

11. Chun TW, Stuyver L, Mizell SB, et al. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proc Natl Acad Sci U S A*. 1997;94:13193-13197.
12. Wong JK, Hezareh M, Gunthard HF, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science*. 1997;278:1291-1295.
13. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4<sup>+</sup> T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med*. 1999;5:512-517.
14. Morgan DA, Ruscetti FW, Gallo RC. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science*. 1976;193:1007-1010.
15. Smith KA. Interleukin 2: inception, impact and implications. *Science*. 1988;240:1169-1176.
16. Lenardo M, Chan KM, Horung F, et al. Mature T lymphocyte apoptosis: immune regulation in a dynamic and unpredictable antigenic environment. *Annu Rev Immunol*. 1999;17:221-253.
17. Kovacs JA, Vogel S, Albert JM, et al. Controlled trial of interleukin-2 infusions in patients infected with the human immunodeficiency virus. *N Engl J Med*. 1996;335:1350-1356.
18. Mellors JW, Rinaldo CW Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272:1167-1170.
19. Schmitz JE, Kuroda MJ, Santra S, et al. Control of viremia in simian immunodeficiency virus infection by CD8<sup>+</sup> lymphocytes. *Science*. 1999;283:857-860.
20. Chun TW, Engel D, Mizell SB, et al. Effect of interleukin 2 on the pool of latently infected, resting CD4<sup>+</sup> T cells in HIV-1-infected patients receiving highly active anti-retroviral therapy. *Nat Med*. 1999;5:651-655.
21. Kovacs JA, Baseler M, Dewar RJ, et al. Increases in CD4 T lymphocytes with intermittent courses of interleukin 2 in patients with human immunodeficiency virus infection. *N Engl J Med*. 1995;332:567-575.
22. Jacobson EL, Piaro F, Smith KA. Rational interleukin 2 therapy for HIV-positive individuals. *Proc Natl Acad Sci U S A*. 1996;93:10405-10410.
23. Davey RT Jr, Murphy RL, Graziano FM, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: a randomized controlled trial. *JAMA*. 2000;284:183-189.
24. Arno A, Ruiz L, Juan M, et al. Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with  $\leq 250/\mu\text{L}$  CD4 T cells and undetectable plasma virus load. *J Infect Dis*. 1999;180:56-60.
25. Connors M, Kovacs JA, Krevat S, et al. HIV infection induces changes in CD4<sup>+</sup> T-cell phenotype and depletions within the CD4<sup>+</sup> T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. *Nat Med*. 1997;3:533-540.
26. Carr A, Emery S, Lloyd A, et al. Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;178:992-999.
27. Hengge UR, Goos M, Esser S, et al. Randomized, controlled phase II trial of subcutaneous interleukin-2 in combination with highly active antiretroviral therapy (HAART) in HIV patients. *AIDS*. 1998;12:F225-F234.
28. Davey RT, Bhat N, Yoder C, et al. HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. *Proc Natl Acad Sci U S A*. 1999;96:15109-15114.

## Will Blood Transfusion Ever Be Safe Enough?

Harvey G. Klein, MD

**I**S BLOOD TRANSFUSION SAFE, OR IS BLOOD ONE OF THE MOST dangerous drugs in the physician's therapeutic armamentarium? The articles by Glynn et al<sup>1</sup> and Ling et al<sup>2</sup> in this issue of THE JOURNAL embody the quintessential paradox of blood transfusion: blood is safer than ever, but the usual notions of safety do not necessarily apply where transfusion is concerned.<sup>1,2</sup> Perhaps it is the mythical and spiritual significance that has been attached to blood by many cultures, or perhaps the devastation inflicted on the recipients of blood infected with the human immunodeficiency virus (HIV). Whatever the reason, blood seems to have gained a singular status—simultaneously feared and revered. Developed countries have come to demand absolute freedom from transfusion-transmitted infection, while simultaneously conceding that zero-risk transfusion is unlikely to ever be achieved.

Blood collection in the United States depends on a system of safeguards to reduce the risk of infection. Sensitive screening tests are necessary but represent only 1 component of this system. Other "layers of safety" include detailed donor education; stringent screening, selection, and deferral procedures; postdonation product quarantine; and donor tracing and notification when instances of transmission of an infectious agent occur. Each element plays a role in preventing "tainted" units from entering the blood inventory. In addition, the Department of Health and Human Services has constructed a comprehensive safety vigilance system to address unknown and emerging infectious

threats.<sup>3</sup> Blood components provided through such a system should prove safe and inspire public confidence.

By and large, the protective system has proved effective. Glynn et al measured markers of viral exposure in 1.9 million volunteer blood donors at 5 regional blood centers between 1991 and 1996, and they report an extremely low risk for the major transfusion-transmitted viruses. The prevalence of HIV and hepatitis C virus (HCV) among first-time donors was far lower than that of the general population and continued to decline during this interval. The seroconversion rate among repeat blood donors was so infrequent, even using mathematical modeling for rare events, that trends were difficult to interpret.

These new data support previous risk estimates of viral transmission from volunteer donor blood, now so low that they are generally expressed as the number of cases per million units transfused.<sup>4</sup> In fact, according to Centers for Disease Control and Prevention (CDC) data, only 38 adults and 2 children have developed the acquired immunodeficiency syndrome (AIDS) after receiving a transfusion in the United States in the 15 years that blood has been screened for HIV, and not a single new case of transfusion-associated HCV has been detected by the CDC Sentinel Counties Viral Hepatitis Surveillance System since 1994.<sup>5,6</sup> Even if surveillance underestimates the cases by a factor of 2 or 3, this achievement is still remarkable. However, lest clinicians become complacent, the constant, if low, prevalence of hepatitis B

**Author Affiliation:** Department of Transfusion Medicine, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md.

**Corresponding Author and Reprints:** Harvey G. Klein, MD, Department of Transfusion Medicine, National Institutes of Health, Bldg 10, Room 1C711, MSC-1184, Bethesda, MD 20892-1184.

See also pp 210 and 229.

virus (HBV) among first-time donors in the study by Glynn et al (approximately 0.2% for hepatitis B surface antigen [HbsAg] positivity), which may have been less affected by the improvements in the screening procedures used in the last 25 years, provides additional incentive to pursue an aggressive HBV vaccination program.

Despite the dramatic improvement in blood safety and the low risk of viral transmission, substantial effort and resources continue to be expended to eliminate the few transmissions that remain. In the United States, the major concern has been donations during the interval between infection and seroconversion, the “window period” of infection involving “immunosilent” donors who are infected but test negative by standard serological screening techniques.<sup>7</sup> One proposed solution has been to introduce methods of direct viral detection using nucleic acid amplification tests (NATs) for HIV, HCV, and HBV into the screening process.<sup>8,9</sup> Currently, small pools (“mini-pools”) of donor specimens are analyzed using sophisticated semiautomated molecular assays. The pooling strategy lowers testing costs at the price of slightly reduced test sensitivity and increased operational complexity. Single-unit NAT testing will almost certainly become standard practice as soon as automated multiplex assays are developed. However, the incremental improvement in safety will come at a high price, about \$2 million per quality-adjusted life year for HIV alone<sup>10</sup> and will not eliminate viral transmission.

The article by Ling et al demonstrates the failure of techniques using dilutions comparable to those used in mini-pool NAT testing to detect an infected donor in the window period. Given the findings of this study, it would appear that unless the viral load is greater than 40 copies/mL, there is a valid concern regarding the continuing risk of transfusion-transmitted infection. The results of this study would seem to confirm that testing of individual units is inevitable. An HCV transmission undetectable even by current single-unit NAT testing methods has previously been reported.<sup>11</sup> It would be naive not to expect that additional cases with these and other agents will occur.

Other promising if expensive technological approaches to blood safety include methods to inactivate pathogenic agents in blood, production of recombinant blood proteins, and development of blood substitutes. Pathogen inactivation techniques have been licensed for plasma and protein fractions, and methods are under development to inactivate pathogens in cellular components.<sup>12,13</sup> Several candidate red cell substitutes are currently in clinical trials, but none has yet proven safe and effective.<sup>14</sup> Recombinant clotting factor concentrates are used widely. These approaches are attractive because they address the inevitable infectious agents of the future as well as the recognized microbes of the present. In today's global village, it is possible to anticipate the intrusion of variant retroviruses, protozoa, and other exotic agents not detected by current screening methods. However, each of these alternatives to trans-

fusion has its limitations and adverse effects; any new treatment will have to compete with a very safe product and one with a long track record.<sup>15</sup> Those who believe that the new miracle treatments will come without risk are confusing faith with science.

Safe is not enough, and blood availability has increasingly become a safety issue. Average blood inventories do not tell the complete story. Emergency appeals during blood shortages are common in the United States. In the most recent national survey of blood availability, 8% of hospitals polled postponed elective surgery because of a lack of blood, and 25% delayed transfusion for 1 or more days.<sup>16</sup> The quest to eliminate the last potentially risky blood donor has caused the loss of thousands of healthy donors. Yet, stung by criticism for slow reaction to the AIDS epidemic, policymakers and their advisory boards now disqualify groups of potential blood donors who have only a hypothetical risk of disease transmission.<sup>17</sup> Fortunately, the temporary deferral of 10 000 National Guard members exposed to ticks during outdoor training exercises, and of 500 000 Desert Storm veterans possibly exposed to *Leishmania donovani* had little permanent effect on blood availability.<sup>18</sup> The indefinite deferral for relatives of patients with Creutzfeldt-Jakob disease affected relatively few potential donors. However, the recent decision in the United States<sup>19</sup> to defer indefinitely individuals who have spent at least 6 months in the United Kingdom between 1980 and 1996 on the chance that they might transmit some agent associated with bovine spongiform encephalopathy (“mad cow” disease) threatens to eliminate more than 2% of otherwise qualified blood donors.<sup>20</sup> New diseases and new infectious agents will continue to be reported. The challenge in the AIDS era will be to base decisions on the best scientific evidence available and on expert assessment of risk and benefit.<sup>21</sup>

Perhaps the most vexing question involves the definition of “acceptable risk.” When blood is involved, the developed world increasingly poses costly technological solutions for risks that seem vanishingly small. Perhaps that is the prerogative of wealthy nations where nothing less than zero-risk transfusion has become acceptable. In the final analysis, it is the patient's perception of risk, not that of the physician or the health care insurer, that must be balanced against statistics involving death, disability, and dollars—as long as the patient is willing and able to pay. This is hardly a responsible global outlook. Cost places even the rudimentary transfusion safeguards beyond the reach of many developing nations. More than two thirds of the world's nations do not have adequate policies to ensure a safe blood supply.<sup>22</sup> An estimated 13 million blood donations globally are not tested for HIV, HBV, and HCV, primarily in developing countries where the number of infected persons in the donor population is high.<sup>22</sup> As for supply, 25% of maternal deaths from pregnancy-related causes are associated with loss of blood.<sup>22</sup> If such statistics do not prompt international action, they should at least give travelers pause.

The slogan used by the American National Red Cross blood program rightfully refers to blood as the “gift of life.” During the past 2 decades, however, there has been a clear shift in the perception of the value of transfusion. Confidence in the nation’s blood supply became an early casualty of the AIDS epidemic and disproportionate fear of transfusion a feature of its unfortunate legacy. While new, expensive measures that increase blood safety even marginally continue to be instituted in the developed world, they may have unintended consequences. The therapeutic index of blood still exceeds that of many common medications and medical procedures. Blood is not entirely safe, but neither is it the most dangerous drug currently available. Like many good things, it comes with risks.

## REFERENCES

- Glynn SA, Kleinman SH, Schreiber GB, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. *JAMA*. 2000;284:229-235.
- Ling AE, Robbins KE, Brown TM, et al. Failure of routine HIV-1 tests in a case involving transmission with preseroconversion blood components during the infectious window period. *JAMA*. 2000;284:210-214.
- Busch M, Chamberland M, Epstein J, et al. Oversight and monitoring of blood safety in the United States. *Vox Sang*. 1999;77:67-76.
- Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *N Engl J Med*. 1996;334:1685-1690.
- Centers for Disease Control and Prevention (CDC). Table 5: AIDS cases by age group, exposure category and sex. *HIV/AIDS Surveill Rep*. 1999;11(1):12.
- Centers for Disease Control and Prevention (CDC). Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-19):1-39.
- Imagawa DT, Lee MH, Wolinsky SM, et al. Human immunodeficiency virus type 1 infection in homosexual men who remain seronegative for prolonged periods. *N Engl J Med*. 1989;320:1458-1462.
- Allain J. Genomic screening for blood-borne viruses in transfusion settings. *Clin Lab Haematol*. 2000;22:1-10.
- Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus and HIV-1 in a blood-bank setting. *Lancet*. 1999;353:359-363.
- Aubuchon JP, Birkmeyer JD, Busch MP. Cost-effectiveness of expanded HIV test protocols for donated blood. *Transfusion*. 1997;37:45-51.
- Schuttler CG, Caspari G, Jursch CA, et al. Hepatitis C virus transmission by a blood donation negative in nucleic acid amplification tests for viral RNA. *Lancet*. 2000;355:41-42.
- Horowitz B, Bonomo R, Prince AM, et al. Solvent/detergent-treated plasma: a virus-inactivated substitute for fresh-frozen plasma. *Blood*. 1992;79:826-831.
- Corash L. Inactivation of viruses, bacteria, protozoa, and leukocytes in platelet concentrates. *Vox Sang*. 1998;74(suppl 2):173-176.
- Winslow RM. New transfusion strategies: red cell substitutes. *Annu Rev Med*. 1999;50:337-353.
- Klein HG. The prospect of red-cell substitutes. *N Engl J Med*. 2000;342:1666-1668.
- National Blood Donor Resource Center. *Report on Blood Donation and Transfusion in the United States in 1997*. Bethesda, Md: National Blood Donor Resource Center; 1999.
- Leviton LB, Sox HC Jr, Stoto MA, eds. *HIV and the Blood Supply: An Analysis of Crisis Decisionmaking*. Washington, DC: National Academy Press; 1995.
- American Association of Blood Banks. FDA issues statement on blood donors possibly exposed to tick-borne pathogens. *Wkly Rep*. 1997;3(28):1-2.
- Food and Drug Administration. *CBER Guidance: Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob disease (nvCJD) by Blood and Blood Products*. Washington, DC: Food and Drug Administration; August 17, 1999.
- Drohan WN. Safety of blood products: are transmissible spongiform encephalopathies (prion disease) a risk? *Thromb Haemost*. 1999;82:486-493.
- Foster KR, Vecchia P, Repacholi MH. Science and the precautionary principle. *Science*. 2000;288:979-981.
- World Health Organization and International Federation of Red Cross and Red Crescent Societies. *Safe Blood Starts With Me*. Geneva, Switzerland: World Health Organization; 2000:12.