CONSENSUS PERSPECTIVE

Perspectives on the 2026 ISHLT Consensus Statement on Clinical Cardiac Xenotransplantation

Mandeep R. Mehra, MD, MSc, FRCP,[a] Muhammad M. Mohiuddin, MD, DSc,[b] Bruno Reichart, MD PhD,[c] Jan-Michael Abicht, MD,[d] Jacinthe Boulet, MDCM, MPH,[e] David K.C. Cooper, MD, PhD,[f] Peter J. Cowan, PhD,[g] Maria G. Crespo-Leiro, MD,[h] Joachim Denner, PhD,[i] Jay A. Fishman, MD,[j] Bartley P. Griffith, MD,[b] Wayne J. Hawthorne, MD, PhD,[k] Emer Joyce, MD, PhD,[l] Igor E. Konstantinov, MD, PhD,[m] Anuradha Lala, MD,[n] Matthias Langin, MD,[d] Robert F. Padera Jr. (MD, PhD,[o] Richard N. Pierson III (MD,[f] Angelika Schnieke, PhD,[p] Linda Scobie, PhD,[q] Patricia A. Uber, Pharm D,[r] Eckhard Wolf, DVM,[s] and Ann E. Woolley, MD, MPH[t]

[a]Mass General Brigham Heart and Vascular Institute and Harvard Medical School, Boston, MA; [b]Department of Surgery, University of Maryland School of Medicine and University of Maryland Medical Center, Baltimore, MD; [c]Walter Brendel Center of Experimental Medicine, Ludwig-Maximilians-University Munich, Munich, Germany; [d]Department of Anaesthesiology, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; [e]Department of Medicine, Montreal Heart Institute, Université de Montréal, Montréal, QC, Canada; [f]Department of Surgery, Massachusetts General Hospital/Harvard Medical School, Boston, MA; [g]Immunology Research Centre, St. Vincent's Hospital Melbourne, and Department of Medicine, University of Melbourne, Melbourne, VIC, Australia; [h]Advanced Heart Failure and Heart Transplant Unit, Complexo Hospitalario Universitario A Coruña, CIBERCV, A Coruña, Spain; [i]Institute of Virology, Free University Berlin, Berlin, Germany; [j]Transplant Infectious Disease and Compromised Host Program, Massachusetts General Hospital and Harvard Medical School, Boston, MA; [k]Department of Surgery, School of Medical Sciences, University of Sydney, Westmead Hospital, Westmead, NSW, Australia; [l]Mater University Hospital and University College Dublin, Dublin, Ireland; [m]Department of Cardiothoracic Surgery, Royal Children's Hospital, Department of Pediatrics, University of Melbourne, Heart Research Group, Murdoch Children's Research Institute, Melbourne, Australia; [n]The Mount Sinai Fuster Heart Hospital, Icahn School of Mount Sinai, New York, NY; [o]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [p]Chair of Livestock Biotechnology, School of Life Sciences Weihenstephan, Technische Universität München, Freising, Germany; [q]Biological and Biomedical Sciences, Glasgow Caledonian University, Scotland, United Kingdom; [r]Department of Pharmacy, Atrium Health Wake Forest Baptist Medical Center, Winston Salem, NC; [s]Chair for Molecular Animal Breeding and Biotechnology and Center for Innovative Medical Models (CiMM), Ludwig-Maximilians-Universität München, Munich, Germany; [t]Division of Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

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Corresponding author: Mandeep R. Mehra, MD, MSc, FRCP, Brigham and Women's Hospital Heart and Vascular Center, Center for Advanced Heart Disease, 75 Francis Street, Boston, MA 02115.
E-mail address: mmehra@bwh.harvard.edu.

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1. INTRODUCTION

In 2000, the International Society for Heart and Lung Transplantation (ISHLT) issued its first consensus on xenotransplantation, cautioning that thoracic organ xenotransplantation was not yet ready for human trials. Significant immunologic barriers, infection concerns, and ethical considerations demanded more research before clinical application could be contemplated. Two decades of scientific progress — in genetic engineering of donor pigs, immunosuppressive strategies, organ preservation, and preclinical non-human primate models — have brought the field to an inflection point. Two genetically modified pig-to-human heart transplants have been performed, revealing both the promise and the complexities of this frontier.

The 2026 ISHLT Consensus Statement on Clinical Cardiac Xenotransplantation[1] distills current knowledge into a pragmatic blueprint that reviews the pilot cases and their learnings, ascertains clinical trial readiness and the successes necessary to pursue such a pathway, and the infrastructure and technological readiness needed to responsibly advance the field. This perspective summarizes the most critical guidance from that statement, offering an accessible entry point for clinicians, researchers, and regulatory stakeholders.

2. TOP TAKEAWAYS

- ***Preclinical Evidence Threshold*** – Before human trials can be recommended, we require data from at least 5–10 non-human primate models across multiple centers, each demonstrating ≥6 months of survival with normal xenograft function achieved on stable maintenance immunosuppression.
- ***Initial Clinical Candidates*** – We recommend that individual 'expanded access' cases should continue to be brought forward to contribute to the clinical experience in an ethical and careful manner. In such cases, adults ineligible for durable mechanical circulatory support or allotransplantation, and infants/children with complex congenital heart disease lacking other options could serve as suitable initial candidates. Initial recipients should have low anti-donor porcine antibody levels (at a minimum a negative complement-dependent cytotoxicity crossmatch and no more than low-level anti-donor IgG or IgM by Flow cross match).
  If results of 'compassionate' initial experiences meet thresholds for success, a pivotal/pilot trial in 'destination' patients may be considered. The patients suitable for such initial and pivotal experiences could include the elderly (e.g. > 75 years), highly sensitized individuals with or without an artificial heart pump option, those with cancer of recent onset but currently with no evidence of active disease, individuals with tropical cardiomyopathies, amyloidosis unable to receive immunoablative therapy (but without severe non-cardiac organ dysfunction), those with severe restrictive cardiomyopathy and small chamber size who are unable to be supported with mechanical circulatory support. Additionally, infants after a Norwood procedure and those with complex congenital heart disease without other options could be considered.
- ***Source Pig Genetic Modifications*** – At minimum: deletion of αGal, Neu5Gc, and Sda antigens; expression of human complement and coagulation regulatory proteins. Consider anti-inflammatory and immune-modulatory transgenes for added protection.
- ***Organ Size Matching*** – Use imaging (CT or echocardiography) to ensure adequate donor organ size. Stroke volume estimation is a reliable surrogate when echocardiographic imaging is poor.
- ***Organ Recovery and Preservation*** – In adults, employ hypothermic oxygenated continuous perfusion with Steen solution to reduce early dysfunction. Alternative solutions and preservation methods remain under investigation, especially for pediatric use.
- ***Intraoperative and Immediate Postoperative Management*** – Avoid proarrhythmic catecholamines; use prophylactic antiarrhythmics. Maintain strict electrolyte control and manage blood pressure to prevent hypertrophy. Minimize transfusions unless screened for low anti-pig antibody content.

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- ***Immunosuppression Strategy*** – Perioperative T- and B-cell depletion plus complement inhibition for all cases. Incorporate costimulation blockade (anti-CD40 or anti-CD154) alongside steroids, calcineurin inhibitor, and mycophenolate mofetil. Use proliferation signal inhibitors if hypertrophy develops.
- ***Immunologic Surveillance*** – Regular endomyocardial biopsies, negative crossmatch against donor phenotype, and antibody monitoring are essential. Consider experimental biomarkers (e.g., porcine cell-free DNA, troponin trends) as adjuncts.
- ***Infectious Disease Risk Mitigation*** – Exclude zoonotic and xenozoonotic pathogens from breeding herds. Prefer PERV-C negative donors and screen for microchimerism. Maintain validated, sensitive assays for porcine-specific viruses in both donors and recipients.

3. CONCLUSION

The 2026 ISHLT consensus marks a pivotal transition from theoretical readiness to structured, measured clinical application in cardiac xenotransplantation. The outlined recommendations balance innovation with patient safety, providing a roadmap for early pilot cases, regulatory engagement, and eventual trial-scale deployment.

While many scientific, immunologic, and ethical questions remain, the field now stands on a foundation built by two decades of rigorous research and cautious clinical forays. By adhering to these principles, the transplantation community can responsibly expand the donor organ pool and offer life-saving options to patients who would otherwise have none.

Reference

1. Mehra MR, Mohiuddin MM, Reichart B, et al. 2026 International Society for Heart and Lung Transplantation Consensus Statement on Clinical Cardiac Xenotransplantation. J Heart Lung Transpl 2026. (xx:xxx–xxx).

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