Effect of sleep deprivation on response to immunizaton

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Occupational Transmission of Hepatitis C Virus

To the Editor: Dr Sulkowski and colleagues[1] present a case of occupational hepatitis C virus (HCV) infection in a medical intern following a needlestick from an intravenous (IV) catheter stylet. In reviewing the occupational risk of HCV infection, they state that "HCV transmission following a single needlestick accident occurs approximately 10 times more often than HIV [human immunodeficiency virus] transmission." This estimate appears to derive from studies reported in their Table 1, which reported a total of 333 HCV-exposed health care workers (HCWs), 14 of whom became infected, for an overall transmission rate of 4.2%.

Integrating these studies published from 1992 through 1994 with several more recent reports shows that more than 11 000 HCV-exposed HCWs have been collectively followed up in 6 countries, with increasingly consistent results (TABLE). The simple average transmission rate for all reports is 0.5%, a rate similar to that for occupational HIV transmission, and much lower than the rate that Sulkowski et al report.

Regarding the recommended follow-up schedule, we agree that HCV RNA testing should be performed only when early detection of HCV infection would alter clinical care. Given a 0.5% average infection rate, if performed routinely, 99.5% of such tests would have negative results. Thus, selective testing of cases with a higher than average transmission risk may be an alternative strategy. Transmission risk appears to increase if the source patient is coinfected with HIV, an observation supported both by surveillance studies[2,3] and anecdotal reports (including the case reported by Sulkowski et al). Also, most cases of transmission resulted from needlesticks involving hollow-bore, blood-filled needles, which represent a small proportion of all needlesticks. HCV RNA tests targeting these circumstances may be justified.

Most high-risk needlesticks from conventional IV catheter stylets are preventable through the use of safety-engineered IV catheters, which have been shown to be from 83% to 95% effective in preventing needlesticks.[4-6] But the use of such protective devices to reduce risk of bloodborne infection is not merely a good idea—in the United States it is the law. The Needlestick Safety and Prevention Act,[7] requiring these devices, went into full effect in July 2001. Consequently, not only is the risk of infection with HCV after an occupational exposure only a small fraction of what it was initially believed to be, but the risk of being exposed to HCV by a conventional IV catheter stylet can be reduced by more than 90% by complying with US regulations requiring the use of protective IV catheters and other needle devices.

Janine Jagger, PhD, MPH
Department of Internal Medicine
University of Virginia School of Medicine
Charlottesville

Vincenzo Puro, MD
Gabriella De Carli, MD
Department of Epidemiology
National Institute for Infectious Diseases "L. Spallanzani"
Rome, Italy

1. Sulkowski MS, Ray SC, Thomas DL. Needlestick transmission of hepatitis C. *JAMA*. 2002;287:2406-2413.
2. Serra C, Torres M, Campins M. Riesgo laboral de infeccion por el virus de la hepatitis C despues de una exposicion accidental [in Spanish]. *Medicina Clinica*. 1998;111:645-649.
3. Campbell SR, Srivastava P, Williams I, Alter M, Cardo D, and the NaSH Surveillance Group. Hepatitis C virus infection after occupational exposure. *Infect Control Hosp Epidemiol*. 2000;21:107.
4. Jagger J, Bentley MB, for the Collaborative EPINet Surveillance Group. Injuries from vascular access devices: high risk and preventable. *J Intraven Nurs*. 1997;20 (suppl 6):S33-S39.
5. Mendelson MH, Chen LBY, Finkelstein LE, Bailey E, Kogan G. Evaluation of a safety IV catheter (Insyte Autogard, Becton Dickinson) using the Centers for Disease Control and Prevention (CDC) National Surveillance System for Hospital Healthcare Workers database. Abstract presented at: 4th Decennial International Conference on Nosocomial and Healthcare Associated Infections; March 5-9, 2000; Atlanta, Ga.
6. Mendelson MH, Lin-Chen BY, Finkelstein-Blond L, Bailey E, Kogan G. Evaluation of a safety IV catheter (IVC) (Becton Dickinson, INSYTE AUTOGARD). Abstract presented at: 11th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America; May 2001; Toronto, Ontario.
7. Needlestick Safety and Prevention Act of 2000. Pub L No. 106-430, 114 Stat 1901 (2000).

To the Editor: Dr Sulkowski and colleagues[1] demonstrated that even a superficial scatch can transmit HCV. Although the intern in their case washed the involved area immediately, it is possible that topical treatment with a virucidal medication would have aborted the infection. Tincture of iodine is virucidal at very low concentration.[2] Also, the ethanol in tincture of iodine "enchances germicidal activity and also increases dispersibility and penetrance, and the action of iodine will persist on the surgeon's gloved hands for several hours."[2]

Arthur J. Lunsk, MD
Long Beach, Calif

1. Sulkowski MS, Ray SC, Thomas DL. Needlestick transmission of hepatitis C. *JAMA*. 2002;287:2406-2413.
2. Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmaceutical Basis of Therapeutics*. 7th ed. New York, NY: Macmillan; 1985.

In Reply: The data presented by Dr Jagger and colleagues suggest the rate of HCV transmission following percutaneous oc-

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

Table. Infection Rates Among HCV–Exposed Health Care Workers*

Source	Country	Cases, No.		Infection Rate (95% CI), %
		Exposed	Infections	
Hernandez et al. *J Hepatol*. 1992;16:56-58	Spain	81	0	0 (0-4.4)
Mitsui et al. *Hepatology*. 1992;16:1109-1114	Japan	68	7	10.3 (3.0-17.5)
Sodeyama et al. *Arch Intern Med*. 1993;153:1565-1572	Japan	90	2	2.2 (0.2-7.8)
Lanphear et al. *Infect Control Hosp Epidemiol*. 1994;15:745-750	United States	50	3	6.0 (1.2-16.5)
Zuckerman et al. *Lancet*. 1994;343:1618-1620	United Kingdom	24	0	0 (0-14.2)
Monge et al. *Accidentes Biologicos en Profesionales Sanitarios*. 1995	Spain	603	2	0.3 (0.04-1.2)
Arai et al. *Liver*. 1996;16:331-334	Japan	56	3	5.4 (1.1-14.9)
Serra et al. *Medicina Clinica*. 1998;111:645-649	Spain	443	3	0.7 (0.1-2.0)
Takagi et al. *J Gastroenterol Hepatol*. 1998;13:238-243	Japan	250	4	1.6 (0.4-4.0)
Hasan et al. *Hepatogastroenterology*. 1999;46:1678-1681	Kuwait	24	0	0 (0-14.2)
Kidouchi et al. Surveillance of blood and body fluid exposures in Japan. 4th International Conference on Occupational Health for Health Care Workers; 1999	Japan	4836	15	0.3 (0.1-0.5)
Petrosillo et al. *Br J Infect Control*. 2001;2:15-17	Italy	4292	19	0.4 (0.2-0.6)†
Baldo et al. *Infect Control Hosp Epidemiol*. 2002;23:325-327	Italy	68	0	0 (0-5.3)
Evans, 2002‡	United Kingdom	439	1	0.2 (0.006-1.3)
Total		**11 324**	**59**	**0.5 (0.39-0.65)**

*Only the most recent report by the same group of investigators was included. HCV indicates hepatitis C virus; CI, confidence interval.
†Percutaneous exposure infection rate, 0.5%; mucocutaneous infection rate, 0.4%.
‡Evans B, Communicable Disease Surveillance Centre, Public Health Laboratory Service, written communication, April 24, 2002.

cupational exposure may be lower than previously recognized. It is difficult for us to fully evaluate several of the studies they cite, because most were not published in English. Still, heterogeneity in reported transmission risk is not surprising since so many factors influence transmission,such as the number of virions in the inoculum and the susceptibility of the exposed tissues. Available data suggest that virions must penetrate skin and that larger inocula are more infectious, as would be expected with exposure to hollow-bore needles containing blood from persons with a high serum HCV RNA level. Consequently, the overall risk of transmission from various investigations will vary according to the nature of the exposures studied. To a lesser extent, differences in ascertainment of HCV exposure and infection in studies of HCWs may also affect estimates of transmission risk. It is probably most useful to consider transmission risk according to at least 3 factors: whether the exposure was (1) via mucous membrane, intact skin, or percutaneous; (2) from a solid-bore or a hollow-bore needle, or (3) from blood with high, low, or undetectable HCV RNA levels. Further research is clearly needed to provide precise estimates in each of these categories. In the meantime, as Jagger et al point out, HCWs with all but percutaneous exposure to hollow-bore needles contaminated with HCV RNA–containing blood (or other deep inoculations) can be reassured that the risk of HCV infection is very low.

This heterogeneity notwithstanding, we feel there is ample evidence to suggest that HCV is more transmissible than HIV following most percutaneous exposures. In addition to the studies of accidental needlestick previously cited, the incidence and prevalence of HCV are much higher among persons who inject illicit drugs,[1-3] although the exact magnitude of the difference is unknown. In the era of effective postexposure prophylaxis for HIV and pre-exposure and postexposure prevention of hepatitis B, HCV remains an important blood-borne occupational infection.

Dr Lunsk asks if iodine should be applied to wounds to diminish transmission of HCV and other blood-borne infections. Although we are not aware of direct evidence to test this hypothesis (and very little is known about which cells HCV infects and how rapidly infection occurs), most particles (and thus probably viruses) are too rapidly transported across tissues for this type of intervention to interdict transmission. Likewise, washing the wound with soap and water is advisable to prevent future bacterial contamination, but is not expected to diminish transmission of viruses already inoculated into the wound. Accordingly, the US Public Health Service recommends that "wounds and skin sites that have been in contact with blood or body fluids should be washed with soap and water; mucous membranes should be flushed with water. No evidence exists that using antiseptics for wound care or expressing fluid by squeezing the wound further reduces the risk of bloodborne pathogen transmission; however, the use of antiseptics is not contraindicated. The application of caustic agents (eg, bleach) or the injection of antiseptics or disinfectants into the wound is not recommended."[4]

Mark S. Sulkowsky, MD
Stuart C. Ray, MD
David L. Thomas, MD
Johns Hopkins University School of Medicine
Baltimore, Md

Financial Disclosures: Please see original article (2002;287:2406-2413).

1. Villano SA, Vlahov D, Nelson KE, Lyles CM, Cohn S, Thomas DL. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol*. 1997;35:3274-3277.
2. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health*. 1996; 86:655-661.
3. Gerberding JL. Incidence and prevalence of human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and cytomegalovirus among health care personnel at risk for blood exposure: final report from a longitudinal study. *J Infect Dis*. 1994;170:1410-1417.
4. Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines on the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR Recomm Rep*. 2001;50:1-52.

Coin Rubbing and Camphor Intoxication

To the Editor: In their Research Letter, Dr Bächli and colleagues[1] describe a case of camphor intoxication after cao gío (coin rubbing). We disagree that this patient experienced camphor intoxication. The authors describe a 1-week history of vomiting and diarrhea followed by several hours of progressive confusion. The patient's laboratory tests were significant for a sodium level of 117 mEq/L, hypokalemia, and slightly elevated liver enzymes. Based on the authors' description we feel that the primary etiology of the altered level of consciousness was hyponatremia, not camphor intoxication. Although dermal exposure to camphor has been associated with hepatotoxicity,[2] we are not aware of an association of camphor (by any route of exposure) with hyponatremia. In addition, the patient apparently did not have convulsions, a manifestation typical of camphor poisoning.[3] Furthermore, the fact that the patient had detectable camphor by gas chromatography/mass spectrometry merely confirms the presence of camphor and by no means proves that the patient was intoxicated from it.

Aaron B. Schneir, MD
Richard F. Clark, MD
Division of Emergency Medicine and Medical Toxicology
University of California, San Diego Medical Center

1. Rampini SK, Schneemann M, Rentsch K, Bächli EB. Camphor intoxication after cao gío (coin rubbing). *JAMA*. 2002;288:45.
2. Aliye UC, Bishop W, Sanders K. Camphor hepatotoxicity. *South Med J*. 2000; 93:596-598.
3. Theis JGW, Koren G. Camphorated oil: still endangering the lives of Canadian children. *CMAJ*. 1995;152:1821-1824.

In Reply: Acute gastrointestinal illness prompted the patient to use cao gío (coin rubbing), and a few hours later, he had onset of confusion that led to his admission to our emergency department. We did not imply that camphor intoxication explained all signs and symptoms of the patient. We agree that there is no known association of hyponatremia and camphor intoxication. The probable cause of hyponatremia was the gastrointestinal illness.

It is possible that hyponatremia could explain our patient's altered mental status, although the confusion was temporally associated with the coin rubbing. At admission vomiting and diarrhea were no longer present. While we asserted that the elevated liver enzymes were caused by camphor intoxication, more importantly, they cannot be attributed to hyponatremia.

E. B. Bächli, MD
S. K. Rampini, MD
M. Schneemann, MD
Department of Medicine
University Hospital Zürich
Zürich, Switzerland

RESEARCH LETTER

Effect of Sleep Deprivation on Response to Immunizaton

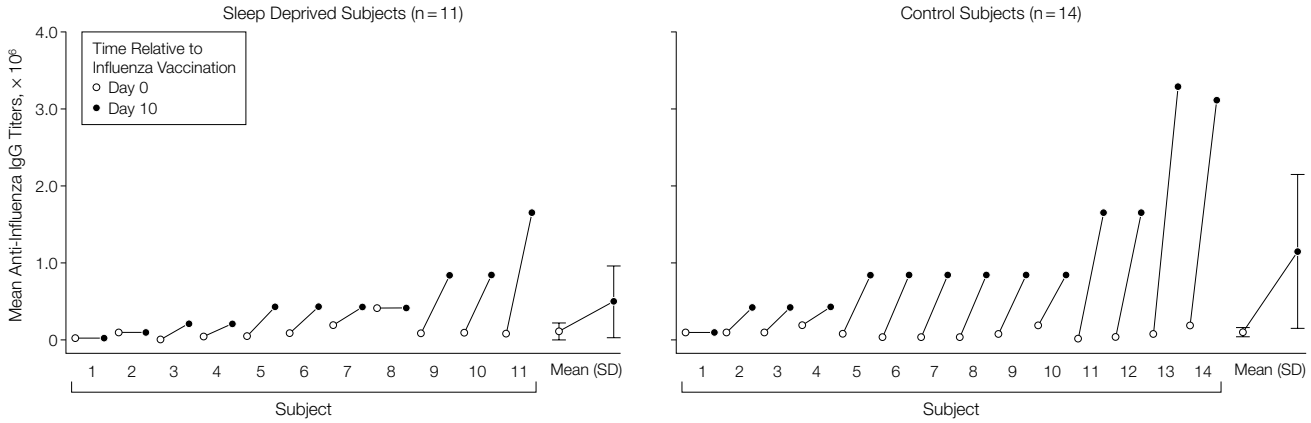
To the Editor: Popular wisdom holds that not getting enough sleep increases the propensity of catching a cold or other ailments. In America, sleep duration has steadily declined from nearly 9 hours in 1960 to less than 7 hours currently.[1,2] Although adverse effects of sleep deprivation on immune parameters have been documented,[3] the clinical implications of these findings are unclear. We examined the effect of sleep deprivation on immune response to influenza vaccination.

Methods. Subjects were 25 healthy young men (mean age, 23 years) who consented to participate in a protocol approved by our institutional review board. Eligibility criteria included bedtime between 11 PM and 1 AM, waking time between 7 and 9 AM, and time in bed of 7.5 to 8.5 hours. None of the subjects had been immunized against influenza during the preceding 3 years. Eleven subjects had their bedtime restricted to 4 hours (1-5 AM) for 6 nights and then extended to 12 hours per night for 7 nights to recover from sleep loss.[4] Between 9:00 and 10:00 on the morning following the fourth short night, they were immunized against influenza (0.5-mL intramuscular injection, Influenza Virus Vaccine, Trivalent Types A and B, Fluogen, 1996-1997 influenza season, Parke-Davis, Morris Plains, NJ). A second group of 14 subjects served as controls and maintained their usual bedtimes prior to receiving the same vaccine under the same conditions. The 2 groups were recruited from the same pool of subjects, fulfilled the same inclusion criteria, and did not differ in terms of age, body mass index, and ethnic background. All subjects were seropositive for anti-influenza IgG antibody at baseline and mean titers were similar in both groups.

To assess anti-influenza IgG antibody titers throughout the major phases of the antibody response, a morning blood sample was taken immediately before vaccination (baseline), as well as 10 days (during the log phase, when antibody titer increases logarithmically) and 21 to 30 days (during the plateau phase, when antibody titer stabilizes) after vaccination. Antibody titers were measured in all samples using an enzyme-linked immunosorbent assay, with the vaccine used to immunize the subjects as the antigen.[5]

Results. Ten days after vaccination, mean (SD) antibody titers in subjects who were immunized in a state of sleep debt

Figure. Antibody Titers at Baseline and 10 Days Following Influenza Vaccination



were less than half those measured in the subjects with normal sleep times (0.50×10^6 [0.46×10^6] vs 1.15×10^6 [1.00×10^6], respectively; $P = .03$ by Mann-Whitney test; FIGURE). At 3 to 4 weeks after vaccination, antibody titers were no longer significantly different. Repeated-measures analysis of variance of natural log-transformed antibody titers with sleep condition as a factor revealed a significant ($P = .04$) effect of sleep duration on antibody titers.

Comment. Sleep deprivation at the time of vaccination reduced the response during the log phase of antibody production despite a prolonged period of sleep recovery after vaccination. These results suggest that the response to influenza vaccination may be impaired in individuals with chronic partial sleep restriction. Because adults who show poorer responses to vaccines and other antigenic challenges also experience higher rates of clinical illness,[6] our findings support the concept that adequate amounts of sleep are needed for optimal resistance to infectious challenge.

Karine Spiegel, PhD
Department of Medicine
University of Chicago
Chicago, Ill
John F. Sheridan, PhD
Departments of Oral Biology and Molecular Virology and Immunology
the Ohio State University
Columbus
Eve Van Cauter, PhD
Department of Medicine
University of Chicago

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1. Kripke DF, Simons R, Garfinkel L, Hammond E. Short and long sleep and sleeping pills: is increased mortality associated? *Arch Gen Psychiatry*. 1979;36:103-116.
2. National Sleep Foundation (NSF). *2000 Omnibus Sleep in America Poll*. Washington, DC: NSF; 2000. Available at: http://www.sleepfoundation.org/publications/2000poll.html. Accessibility verified August 13, 2002.
3. Krueger JM, Fang J, Floyd RA. Relationship between sleep and immune function. In: Turek FW, Zee PC, eds. *Regulation of Sleep and Circadian Rhythms*. New York, NY: Marcel Dekker Inc; 1999:427-464.
4. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354:1435-1439.
5. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci U S A*. 1996;93:3043-3047.
6. McGlone FB, Arden NH. Impact of influenza in geriatrics and action plan for prevention and treatment. *Am J Med*. 1987;82(suppl A):55-57.