Physicians Seek To Expand Kidney Donor Pool

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are seeking to overcome the limitations presented by the small donor pool available for kidney transplantation by aggressively pursuing several strategies that aim to solve the problem of blood-type incompatibility as well as other issues. Ultimately, the goal is to save lives.

Columbia researchers are studying the potential for transplantation of kidneys across blood groups by conducting plasmapheresis to remove antibodies directed at the foreign blood group. They are also developing procedures to “swap” kidneys when donors can be better matched to a different recipient.

Each approach has its advantages and challenges and is selected according to the specific circumstances of the patient, but each has the potential to increase the pool of candidates who undergo successful transplantation.

“Since we started these programs, we have performed 22 kidney transplants in patients who otherwise would not have received a transplant,” noted Lloyd Ratner, MD, adding that these new approaches appear to be viable and promise long-term graft survival.

Plasmapheresis to remove antibodies in patients with either blood group or cross-match incompatible grafts also removes antibodies important to immune defenses, so Dr. Ratner and his team have developed a protocol for
Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital have been involved in many of the key innovations in islet cell transplantation, an intervention that has the potential to cure type 1 diabetes mellitus.

Currently, the work performed in steroid-sparing regimens by Sandip Kapur, MD, and Manikkam Suthanthiran, MD, has been important because the research has an impact on the toxicity that steroids pose to islet cells. Mark Hardy, MD, has also been an innovator in modifying and titrating immunosuppressive drug regimens to reduce toxicity without jeopardizing graft survival.

The progress in steroid-sparing immunosuppression was pioneered in renal transplantation. Due to the advances in preventing rejection after transplant, some of the focus on improving long-term survival has turned to preventing long-term complications, such as atherosclerosis, which are associated with immunosuppressive regimens. Lessons generated from extensive experience in other types of organ transplantation are being applied in islet cell transplantation.

The islet transplantation program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center was initiated 2 years ago, with the first transplantation performed in 2004. According to Dr. Kapur, the program is “a true multidisciplinary effort that involves transplant specialists and endocrinologists” who work together to select candidates and plan preoperative, intraoperative, and postoperative care. The first patient to receive islet cell transplantation has been able to abandon insulin completely due to the ability of the transplanted cells to respond appropriately to physiologic demands.

The second successful transplant was completed recently, and the patient is rapidly being weaned off insulin with islets from a single pancreas. Dr. Suthanthiran credited “refinements in the islet isolation procedure,” implemented by Hua Yang, MD; “the high level of expertise of our interventional radiologist,” David Trost, MD; and the “meticulous posttransplant care” by Dolca Thomas, MD, and Meredith Aull, MD. “This is a great achievement because it potentially means she will be cured with islets from just 1 donor, compared to standard islet transplants that require at least 2 donors,” noted Dr. Kapur.

One reason to anticipate further progress in transplant survival is the work being done on early detection of rejection. According to Dr. Suthanthiran, gene-based diagnostic assays have demonstrated significant promise and have the added advantage of being minimally invasive procedures. Such an approach permits more frequent surveillance, earlier modification of the immunosuppressive regimen, and an optimized immunosuppressive drug maintenance.

“If we can identify signs of rejection in the earliest stages, we can adjust therapies rapidly,” said Dr. Suthanthiran, “and keep patients on the lowest doses and best tolerated immunosuppressive drugs until they need more aggressive therapy.”

Currently, criteria for islet cell transplantation candidates at NewYork-Presbyterian/Weill Cornell include frequent episodes of hypoglycemia despite optimal management that includes exogenously administered insulin. The program is evolving quickly, and the selection criteria may change as more is learned about optimal techniques and long-term outcomes. Transplantations at NewYork-Presbyterian Hospital/Columbia University Medical Center are being restricted to diabetics who have already had a renal transplant. Candidates must have a kidney that is free of progressive diabetes-induced damage. Appropriate immunosuppression is the key to survival of both the renal and the islet cell grafts.

“We are understanding much more about both the short-term and long-term toxicities of immunosuppressive agents, [which] is helping us to better choose drugs and regimens that provide the greatest likelihood of a favorable outcome,” Dr. Hardy observed. He noted that careful monitoring of signs of rejection has also been important in achieving an optimal balance between preventing episodes of rejection while reducing the risk of toxicities or excessive immunosuppression. With the
work of Kevan Herold, MD, as well as collaboration with Paul Harris, MD, Peter Witowski, MD, and Ronald Van Heertum, MD, a radiologist, significant progress has been made in detecting viable islet tissue in experimental studies using positron emission tomography. This could permit rapid detection of islet rejection and may offer the opportunity for more effective modification of immunosuppressive therapy.

One of the greatest challenges to islet cell transplantation has been acquiring donor tissue. According to Dr. Hardy, the pancreas is not being recovered from donors in the same numbers as other commonly transplanted organs, particularly the kidney and the liver. However, unlike whole pancreas transplantation, there are fewer restrictions on candidate donors when only islet cells are used.

“Donors over the age of 50 or who have a body mass index greater than 29 are not generally considered an acceptable source of a whole pancreas, but these individuals may be appropriate donors of islet cells,” said Dr. Hardy. However, he noted that even with fewer restrictions, islet cell transplantation will continue to be limited by donor supply.

“The success of islet cell transplantations so far provides a proof of principle that this is a viable procedure.”

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Research Demonstrates Positive Outcomes with Extended Donor Lungs

Columbia researchers at NewYork-Presbyterian Hospital have found that recipients of transplanted lungs from “extended donor pools” have the same survival rate as patients who receive lungs that meet the formal criteria for transplant acceptability. Because lung transplantation is currently limited by the number of suitable donor organs, according to Selim Arcasoy, MD, senior author of a recently published study, many lung transplant programs have begun using extended donor lungs or lungs that do not meet the formal criteria for acceptability. The ideal criteria for lung transplantation are based on very little evidence, noted Dr. Arcasoy. “Instead, they’re based on experience and opinion,” he said.

Indeed, results from the new study at NewYork-Presbyterian Hospital/Columbia University Medical Center—published in the noted journal Transplantation (2005;79:310-316)—indicate that transplant surgeons can safely continue to use what have been considered unusable lungs with good results. “This can further increase the pool of special donors and help decrease the organ donor shortage,” said study co-author Joshua R. Sonett, MD.

Drs. Arcasoy and Sonett and their colleagues performed a retrospective cohort study of all patients who had undergone lung transplantation at NewYork-Presbyterian/Columbia from July 2001 to July 2003. They compared the outcomes of recipients of extended donor lungs with those of recipients of optimal donor lungs. Twenty-seven (53%) of 51 patients received extended donor lungs. Overall, the results showed no differences in the 30-day and longer-term survival rates of recipients of extended and optimal donor lungs. Recipients of extended donor lungs, however, did have a longer stay in the intensive care unit and a longer time to hospital discharge than did recipients of optimal donor lungs. In addition, extended donor recipients had a lower forced expiratory volume at 1 year than did optimal donor recipients. However, this was a measured difference and did not appear to have a clinical effect on patients, explained Dr. Sonett.

Pulmonary function may have been poorer in the recipients of extended donor lungs because of older donor age, cigarette use, or lung abnormalities that appeared on X-ray films, explained Dr. Arcasoy. However, the real significance of recipients of extended donor lungs with those of recipients of optimal donor lungs.

“We could use donors that we haven’t considered or used in the past with very few problems in the short and long term. Certainly, a larger data analysis from different centers, in a prospective fashion, would be quite important in trying to glean what the most significant factors are when we choose donors.”

—Selim Arcasoy, MD

Chest radiograph before and after lung transplantation.
of a lower level of pulmonary function is unclear, he added. Furthermore, researchers are uncertain about what mechanism reduces pulmonary function. It may be related to poorer donor quality compared with ideal donors, he said.

The researchers concluded that the criteria for the optimal lung donor should be reevaluated considering the current shortage of acceptable organs. However, larger, multicenter studies need to be conducted.

“We could use donors that we haven’t considered or used in the past with very few problems in the short and long term,” said Dr. Arcasoy. “Certainly, a larger data analysis from different centers, in a prospective fashion, would be quite important in trying to glean what the most significant factors are when we choose donors.” Further studies could also be developed to identify the genetic makeup of donors and recipients, helping to determine short- and long-term outcomes, he added.

Columbia researchers at NewYork-Presbyterian Hospital are currently working toward enhancing and preserving donor lungs. All such endeavors are directed toward alleviating the problem of a shortage of donated organs, according to Dr. Sonett. Additionally, researchers still need to evaluate how to match donor lungs with recipients. A recipient who is more robust might more easily receive an extended donor lung than a recipient who is frail and likely to require intensive care or a longer hospital stay.

“Sometimes, the outcomes we see are due to donor quality,” said Dr. Arcasoy. “Sometimes, they’re due to recipient quality.”

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reinfusing those antibodies that restore protection from infection. During posttransplant recovery, conventional anti-rejection medications are titrated to prevent rejection episodes.

Blood group incompatibility between patients and their donors has also been a major focus of Weill Cornell researchers’ efforts to increase the pool of patients receiving successful transplants. It is currently estimated that about one third of patients who need a kidney can provide a donor but face incompatibility issues. According to Choli Hartono, MD, resolving blood group incompatibility is one of the most promising approaches for reducing transplant waiting lists.

“The desensitization program we are using involves rituximab, plasmapheresis, and intravenous immunoglobulin, which is effective for bringing down antibody levels to permit cross-matching,” reported Dr. Hartono, who is serving as a principal investigator on several clinical trials testing these protocols. He emphasized that the work at NewYork-Presbyterian Hospital/Weill Cornell Medical Center is highly collaborative. The desensitization protocol has proven effective both for transplanting organs across blood groups and for transplanting organs in patients who are sensitized due to a previous transplantation, blood transfusion, or pregnancy.

“The incompatibility issue is certainly one that deserves to be a major focus of attention, because the ability to increase the proportion of patients who can be successfully transplanted across blood groups is one of our best opportunities to allow patients to avoid the long wait for a compatible organ,” Dr. Hartono observed. He suggested that the NewYork-Presbyterian Hospital programs, where many of the innovations have taken place, have been among the most aggressive in seeking ways to increase the donor pool.

For the transplant kidney exchange program (or donor swapping program) at NewYork-Presbyterian/Columbia, which has been used in 12 patients (6 donors and 6 recipients) so far, patients with donors who are incompatible swap live donors so that each recipient receives a kidney from a donor who is compatible. Due to the very real possibility of the second donor withdrawing from the agreement once the first procedure is performed, leaving one of the potential recipients without an available organ, a large transplant program with sufficiently skilled surgeons is needed.

“To make sure that no one backs out once their loved one gets a kidney, both donors undergo anesthesia and have the surgery at the same time,”

—Choli Hartono, MD

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Use of ‘Expanded Criteria’ Livers Increases Access to Transplantation

Approximately 30% to 50% of donated cadaver livers available for transplantation are considered less than ideal and placed in the category known as “expanded criteria” organs. Nonetheless, most are used, with successful outcomes, at centers such as NewYork-Presbyterian Hospital, which has taken the lead in “informed disclosure”—a process designed for patients receiving these organs.

The use of these organs, regarded as less than ideal because of the donor’s age or medical condition, has doubled patients’ access to liver transplants in recent years, said John F. Renz, MD, PhD. Still, the transplantation of livers that may carry a somewhat higher risk for patients raises medical, legal, and ethical questions about how much information should be conveyed to patients in critical need of liver replacement.

To address these issues, the New York State Health Commissioner last year convened a working group of experts to develop informed consent guidelines related to extended criteria livers. The working group included representatives from the 5 centers in New York authorized to perform liver transplantation surgery in addition to other experts in medicine and medical ethics.

Milan Kinkhabwala, MD, represented NewYork-Presbyterian Hospital, where approximately 120 surgical procedures are performed each year as part of an active and successful liver transplant program. Approximately 20% of the surgeries at NewYork-Presbyterian Hospital involve living donors, and up to half of the rest use expanded criteria organs.

According to Dr. Kinkhabwala, the working group was formed to find answers to questions about whether liver transplant centers in New York are using expanded donor organs more aggressively than centers in other regions.

“It is probably true,” he said, because of “the specific supply-demand imbalances in New York, which are greater than those in other parts of the United States. In our view—and this is shared by the other centers in New York—the use of expanded criteria organs has done a lot to shorten the waiting time and reduce the likelihood of patients dying while waiting. If we didn’t use these organs, we would lose almost half of our potential cadaver livers, and there would be a big penalty for access to liver transplants.”

The working group, continued Dr. Kinkhabwala, studied issues that included the definition of expanded-criteria donors, the actual risk for patients, and the outcomes of transplantation procedures performed with expanded criteria donors. The members also discussed appropriate procedures for informing patients about the risks involved. The result of these meetings is a consensus report that will be presented to the state health commissioner, according to Dr. Kinkhabwala.

One important recommendation outlines a more vigorous process of informed patient consent. For the past 2 years, the Center has used a 3-stage process to educate patients about the risks and benefits of liver transplantation. As a first step, transplant candidates receive a letter during their evaluation that fully describes their options.

“If patients consent to receive an expanded donor liver after having read the information, they sign the letter and we put that in their file,” Dr. Kinkhabwala said. “They are then allowed increased access to transplantation by being eligible to receive either an expanded donor organ or a standard deceased donor organ. If an expanded donor organ becomes available in the middle of the night, we know who we can call.”

Patients going on the waiting list are also told about the different pathways available to shorten their waiting time. In addition to receiving an expanded criteria organ, patients can apply for living donation and simultaneous listings at centers outside New York. Multiple listings offer the chance that an organ will become available sooner in another region where not as many patients are waiting.

In New York, the average wait is now somewhere between 6 months and 1 year. However, the use of expanded criteria donors can cut that waiting
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according to Jonathan M. Chen, MD. One explanation for this improved survival rate may be that Hospital physicians are aggressive in getting young children into surgery as soon as possible. A shorter waiting time often means a lower mortality.

Once children have undergone heart transplant, evaluating long-term survival is crucial. Today, according to Dr. Chen, many patients have survived 20 years with palliative surgery, and some have undergone an additional 4 or 5 heart operations. Many researchers question how well these patients fare when they are reconstructed or need new transplants. Dr. Chen and his colleagues evaluated data (Ann Thorac Surg 2004;78:1352-1361) that showed congenital heart disease patients who underwent transplant surgery years later had outcomes similar to those with cardiomyopathy. This may be due to technical improvements such as the ability to reconstruct pulmonary arteries and route blood back to where it should be flowing.

NewYork-Presbyterian Hospital is the first institution in the United States to perform ABO-incompatible heart transplants (meaning that donors and recipients have different blood types) in pediatric patients. Dr. Chen noted that when surgeons follow protocol, survival is the same as in children who receive ABO-compatible hearts (N Engl J Med. 2001;344:793-800).

Prior to transplant surgery, physicians exchange the patient’s blood, washing away any preformed antibodies that may be present. The patient also receives immunosuppressant drugs. “We almost trick the body into not making antibodies against the incompatible blood type,” said Dr. Addonizio. “This doesn’t mean that they won’t experience rejection, but they won’t make antibodies against that blood group.”

“There’s no reason why we can’t be the biggest transplant center for children in the United States. We’re almost there.”

—Jonathan M. Chen, MD

According to Dr. Chen, an evolving area of surgery is the use of ventricular assistance devices (VADs) in pediatric pretransplant patients. Currently, surgeons at the Hospital use VADs in 1 or 2 patients a year. Dr. Chen envisions that 5 years from now, surgeons will be using the procedure in 25 to 50 children annually. VADs support the heart and stabilize the pretransplant patient, a process called “bridging.” This becomes important as younger patients “will wait quite a while before surgeons can locate a heart that is the right size,” he explained.

Overall, the outlook for pediatric transplant patients has improved in the last 20 years. With Dr. Addonizio as co-founder, the NewYork-Presbyterian Pediatric Cardiac Transplant Program has been at the forefront in the management of children after heart transplantation. The Hospital also has a leadership role in the Pediatric Heart Transplant Study Group, which consists of 23 institutions across North America and is responsible for a significant proportion of multi-institutional research related to pediatric heart transplantation today. The Hospital plans to expand its organ transplant initiative in pediatric patients with the creation of the Morgan Stanley Children’s Hospital Pediatric Transplant Institute. This facility would house transplant teams for all types of solid organs, as well as specialists in immunosuppression, rehabilitation, and neurocognitive development.

“There’s no reason why we can’t be the biggest transplant center for children in the United States,” said Dr. Chen. “We’re almost there.”

Linda Addonizio, MD, is Medical Director and Co-founder, Pediatric Cardiac Transplant Program at Morgan Stanley Children’s Hospital Pediatric Transplant Institute. This facility would house transplant teams for all types of solid organs, as well as specialists in immunosuppression, rehabilitation, and neurocognitive development.

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said Dr. Ratner, noting that he developed this program at NewYork-Presbyterian/Columbia because the facility has the capacity to undertake such a program. “We need 4 operating rooms, 4 surgical teams, and 4 sets of anesthesiologists. The logistics need to be synchronized perfectly.”

One of the most common obstacles to transplantation is the problem of pre-existing antibodies to grafts due to a previous transfusion or a previous organ transplantation. Progress in removing antibodies to these antigens has permitted NewYork-Presbyterian/Columbia surgeons to perform 10 transplantations in the past year in patients with antibodies directed against the donor antigens at baseline. In 2 additional cases, patients were both blood group incompatible and incompatible due to donor-specific antibodies.

“The demand for kidneys is expected to increase due to the rising rates of renal failure, but the donor supply is likely to remain limited. These approaches are increasing the opportunities to complete a successful transplant in those who need them.”

—Lloyd Ratner, MD

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