torical control group of the last 50 consecutive patients with cirrhosis and sepsis in whom adrenal function was not assessed and no steroid therapy was given. All patients were treated with a standard protocol that differed only in the assessment of adrenal function and included antibiotic therapy, central venous and urinary catheterization, goal-directed plasma volume expansion and vasopressor therapy, albumin administration in cases of spontaneous bacterial peritonitis, and continuous venovenous hemofiltration and mechanical ventilation as indicated.

Within the prospective cohort, 17 of 25 patients had RAI. A trend toward higher rates of RAI in patients with Child–Pugh class C cirrhosis was noted ($P = .08$), although no statistically significant differences in clinical characteristics were identified between patients with and without adrenal insufficiency. Compared with historical controls, patients in the prospective cohort had similar baseline clinical characteristics, except for a statistically significant lower serum albumin concentration (2.3 ± 5 g/dL vs 2.7 ± 5 g/dL; $P < .05$). Clinically important outcomes were improved in the prospective cohort compared with controls, including resolution of shock (96% vs 58%; $P = .001$), time to shock resolution (48% vs 18% within 48 hours of ICU admission; $P = .01$), ICU and hospital survival (68% vs 38% [$P = .03$]; 64% vs 32% [$P = .003$], respectively). Two patients treated with hydrocortisone died of fungal infection; no other serious adverse events were reported in the hydrocortisone treatment group.

Comment. The sepsis syndrome is a major precipitant for acute-on-chronic liver failure, thereby leading to hypotension, worsening hepatic function, hepatorenal syndrome, multisystem organ failure, and death (Gut 2005; 54:718–725). Broad-spectrum antibiotic therapy and early goal-directed therapy (with target values for targets for central venous oxygen saturation, central venous pressure, and mean arterial pressure) have been demonstrated to improve short-term survival in patients with sepsis not necessarily associated with cirrhosis (N Engl J Med 2001; 345:1368–1377). Strategies for the management of septic shock need to be prospectively evaluated in patients with liver disease, among whom infection remains a major cause of death.

The hemodynamic derangements of cirrhosis mirror those of septic shock and adrenal insufficiency. Recent data have emerged regarding the association of RAI in patients with liver dysfunction and sepsis. In patients with acute liver failure, RAI was present in 62% of patients and was associated with lower transplant-free survival (Hepatology 2002;36:395–402). A series of cirrhotic patients with septic shock revealed that RAI was present in 51.5% of patients and was associated with significantly higher ICU and hospital mortality rates. Cumulative 90-day survival rates were 15.3% and 63.2% in adrenal-insufficient and normal adrenal function groups, respectively (Hepatology 2006;43:673–681).

The rates of RAI reported by Fernández et al were similar to, if not higher than, previously reported rates. In concordance with prior reports, RAI was more common in patients with more advanced liver disease. Whether this is directly related to impaired hepatic cholesterol synthesis and steroid metabolism, the proinflammatory cytokine milieu, or whether adrenal insufficiency is simply a marker of multisystem organ failure remains unclear. That RAI is frequently present in patients with acute liver failure without evidence of sepsis (Hepatology 2002;36:395–402) suggests that hepatocellular dysfunction may play a significant role. Notably, a specific bacterial etiology for the sepsis syndrome was not identified in 36% and 24% of patients in the prospective and control groups, respectively. The role of RAI and steroid therapy in cirrhotic patients with noninfectious precipitants for the systemic inflammatory response syndrome (such as gastrointestinal hemorrhage or surgery) remains to be determined.

Although the overall mortality rate was improved in patients receiving steroid therapy, 2 of 17 patients receiving hydrocortisone therapy developed fatal fungal infections. The site of infection and portal of entry was not reported by the authors. A prior study utilizing higher doses of steroid replacement (hydrocortisone 300 mg/d) reported an increased rate of resistant bacterial infections (Liver Int 2003;23:71–77). No resistant bacterial infections were noted in the current study.

The major limitation of the current study is the absence of a contemporary, blinded, placebo-controlled arm. Although the use of clinical management protocols in a single, specialized liver ICU minimized the variability in care between the prospective and historical cohorts, it is possible that the improved survival in the contemporary (prospective) cohort may be due to an unidentified factor other than adrenal replacement therapy. Although this study provides valuable insight into the care of the septic cirrhotic patient, the results need to be validated in a larger, multicenter, placebo-controlled trial before routine use of hydrocortisone for RAI in cirrhotic patients with sepsis can be recommended.

WILLIAM SANCHEZ
PATRICK S. KAMATH

SEX, DRUGS, AND HEPATITIS C VIRUS IN MEN WHO HAVE SEX WITH MEN: EVIDENCE FOR PERMUCOSAL TRANSMISSION

Danta M, Brown D, Bhagani S, et al. **(HIV and Acute HCV group, UCL Institute of Hepatology, Royal Free and University College Medical School, London, En-**

gland). Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS 2007;21:983–991.

New acquisition of hepatitis C virus (HCV) at present is most strongly linked to injection drug use (IDU). For a given person with human immunodeficiency virus-1 (HIV-1), another blood-borne virus, the risk of HCV is much higher for those with IDU as a risk factor than for those who acquired HIV-1 by sexual routes. This phenomenon is attributed to the inefficiency of permucosal infection by HCV. However, several outbreaks of HCV among HIV-1–infected men who have sex with men (MSM) have been reported in the past few years, identifying a novel subgroup of individuals at risk for incident HCV infection (HIV Med 2004;5:303–306; J AIDS 2005; 40:41–46; J AIDS 2006;41:31–36; Clin Infect Dis 2005; 41:395–402; J Infect Dis 2007;196:230–238).

Danta et al have performed a phylogenetic study of E1/E2 sequences derived from HCV incident strains acquired in a large ongoing epidemic of HCV in HIV-1–infected MSM in Southern England. A parallel epidemiologic study collected information via a very detailed, self-administered questionnaire regarding a wide range of risk behaviors revolving around sexual practices and recreational drug use, all of which are possibly associated with HCV acquisition. The comparisons were between HIV-1–infected MSM who acquired HCV (cases) and HIV-1–infected MSM who were negative for HCV (controls). The case-control study design allowed for matching by age, duration of HIV-1 infection, race, and antiretroviral exposure.

The phylogenetic analysis of 93 sequences revealed 7 distinct clusters, including 5 separate genotype 1a clusters comprising 78% of the sequences. The other 2 clusters were genotype 1b and 3a. A handful of genotype 4 sequences were not characterized, and a few genotype 1 sequences fell outside of known clusters. Molecular clock analysis revealed that the likely year of origin for the majority of these sequences was before 1995.

The behavioral questionnaires compared 60 cases with 130 controls. Although safe sex practices (ie, anal intercourse with condoms) were equivalent between the 2 groups, risky behaviors were significantly higher in cases than controls. In particular, the rates of receptive unprotected anal intercourse, group sex, and practices associated with trauma to rectal mucosal surfaces were significantly higher among MSM contracting HCV than those who remained HCV negative.

A very high rate of recreational drug use over the previous 12 months was reported in both populations (70.9% controls, 96.7% cases). The predominant drugs used among cases were amyl nitrites (poppers), ketamine, ecstasy, and cocaine. The rate of injecting practices was higher in HIV-1–infected MSM with HCV infection than those without (17.2 vs 6.6%; $P = .08$) and can therefore only account for a minority of cases.

The authors conclude that HCV has been introduced several times into the HIV-1–infected MSM population of London and Brighton. Moreover, because of the presence of genetically distinct clusters of HCV, they conclude that viral adaptation is not the primary factor driving these outbreaks. Rather, HCV acquisition was strongly associated with group sex and high-risk sexual practices traumatic to mucosal surfaces, especially the rectum. These sexual practices were too tightly linked to recreational drug use to determine whether they each independently confer risk of HCV acquisition. Recommendations include enhanced screening for HCV for individuals engaging in unsafe sexual and drug practices and targeted public health interventions.

Comment. Sexual transmission of HCV is not considered efficient, despite the presence of this virus in genital secretions. This statement is based on several studies of discordant heterosexual couples (one partner infected, the other susceptible) that demonstrated the rarity of HCV transmission in the context of monogamous relationships (Blood 1993;81:1077–1082; Lancet 1995;345: 1209–1211). Based on this low risk, condom use is not specifically recommended for the prevention of HCV between discordant monogamous couples (NIH Consensus Statement, 2002).

As emphasized in this study, sexual transmission is apparently epidemic in HIV–infected MSM (AIDS 2007; 21:983–991). Barring a gross underreporting of IDU (possible given the overall 54% return rate among cases), the findings strongly suggest that percutaneous injection does not account for the vast majority of HCV acquisition in this population. Therefore, other modes of transmission are likely important, and the authors posit that group sex and sexual practices traumatic to the rectum are primary risks, once again suggesting sexual acquisition of HCV. Use of other drugs was exceptionally prevalent, especially recreational drugs closely associated with high-risk sexual behaviors. These data add to other reports that indicate HCV's emergence as a sexually transmitted infection among a subgroup of HIV-positive MSM and are novel in delineating some of the specific practices highly associated with HCV acquisition.

These outbreaks reflect a "perfect storm" of the risky behaviors outlined and biological factors related to HIV-1 and HCV infections. With regard to HCV-related factors driving this epidemic, one possibility is that HCV has undergone mutational changes that confer adaptations that facilitate transmucosal infection. This study does not provide evidence supporting this hypothesis given the lack of a commonality between clusters, although a more powerful comparison would have been between these incident strains to other prevalent strains in the area rather than to sequences already published. Defini-

tive evidence to prove or disprove this hypothesis may be difficult given the lack of experimental models for transmucosal HCV infection.

In terms of HIV-1 as a cofactor, this study raises the following question: Why are these outbreaks of HCV occurring among MSM who are HIV-1 positive but not among those without HIV-1 who are engaging in the same practices? Thus far, outbreaks of HCV in HIV-negative MSM in the same cities have not been detected. This could be due to lower rates of risk behaviors and fewer intersections with health care in HIV-negative MSM, but it is also highly likely that HIV-1 independently confers a greater likelihood of transmucosal HCV acquisition. First, higher viral loads are observed in HIV-1 coinfection, and may be a donor-related factor; these are associated with infection even in monogamous heterosexual relationships. In terms of recipient-related factors, it has been recently appreciated that the gut-associated lymphoid tissue is depleted of CD4 T cells early in HIV-1 infection, well before CD4 T cells measured in peripheral blood decline (J Exp Med 2004;200:761–770). This likely represents one of several immunologic lesions in HIV-positive MSM, as local responses to pathogens at mucosal surfaces are impaired and dysregulated. This could also explain why HIV-positive individuals seem to have enhanced susceptibility to HCV acquisition at all levels of peripheral CD4 counts, as observed in the present study. Other related cofactors that may facilitate HCV transmission in this setting include other concomitant STDs that enhance HCV transmission, especially if it produces ulcerative disease within the rectum.

What are the practical, take-home messages from this study? First, clinicians seeing high-risk populations need to maintain a high index of suspicion to identify acute HCV, because most presenting with this syndrome are not symptomatic, as confirmed in the present study in which >90% of acute HCV cases had no symptoms. The rationale for identifying acute HCV includes greater opportunities to prevent further transmission (because there are higher viral titers during the acute phase), provide education, and administer immunizations against other hepatitis viruses. Moreover, coinfection with both HCV and HIV-1 is associated with faster rates of progression and poorer responses to interferon-based treatments. HCV has emerged as a leading cause of morbidity and mortality among persons with HIV-1 infection and we should not miss a valuable opportunity to consider interferon-based regimens, especially given enhanced treatment outcomes when treating during the acute phase when compared to the chronic phase (N Engl J Med 2001;345:1452–1457; J Viral Hepat 2005;12:207–211; Clin Gastroenterol Hepatol 2006;4:1278–1282). This becomes especially true when one considers the even more limited success of pegylated interferon and ribavirin therapy for chronic HCV in the HIV-coinfected person (N Engl J Med 2004;351:451–459; N Engl J Med 2004;438–450).

Current guidelines for the care of HIV-infected persons recommend screening for hepatitis viruses at baseline and targeted repeat testing for ongoing risk, generally IDU. Given these recent reports, repeat HCV antibody testing for MSM with high-risk sexual encounters is warranted. Targeted liver function and nucleic acid testing screening should be implemented, because antibodies can be negative in the first several weeks after HCV acquisition. Possible locations for screening include clinics oriented to MSM, those living with HIV, and those desiring testing for STDs.

Second, the social factors driving these particularly risky behaviors need to be addressed. Changing attitudes with regard to the dangers of HIV-1 infection, Internet use to facilitate partnering, and widespread use of recreational drugs are each driving forces in this epidemic. These issues are important not only for the individual patient's health, but for the public health. The complexity of changing behavior requires significant effort from health care providers and public health officials, working together with advocacy groups, with the ultimate goal of providing novel and effective behavioral interventions to stem this epidemic.

ARTHUR Y. KIM, MD
RAYMOND T. CHUNG, MD

Reply. Our study supports the permucosal transmission of HCV in HIV-1–positive MSM with cohorts also reported in Europe, the United States, and Australia. Recently, the Health Protection Authority of the United Kingdom confirmed an increasing incidence of HCV in the UK HIV-positive MSM population since 2002 (Giraudon, European Intervention Epidemiology Training Programme Scientific Seminar, Mahon, Spain, October 2006). An international collaborative phylogenetic study exploring HCV transmission has been initiated combining reported UK, European, and Australian cohorts. Provisional analysis has revealed a large HCV transmission network with country mixing (4th IAS conference, Sydney, Australia, July 2007).

Both risk behavior and HIV-1 are probably contributing to the increase in the permucosal transmission of HCV in this population. Since the late 1990s there has been an increase in sexual risk behaviors among MSMs, particularly in HIV-1–positive men, related to serosorting, which often involves unprotected anal intercourse in men of the same HIV serostatus (AIDS 2005;19:2171–2173). Although obviating the risk of primary HIV infection, it presents a significant risk of STDs, HIV superinfection, and now probably HCV. Interestingly, phylogenetic analysis supports an increase in the transmission of HCV since the mid-1990s. In our study, controls also appeared to have high levels of risk activity, including participation in group sex (52%) and

sharing of intranasal drugs (49%) suggesting a larger "at-risk" population.

The role of HIV-1 was not explored in our study. In addition to the reviewers' comments, we would add that HIV-1 infection is associated with increased proportion of detectable HCV in semen, present at higher loads (AIDS 2005;19:1827–1835). Our group has also reported that in the UK cohort, HIV-1 infection was associated with higher serum HCV loads and significantly less detectable CD4 responses to HCV antigens compared with monoinfected acute HCV cases (Hepatology 2006;44: A163). These factors probably contribute to increased transmission or reduced clearance of HCV.

To further dissect the mechanism of HCV transmission in this population, detailed qualitative data are required to explore the complex interaction of drug and sexual practices. At present, education about transmission risk and screening of high-risk individuals, such as those who participate in group sex, should be recommended.

MARK DANTA, MD, FRACP

SHIGELLA: A SEXUALLY TRANSMITTED INFECTION IN MEN WHO HAVE SEX WITH MEN

Aragon TJ, Vugia DJ, Shallow S, et al. **(San Francisco Department of Public Health, City and County of San Francisco, San Francisco, California). Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis 2007; 44:327–334.**

In the United States, 450,000 people are infected with *Shigella* species each year, with 6200 hospitalizations and 70 deaths. Transmission is by the fecal–oral route, and as few as 10 organisms can cause clinical infection. Children <10 years of age are the most commonly affected group. In the mid 1970s, increased rates of shigellosis in men who have sex with men (MSM) were attributed to sexual practices including oral–anal contact. A study in San Francisco in 1996 showed an increase in human immunodeficiency virus (HIV) infection that paralleled an increase in shigellosis, suggesting that *Shigella* was more severe in HIV infected persons or that shigellosis was an important risk factor for HIV in MSM. In the same geographic area, these authors performed a population-based epidemiologic analysis to evaluate the role of HIV infection and sexual behavior in transmission of *Shigella* species. They conducted a case-control study of culture confirmed cases of *Shigella* over a 2-year period (1998–1999), made possible by the laboratory-based active surveillance of the California Emerging Infections Program. A database of 174 adult cases was identified, of whom 76 were eligible for study. There were 147 control subjects. *Shigella flexneri* was the most common organism (52.6%); *S sonnei* was second (45.1%), and 1 case had *S dysenteriae.* Shigellosis was associated with MSM, as well as direct and indirect anal contact. It was also associated with foreign travel and drinking untreated water. Among women, only foreign travel was associated with shigellosis. Foreign travel was still the biggest risk factor for men and women (odds ratio [OR], ≥20; $P < .001$). Among MSM, HIV infection and direct anal contact were independently associated with shigellosis. This is the first population-based study of risk factors for shigellosis that evaluates sexual practices, and HIV status. This strongly supports shigellosis as a sexually transmitted disease (STD). HIV infection may contribute to transmission by increasing host susceptibility.

Comment. In 1974, Dritz et al (N Engl J Med 1974;291: 1197) suggested possible sexual transmission of *Shigella,* reporting an outbreak of *Shigella flexneri* enteritis in adult men from the gay community in San Francisco. They postulated oral sexual practices as the probable mode of transmission. Before this, *Shigella,* like hepatitis B, was not considered a sexually transmitted pathogen. However, since the 1970s, outbreaks of shigellosis among MSM have been documented in major cities in the United States, Europe, and Australia. In the United States, *Shigella* remained a relatively common pathogen among MSM until the early 1980s. Rates of decrease paralleled increased rates of HIV infection, and it is likely that changes in sexual practices to decrease transmission of HIV led to decreases in other STDs, as well as shigellosis.

There has been a documented resurgence of shigellosis among MSM in the past 10 years. In Chicago, an increase in *S flexneri* infection in 2003–2004 was seen in adult men (rates rose from 5 to 15.5 cases per year) with a parallel decrease in women and children (5.9 to 3.0 cases per year). In analysis, 22 of 25 (88%) were MSM, and this was the only risk factor. Of 14 isolates from MSM, 12 were *S flexneri* subtype 3a and 2 were *S flexneri* subtype 3b (Morbid Mortal Weekly Rep 2005;54;820–822).

In San Francisco, there was an outbreak of *S sonnei* infection among MSM in 2000–2001. Rates of infection among MSM was 259 per 100,000 population compared with 16 per 100,000 for all other groups (Morbid Mortal Weekly Rep 2001;50:922–926). In previous epidemics among MSM, *S flexneri* was the more common pathogen. This large community outbreak of *S sonnei* followed a 10-year decline in STDs and enteric infections among MSM (San Francisco Epidemiologic Bulletin 1986;2:1–3; www.dph.sf.ca.us/PHP/AIDSSurvUnit.htm). There was a parallel change to more high-risk sexual behaviors that transmit HIV and other infections (Morbid Mortal Weekly Rep 1999;48:45–48). The role of sexual practice in transmission is important, as is the relationship of *Shigella* infection with HIV infection. HIV-positive men