# Xenotransplantation

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**ABSTRACT**

Xenotransplantation is transplantation of living cells, tissues or organs from one species to another. There is a large number of patients who need to wait for allotrasplantation due to limited donors. This drives a need for the transplant of tissue from animals to humans. However, immune rejection and infections are major risks that may prevent a good outcome of xenotransplantation. Proper documentation and sterilisation of tissues is indispensable. This article highlights the present day prespectives of Xenotransplantation.

**Keywords:** Xenotransplantation

## INTRODUCTION

Xenotransplantation (*xenos means* "foreign") is the transplantation of living cells, tissues or organs from one species to another.[1] Some authors believe that for one allotransplantation, there are around ten patients in the waiting list.[2] Various studies have shown that transplant results in less long term mortality and better quality of life compared to patients on artificial helps such as chronic hemodialysis and mechanical pumps.[3] Hence, there is a need for transplant from animals to humans. Xenotransplantation has various advantages such as unending supply of organs, resistance to the human infections and predictable schedule.[4]

## HISTORY OF XENOTRANSPLANTATION

The first attempt at organ xenotransplantation was done by Keith Reemtsma in the 1960s.[5] Reemstma transplanted 13 chimpanzee kidneys to humans. Several transplants failed within 4-8 weeks because of rejection or infectious complications. But one of the patients survived for 9 months but suddenly collapsed and died due to an acute episode of electrolyte imbalance. Since then, there were other attempts at xenotransplantation including the use of baboon kidneys by Tom Starlz[6] and others.[7] James Hardy attempted to transplant a chimpanzee heart in a patient but the transplanted heart failed a few hours later.[8] Another notable attempt was made by Leanord Bailey in 1983 whereby he transplanted a heart from a baboon into a female infant girl. While surgically successful, the transplanted organ underwent xenograft rejection 20 days later.[9] Two of the major concerns facing xenotransplantation are immune rejections and transfer of infections from animals to humans.

## IMMUNE REJECTIONS

Any successes seen in xenotransplantation thus far have required advances in better understanding of pathobiology, genetic engineering, improved perioperative management, and novel immunosuppressive drug regimens to counteract the immune response in the host body.

The major sources of xenotransplants are pigs and non human primates. In the context of pigs, humans develop complement activation against galactosea 1-3 galactose (Gal) epitopes found on bacteria, viruses, and parasites in certain pig cells such as the vasculature.[10] Though attempts have been made to prevent complement activation, it has increased the risk of infection.[11] Transgenic pigs have been engineered to express human complement regulatory proteins including CD46, CD55 or CD59 to confer resistance to the donor organs. However, mean survival time for these transplanted organs is 3 weeks.[12,13] Research has also looked into anti-gal antibodies by either ex-vivo removal or in-vivo blocking of antibodies using non-antigenic Gal-polymers or infused carbohydrates.[14,15] The mean survival time forCD46 heterotropic transplant is 96 days.[16,17,18,19]

Certain research groups have been successful in producing genetically engineered anti-gal knockout pigs (GTKO). In 2005, the first heterotropic cardiac xenotransplantation was conducted that used T-cell and anti-CD154 antibody immune suppression and were able to sustain the survival time between 78-179 days.[20] Improvements have also been made in immune suppression in the recipient, using a combination of ATG induction therapy and B-cell depletion with chronic anti-CD154 immune suppression.[21] There are associated problems with using anti-CD-154 antibodies including a higher incidence of perioperative thrombocytopenia and post-transplant consumptive coagulopathy. Alternative therapies have focused on using anti-CD40 antibodies with survival times upwards of 200 days[1], where some grafts showed remarkable contractility for 945 days.[22]

## XENOTRANSPLANT ZOONOSIS

Though no actual incidence of xenotransplant zoonosis have been reported in literature, the theoretical risk does exist. The recipients are immunosuppressed and are more predisposed to the infection. Apart from being a potential source of infection, it is also a risk for break of widespread

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disease into the human population.[2] These zoonosis can be bacteria, fungi, parasites, and most importantly viruses.[23] Swine influenza and Nipah virus encephalitis are some of the recent epidemics that have jumped from swine to humans. Pigs carry an endogenous retrovirus called PERV that has been shown to infect human cells in vitro. PERV are viruses that have become an endogenous part of the porcine DNA and cannot be excluded from the porcine DNA before the transplantation. Though a lot have patients have received the porcine transplants, till now no single case of PERV transmission has been reported.

It is even more difficult to rear infection free NHP compared to pigs.[24] The infection in NHP may be silent but may cause fatal infections in other species. Some examples are cercopithecine herpesvirus 1 (B virus) from macaque monkeys which causes encephalitis in humans, HIV 1 from chimpanzees and HIV 2 from sooty mangabeys. NHP are also known to have two retroviruses SFV and BaRV which cannot be eliminated easily. The major problem with retroviruses like BaRV is that they cannot be isolated from baboons DNA and have been shown to be xenotropic in laboratory.[23]

**Xenografts**

Xenografts are the use of animal products instead of solid organs. The major advantage is that these product lines do not come directly in contact with the humoral response of the body. This helps it to escape rejection. Xenografts are considered a device and therefore the Center for Devices and Radiological Health (CDRH) department of the FDA regulates them. Xenografts (acellular tissue) are not subject to the same degree of regulation as cellular tissue from animal sources. The current guidelines for medical devices derived from animal sources explicitly exclude in vitro diagnostic device standards (Draft Guidance, 2014).

The FDA recognizes that acellular animal-derived materials in medical devices carry an infectious disease risk when improperly collected, stored, or manufactured.[27] The current guidance document from the FDA is in draft form at this time, and has been updated from the FDA's 1998 guidelines. The guidelines outlined in 1998 focused heavily on preventing bovine spongiform encephalopathy in the wake of the historical outbreak of the disease in Great Britain in the late 1980s. At the writing of the 1998 guidance, the CDRH had

| Herd | Source animal | Facility and processing | Patient |
|---|---|---|---|
| Management of closed herd | Qualification | Harvesting procedure details | Consent, education, follow-up |
| Strain, genealogy of source animal | Screening for infectious agents | Processing of the tissues at the facility | Screening of patients for infection |
| Housing maintenance | Veterinary care | Assay design for detection of infectious agents | Review of protocol |
| Facility accreditation by AAA-LAC Approval of husbandry | Animal history | Animal termination and disposal | Clinical site maintenance |
| | No transportation of source animal | | |
| Recording of details | | | |
| Information that needs to be documented for xenotransplantation[28,36] | | | |

| Device | Processing |
|---|---|
| Pericardial valves (bovine) | -Sheets of bovine pericardium mounted inside or outside a supporting stent.<br>-Sterilization: chemical (glutaraldehyde), radiation (gamma, microwave)[30] |
| Viscera gut sutures (bovine, ovine intestines or from bovine tendon) | -Sterilized with fluid containing ethylene oxide, isopropyl alcohol, distilled water[31,32] |
| Dental implants (bovine bone) | |
| Collagen sheets/dressings/shields (equine, bovine, porcine) | -Cross-linking methods: chemicals (glutaraldehyde, isocyanates, sugars, carbodiimides), mechanical (heat) and/or radiation (UV, gamma) in the presence of activators.<br>-Sterilization methods: chemicals (ethylene oxide or glutaraldehyde), radiation[33] |
| Collagen corneal shield (porcine sclera or bovine dermis) | -Corneal shield crosslinked with UV, supplied in dehydrated form requiring rehydration prior to use. Made of type I and some type III collagen[34] |
| Bioprosthetic valves (porcine) | -3 porcine aortic valve leaflets cross-linked with glutaraldehyde and mounted on a metallic or polymer supporting stent. Now commonly treated with anti-calcification agents as well to improve lifespan of device. Intact porcine aortic valve preserved in low-concentration glutaraldehyde solution - reduces antigenicity and stabilizes tissue against proteolytic degradation.[35] |
| **Processing of example tissues** | |

developed the CDRH Biomaterials Database that continues to maintain an inventory of medical devices which either contain or are exposed to animal-derived materials during manufacturing. The database tracks type of material, animal species and country of origin, and target organ or tissue for each device. Although this database was originally created in response to the historical BSE issue, it was further expanded to include all animal-derived products (including human).

**CDRH guidance (1998) summary**

- Bovine material should not come from cattle in a country with significant risk of BSE (including all countries in Europe).
- Device manufacturer should keep traceable records for each lot of bovine material as well as each lot of FDA-regulated product.
- Country of origin and residence of animals should be included.
- Source tissue should also be indicated.
- If the bovine-derived material is only available from a country with BSE existence, the manufacturer must indicate that BSE is inactivated during the processing using a validation study or other valid scientific evidence; these methods may require review by experts in the TSE field.[26]

**CDRH Draft 2014 (Changes to the 1998 guidance)**

The 1998 guidance focused largely on bovine sources especially in the wake of the bovine spongiform encephalopathy outbreak. The 2014 Draft Guidance broadened the spectrum to include of recommendations for control of transmissible disease related to all transmissible spongiform encephalopathies (not just bovine spongiform encephalopathy) as well as viruses and bacteria. It also contains recommendations for documenting source of animal tissue and conducting viral inactivation validation studies.

**The information that need to be documented**

- Species and age of animal (herds that have been properly screened for diseases should be used, the history of exposure to infections such as TSE needs to be properly documented),
- Specific tissues used,
- Animal country of origin and residence (as far as possible the use of animals from USA should be preferred, the animal cannot be sourced from any country in which TSE is known to be prevelant)
- Methods for monitoring the health of the herd and the health of specific animals from which tissues are collected (vaccinations, active surveillance for human pathogens, screening frequency , methodology needs to be mentioned)
- USDA status of the abattoir(animals from abattoirs should be avoided as far as possible),
- Methods and conditions for transport of tissue,
- Procedures for maintaining above mentioned records[27]

## METHODS OF DOCUMENTATION

- Test methods and release criteria permitting animal tissues to be further processed,
- Quarantine procedures for tissues until they have met/failed release criteria,
- Test methods and acceptance criteria for assessing in-process and final product bioburden or sterility,
- Methods for facility decontamination/sterilization so that cross-contamination is avoided,
- Procedures for maintaining above mentioned records

Manufacturers should also demonstrate and validate equipment cleaning, decontamination, and sterilization relative to the specific pathogen exposure, documenting results.

**Some of the Examples of xenografts used in humans are**

*Bovine* – Pericardium used in heart valves, viscera used in gut sutures, bone used in dental implants, collagen used in lacrimal plugs, human cells grown in media containing fetal calf serum, tissue culture cells exposed to bovine trypsin.

*Porcine* – Heart valves, collagen corneal shields, blood vessels in vascular grafts, collagen in wound dressings

*Device Components* – Pericardium, viscera, bone, hyaluronic acid, collagen

*Manufacturing reagents* – Tissue culture media, enzymes
These tissues require proper sterilization

## CONCLUSION

These advances in the last few years alone have been encouraging. As reflected here, xenotransplantation is a multi-steps process and multiple prong approach will have to be adopted to ensure the success of xenotransplated organs. As the scientific community tackles the physiological and immunological barriers to xenotransplantation, discussions should also be underway regarding the ethical, moral, and psychosocial challenges associated with the individual and public acceptance of xenotransplantation.

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