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**INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
ISSUES COMPREHENSIVE GUIDELINES ON HOW AND WHEN
TO PROCEED WITH ANIMAL-TO-HUMAN HEART AND LUNG TRANSPLANTS**

DALLAS, Dec. 15 -- Despite the critical shortage of human donor organs, transplants involving hearts or lungs from pigs should not be permitted at the present time. But clinical trials of such transplants would be justified and should be encouraged when researchers achieve acceptable results in animal studies, but only if, at that time, experts determine there to be little potential for the spread of animal viruses to humans.

These and other recommendations are being made by a group of leading scientists, physicians and surgeons brought together by the International Society for Heart and Lung Transplantation (ISHLT) to review the current status of cross-species transplantation -- or xenotransplantation -- and its potential in the treatment of patients with end-stage heart and lung diseases. This first-ever comprehensive review specific to these vital organs is published in this month's *Journal of Heart and Lung Transplantation*.

With about 1,200 patients dying each year on heart and lung transplant waiting lists in the United States alone, researchers are constantly looking for ways to expand the number of donor organs that become available. While there is no question that human organs are best suited for humans, xenotransplantation research should be pursued, say the authors, because animals, such as the pig, could offer an unlimited supply of organs and allow the transplant procedures to be scheduled on an elective basis. The pig is considered to have the best potential as a donor, but because of its genetic differences to humans, researchers must devise strategies to overcome the rejection of pig organs. Rejection and a number of other hurdles must be overcome before testing can be permitted to evaluate xenotransplantation's full potential in patients. Several strategies, such as "humanizing" the pig organs by introducing certain human proteins into the pig, show promise.

Given the early stage of research into xenotransplantation of the lung, lung transplantation using a pig organ is at present far from becoming a reality. Continued

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advancements, however, could make pig-to-human heart transplants feasible within a few years, say the authors, who provide goals they would like to see achieved in the experimental laboratory before considering a trial in patients.

"We would require sufficient evidence from animal studies to assure us that the donor organ could meet the physiological needs of a human recipient, and that the methods used to prevent rejection would not otherwise compromise the patient's health and quality of life," explains lead author David K.C. Cooper, M.D., Ph.D., FRCS., of Massachusetts General Hospital and Harvard Medical School, who co-chaired the ISHLT Xenotransplantation Advisory Committee.

Specifically, the authors recommend that, if the clinical trial were intended to provide long-term support of the patient, then laboratory evidence would need to be provided to indicate that the transplanted pig heart could support a good quality of life for at least six months. This would need to be achieved in the absence of life-threatening complications from the immunosuppressive drugs required to control rejection. Currently, in studies of orthotopic heart transplants, where the donor organ is placed in the normal life-sustaining position in the chest, the longest a nonhuman primate has survived supported by a pig heart has been 39 days, a result that the authors nonetheless see as encouraging.

Provided the necessary research advances are made and other questions are satisfactorily resolved -- regarding the potential risks of animal-derived infections being introduced into the community, for example -- then a trial would be justified. Patients considered for an initial clinical trial should be those who are either currently excluded from receiving a human heart or are unlikely to survive the wait for a human heart and do not qualify for mechanical heart support. While several ethical questions surround the inclusion of infants and children in such a trial, the report recommends that, if there is no alternative for them except death, they should not be absolutely precluded.

"These are very difficult decisions," says Anne Keogh, M.B., B.S., M.D., of St. Vincent's Hospital at the University of New South Wales in Sydney, the advisory committee co-chair and current president of the ISHLT. "But we gave every issue our most careful consideration, from close inspection of the science to discussion of the ethical and social implications." The advisory committee calls for an ongoing review of the scientific and ethical issues, and strongly advocates appropriate oversight of any studies in patients by national regulatory bodies and international organizations, such as ISHLT.

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One issue the authors considered in detail is whether a transplanted pig heart would be preferable to an artificial (mechanical) heart. They acknowledge that, for some patients with heart failure, there already exists the option of a mechanical heart, at least as temporary support (a “bridge”) to maintain life until a human heart transplant can be performed. And researchers are working to develop better mechanical devices for long-term or permanent support, some of which are presently being tested in patients.

While the experts agree that a human organ transplant is a patient’s best option, and efforts to raise awareness about organ donation must continue to be a priority, they also acknowledge that research into the use of animal organs and mechanical hearts holds much promise.

"Further developments in implantable mechanical devices or major advances in xenotransplantation would appear to represent the most likely potential solutions (to the shortage of human donor hearts) in the medium term," concludes the ISHLT committee. An implantable artificial lung, however, seems unlikely to be developed in the foreseeable future.

There has never been an attempt to transplant an animal’s lungs into humans, but animal hearts have been transplanted on a number of occasions dating back to 1964 when surgeons tried unsuccessfully to sustain a patient's life with a chimpanzee's heart. Probably the most famous patient was Baby Fae, who survived 20 days with a baboon heart in 1984. The only known cases of pig-to-human heart transplants were in 1991 in Poland and in 1996 in India. Neither involved the use of a humanized or transgenic pig, and the organs failed in less than 24 hours.

“It’s important to understand that at present by far the best option for patients with heart and lung failure is transplantation with human organs, and it is the altruism of people willing to donate their loved ones’ organs that makes it possible for countless lives to be saved,” asserts Dr. Keogh.

In addition to Drs. Cooper and Keogh, other authors and members of the ISHLT Xenotransplantation Advisory Committee are: Johan Brink, MB, ChB, FCS (SA) (South Africa); Paul A. Corris, M.D., FRCP (UK); Walter Klepetko, M.D. (Austria); Richard N. Pierson, III, M.D. (USA); Michael Schmoeckel, M.D. (Germany); Ryota Shirakura, M.D. (Japan); and Lynne Warner-Stevenson, M.D. (USA). The committee was assigned its charge in 1999 by Robert Kormos, M.D., then president of the ISHLT, who is affiliated with the University of Pittsburgh Medical Center.

Following are some of the committee's conclusions and recommendations. For a complete listing of the conclusions and recommendations, as well as information about the clinical history of heart and lung xenotransplantation, please go to www.ishlt.org. The site also includes an executive summary and the advisory committee's entire report.

Conclusions:

- There is a worldwide need for an increased supply of donor thoracic organs, and xenotransplantation offers the possibility of an unlimited number of organs that could be made available as required.
- Unresolved questions relate to immune barriers, the function and growth of pig organs in a human metabolic environment, and whether a pig heart used as temporary support (a "bridge") would affect the outcome of a subsequent human heart transplant.
- Current experimental results indicate that a clinical trial of heart xenotransplantation is premature. Experimental lung xenotransplantation is at an extremely primitive stage of development and no consideration for a trial can be given at the present time.
- There is an undetermined yet potential risk that an infectious organism could be transferred from the donor pig organ to the recipient, and possibly to members of the community.

Recommendations:

- Every effort should be made to improve medical treatment for patients with advanced heart and lung disease in order to minimize the number needing organ transplants. Likewise, every effort should be made to improve human organ donation rates.
- A clinical trial of pig organ transplantation should be undertaken only when experts in microbiology and the relevant regulatory authorities consider the potential risks of transfer of a pig-related infection to members of the community to be minimal.
- All xenotransplant trials should be regulated by national bodies that have far-reaching government-backed control, including the authority to halt them if deemed necessary. An international body, such as the ISHLT, should monitor the trials and serve as a registry of information and data.
- A clinical trial for permanent placement of a pig heart should be considered only when studies of pig-to-primate life-supporting transplants achieve a 60 percent survival for a minimum of 3 months in at least 10 animals, and evidence is provided that 6 months survival can be attained. It must be demonstrated that the immunosuppressive regimen will not produce life-threatening complications.
- Initial patients should be those not acceptable for transplantation using a human donor organ but who are not so sick that the potential for success of the trial is diminished. Other patients could be those not likely to survive the wait for a human donor organ and for whom mechanical bridging is not possible. Infants and children should not be absolutely precluded from the trial.
- An initial clinical trial should be limited to a small number of patients, and should only be carried out as an extension of a planned experimental program and by those involved in the development of the protocol.

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