Editorial

Xenotransplantation: Is the Future Upon Us?

Michele L. Pearson, MD; William R. Jarvis, MD; Thomas M. Folks, PhD; Louisa E. Chapman, MD

Over the past decade, the number of solid organ transplant procedures done in the United States each year has increased substantially, from approximately 13,000 in 1988 to 20,000 in 1996.[1] Despite the increased availability of these procedures, the number of potential recipients awaiting organ donation has more than tripled since 1988. At the end of 1996, an estimated 50,000 persons were awaiting organ donations.[1] This shortage of available human allografts has prompted the development of investigational therapeutic approaches that use animal tissues or organs (xenografts) in human recipients. Xenotransplantation refers to any procedure that involves the use of live cells, tissues, or organs from a nonhuman animal source for transplantation, implantation, or ex vivo perfusion in humans.

In the United States, the modern era of xenotransplantation began with the transplantation of chimpanzee kidneys into patients with chronic renal failure.[2] It is likely that, in 1964, when this procedure was introduced, it was viewed as one with limited clinical utility and a procedure for the future. However, recent scientific and biomedical advances have made possible more extended use of animal tissues or organs for human clinical applications beyond organ transplantation; animal cells, tissues, or organs have been used for extracorporeal perfusions of patients awaiting organ donation and as a treatment for medical conditions such as Parkinson's disease, diabetes, and human immunodeficiency virus (HIV) infection. Although xenotransplantation may be one partial solution to the unmet demand for human organ and tissue donations, its use raises some unique public health concerns, most notably the potential for transmission of infections of animal origin (xenozoonoses) to humans.[3]

In this issue of the Journal, Borie and colleagues have provided an overview of the potential infectious agents and infectious risks associated with use of tissues harvested from pigs, one of the primary species proposed as a source for xenografts.[4] While considerable debate has centered around the question of whether one animal source or species may pose a greater risk for xenotransplant-related infection than another, the article raises global and provocative questions about the potential infectious risks that may accompany the use of xenotransplantation as a routine therapeutic modality: What is the risk of transmitting endogenous animal pathogens to the human recipient? What is the risk of secondary transmission of xenozoonoses from the recipient to their contacts (eg, family members, healthcare providers)? Lastly, what risk do xenozoonoses pose to the general population?

Currently, the infectious risks posed by xenotransplantation are unknown. However, experience with human allografts has shown that infectious agents (eg, hepatitis B virus, hepatitis C virus, rabies virus, HIV, *Candida albicans,* and Creutzfeldt-Jakob agent) can be transmitted via transplanted human tissues or organs.[5,6] Some investigators have suggested that the ability to produce and use pathogen-free animal sources to obtain "clean" xenografts would eliminate both the infectious risks associated with the use of human allografts and the risk of transmitting recognized zoonoses. However, caution should

From the Hospital Infections Program (Drs. Pearson and, Jarvis), National Center for Infectious Diseases; the Division of AIDS, STD, TB Laboratory Research (Drs. Folks and Chapman), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

Address reprint requests to Michele L. Pearson, MD, Hospital Infections Program, Mailstop E-69, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30333.

97-ED-015. Pearson ML, Jarvis WR, Folks TM, Chapman LE. Xenotransplantation: is the future upon us? Infect Control Hosp Epidemiol *1998;19:305-307.*

be exercised regarding assumptions about both the safety and risk associated with xenotransplantation (especially from infectious agents not recognized as zoonoses) until the science is adequate to establish a solid basis for risk assessment.

Presumably, the recipient is at greatest risk for acquiring xenozoonoses; thus, available data have focused primarily on the risk posed to the recipient of the organ or tissue. However, might not animal handlers, surgical team members who harvest and implant the xenografts, laboratory workers who handle clinical specimens from xenotransplant recipients, and personnel who provide medical care to the transplant recipient after the procedure also be at risk? Additionally, we have a public health responsibility to assess the risk of propagation of xenozoonoses within the general population.

In assessing the risk to the public at large, one must consider the ability for the agent to be transmitted by person-to-person spread and the ability for the agent to cause subclinical, latent, or clinical disease. Clearly, some agents may pose a greater risk to the public health than others. If the agent is not transmissible by person-to-person spread and its potential to cause disease is low, then the public health risks of the infection may be viewed as small. Conversely, if the agent is transmissible by person-to-person spread and the risk of disease is high (eg, filoviruses), then the risk may be considered too great to permit the procedure. Previously unrecognized agents, viruses, and prions may pose the greatest risk for dissemination into the general community. However, these risks may vary from pathogen to pathogen. For example, retroviral infections may be followed by prolonged periods of clinical latency before recognition of malignancies or other chronic sequelae, thereby allowing an emerging infectious agent to transmit silently and become established in a susceptible population before being recognized.

Additional challenges to assessing the risks and ensuring the safety of xenotransplantation include the potential for zoonotic strains to recombine with human strains, resulting in new homologous or heterologous recombinant variants of uncertain virulence and pathogenicity; the possibility that immunosuppressive drugs used during transplantation may facilitate cross-species transmission of infectious agents; the availability of accurate diagnostic tests for detection of infection in animal herds and tissues and humans; and availability of effective therapies. Whereas many of the infectious agents responsible for zoonoses (eg, *Salmonella* species, *Toxoplasma* species, herpes B virus) are well-characterized and identifiable through available diagnostic tests, other potential zoonoses are not known, and no standardized tests are available for their detection. Moreover, some new and emerging infectious agents may not be identifiable by current diagnostic methods.

Despite these challenges and the current lack of scientific data, there are steps that can be taken to monitor and minimize the potential infectious risks associated with xenotransplantation. First, we can require rigorous scientific review and justification of all protocols involving the use of animal cells, tissues, or organs before they are allowed to proceed to clinical trial. In the United States, the Food and Drug Administration requires that all clinical trials in xenotransplantation proceed under their regulatory oversight.

Second, we can require that clinical trials proceed only if they are accompanied by a plan for monitoring infections that may result from the procedure. The risk of transmitting infectious agents during xenotransplantation can be reduced by developing a standardized approach for selecting and screening source animals. This approach should be tailored to consider the animal donor source, infectious agents indigenous to that species, available diagnostic capability, and the anticipated clinical application of the organ or tissue. The development of lists of potential infectious agents undoubtedly will be a necessary working tool for persons involved in the development and review of xenotransplant clinical protocols; such working lists should be generated by a multidisciplinary team, including veterinarians, infectious diseases experts, microbiologists, epidemiologists, pathologists, and public health specialists. However, attempts to develop a template, or master list, of infectious agents cannot replace applied expertise and considered reasoning, and any working list will become outdated rapidly and therefore must undergo frequent review and updating. Finally, the use of such a list should not allow us to become complacent. It should be remembered that it is the unanticipated agents that may pose the greatest risks to the recipient and the general public. Pretransplant screening of donor animals followed by posttransplant surveillance of xenotransplant recipients and their contacts will facilitate recognition of known and new pathogens.

Third, we can develop national and international consensus standards to ensure the quality and safety of xenotransplantation clinical trials. Although consensus standards for xenotransplantation do not yet exist, the US Public Health Service has developed

draft guidelines to decrease the risks of human disease resulting from xenozoonoses.[7] These guidelines are designed to reduce transmission of known zoonoses and new and emerging infectious agents arising from xenotransplantation. More specifically, the guidelines provide guidance in determining the composition of the xenotransplant team, pretransplant screening procedures for animal sources to minimize potential for cross-species transmission of infectious agents, posttransplant surveillance to monitor for infection in the recipient and secondary transmission of infectious agents, and infection control practices to reduce the risk of nosocomial transmission of xenogenic infectious agents. Lastly, to address the public health concerns posed by xenotransplantation, the Public Health Service guidelines have proposed the establishment of a national registry or centralized database to evaluate the long-term safety of xenotransplantation. Such a registry would facilitate identification of clusters of unusual health events and notification of recipients and clinical centers, and enable monitoring of adverse infectious and noninfectious outcomes following xenotransplantation. Data collected through the registry could help expand the epidemiological understanding of xenotransplantation, thereby allowing for a more accurate assessment of risks and potential prevention strategies.

Borie and colleagues should be commended for their systematic review of the state of knowledge regarding the endemic infectious flora of pigs. Comprehensive, scientific reviews of existing knowledge, such as they have provided, help frame unanswered questions and identify areas where research is needed.

The future is, indeed, upon us. We now must prepare ourselves to answer the difficult questions raised by xenotransplantation. Only with the systematic collection of data on xenotransplant recipients and their contacts will we be able to answer the following questions: What are the risks? How can the risks be prevented or minimized? And, finally, are the residual risks outweighed by the potential benefits?

REFERENCES

1. 1997 Annual Report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network—Transplant Data: 1988-1994. UNOS Richmond, Virginia and the Division of Transplantation, Bureau of Health Resources Development, Health Resources and Services Administration. Rockville, MD: US Department of Health and Human Services; 1997.
2. Reemstma, K. Renal heterotransplantation from nonhuman primates to man. *Annals of the New York Academy of Science* 1969;162:412-418.
3. Michaels MG, Simmons RL. Xenotransplant-related zoonoses: strategies for prevention. *Transplantation* 1994;57:1-7.
4. Sachs DH. The pig as a potential xenograft donor. *Veterinary Immunity and Immunopathology* 1994;43:185-191.
5. Eastlund T. Infectious disease transmission through cell, tissue, and organ transplantation: reducing the risk through donor selection. *Cell Transplant* 1995;4;455-477.
6. Centers for Disease Control and Prevention. Candida albicans endocarditis associated with a contaminated aortic valve allograft—California, 1996. *MMWR* 1997;46:261-263.
7. U.S. Public Health Service. Draft public health service guideline on infectious disease issues in xenotransplantation. *Federal Register* September 23, 1996;61:49920-49932.