why these responses are inadequate to clear the infection include the possibility that the responses are downregulated as a result of the HCV viremia (126, 193, 194) and that the magnitude of the response is inadequate or that the overall quality of the immunological response may be too narrow, or not be directed specifically against key protein or peptide antigens. Other investigators have incriminated an inadequate CD8 response as a major contributor to viral persistence and chronic infection (132, 362).

Takaki and colleagues studied a cohort of women who had been inadvertently exposed to a single HCV strain of known sequence in a point source epidemic and found that, despite documented exposure, circulating HCV-specific antibodies were undetectable in many patients 20 years after recovery (332). Conversely, these investigators found that the same individuals who lacked anti-HCV antibodies had detectable levels of helper and cytotoxic T-cell responses directed against HCV antigens. These authors argue that these HCV-specific cellular immune responses serve as more reliable biomarkers for previous HCV exposure or infection than do tests for specific anti-HCV antibody (332). They also emphasize that because anti-HCV antibodies are not detectable in a substantial fraction of exposed or previously infected individuals and because the current screening tests for exposure are based entirely on detecting anti-HCV antibodies, the true incidence of self-limited HCV infection may be considerably underestimated (332).

In summary, although the precise mechanics of the successful immunological response to HCV have not been delineated, and despite the fact that the relative importance of humoral, cellular, and natural immunity in host defense against HCV remains a matter of substantial controversy, one can mount a reasonable argument that both cellular and humoral immune responses play important roles in determining the outcomes of HCV infection. As yet, we do not understand either why some individuals develop balanced, aggressive, persistent responses that are effective in clearing the virus and others do not, or why some individuals develop a persistently bland, slow, or nonprogressive infection and others develop aggressive fibrosis and cirrhosis.

RISKS FOR HEALTH CARE WORKERS

Prevalence of HCV Infection

Studies of the prevalence of HCV infection in health care workers have generally demonstrated that health care workers are at only minimally increased risk for HCV infection compared with the population at large (summarized in reference 181). Interpreting the results of these studies is complex because of all of the potentially confounding variables that may influence such studies, e.g., geographical differences in prevalence (361), genetics, socioeconomic factors, race, and environmental factors, most of which were not investigated in these studies. In addition, appropriate control groups are not always included, and many of the studies (because of the convenience of the data) inappropriately employ blood donors as controls. As a group, blood donors are probably not the best controls, since individuals who are at risk for blood-borne infection or have a history of hepatitis have been specifically excluded (310). Factors that have been associated with increasing HCV prevalence in at least one study include increasing seroprevalence with increasing age, increasing seroprevalence with increasing number of years in a health care occupation, history of transfusion of blood or blood products, and having sustained needle stick injuries (summarized in reference 181).

Case Reports

Several case reports describing instances of well-documented occupational HCV infection have been published since serological and molecular testing for HCV has been developed (46, 210, 223, 230, 237, 238, 282, 284, 293, 297, 299, 300, 325, 330, 349, 351). I would stress that the nosocomial epidemiology of occupational HCV infection remains somewhat unclear. The overwhelming majority of infections are associated with parenteral exposures (46, 210, 223, 230, 237, 238, 282, 297, 299, 300, 325, 330, 349, 351), although two of the anecdotal reports describe infection associated with mucosal splashes (284, 293). Delineating additional factors associated with occupational risk has been difficult for a variety of reasons, the most problematic of which is the fact that our current understanding of the pathogenesis, host response, and other early events in HCV infection is not precise. Factors that have been shown to influence risk for other blood-borne pathogen infections, such as the presence of visible blood on the injuring device, the depth of the injury, the device inserted into a vascular channel, and viral titer in the source patient (45), have not yet been linked to HCV exposures and infection. Nonetheless, it seems entirely reasonable and logical to assume that factors that relate directly to inoculum size are very likely to operate in HCV infection as they do in HIV and hepatitis B virus infection in this setting.

Cohort Studies

Investigators in four studies have attempted to determine the number of incident HCV infections among cohorts of previously uninfected health care workers (73, 86, 123, 187). Taken together, these studies clearly document some risk for HCV infection, though clearly not of the same magnitude as for hepatitis B infection and slightly higher than for HIV in-

fection (123). Cooper and coworkers retrospectively evaluated 960 dental health care workers over a 2-year period and found an incidence of 0.15 HCV infections per 100 person-years of follow-up (73). Lanphear and colleagues evaluated hospital staff over a 10-year period and found six incident cases of non-A, non-B hepatitis, four of which could be serologically proven to be HCV infection, an incidence of 21 cases per 100,000 health care workers per year (187). This incidence in this health care worker cohort was approximately three times higher than that for non-health care workers. DiNardo et al. evaluated 765 hospital workers over a 6-year period and found one incident infection, an annual incidence of 0.02% (86). Gerberding evaluated a population of health care workers working at a large public hospital in San Francisco for 8 years and identified one incident infection (123). From these data, the investigators calculated an incidence density of 0.08 per 100 person-years (123). Together, these cohort studies demonstrate a small but measurably increased risk for health care providers to acquire HCV infection as a result of occupational exposure.

As noted above, in the National Health and Nutrition Examination Survey, Alter and coworkers did not identify an association between a health care occupation and HCV infection (15). In fact, in this study, in the three ethnic groups studied and in the total population surveyed, the prevalence of HCV was actually lower among those who had ever worked in a health care setting compared with those who had not (15). These data were not corrected for either socioeconomic status or other potentially confounding risk factors. Nonetheless, whatever contribution to risk is made by working in health care occupations is dwarfed by these other factors. Conversely, in an Italian population-based survey for acute viral hepatitis (a suboptimal marker for HCV infection that would tend to underestimate risk because of the infrequency with which HCV infection presents as acute hepatitis), health care workers were nearly three times as likely to acquire acute hepatitis C as were members of the general population (322). When the study was repeated 3 years later, health care workers were only 1.7 times more likely to have acute HCV-induced hepatitis (322).

Longitudinal Studies

Several studies have attempted to assess the magnitude of risk for infection associated with parenteral (and in some cases mucosal) occupational exposures to HCV in the health care setting (18, 22, 86, 116, 137, 140, 147, 152, 174, 187, 222, 223, 244, 249, 267, 268, 270, 277, 309, 318, 320, 380; G. Ippolito, V. Puro, and G. De Carli, 10th Int. Conf. AIDS, 1994, abstract 271 B/D; A. Veeder, K. Stellrecht, A. Steinmann, K. Putnam, W. Caldwell, and R. Venezia, Eighth Annu. Meet. Soc. Health Care Epidemiol. Am., 1998, abstr. 31). Whereas most of the studies employed anti-HCV antibody as the primary detection system for HCV infection, seven of the studies used PCR technology to attempt to detect HCV RNA as a marker of infection among individuals who had been parenterally exposed to blood from patients known to harbor HCV (18, 22, 137, 140, 222, 223, 320; Veeder et al., abstr. 31).

Table 1 lists the published longitudinal studies of health care workers' occupational risk for HCV infection following parenteral exposure to blood from individuals known to be infected

with HCV. Transmission rates in these studies range from 0% (9 of the 25 studies) to 22.2%. The reasons for the substantial variation in transmission rates include different infection detection systems with different sensitivities, the possibility that different exposures may pose different levels of risk, geographic differences and, likely, genetic differences in the populations being studied, substantial differences in sample sizes, the potential for variable infectivity of source patients (i.e., viral burdens), different viral genotypes, the presence of other cofactors (e.g., HIV infection) in source patients, and a veritable host of other potentially confounding risk factors and variables. Additional limitations of the studies that have employed HCV RNA-PCR testing include not knowing what fraction of individuals who are exposed to HCV may have intermittent PCR spikes, with or without developing productive HCV infection, and the fact that nucleic acid-based tests may also be technically difficult to perform reproducibly and may be falsely positive or negative if samples are not handled or processed appropriately. Nucleic acid contamination is a major problem in many laboratories that conduct these tests. Nonetheless, if one ignores the limitations of the data, the differences in study design, and the substantial differences in testing methods employed and combines the data from all of the studies, the average infection risk following parenteral exposure is 1.9%. This risk places HCV occupational risk squarely between the risk for transmission of hepatitis B virus (about 30% per parenteral exposure to blood from an e antigen-positive patient) (306, 364) and that for HIV (approximately 0.3% per parenteral exposure) (146, 148).

Recent data (discussed above) from studies of the immunology and immunopathogenesis of HCV infection suggest that none of these techniques may provide a true denominator of who has been "exposed" to HCV. One anecdotal case report documents HCV RNA circulation in an individual who never made anti-HCV antibody despite the development of HCV infection with circulating viral burdens of 10^6 , 10^6 , and 10^3 copies/ml at 2, 3, and 4 weeks, respectively (224). Additionally, some studies have suggested that the most reliable marker of past exposure is an assessment of specific cellular immunity directed against HCV (332) (not used in any of these longitudinal studies); these investigators suggest that both antibody tests and tests for circulating HCV RNA underestimate the true number of exposures.

From these data, one can conclude that the risk associated with an occupational exposure is likely to be less than the 1.9% summary risk presented above. How much less than 1.9% is, at this time, uncertain. A reasonable estimate, based on studies of exposed health care workers combined with the studies of Takaki et al., is that between 1% and 2% of those who are exposed develop markers of infection. As noted above, this estimate places the occupational HCV risk directly between the risks for occupational hepatitis B virus and HIV infections, approximately 10-fold less than the hepatitis B virus risk, and approximately 10-fold higher than the HIV risk.

Based on the data summarized above, the risks for occupational transmission of hepatitis C are incompletely characterized. Whereas the parenteral route of transmission of HCV is definitively established as an important mode for both transmission recipients and intravenous substance users, transmission

TABLE 1. Longitudinal and prospective studies of risk for infection with hepatitis C virus following parenteral occupational exposure to blood from infected patients

Reference	Yr	Location	No. of parenteral HCV exposures	No. of HCV infections	% Of subjects infected	Testing method(s) ^a	Comments
Kiyosawa ^b (174)	1991	Japan	110	3	2.7	EIA-1, RIBA-1	
Francavilla (116)	1992	Italy	30	0	0	EIA-2	
Hernandez (152)	1992	Spain	81	0	0	EIA-2, RIBA	
Marranconi (210)	1992	Italy	117	3	2.6	EIA, RIBA	
Mitsui (222)	1992	Japan	68	7	10.0	EIA-2, PCR	
Stellini (320)	1993	Italy	30	0	0	EIA-1, RIBA-1, PCR	
Sodeyama (318)	1993	Japan	62	3	4.8	EIA-2	
Lanphear (187)	1994	U.S.	50	3	4.2	EIA-2, SN	
Perez-Trallero (244)	1994	Spain	53	1	2.0	EIA-2, EIA-3	
Petrosillo (249)	1994	Italy	61	0	0	EIA-2, RIBA-2	Dialysis settings
Ippolito et al. ^c	1994	Italy	123	2	1.6	EIA-2, RIBA-2	HIV-coinfected sources
Zuckerman (380)	1994	U.K.	24	0	0	EIA-2, RIBA-2	
Puro (268) ^d	1995	Italy	97	1	1.0	EIA-2, RIBA-2	
Puro (269) ^d	1995	Italy	436	4	0.6	EIA-2, RIBA-2	
Puro (270) ^d	1995	Italy	61	0	0	EIA-2, RIBA-2	HIV-uninfected sources
Arai (18)	1996	Japan	56	3	5.4	RIA-1, PHA-2, PCR	
Mizuno (223)	1997	Japan	37	2	5.4	EIA-2, PCR, sequencing	
Serra (309)	1998	Spain	443	3	0.7	EIA-2, EIA-3	
Takagi (309)	1998	Japan	251	4	1.6	EIA-1, EIA-2, PCR	
Veeder et al. ^e	1998	U.S.	9	2	22.2	EIA, PCR	
Hamid (137)	1999	Pakistan	53	2	3.8	EIA-2, PCR	
Hasan (140)	1999	Kuwait	24	0	0	EIA-2, RIBA	
Baldo (22)	2002	Italy	68	0	0	EIA-3, RIBA-2, PCR	
Regez (277)	2002	Netherlands	23	0	0	EIA-3, RIBA-2	
Wang (277)	2002	Taiwan	14	1	7.1	EIA-3, RIBA-2	
Total			2,357	44	1.9		

^a EIA-1, first-generation enzyme immunoassay; EIA-2, second-generation immunoassay; EIA-3, third-generation immunoassay; RIBA-1, first-generation recombinant immunoblot assay; RIBA-2, second-generation recombinant immunoblot assay; RIA, radioimmunoassay; PHA, passive hemagglutination; SN, supplemental neutralization.

^b Some patients may overlap with those in reference 318.

^c Ippolito et al., 10th Int. Conf. AIDS, 1994, abstract 271 B/D.

^d Some patients may be counted more than once in these studies by the same set of investigators.

^e Veeder et al., 1998, abstr. 31.

to health care providers as a result of occupational parenteral exposure remains a relatively uncommon event.

PREVENTING OCCUPATIONAL TRANSMISSION

Lessons from Chronic HCV Infection

The treatment of chronic hepatitis C infection has met with increasing, albeit modest, success over the past 15 years (34, 82, 155, 201). The cornerstone of therapy was initially alpha interferon. Initial treatment regimens with interferon alone resulted in response rates of from 20% to 35%; however, cures or sustained remissions occurred in less than 10 to 20% of patients (255, 334). Therapy has been particularly problematic for patients infected with genotypes 1a and 1b. In the 1990s, the nucleoside analog ribavirin was shown to decrease alanine aminotransferase levels in patients and to improve the hepatic histology with chronic HCV infection. A number of trials subsequently demonstrated that combination therapy with interferon and ribavirin is superior to interferon alone in terms of percent responding, percent with sustained responses, and histological improvement in the liver (175). The combination produced sustained responses in the range of 30 to 40% (47, 201), although not all studies have found a substantial benefit with the combination (57).

The next significant advance in treatment was the modifica-

tion of interferon with polyethylene glycol to improve drug pharmacokinetics and to provide long-term activity. Compared to interferon, so-called pegylated interferon or peginterferon has similar activity and far superior pharmacokinetics (359). Use of pegylated interferon in combination with ribavirin has produced sustained response rates in some studies that are greater than 50%, with some approaching 60% (77, 82, 119, 154, 206, 236).

Other candidate therapies that are currently in evaluation include alternative interferons, amantadine, micophenolate, nucleoside analogs, α 1 thymosin, Maxamine (histamine), HCV-specific protease, helicase and polymerase inhibitors, antisense oligonucleotides, and interleukin-10 (158, 214). Whereas interferon has both immunomodulatory and direct antiviral activity (234), and some antiviral agents specifically directed against HCV are on the horizon, the majority of the agents being evaluated are immunomodulators.

What lessons have been learned from the treatment of chronic HCV infection? First, even with the current gold standard therapy, the outcomes associated with therapy remain suboptimal and somewhat discouraging. Second, the primary approach to therapy (i.e., the interferons) has mainly been immunomodulatory, and such interventions are not likely directly comparable in the postexposure management setting to the use of antiviral compounds as postexposure prophylaxis for

occupational exposure to other blood-borne pathogens (e.g., HIV). Third, the long courses of treatment required (i.e., 6 months to a year) and substantial toxicities in therapy recipients are daunting.

Lessons from Acute HCV Infection

The experience of treating acute hepatitis C infection has been somewhat more favorable (6, 44, 153, 161, 162, 354). In general, these studies (although many of the studies have limitations in study design) have shown higher resolution rates and lower rates of chronic infections among patients who received treatment for their acute infections than is the case with therapy for chronic infection (34, 82, 155, 201). These data should be interpreted with caution in light of the fact that we do not yet have a clear understanding of the early events in the pathogenesis and host response to hepatitis C virus exposure and infection (see discussion of immunopathogenesis, above).

Special mention should be made of the study recently published by Jaeckel and coworkers (161). In this study, the authors treated 44 German patients who had acute hepatitis C with 5 million units (MU) of interferon $\alpha 2b$ daily for 4 weeks and then three times weekly for the ensuing 20 weeks. Of the 44 patients studied, 9 acquired HCV infection through needle sharing in intravenous substance use; 14 were health care workers who acquired HCV infection as a direct result of an occupational needle stick exposure; 7 acquired infection as a result of patient-to-patient spread in a health care institution or as a result of nosocomial spread of the virus; 10 were thought to have acquired infection following sexual exposures; and four had acute infection, the etiology of which could not be determined (161). The patients with acute hepatitis received single-agent therapy with interferon $\alpha 2b$. At the conclusion of treatment as well as after 6 months of follow-up, HCV RNA was undetectable, and alanine aminotransferase levels were entirely normal in 43 of 44 patients (98%) (161).

These results are strikingly different from (and strikingly better than) those in published studies of even the best and most effective treatments for chronic HCV infection (154). I would underscore that the outcomes and therapeutic responses that result from treating patients who present with acute hepatitis caused by hepatitis C are very likely substantially different from those in studies describing the treatment of patients who have asymptomatic HCV viremia, those who have an indolent presentation of HCV infection, and those who present with chronic, progressive infection. As noted above, the immunological response to HCV is exceedingly complex, and it could be argued that individuals who develop acute hepatitis at the time of infection may do so because they are mounting a more robust immunological response. Although many such patients may well clear their infections spontaneously, having 98% of patients clear the infection is essentially unprecedented.

Whereas the authors refer to this collection of 44 patients as having "acute hepatitis," the patients themselves represent a truly nonhomogenous group, having substantial differences in severity of presentation, route of exposure, source of infection, gender, and age. The time from hepatitis C virus exposure to development of the first symptoms of the acute hepatitis syndrome in this population ranged from 15 to 105 days (mean, 54 days), and the time from exposure and infection until initiation

of therapy ranged from 30 to 112 days (average, 89 days) (161). Nonetheless, a 98% success rate cannot be discounted.

Vogel and coworkers previously reported success in treating a similarly nonhomogenous group of 24 individuals with acute HCV infection (355). Twenty-two of the patients completed therapy, and 20 of those cleared their infections and remained PCR negative for HCV for 6 months. Eighteen of these patients remained PCR negative for more than 18 months (355). In a smaller study, Pimstone and coworkers treated seven patients with acute HCV infection with a regimen that included 5 MU of alpha interferon for 12 weeks followed by 3 MU three times a week for the remainder of a year. All seven were PCR negative for HCV RNA at 6 months following the completion of treatment (252). A number of additional single case reports or small studies also document the success of treating acute hepatitis in health care workers who sustained an occupational exposure and developed evidence of productive HCV infection (98, 237, 241, 294, 331, 347, 358). These studies used different doses of different interferon products; however, none of the subjects in these studies progressed to chronic infection, unlike the case reported by Nakano et al. (230). In the cases in which the disease did not progress to chronic infection, the majority were treated between 5 and 25 weeks following the exposure; the majority had acute hepatitis; and all had PCR tests positive for HCV RNA (though the tests several were positive at a very low level). In the case in which the disease did become chronic, a short course of interferon was administered prophylactically (i.e., in the immediate post-exposure period, prior to the development of either symptoms or viremia) (230) (discussed in more detail below).

What have we gleaned from the studies evaluating the treatment of acute hepatitis C? First, even with the limitations of these studies, data are accumulating that conclusively suggest that treatment of acute infection may be advantageous. Second, some aspects of the experience with treatment of acute infection may be directly relevant to the management of health care workers who have sustained occupational exposures to HCV (discussed in more detail below). In fact, in two of the three studies cited above, 15 of the patients studied were health care workers who had sustained occupational exposures and progressed to the development of the acute hepatitis C syndrome. Third, the investigators were able to achieve extremely high regimen adherence rates despite the rigorous regimens outlined and their obvious toxicities. Despite the use of very high doses of interferon in one of the studies (5 MU of alpha interferon subcutaneously daily for 4 weeks and then the same dose administered three times per week for another 20 weeks [161]), combining data from all three studies, only 3 of 75 individuals (4%) failed to complete the half-year to year-long regimens.

Management of Health Care Workers after Exposure

Immediate management and follow-up strategies. Administering first aid to a person subjected to an occupational exposure makes implicit sense. If the worker her- or himself has not already cleansed and decontaminated the exposure site, the Occupational Medicine staff should assist in this process as soon as possible after the exposure. To my knowledge, however, no data have demonstrated any direct benefit from first

aid in terms of preventing occupational infections. Puncture wounds and other open wounds should be washed with soap and water. Some authorities have recommended that open wounds be flushed with sterile saline or a disinfectant solution (125). For splash exposures involving the mouth and nose, I recommend rinsing aggressively with water. Splash exposures to the eye should be flushed with water or with irrigation fluids designed for irrigating the eye.

Each institution should develop streamlined mechanisms that facilitate both the reporting of occupational exposures and the provision of follow-up care for workers sustaining exposures. Institutions should publicize these procedures widely so that employees at all levels of the organization are aware of the importance of immediately reporting such exposures as well as the importance of follow-up. Underreporting of occupational exposures to blood-borne pathogens remains a significant problem in the health care workplace (28, 31, 138, 150, 205).

Irrespective of the source patient's underlying infection status, protecting the medical privacy and confidentiality of both the source patient and the exposed health care workers should be a major priority. In our institution, we manage records of occupational exposures separately from both employee health records and source patients' medical records.

As would be the case for an occupational exposure to any blood-borne pathogen, baseline testing of the source patient (to make certain an exposure has occurred) and baseline testing of the exposed health care worker (to make certain that the individual is not already infected) are both recommended.

Since not all exposures are directly linked to an obvious source patient, it is important to emphasize that making the effort to identify the source, whenever even remotely possible, is worth the effort. Source patients should be evaluated clinically and epidemiologically for evidence of infection with all relevant blood-borne pathogens (e.g., HIV, hepatitis B virus, and HCV), and the examining physician should consider other potentially transmissible infectious diseases, based on the source patient's clinical history and condition. When the source patient cannot be identified, we attempt to make an epidemiological assessment of the likelihood of exposure to blood-borne pathogens (147). Employees sustaining a "source unknown" exposure should be managed on a case-by-case basis but should, at a minimum, be offered follow-up to assess whether a blood-borne pathogen has been transmitted.

Even when the source patient is hospitalized because of hepatitis C infection, testing for other blood-borne pathogens (because of the similarities in epidemiologies) is appropriate. I recommend baseline testing of the source patient for hepatitis B surface antigen, hepatitis C antibody, and HIV. Testing for hepatitis B surface antigen usually does not require informed consent (125), nor does testing for antibody to hepatitis C in most jurisdictions. In addition, I recommend that the source patient be tested for antibody against HIV. In some states and jurisdictions, this process requires informed consent. In those instances, I recommend that the testing be discussed appropriately with the source patient and that consent be obtained. Most source patients agree to testing voluntarily. As noted above, every effort should be made to preserve the medical privacy and confidentiality of both the source patient and the health care worker. Where permitted by statute, it may be possible for the managing physician to obtain consent for se-

rological testing from the source patient's immediate next of kin, from the individual holding the source patient's durable power of attorney, or from another individual who has been identified as legally able to make the decision. This permission may allow source patient assessment when testing would otherwise not be possible. Because there are substantial differences in state and local regulations concerning testing for blood-borne pathogen exposures, each institution should create procedures that facilitate postexposure management and both source and health care worker testing that are consonant with state and local laws relevant to these blood-borne diseases.

Screening by antibody tests alone is subject to the limitations of these tests. As noted above, none of the tests, even the current generations, are capable of identifying 100% of those who have been infected previously (332). In fact, Alter and coworkers suggest that as many as 10% of patients who harbor hepatitis C infection may not be detected by currently available antibody tests (16). Furthermore, finding antibody directed against HCV in the serum of the source patient for an occupational exposure is not a totally accurate indicator of HCV infectivity of the source patient. Some individuals with anti-HCV antibodies have no or very low levels of circulating HCV, and some of these individuals may have totally resolved HCV infection. Nonetheless, in the acute setting of occupational exposure, sources found to be positive by the antibody screening test should be assumed to be infectious.

Currently, the U.S. Public Health Service (55) recommend the following approach for follow-up of health care workers who sustain parenteral or mucosal occupational exposures to HCV: testing the source patient for antibody directed against HCV; testing the exposed health care worker at the time of exposure and at 6 months following the exposure for antibody directed against HCV and for alanine aminotransferase levels; using supplementary HCV antibody tests to confirm any positive results of HCV antibody testing; not using postexposure prophylaxis with immunoglobulin, antiviral agents, or immunomodulators; and educating the exposed worker about the risk of infection, nosocomial epidemiology, and secondary transmission as well as about strategies effective in preventing transmission of blood-borne pathogens, including hepatitis C virus in occupational settings (55).

At our institution, we monitor health care workers who have sustained occupational exposures to HCV at 2-week intervals with an HCV RNA PCR assay. In addition, anti-HCV antibody studies are performed at three-month intervals or whenever HCV RNA is detected by PCR. If an individual is found to be repeatedly positive by PCR, she or he is referred to our hepatology service for follow-up and management. This team is currently conducting a study of occupational infections and is evaluating the watchful waiting strategy outlined below.

Immunoglobulin

Unlike the case for hepatitis B infection, immunoglobulin prophylaxis is of no value in managing occupational exposures to hepatitis C. Studies conducted prior to the identification of hepatitis C as the cause of the overwhelming majority of cases on so-called non-A, non-B hepatitis suggested a possible benefit of immunoglobulin prophylaxis for the prevention of this

syndrome (177, 291, 307); however, since we have become aware of HCV as a significant cause of posttransfusion hepatitis, no study to date has demonstrated any benefit of immunoglobulin prophylaxis. Although the Advisory Committee on Immunization Practices from the Centers for Disease Control and Prevention previously recommended (for parenteral occupational exposures to patients who had non-A, non-B hepatitis) that "it may be reasonable to administer immunoglobulin as soon as possible after exposure," currently the committee actually recommends not administering immunoglobulin (53, 55).

Whereas the pooled "standard lot" immunoglobulin product once contained antibody directed against hepatitis C virus (112), plasma donors are now screened and eliminated from the donor pool if they are HCV positive. These immunoglobulin products no longer contain antibodies to HCV and thus offer even less theoretical benefit (221). In addition, in one series of experiments, neither anti-HCV-negative intravenous immunoglobulin nor immunoglobulin that contained high-titered antibody directed against hepatitis C administered 1 h after exposure to HCV-containing blood prevented transmission of HCV infection in chimpanzees (183). Finally, it should be noted that administration of intravenous immunoglobulin preparations has been incriminated as transmitting HCV in Spain, France, Italy, Scandinavia, the United Kingdom, and the United States (32, 38, 43, 52, 61, 68, 93, 108, 114, 128, 141, 142, 163, 164, 197, 203, 226, 240, 272, 276, 288, 298, 369, 370, 373). Newer approaches, such as solvent or detergent treatment and heating at low pH, have reduced the risk of HCV transmission from these products (37, 58, 289), but the clusters of infection linked to intravenous immunoglobulin treatment clearly underscore the lack of value of immunoglobulin as postexposure prophylaxis.

Immunomodulators

Despite oblique inferences in the literature suggesting the use of immunomodulating substances in the immediate post-exposure prophylaxis setting, for a variety of reasons, among them the toxicity associated with the administration of immunomodulators, the long courses of treatment needed, and a paucity of data suggesting their efficacy in the setting of post-exposure prophylaxis, to my knowledge no one has formally recommended that individuals sustaining an occupational exposure to HCV be "prophylactically" treated with immunomodulators (17). The one instance reported in the literature in which this approach was tried indicated that it was not successful in preventing infection (230). Additionally, should an effective vaccine directed against HCV infection be developed, its use would also likely become part of an effective postexposure management program (i.e., analogous to the use of the hepatitis B vaccine after occupational exposures to hepatitis B virus).

Antiviral Agents

As yet, other than alpha interferon, no agents with clearly defined antiviral activity (as opposed to immunomodulatory activity) are either marketed or in late-stage development for the treatment, preemptive therapy, or prophylaxis of hepatitis

C. Agents with antiviral properties (e.g., specific protease, helicase, and polymerase inhibitors) are in development, as noted above. In the absence of data about the efficacy of these and other compounds in the postexposure setting, no recommendation can be made about their potential use for postexposure prophylaxis. Should compounds that are relatively safe and have efficacy against HCV be developed, this subject should clearly be revisited, especially in light of the animal and human data developed over the past decade demonstrating that antiviral compounds are likely effective in preventing occupational infection with human immunodeficiency virus (summarized in reference 144).

Preemptive Therapy versus Watchful Waiting

One postexposure strategy that has been advocated by some authorities working in this field (and parenthetically, a strategy that is in relatively widespread use in the United States [17]) involves the periodic monitoring of health care workers who have experienced occupational exposures by PCR for HCV RNA at approximately 2-week intervals following the exposure and aggressive implementation of interferon therapy if HCV infection is documented to have occurred, as measured by repeated positive RNA assays for HCV in the serum of the exposed health care provider (preemptive therapy of documented early HCV infection). Schiff, in an editorial in *Hepatology*, first suggested this strategy in 1992 (295). One can marshal a substantial intellectual argument that this strategy is sensible, in that therapy would be initiated at a time when one would likely be dealing with one or only a limited number of HCV quasispecies and when nonspecific stimulation of the cellular immune system might be of maximal benefit.

Other investigators have argued for a "watchful waiting" strategy. Following this line of thinking, clinicians would monitor the exposed health care worker biweekly by PCR and then monitor those who develop viremia over time to see if chronic infection develops. One suggestion has been to treat only individuals who remain positive for HCV RNA by PCR and have elevated alanine aminotransferase levels 2 to 4 months into the course of their infections (6, 154). Under this scenario, individuals who spontaneously resolve their infections would be spared the toxicities (and the expense) (154) of lengthy courses of interferon. Nonetheless, in the most recent National Institutes of Health Consensus Conference on the Management of Hepatitis C Infection (304), Alberti et al. concluded that the currently available evidence base supports the treatment of individuals who have acute hepatitis C (6). He points out, however, that the current evidence does not permit clear identification of which patients should be treated, when therapy should be initiated, or what regimen should be chosen for treatment (6).

Despite the interesting and very encouraging data addressing the efficacy of early pharmacological and immunomodulatory intervention to treat acute HCV infection (summarized above), we do not have data, at least as yet, definitively establishing the ability of this interventional strategy to manage occupational exposures to HCV. Based on our experience with HIV postexposure prophylaxis, such information may be extremely difficult to obtain, both because of health care workers' unwillingness to participate in placebo-controlled trials (S. W.

LaFon, B. D. Mooney, and J. P. McMullen, 30th Intersci. Conf. Antimicrob. Agents Chemother., 1990) and because occupational HCV transmission events are sufficiently rare and sufficiently complex to require a very large population in both arms of a placebo-controlled trial to achieve statistical significance (17, 145).

Several anecdotal reports have reported the success of the preemptive therapy approach to the management of occupational HCV exposures (18, 237, 241, 331, 358). Unfortunately, as is the case with almost all infectious diseases, not all of the case reports demonstrate success (230). The case report describing failure of a postexposure interferon intervention may be instructive nonetheless. In this case, an individual sustained a deep needle stick exposure to blood from a patient known to have chronic HCV infection. In an attempt to prevent transmission of HCV, the individual was given true postexposure prophylaxis with alpha interferon, 5 MU per day intramuscularly for 4 days, beginning the day of the exposure (230). By 1 month following the exposure, the individual had elevated aminotransferase levels and was positive for HCV RNA by PCR (230). At 11 weeks following the exposure, the patient's anti-HCV antibody test became positive, and at 6 months after the exposure, a liver biopsy demonstrated chronic persistent hepatitis. The patient was subsequently treated with a 6-month course of alpha interferon (total dose, 720 MU) and became disease free and PCR negative for a year of follow-up (230). In this case, postexposure prophylaxis with interferon for 4 days was not successful, whereas the watchful waiting approach of treating established infection for 6 months to 1 year resulted in a favorable outcome. Conversely, in some of the cases described in the literature, individuals who had reproducibly positive HCV RNA tests were treated immediately (and successfully) upon identification of the viremia, in some instances without the exposed individual's ever seroconverting to HCV antibody positivity (224).

The lessons learned from the treatment of acute HCV infections (see above) may be relevant to the use of preemptive therapy; however, the data should be interpreted with caution for a variety of reasons. First, as noted above, we do not yet have a clear understanding of the complex early events in the pathogenesis of HCV infection that determine the outcome of HCV infection. Specifically, we do not know what fraction of individuals who are infected with the small inoculum on a needle will mount a brisk cellular immune response, completely resolving the infection without ever developing antibody against HCV-associated antigens (5, 161, 224, 332). Investigators need to gain much more insight into the early events in HCV infection in order for us to understand the pathogenesis, immunopathogenesis, and appropriateness and efficacy of immunomodulating interventions in the postexposure management setting. Second, a substantial fraction of individuals who are infected with HCV via transfusion spontaneously clear the infection despite the arguably large inoculum of virus received. Seeff and colleagues found that more than 20% of patients who acquired transfusion-associated HCV infection cleared the infection spontaneously (303). Administering interferon to all individuals detected as having circulating HCV by PCR would unnecessarily expose the 20% of individuals who will spontaneously clear the infection to the toxicities of the agent with no potential benefit. For individuals

who develop the acute HCV hepatitis syndrome, as many as 50% (or perhaps even more) may recover spontaneously (6, 127, 188, 242, 353).

Third, information about the treatment of acute hepatitis may only be relevant to individuals who present with this relatively unusual form of HCV infection. As noted above, individuals who develop acute hepatitis have higher rates of spontaneous resolution of the infection, and these individuals, as a group, make more robust humoral and cellular responses to viral antigens. Fourth, available information on which a decision to base therapy would rely is limited to the anecdotal evidence described above and the studies of the therapy of acute infection (most of which are un- or poorly controlled). Fifth, the use of immunomodulating agents in the postexposure prophylaxis setting is substantially different from the use of antiviral agents directed against specific viral targets (compared with postexposure prophylaxis for HIV exposures, where antiretrovirals are the mainstay of therapy). Sixth, some individuals have suggested that administering interferon before the infection is established, and therefore before the cellular immune response has begun in earnest, might be ineffective (6, 29, 133, 246). In fact, in one instance in which a short course of alpha interferon was administered prophylactically (i.e., immediately after a needle stick injury), the recipient went on to develop acute HCV infection (230).

Despite all these limitations, and despite the absence of U.S. Public Health Service support for such an approach, a substantial proportion of institutions in the United States have adopted either the preemptive therapy or watchful waiting approach to the management of occupational exposure to HCV (17). Both the preemptive therapy and watchful waiting models represent entirely reasonable approaches to the management of occupational HCV exposure based on the currently available information. From my perspective, monitoring for viremia by PCR, monitoring hepatic function by alanine aminotransferase levels, and then making the decision whether to intervene from the clinical and chemical data obtained represent a far superior approach to postexposure management than the 3-month to 6-month antibody testing previously recommended for follow-up of these exposures (29, 53, 55). As noted above, the watchful waiting strategy is the approach to this problem that is currently taken in my institution.

PRIMARY PREVENTION

Standard Universal Precautions and Exposure Avoidance

No discussion of prevention would be complete without emphasizing primary prevention activities in the health care setting. Perhaps the best strategy to prevent occupational and nosocomial transmission of all blood-borne pathogens is to prevent health care worker injuries and occupational exposure to blood (124). To minimize the bidirectional risk of blood-borne pathogen transmission, health care providers should follow standard universal precautions (50, 51, 121). Effective use of these precautions, which have been shown to be effective in reducing occupational exposures to blood (26, 101), will substantially reduce blood exposures and thus the risk for transmission of HCV in either direction. Elements of these precautions (summarized in detail in references 50, 51, and 121)

include hand hygiene, use of protective barriers (especially gloves), and attention to the appropriate use and disposal of needles and other sharp objects. Numerous strategies have been shown to be effective in reducing occupational injuries, including educating staff about the occupational risks prevalent in the health care workplace, modifying procedures and work practices that are intrinsically risky, and monitoring adherence to standard universal precautions (26). Institutions should also continually scan the health care marketplace for devices and technological advancements that can be used to reduce occupational risk. Furthermore, institutions should collect data about all occupational exposures and use these data to reduce exposures. Finally, the appropriate use of vaccines, (e.g., hepatitis B vaccine) is also a key part of primary prevention.

Active Immunoprophylaxis and Vaccine Development

The hepatitis B vaccine significantly reduced the occupational risk of transmission of this blood-borne pathogen in the health care setting. Clearly, the development of a vaccine for hepatitis C virus infection would represent a major advance and would have a similarly substantial impact on occupational risk for HCV infection in health care. Nonetheless, in 2002, there are still many barriers to the development of an HCV vaccine (summarized in references 115 and 258). Among these challenges are the heterogeneity of isolates, the virus's ability to modify envelope (and other) proteins rapidly in the face of immunological pressure, incomplete understanding of the pathogenesis and immunopathogenesis of HCV infection, the likely need to develop a vaccine that stimulates both humoral and cellular immunity against HCV, and the inability to culture the virus (115). Although several investigators are aggressively pursuing a variety of approaches to vaccine construction, no clear candidate is even on the distant horizon.

MANAGING HCV-INFECTED PROVIDERS

Transmission of HCV from health care providers to patients has been reported infrequently, although several instances of iatrogenic transmission have been reported in the past few years, primarily in the United Kingdom (discussed in detail above) (35, 36, 41, 71, 90, 97, 259–261, 263–265, 286). As is the case for health care worker who carry other blood-borne pathogens, chronically HCV-infected workers are unlikely to transmit infection during routine (i.e., noninvasive) patient contact. In addition, the risk for provider-to-patient HCV transmission during the performance of “invasive” procedures is very small and is likely to be intermediate between the remote risk of HIV transmission and the small but measurable risk of transmission of hepatitis B (27). Based on the experience in the United States to date, transmission from infected providers to their patients is likely to occur very uncommonly, will likely be associated with clear instances of exposure of patients to providers' blood, and will likely also be associated with providers who have relatively higher circulating titers of HCV RNA.

Because of an increasing number of instances in which provider-to-patient transmission of HCV has been documented in the United Kingdom, practice restrictions have now been implemented for HCV-infected providers (79, 80, 151, 262); how-

ever, not all authorities in the United Kingdom believe that these restrictions are warranted (70). In the United States, neither the Public Health Service (49) nor professional organizations have recommended restricting the practices of health care workers who perform so-called invasive procedures (149). Discounting the experience in the United Kingdom, such restrictions seem unnecessary unless transmission has been definitively linked to an individual provider. If the experience in the United Kingdom is ultimately shown to represent the risks accurately and the risk of iatrogenic transmission is substantially larger than it currently appears to be in the United States, the issue of managing HCV-infected providers will clearly need to be revisited by public health officials. As is the case for all instances of managing providers infected with blood-borne pathogens, each provider should be evaluated individually.

The existing public health guidelines for managing providers infected with blood-borne pathogens were primarily designed to address the risks of hepatitis B and HIV infection. Because so little was known about the risks for HCV transmission at the time of their creation, little is said about the management of HCV-infected providers (summarized in detail in reference 147). These guidelines did, however, suggest that health care providers who were high-titered carriers of hepatitis B virus or infected with HIV notify “prospective patients of the health-care worker's seropositivity before they undergo exposure-prone invasive procedures” (49). The guidelines did not define “exposure-prone invasive procedures”; rather, they summarized the characteristics of procedures that might be considered exposure prone (49). Ultimately, after considerable discussion in the health care community, each state was encouraged to consider this problem independently, and many states crafted guidelines, resulting in uneven guidelines for this circumstance across the country.

The issue of blood-borne pathogen-infected providers is an extremely difficult one, both for medicine and for society. The risk for transmission of these pathogens to patients is miniscule; however, the consequences of transmission may be substantial. To craft a sensible approach to this problem, medicine needs more information than is currently available, including better quantification of the magnitude of risk for provider-to-patient transmission of these blood-borne pathogens; factors that might be used as intervention or prevention strategies that might lessen the risk for patient exposures and, therefore, patient infections; a clearer understanding of the ethics of this complex issue; and definitive understanding of the sociopolitical and legal consequences of issuing either restrictive or non-restrictive guidelines (147). At the time this article is being written, none of these questions can be answered definitively.

Perhaps most perplexing among these difficult questions are the ethical, legal, and sociopolitical issues associated with managing HIV-infected providers. Basically, we find ourselves in a circumstance in which the rights of the practitioner (i.e., medical privacy, right to practice) intersect directly with the rights of the patient (147). Arguments of substance have been made on both sides of this issue, and society continues to wrestle with this difficult problem (summarized in reference 147).

Our society manages risk and even perceives risk in a less than even manner and is willing to accept voluntary risks (some of which are not truly voluntary) while eschewing so-called involuntary risks. For example, some individuals elect to

smoke, to drive automobiles, and to consume alcohol. Some talk on cellular telephones while driving. These voluntary risks are often accompanied by hidden involuntary risks. One cannot determine, for example, how much alcohol the person driving on the other side of the road or immediately behind you on the road has consumed. Instances of transmission of blood-borne pathogens from infected providers to their patients (despite their rarity) serve as lightning rods in society. These cases receive wide publicity and often provoke almost visceral responses among members of society at large.

I would be remiss in not mentioning a fundamental principle of health care provision, *primum non nocere*, that is, that providers first do no harm. A major difficulty for medicine and society is the need to place the potential for harm associated with allowing an infected provider to practice in the appropriate perspective. Virtually every aspect of health care is associated with risks (some of them less well defined, and likely substantially larger, than the provider-to-patient transmission risk). Restricting the practices of infected providers because of risks that society considers negligible in other circumstances may have other significant adverse effects (147). This extremely complex issue needs excellent public health and political leadership for resolution. As additional information about these risks and the factors that might influence or reduce them becomes available, the public health leadership should revisit the issue. Leadership must develop a balanced, science-based analysis of all these risks for society and for political leaders (147).

In deciding about the management of infected providers, several additional issues should be considered. First, provider-to-patient transmission accounts for only a minimal part of the burden of illness attributable to these viruses (124). Mandatory practice restrictions could result in a disincentive to surgeons and others conducting invasive procedures to treat infected patients (124). As noted above, the most effective method for preventing transmission is preventing parenteral exposure. Treatment of infection (e.g., antiretroviral therapy for HIV and immunomodulator therapy for HCV) may also decrease iatrogenic risks for transmission by lowering circulating viral burdens (although this concept has not been definitively demonstrated in the postexposure prophylaxis setting). One codicil should be inserted, however, about therapy of blood-borne pathogen infections in health care providers. The administration of these agents to health care providers may result in toxicities that lead to impaired performance, at least over the short run. This statement is particularly germane to long-term interferon therapy for hepatitis C infection.

Finally, one should also consider the fact that many, if not all, of the successful prevention strategies currently in place were not being used at the time the risk estimates for iatrogenic transmission of hepatitis B virus, HCV, and HIV were developed. Use of these prevention strategies should substantially reduce the already extremely small risks for provider-to-patient transmission of these blood-borne pathogens.

CONCLUSIONS

Information gleaned from the past 15 years' investigation of hepatitis C has yielded a better understanding of the virology, natural history, immunological responses, and therapy of acute and chronic hepatitis C infections. These data are now being

incorporated into management strategies for health care workers who are occupationally exposed to hepatitis C. Furthermore, the past 15 years have seen the accurate characterization of the nosocomial epidemiology and the magnitude of risk associated with occupational exposure to hepatitis C in the health care workplace.

Because data demonstrating the efficacy of any intervention are not yet available, no definitive recommendations can be made about the use of immunomodulating therapy for health care workers who are exposed to hepatitis C. Based on data gleaned from a variety of other relevant settings, however, the preemptive therapy and watchful waiting strategies outlined in this article represent reasonable interim approaches to this complex problem, at least until more definitive data become available.

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