A Potential Hidden Source of Hepatitis C Infection Among Noninjecting Drug Users†

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Abstract—Hepatitis C virus (HCV) is a major cause of chronic liver disease in the United States and worldwide. It is primarily transmitted through blood-to-blood contact with an infected individual. HCV is hyperendemic among injection drug users (IDUs), who contract the virus through contaminated syringes and drug preparation equipment shared with other IDUs. The prevalence of HCV is also high, to a lesser degree, among noninjection drug users, many of whom report no identifiable HCV risk exposures. This article reviews the epidemiological and virological evidence bearing on a potential hidden source of HCV infection among noninjection drug users: namely, the oral or intranasal transmission of HCV through the sharing of noninjection drug-use implements such as pipes or straws. While there is some epidemiological evidence supporting both oral and intranasal HCV transmission, most studies are hampered by methodological limitations. Thus, there is a need for prospective studies designed specifically to examine these potential routes of transmission. Current biological evidence does not refute either oral or intranasal transmission as possible sources of HCV infection, although more research is needed in the areas of oronasal HCV pathogenesis and the detection of HCV RNA in the nasal mucosa of intranasal drug users.

Keywords—HCV transmission, hepatitis C virus, intranasal drug use, noninjection drug use, review

Chronic active hepatitis C is a mildly symptomatic and slowly progressive illness that can lead to severe liver disease, including cirrhosis and the development of hepatocellular carcinoma, within two to three decades of infection (Ebeling 1998; Alter et al. 1992). There is no known cure or vaccine, and current therapeutic treatments have shown limited efficacy. The prevalence of hepatitis C virus (HCV) among the general population in the United States has remained relatively constant at roughly 2.0%, with about 25,000 new infections occurring annually (CDC 2002; Alter et al. 1999; McQuillan et al. 1997). However, HCV is hyperendemic in certain sectors of the population, most notably among injection drug users (IDUs) and hemophiliacs who received a blood transfusion prior to 1992. This pattern of endemicity reflects the known etiology of the virus—it is primarily transmitted parenterally through blood-to-blood contact. Several studies have reported low

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levels of suspected nonparenteral HCV transmission through sexual contact and the sharing of household implements (Wejstal 1999; Caldwell et al. 1995).

Although much is known about the transmission of HCV, a substantial proportion of infected individuals report no identifiable source of exposure. This is particularly true of drug users who have never injected and report no other risk factors for HCV (Tortu et al. 2001; Flamm, Parker & Chopra 1998). This article reviews the evidence surrounding a potential hidden source of HCV infection among noninjecting drug users: namely, the transmission of HCV through the sharing of noninjection drug use implements, such as pipes, straws and spoons.

KNOWN ROUTES OF HCV TRANSMISSION

By far the strongest risk factors for HCV infection are related to injection drug use. Syringes shared among IDUs can transmit viral-contaminated blood to uninfected individuals (Robinson, Reynolds & Robinson 1995), and recent studies indicate that HCV transmission can also occur through shared injection drug preparation equipment, such as cookers, filters and rinse water (Hahn et al. 2002; Thorpe et al. 2002; Green et al. 2001; Hagan et al. 2001). Currently, about 60% of all new cases of acute HCV infection in the United States can be attributed to injection drug use (CDC 1998; Alter 1997).

Other parenteral modes of HCV transmission account for substantially fewer infections. Acquisition of HCV from blood transfusion, once a major source of infection, has become rare since donor screening for viral hepatitis C was introduced in 1992 (Kleinman & Busch 2000; Holland 1996). Tattooing and body piercing with improperly sterilized needles are also potential modes of viral transmission, but few studies have shown these to be significant predictors of HCV infection in U.S. populations (Alter 1999; Flamm, Parker & Chopra 1998; Conry-Cantilena et al. 1996). Purported nonparenteral routes of HCV transmission, such as through sexual or household contact, have been reported in several studies, but the efficiency of these routes of transmission is apparently quite low (Terrault 2002).

UNEXPLAINED HCV CASES

Despite the growth of awareness concerning the routes of HCV transmission, a substantial proportion of anti-HCV reactive individuals report no known source of infection. Early estimates that 40% or more of all acute HCV cases had no identifiable source of infection tended to discount nonpercutaneous routes of transmission (Zeuzem et al. 1996; Alter et al. 1989). Revised estimates, which take into account a broader spectrum of risk factors, tend to be much lower. Yee and colleagues (2001) found that seven of 148 (4.7%) HCV seropositive patients from two clinical care centers reported lack of exposure to any known sources of infection. In a study involving 301 consecutive patients with chronic HCV, Flamm, Parker and Chopra (1998) found that 12% had no history of risk exposure. These data have generally been interpreted in one of two ways: either the study participants have not accurately reported their past exposure history, or at least one as-yet unidentified source of HCV infection is present.

INACCURATE REPORTING OF HCV RISK FACTORS

The notion that unexplained HCV cases, especially among drug users, are due to nonreporting of previous percutaneous (i.e., skin piercing) exposures deserves serious attention (Alter 1999). Due to its stigmatized nature, past or present drug injection may be underreported in certain contexts. Conry-Cantilena and colleagues (1996) noted that many of the blood donors who participated in their study had not been forthright about their past injection drug use at initial screening. The high frequency of intravenous drug use was unexpected, since these participants had denied such use when they were questioned directly about it at the time of their blood donations" (p. 1693). Similarly, Flamm, Parker & Chopra (1998:599) uncovered previously unreported risk factors in a sample of 301 patients with chronic HCV infection, and noted that "[i]n nearly all cases, the initially unreported risk factor for HCV transmission was a remote history of IVDU." These observations highlight the importance of the methods used to obtain drug use histories and other stigmatized behaviors. This is supported by research showing that self-reported injection drug use is reliable under appropriate conditions and methods of data collection (Darke 1998; Goldstein et al. 1995; McElrath et al. 1994).

UNIDENTIFIED SOURCES OF HCV INFECTION

An alternative hypothesis is that unexplained cases of HCV derive from a source or sources of HCV infection that have not yet been identified. Potential hidden sources of HCV infection among noninjecting drug users may include the sharing of drug use implements such as pipes and straws. These implements may come into contact with blood or other bodily fluids in the nose and/or mouth and, ostensibly, serve as conduits through which HCV and other pathogens travel from person to person. It is important to keep in mind that the potential routes of intranasal versus oral transmission of HCV are biologically and behaviorally distinct, and this distinction is not always acknowledged, especially in epidemiological studies.

Epidemiological Evidence

One of the first studies to examine noninjection drug-use behavior as a potential risk factor for HCV was

performed by Conry-Cantilena and colleagues (1996; see also Alter et al. 1997). These investigators found that among 481 U.S. blood donors the likelihood of HCV infection was eight times greater among donors who reported a history of intranasal cocaine use than among those who reported no such drug use, after controlling for other significant risk factors. This finding suggested that cocaine sniffing may be associated with some form of risk behavior for HCV acquisition, presumably nasal-to-nasal transference of HCV-contaminated blood or other secretions carried in an implement such as a straw shared by two or more users.

A similar finding has been reported by Ladron-de Guevara and colleagues (2002) in a study of HCV prevalence and risk factors among 41,957 blood donors in Mexico City. These investigators determined that a history of intranasal cocaine use was an independent risk factor for HCV infection in multivariate analysis.

Alter and colleagues (1999) performed anti-HCV testing on 21,241 participants in the third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 through 1994. Among subjects 17 to 59 years of age, the strongest risk factors associated with HCV infection were lifetime use of cocaine or marijuana. However, the NHANES III survey did not collect data on injection drug use, and the observed association between cocaine or marijuana use and HCV infection may be due to a greater number of IDUs among respondents reporting the use of these drugs compared to those with no reported use. Moreover, cocaine may either be sniffed or smoked and no distinction was made between these two methods of drug administration.

In a recent case-control study of 1,797 blood donors, Murphy and colleagues (2000) evaluated a series of risk factors for HCV infection, including the use of "inhaled drugs." Although drug inhalation was a significant risk factor in the univariate analysis (even when controlling for IDU status), it did not retain significance in the final multiple regression model reported by these authors. However, the use of "inhaled drugs" does not necessarily involve the transference of bodily fluids, such as when vapors from cooked heroin are inhaled (i.e., "chasing the dragon"). Moreover, the term "inhaled drugs" conflates potential intranasal transmission of HCV via shared straws and oral transmission through shared pipes.

With regard to potential oral transmission of HCV through noninjection drug use, Roy and colleagues (2001) examined lifetime risk factors and anti-HCV reactivity among 437 itinerant street youths in Montreal, and found that smoking crack cocaine was an independent predictor of HCV infection, after controlling for injection drug use, tattooing and other risk factors.

A limitation common to all of the aforementioned studies is that none measured the *sharing* of noninjection drug use implements; nor did the studies examine both intranasal and oral routes of transmission according to the type of drug used. To overcome these limitations, Tortu and colleagues (In press) administered an HCV risk questionnaire to a sample of 123 women drug users from East Harlem, all of whom were participants in a larger study on the social context of HIV risk behavior (Tortu et al. 2000). The questionnaire included items on lifetime sharing of noninjection drug-use implements with IDU and non-IDU partners, categorized by implement, mode of drug ingestion, and type of drug shared. The women in this sample all underwent voluntary testing for HIV and hepatitis B and C, and reported no history of drug injection. Twenty-four (19.5%) of the 123 women tested anti-HCV positive. Multiple logistic regression analysis revealed that a history of sharing both oral and intranasal noninjection drug use implements was a significant predictor of HCV infection, after accounting for other known routes of HCV transmission. The study further revealed that HIV seropositivity moderated the association between HCV infection and sharing noninjection drug use implements, suggesting that HIV may facilitate the transmission of HCV through noninjecting routes (Tortu et al. In press). However, limitations to this study included the use of a cross-sectional design, and a small sample size affording limited power.

Another body of epidemiological research concerning potential oral transmission of HCV comes from the dental health care profession. Several early studies showing higher than expected prevalence of HCV infection among dentists in New York City (1.8% versus 0.14% in controls) and elsewhere raised the possibility of oral transmission (Tibbs 1995; Klein et al. 1991). Most subsequent studies, however, have found no elevated occupational or nosocomial risk of HCV infection among dental health care workers (e.g., Porter & Lodi 1996; Hindy, Abdelhaleem & Aly 1995). Given the ubiquitous use of universal precautions against viral hepatitis by Western dentists and oral surgeons, this finding is not unexpected. Olubuyide and colleagues (1997) documented a high prevalence of HCV among physicians and dentists at a Nigerian hospital, and most reported using universal precautions in fewer than 50% of patient procedures. Currently, there is little consensus regarding an efficient oral route of HCV transmission to oral health care workers.

Virological Evidence

Although epidemiological evidence suggests that noninjection drug use may be a risk factor for HCV infection, certain virological preconditions must exist for drug-related oral or intranasal HCV transmission to occur. HCV RNA must be present in the oral or nasal secretions of infected individuals. If present, the source of HCV RNA in oronasal fluids may be due to blood spillover from lesions (parenteral) or from exocrine secretions directly (nonparenteral). This distinction has important consequences for the potential efficiency of HCV transmission through oral or nasal routes. If HCV pathogenesis is limited

to parenteral transmission, then both the infected individual and the potential host must present with oral or intranasal hemorrhage for transmission to occur. However, if HCV RNA replication occurs in exocrine glands and is released in oronasal secretions, then oral or intranasal hemorrhage is not required for transmission. Since the virological evidence concerning these issues is distinct for oral versus intranasal HCV transmission, each will be discussed separately.

HCV in saliva and potential oral transmission. Due to concerns regarding HCV transmission among dental health care professionals, much research has been conducted on the biological plausibility for oral transmission of HCV. There is now abundant evidence indicating that HCV RNA is present in the salivary fluid of many (between 15% to 52%) plasma-positive individuals (Hermida et al. 2002; Maticic et al. 2001; Rey et al. 2001; Kage et al. 1997; Taliani et al. 1997; Tang et al. 1996; Chen et al. 1995; Liou et al. 1992). The detectability of HCV RNA in saliva has been correlated with increased plasma viral load (Hermida et al. 2002), although levels of HCV viral titer in saliva are generally much lower than those detected in serum samples (Rey et al. 2001; Taliani et al. 1997). However, no conclusive data exist as to the threshold concentration of HCV required for transmission (Memon & Memon 2002; Nowicki & Balistreri 1995).

While the presence of HCV in oral secretions is unequivocal, debate continues as to the source of salivary HCV. Viral spillover from blood is one confirmed source (Maticic et al. 2001; Talaini et al. 1997), but a recent study by Arrieta and colleagues (2001) using in situ hybridization techniques also established that HCV infects and replicates in the salivary glands of viremic patients (Arrieta et al. 2001; but see Taliani et al. 1997). In addition to detecting HCV in salivary fluid, Maticic and colleagues (2001) reported the presence of HCV RNA in gingival crevicular fluid (GCF), and suggested that GCF was a potential additional source of HCV in the saliva of infected individuals.

HCV infection has been associated with a number of oral diseases, including oral lichen planus, Sjögren's syndrome, and chronic sialadenitis (Biasi et al. 1995; Aceti et al. 1992). Although the role of HCV in the progression of such oral manifestations is not well understood, many are characterized by lesions and bleeding sores which might facilitate parenteral oral transmission of HCV (Arrieta et al. 2001).

HCV in nasal mucosa and intranasal transmission. In stark contrast to the extensive literature on the potential for oral HCV transmission, there is a conspicuous absence of biochemical evidence related to intranasal transmission of HCV. To the authors' knowledge, no studies have been published that attempt to detect the presence of HCV RNA in the cells of nasal mucosa or nasal mucus secretions of HCV seropositive patients. However, the adverse effects on the nasal passages stemming from chronic intranasal drug use are well documented (Smith, Kacker & Anand 2002). The association between intranasal cocaine use and epistaxis (i.e., bleeding from the nose) is complex, since cocaine is both an irritant and a vasoconstrictor; it is perhaps the most commonly applied topical drug for the clinical prevention and cessation of nosebleeds (Feehan, & Mancusi Ungaro 1976). A survey of volunteer blood donors in Maryland and Minnesota revealed that a history of intranasal cocaine use was common (10.4% and 7.2%, respectively); and although most drug users had shared implements, few reported instances of drug-related epistaxis. It is clear, however, that the frequency of drug-related epistaxis is related to degree of previous damage to nasal tissue. For example, a study of 464 adolescents enrolled in seven drug treatment facilities around the U.S. found that 30% of those who had sniffed cocaine less than daily, versus 47% of those who sniffed the drug daily, reported nasal membrane irritation with nasal scabs, recurrent nosebleeds, or both (Schwartz et al. 1989).

SUMMARY

Despite a growing awareness of the routes of HCV transmission, a substantial proportion of HCV cases have no identifiable source of infection, especially among noninjection drug users. One explanation is that past and present HCV risk exposures may go unreported in epidemiological surveys. Underreporting of injection drug use, often a stigmatized behavior, may occur due to respondent misrepresentation, inaccurate recall of injection-related behavior, or inadequate questionnaire methodology. Research has shown, however, that a careful history taken in the proper setting may uncover many previously unreported HCV risk exposures, and that unexplained HCV cases persist even in these settings.

Another explanation is that unexplained cases of HCV derive from a source or sources of infection that have not yet been identified. Potential hidden sources of HCV infection among noninjection drug users may include oral or intranasal transmission through the sharing of viral-contaminated implements such as pipes and straws. Epidemiological studies have shown the use of noninjection drugs (e.g., crack, cocaine, heroin and marijuana) to be risk factors for HCV infection. However, most of these studies are hampered by various methodological limitations, including: (a) inadequate screening for past or present HCV risk exposures, (b) inadequate measures of noninjection drug use and implement sharing, (c) failure to distinguish between oral and intranasal routes of HCV transmission, and (d) use of cross-sectional design or research methods not specifically designed to assess oral or intranasal HCV transmission. Small sample sizes and limited statistical power have also been a limitation in several studies.

Whereas most of the epidemiological studies that have examined noninjection drug use risk factors have focused

on potential intranasal routes of HCV transmission (with far less attention paid to possible oral transmission), the opposite is true of biological studies. Virological evidence related to potential oral transmission of HCV is extensive, whereas similar research into potential intranasal transmission is virtually nonexistent. A few recent studies have shown that HCV RNA infects and replicates in extrahepatic cells, such as in salivary gland and sweat gland epithelia. This finding suggests the plausibility of nonparenteral oral transmission of HCV through viral-contaminated saliva. Although virological studies have reported lower hepatitis C viral titer in saliva compared to blood, the relationship between viral titer and HCV transmission efficiency is not yet understood. The observed association between oral disease manifestations and salivary HCV RNA may indicate an increased potential for parenteral oral HCV transmission. Similarly, frequent epistaxis resulting from nasal mucosa damage caused by chronic intranasal drug use indicates the potential for parenteral intranasal HCV transmission. Virological data pertaining to potential nonparenteral intranasal transmission of HCV is, at present, unavailable.

Current evidence neither confirms nor invalidates the existence of oral or intranasal drug-related HCV transmission. Resolution of this question has significant implications for HCV prevention, drug treatment and harm reduction programs, and blood donor screening policies. Still, major gaps in research exist with regard to these potential sources of HCV infection.

FUTURE RESEARCH DIRECTIONS

Although inconclusive, current epidemiological and virological evidence warrants the support of further research in this area. The preceding review clearly shows that epidemiological evidence bearing on the issue of noninjection drug-related HCV transmission obtain mostly from studies designed to address other research objectives. There is a need for research designed specifically to address the question of oral and intranasal drug-related HCV transmission. More research is also needed regarding the virologic and pathogenic parameters required for oronasal transmission of HCV. Most urgent is the need to understand cell-specific viral titer thresholds required for HCV transmission. Special attention should also be paid to the detection of HCV RNA in the nasal mucus and epistaxis of plasma-positive drug sniffers, as well as the potential for infection and replication of HCV RNA in the nasal mucosa.

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