DeBakey/Cooley Joint Session

The Future of Liver Transplantation

Christine A. O'Mahony, MD
John A. Goss, MD

The most successful treatment for end-stage liver disease is orthotopic liver transplantation (OLT). As of June 2012, more than 17,000 patients in the United States were awaiting a liver transplant. The first successful kidney transplantation in a human being, performed in 1954, prompted several liver-transplantation attempts in 1963 and 1964 in the U.S. and Europe. The initially dismal results led to a moratorium on liver transplantation until 1967, when Thomas Starzl performed the first successful OLT.[1] Refinements in operative techniques, improved patient selection, the development of immunosuppressive medications and preservation solutions, and improvements in postoperative management have contributed to the widespread success of liver transplantation. In the U.S., the expected one-year survival rate after liver transplantation approaches 90%.

Numerous aspects of liver transplantation can still be improved upon. More than 1,700 people died in the U.S. last year while awaiting a liver. Major reductions in waiting-list deaths will require a substantial increase in organ donations. There have been increases in donor-awareness campaigns, professional-education efforts, and legislative changes. Regardless, the number of deceased donors has remained essentially unchanged.

One of the largest expansions in the deceased-donor pool has arisen from the increased use of extended criteria. In part, extended criteria encompass the following: livers from donors of advanced age, blood (ABO incompatibility), steatosis (fatty liver), hepatitis C virus (HCV) and other active infections, Centers for Disease Control and Prevention (CDC) high-risk donors, livers donated after cardiac death, split livers, and living donors.

Advanced-Age Donors. The consensus is not to exclude donors solely on the basis of their older age, especially in view of the allograft shortage.[2] If an advanced-age allograft is evaluated as suitable, it could be appropriate for a recipient who might otherwise wait much longer for a "perfect" allograft.

Blood-Type Incompatibility. Little in the medical literature deals with the effects of ABO incompatibility on OLT. With some exceptions, ABO-incompatible liver allografts are not routinely used beyond emergent need in pediatric recipients.

Steatosis. In the past, steatosis caused many donor livers to be discarded during evaluation; currently, liver allografts with substantial steatosis are being transplanted successfully after careful evaluation of the donors and recipients. As the epidemic of obesity continues within developed countries, even more steatosis may be found during the evaluation of donor allografts.

Virally Infected and High-Risk Donors. Transplantation of liver allografts from donors infected with HCV has increased. Overall, OLT involving HCV-positive allografts into HCV-positive recipients is safe and yields long-term survival outcomes comparable to those of HCV-negative allografts.[3] In addition, hepatitis B core-positive donor livers are routinely used with little effect on postoperative survival rates. The transmission of viruses, such as human immunodeficiency virus (HIV) and HCV, continues to be of concern. According to the CDC, high-risk donors include intravenous-drug users, hemophiliacs, and prison inmates; and persons with a history of prostitution, high-risk sexual activity, or exposure to HIV.

Donations after Cardiac Death. Livers can come from donations after cardiac death (DCD). Using these livers can increase the risk of ischemia to the allograft. With careful donor and recipient selection, the use of DCD allografts has resulted in survival rates similar to those of conventional allografts.[4] Because of ongoing organ shortages, many centers are considering the use of allografts from high-risk and DCD donors,

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From: *Division of Abdominal Transplantation and Hepatobiliary Surgery, Baylor College of Medicine, Houston, Texas 77030*

Address for reprints: *Christine A. O'Mahony, MD, Division of Abdominal Transplantation, Baylor College of Medicine, 6620 Main St., Suite 1425, Houston, TX 77030*

E-mail: *comahony@bcm.tmc.edu*

weighing the risk of transmitting potentially fatal disease against the decompensation or death of the wait-listed recipient.

Split Livers. Split-liver donation, in which one allograft is divided into 2 transplantable allografts, is another way of expanding the donor pool. This method, introduced to decrease mortality rates in wait-listed pediatric patients, has been adapted for adults. Livers have typically been split into one graft for a pediatric recipient and one for an adult patient; however, evidence now supports the implantation of both grafts into size-appropriate adults. Special caution is required: splitting techniques demand technical precision, and not every liver allograft is appropriate for splitting. Survival rates will increase as centers gain experience in this technically difficult type of transplantation.

Livers from Living Donors. Some centers have performed living-donor liver transplantations. Many institutions, including our own, no longer routinely perform these operations in adults. The procedure is ethically charged, because the operative team must weigh the safety of the donor against the risks to the recipient of remaining on the waiting list.

Technological Efforts

The ongoing efforts to expand the current donor pool have had only a marginal effect on the survival rates of wait-listed patients. Support devices exist for patients with respiratory, cardiac, and renal failure. In contrast, no model has bridged patients to liver transplantation with widespread success. Numerous attempts to develop an artificial liver—hemodiafiltration, albumin dialysis, plasma exchange, and bioartificial systems using viable liver cells—have been successful in several instances. However, the impact on outcomes is disputed, and further development is restricted by costs.

Xenotransplantation. Xenotransplantation is controversial. Early results in primate models were dismal. The development of genetically modified pigs has greatly reduced hyperacute rejection. However, the sequelae of severe postoperative thrombocytopenia and the risks of infection transmission are substantial obstacles in liver xenotransplantation.[5]

Immunosuppression

The use of cyclosporine has greatly increased survival rates after OLT. Tacrolimus, introduced in the 1990s, has had a positive impact on postoperative survival. Although the immunosuppressive medications in current use are very effective, their side effects include hypertension, diabetes mellitus, renal failure, seizures, cancer, and bacterial and viral infections.

Immunosuppressive strategies and protocols are rapidly changing. Works in progress include elucidating the mechanisms of allograft rejection, developing medications to inhibit the immune response in various steps, devising protocols to target a patient's individual genetic makeup, and targeting a patient's underlying disease with novel therapeutic modifications. Optimally, the findings in these investigations will minimize the long-term toxic effects of the current immunosuppressive regimens. Ongoing studies of tolerance will precede any declarations of success.

Summary

Improvements in surgical techniques, postoperative care, and donor and recipient selection have all contributed to the increased success of OLT and to higher survival rates in patients with advanced liver disease. This progress in liver transplantation has occurred in only 45 years, since the preliminary work of Dr. Starzl,[1] and provides a basis for future advances.

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