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Determining the Risks of Xenozoonoses

Marian G. Michaels

The use of any biologic agent brings with it a possibility of infection. Accordingly, while xenotransplantation promises to be a solution to the severe shortage of human organs, tissues and cells, it carries the risk of introducing new infections, xenozoonoses.¹ This brief paper reviews methods to determine and limit these risks as the field of xenotransplantation moves forward. Specific principles can be set forth in regard to understanding xenozoonoses (Table 1).

Principle 1: All Biologic Agents Carry a Risk of Infection

As stated above, any biologic agent can carry infectious agents; as such there will never be a no-risk scenario as demanded by some opponents of xenotransplantation. However, other biologics, such as human organs, tissues and cells, have also been inadvertent vehicles for transmitting infections including retroviruses, herpesviruses (cytomegalovirus and Epstein Barr virus), hepatitis viruses (hepatitis B virus, hepatitis C virus, transfusion-transmitted virus) and protozoa, such as plasmodium species.^{2,3} Recognizing this reality has allowed public health service agencies, health care providers and health care industries to limit the risk of infection by setting in place screening practices to detect these microbes and eliminate the sources when possible. The lessons learned from using human products and organs can assist in developing screening practices that attempt to eliminate infections from source animals for xenotransplantation.

Xenozoonoses will be dependent on the source animal used, how it is reared, the type of transplant performed, and the interaction between contaminating microbial agents and the new human recipient.

Limitation of risks involves pre-transplant screening and strict adherence to rearing conditions of source animals.¹ In addition, post-transplant screening and follow-up of recipients will ultimately define the types of infectious complications that occur.

To determine the types of organisms that may be a hazard after xenotransplantation it is necessary to consider potential mechanisms of transmission of infections from a source animal to a human recipient.¹ First, a microbial agent could be pathogenic for both an animal and human such as the protozoa, *Toxoplasma gondii*. Second, a virus that is established in a specific animal species might be similar enough to an analogous human virus that human cell receptors permit entry. This is hypothesized for some viruses of non-human primates.⁴ Viruses, which are nonpathogenic for humans under normal circumstances, may become pathogenic under the immunosuppressed environment of xenotransplantation. Similarly, use of transgenic animals that have altered cell antigens to prevent hyperacute rejection may hinder normal human immune surveillance.⁵ A fourth possibility is recombination between a human and animal virus leading to a more virulent pathogen. Finally, the animal graft might fail either because of infection with a human virus from the recipient or from reactivation of an animal microbe, even if it is unable to infect human cells.

Principle 2: Eliminate Microbial Agents from the Donor

With these mechanisms in mind, the ideal situation would be to eliminate all infectious agents. Rearing animals in gnotobiotic conditions is logistically difficult and may not result in the healthiest animals for organ sources. In addition, endogenous viruses

Marian G. Michaels, M.D., M.P.H.
Associate Professor of Pediatrics
and Surgery
University of Pittsburgh School
of Medicine
Division of Allergy, Immunology
and Infectious Diseases
The Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania, USA 15213
Tel: 412.692.6768
Fax: 412.692.8499
email: michaem@chplink.chp.edu

Table 1 | PRINCIPLES IN UNDERSTANDING XENOZOONOSES

PRINCIPLE
1. All biologic agents carry a risk of infection
2. If the microbial agent is not in the tissue that is transplanted, it cannot be transmitted
3. All laboratory tests have limitations
4. Viruses may behave differently in a new host
5. Modify protocols based on new findings

... use of transgenic animals that have altered cell antigens to prevent hyperacute rejection may hinder normal human immune surveillance.

and vertically-transmitted infections will not be eliminated. Strict adherence to raising animals screened at birth in closed, clean environments may adequately achieve similar results without the difficulties encountered with waste production and poor growth that animals experience with gnotobiotic conditions. While these specific pathogen-free environments will help to decrease the risk of xenozoonoses, they will not completely eliminate it. For this reason, it is important for any recipient of xenogeneic tissue to undergo counseling about potential risks and agree to surveillance for new infections after xenotransplantation. Thus the true epidemiology and risks of xenotransplant infections will ultimately be recognized. Serial samples from the recipient and transplanted tissues should be collected to look for agents that were known or suspected to be in the source animal, such as endogenous viruses. These recommendations have become part of the guidelines recommended by the United States Public Health Services.⁶ Towards this end, Paradis and colleagues reported collaboration between industry and public health services wherein 160 people who had been treated with living porcine tissues were retrospectively evaluated.⁷ Researchers did not find infection with porcine endogenous retrovirus in the blood of these individuals despite some having persistent pig cells up to 8.5 years after exposure. While it is reassuring that the results were negative, it was as important that collaborative efforts could be successfully put into place.

Principle 3: All Laboratory Tests Have Limitations

All tests have certain limitations and testing techniques for screening may prove inadequate at any one time period. Research is progressing on developing techniques to identify microbial agents of animal sources and distinguish them from human microbes.^{4,8} Also, novel infectious agents are continually being identified. Accordingly, archiving samples for future studies are important and should be maintained for prolonged periods.

Principle 4: Viruses May Behave Differently in a New Host

Shared or centralized registries and repositories for archived specimens may help with evaluating potential infectious agents.^{1,6} Registries should more quickly identify unexpected reactions to infection from a source animal or rare trends that would otherwise be missed by an individual research protocol. This is particularly important as infectious agents may behave differently in a new species and thus not be considered in a differential diagnosis of a particular syndrome.

Principle 5: Protocols Should be Modified in the Light of New Findings

All biologic agents have an inherent risk for transmitting infections and our ability to recognize and prevent these infections is continually growing. Medicine is a fluid discipline; as new findings emerge, protocols should change to reflect our increased knowledge base. As the field of xenotransplantation progresses, development of new techniques and strategies to help identify and prevent novel infections must continue as well.

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