Coming of Age

Intestinal Transplantation Gaining in Volume, Survival

Hailed as a "miracle drug," cyclosporine turned the field of organ transplantation upside down with its approval for commercial use in November 1983. Procedures that were technical successes but postoperative failures were given new life through the immunosuppressant's remarkable ability to reduce the likelihood of rejection.

Praised for its ability to safely "switch off" the body's immune system, cyclosporine weakened the body's natural defenses to the point that it could accept a transplanted organ but still knock out infection. Transplants of kidneys, hearts, livers, lungs and pancreases took off. By the end of the 1980s, thousands of lives had been saved and thousands more were lining up for this lifesaving therapy.

But for those suffering intestinal failure, cyclosporine was not the answer. Rejection continued, and patients died.

With FDA approval of tacrolimus in 1994, however, the 1990s could be the decade in which intestinal transplantation at last gains a foothold.

Overcoming rejection

Rejection has always been the major stumbling block to intestinal transplantation, according to Andreas Tzakis, M.D., director of the division of liver and intestinal transplantation at the University of Miami/Jackson Memorial Hospital.

"We have been able to do the transplants technically," he said. "The main problem has been immunosuppression."

Although interest in intestinal transplantation dates back to the 1950s, transplantation of the small bowel, colon and other portions of the gastrointestinal tract have been slow in coming, mainly due to the organs' propensity to reject. Tacrolimus changed all that.

Survival improving

As of February 11, 1997, the University of Pittsburgh had performed 93 intestinal transplants since its first two in 1987. As of January 15, 22 such transplants had been performed at the University of Miami/Jackson Memorial Hospital, which began performing the procedure after Tzakis' arrival in June 1994. Transplants at both institutions include isolated small bowel as well as "cluster" transplants of multiple abdominal organs. Both institutions profess a patient survival rate of 60 percent and a graft survival rate of 50 to 55 percent.

"Isolated small bowel transplants have the best survival rates at about 75 to 80 percent patient survival," maintained Jorge Reyes, M.D., associate professor of surgery, Thomas E. Starzl Transplantation Institute, University of Pittsburgh. Graft survival is about 65 to 70 percent, he said. Liver/bowel and other multivisceral transplants at the University of Pittsburgh have a patient survival rate of approximately 55 to 60 percent, he said.

More than 40 intestinal transplants have been performed at the University of Nebraska Medical Center since its first two in 1990. According to Alan Langnas, M.D., UNMC professor of surgery and chief of transplantation, Nebraska's one-year patient survival rate for isolated bowel is 93 percent; 67 percent for liver/small bowel. Graft survival rate for both categories is 75 percent.

Guarded optimism

Despite a generally positive outlook within the intestinal transplant community, Langnas nonetheless urges caution. Graft and patient survival rates still fall short compared to those for other organs, and although Tacrolimus may be the new "wonder drug" in regards to immunosuppression, monitoring intestinal recipients for rejection is still difficult.

Whereas kidney graft rejection is detectable through creatinine checks and liver graft rejection through bilirubin, there are no specific blood tests to determine intestinal graft rejection, he pointed out. For intestinal transplantation, there are only biopsies, and biopsies are unpopular because it's impossible to obtain a sample containing all layers of the intestinal wall without perforating it. "Pinch" biopsies of the surface are all that's left, but they don't necessarily provide the whole picture.

"With our current abilities and understanding of intestinal transplantation, we're primarily limiting its application to those patients who have life threatening complications of TPN (total parenteral nutrition) or intestinal failure," Langnas said. "We're really not into performing this operation for strictly quality of life issues. I don't think it's evolved to that point."

Physicians are typically reluctant to refer people for intestinal transplantation because of the newness and evolving nature of the procedure, Langnas stated. "They typically wait for the patients who are really quite ill."

Sickest selected

There's no denying that patients seeking intestinal/multivisceral transplantation are ill. Horrendously ill. About half are children who have been in and out of hospitals all their lives. They have never eaten a hot dog, a slice of pizza or a chocolate chip cookie. Most were born with little to no gut and have had numerous operations. They are fed intravenously and require full-time care.

Crohn's disease or inflammatory bowel disease are common indicators for adults. In addition, adults may need transplants because of progressive illnesses or an intra-abdominal catastrophe such as a gunshot wound, stabbing or vehicular accident.

Most of these patients—adults and children—survive off TPN in much the same way patients with kidney failure use dialysis and diabetics take insulin. But TPN can damage or destroy the liver, thus necessitating a liver transplant for which there are no artificial means of support. Clot formations develop in some or infections occur that eliminate venous access, making intra-venous feedings difficult or impossible. And as more and more operations are performed.

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By Caitlin in the arms of her foster mother, Mayda

Caitlin, at Jackson Memorial Hospital in Miami Dec.
1996. Baby Caitlin was returned to her grandparents, Paul
and Donna Emde, after undergoing liver, pancreas, stomach,
kidneys, and small and large intestine transplants.
on the intestine, organs attached to the gastrointestinal tract can be affected, thus warranting transplantation of not only an intestine but several organs.

Living under these conditions can be painful, frightening and frustrating for the patient and emotionally wrenching and physically exhausting for the care giver.

Giving up

With patients this sick who have gone through so much, the hardest decision facing the transplant team is not always how to treat the patient but knowing when to stop.

"This is the toughest decision we have to make," Tzikis acknowledged. "There are no rules. There are not even instructions. We can't tell who is going to succeed and who is not."

Tzikis remembers cases in which children in dire need were transplanted and did well. Others, grossly deteriorated, died shortly posttransplant. If transplantation worked for someone, he said, it's difficult not to propose it for others.

Tzikis can't recall a time when University of Miami/Jackson Children's Hospital refused to transplant a child. He and his colleagues describe the operation and risks to the parents and explain what adjustments the family will have to make posttransplant. The decision is ultimately left up to the family.

"The problem is, they rely on our advice," Tzikis explained. "They trust us with life and death decisions. I think these decisions are much harder than deciding which organs to put in and how to set up the surgery and carry out the technical part."

Postop worrisome

Transplantation itself is just the beginning. Langnas noted. "Completing the operation—that's the only real fun part. After that, it's a lot of work in caring for the patients. Most transplant surgeons know better than to celebrate, because your work is never really done. There's always rejection. There are always opportunistic infections that can develop. And for something as new as intestinal transplantation, the time you get in trouble is when you let your guard down—when you stop paying close attention to even the smallest problems."

Because of the demanding nature of postoperative care, University of Pittsburgh evaluates the parents of pediatric intestinal candidates as closely as it does the children.

"You literally evaluate them in terms of their capacity to be care givers," Reyes said. "The postoperative care that these patients require is very important. You could fail in your transplant outcome simply because the family is not able to or willing to handle the postoperative care."

Simply giving the immunosuppressants at the right time requires a high degree of responsibility, he noted. Parents may need to administer supplemental intravenous fluids to their child for six months to a year. They must also bring the child in for periodic check-ups and watch for signs of rejection or infection.

"We don't shut patients out because of that, but we try to establish a situation of support, foster care or assistance that would permit this child to go through the operation and postoperative period successfully," Reyes added.

Patients registered at any of the three transplant centers are allowed to wait at home rather than relocate. The average wait tends to be anywhere from six months to a year. The patient generally stays near the transplant center for about three months posttransplant.

Multiviscerals

News reports of patients receiving five, six and even seven abdominal organs have made headlines recently, but in reality, transplant specialists say, these procedures aren't noteworthy. They aren't performed often and the number of organs transplanted really isn't relevant.

"It's not how many organs we do, but how we're going to get the patients to accept the organs better," Tzikis stated.

In December, Tzikis transplanted seven organs into Pensacola toddler Caitlin Ernde. Ernde received seven abdominal organs instead of six because the donor's kidneys were so small that receiving just one would not have been enough for her. Those patients receiving six organs could just as easily have received seven if their donor's kidneys had been similarly limited, Tzikis stated.

Added Reyes, "The gastrointestinal tract is a continuum. To [count the] the stomach separate from the duodenum, the jejunum separate from the ileum, the small bowel separate from the colon, seems almost silly to me."

Now that surgeons can transplant kidneys, livers and pancreases, hearts, lungs and intestines, what's next on the horizon?

Revascularization

Tzikis has developed a technique in which he can remodel the blood vessels in the intestine so as to revascularize the liver. Not only does the technique avoid subjecting the patient to multivisceral transplantation, but by doing so Tzikis can avoid adding to an already overcrowded patient waiting list. So far the revascularization been performed successfully on two patients.
Living related transplants

At Tulane University Medical Center in New Orleans, surgeons have performed two living related intestinal transplants and are poised to do more. In both cases, a mother donated a portion of her intestine to her grown child. One patient died 10 months after the transplant due to a resistant fungal infection. At press time the other was alive at 15 months posttransplant. A third living related transplant was scheduled for March.

In the two cases taking place in early 1996, each patient received about 30 percent of the donor's small bowel—an amount large enough to sustain the recipient yet not so large as to endanger the donor. One donor remained in the hospital 48 hours posttransplant, the other 72 hours. Donor surgery lasted about three hours. Suturing the graft took less than an hour. The donors suffered no complications.

Although the intestine, like the liver, can regenerate, the Tulane transplant team does not expect the donor organ to grow back to its original size. Once transplanted, it is expected to grow, although no one knows for sure how large it will become.

Although the transplant team isn't opposed to using cadaveric donors, the current preference is toward living donors.

"It obviously means we get an excellent match," said program director Bernard Jaffe, M.D., professor of surgery and vice chairman of the department of surgery at Tulane. "It also means the ischemia time is less than an hour, and the bowel handles that remarkably well."

"[Living related donation] prevents a number of complications accrued from leaking membranes from a small bowel that's been out for a while," he asserted. "Biopsies after the transplant show perfectly normal, pristine small intestine with no injury pattern in them."

The intestine, like the heart and lungs, doesn't tolerate well insults that can cause ischemic damage to the graft, he said.

Living related donation may be Tulane's answer to the organ shortage. The team will not do living unrelated intestinal donation until more is known, Jaffe said.

"Five years from now, when small bowel transplantation becomes routine, everyone may do it without matching and do it with cadavers. No one has a clue. But unless someone tries this and does it and proves it works or doesn't work, we'll never know."

Abdominal/Thoracics

At the University of Pittsburgh, Reyes believes the next scientific step will not be the transplantation of bladders, ovaries or other parts, but multorgan transplantation involving thoracic and abdominal organs. Although such transplants have been done before, they're rare and usually involve only two or three organs. Reyes believes such transplants will become more common and involve even more organs.

Immunosuppression and postoperative care remain the biggest hurdles. Each organ brings its own components to the picture, making patient management more complex.

"When you combine thoracic and abdominal procedures, you are not only doing a technically larger operation, but you are opening a wider need for surveillance, and very likely a higher level of immunosuppression," Reyes said. "When you get into that scenario, you enter the problems of overimmunosuppressed states and opportunistic infections, and they can occur in any organ."

Acceptance

In the meantime, the University of Pittsburgh is working on protocols to persuade third party payers that intestinal transplantation is no longer experimental and should be reimbursable. The transplant center is also striving to convince OPOs of its success rates, so they will refer more donors.

"I've sent several letters over the past few years reminding them of the results at the most recent international small bowel meeting and relating what was discussed and advancements in the field—trying to stimulate them to request donation," Reyes remarked. "They need to know the results. We, as humans, like to know that what we're doing has a positive impact, and I don't think people have really been impressed. They may feel that the results are still poor, when in fact they have evolved and improved tremendously."

Gaining acceptance should not be insurmountable. After all, it was only 10 to 12 years ago that organ transplantation first garnered widespread attention and only recently that intestinal transplants entered the circle. More than 180 intestinal transplants have been reported worldwide, with at least 150 taking place within the U.S. Experience has shown that in the field of organ and tissue transplantation, nothing is impossible. □

—Esther Benenson

UNOS Member Intestinal Transplant Centers

As of December 4, 1996:

Region 1
Children's Hospital, Boston, Mass.
Massachusetts General Hospital, Boston

Region 2
Johns Hopkins Hospital, Baltimore, Md.
Children's Hospital of Pittsburgh, Pittsburgh, Pa.
University of Pittsburgh Medical Center, Pittsburgh, Pa.

Region 3
Jackson Memorial Hospital, Miami, Fla.
Tulane University Medical Center, New Orleans, La.

Region 4
Baylor University Medical Center, Dallas, Texas
Wilford Hall Medical Center, Lackland AFB, Texas

Region 5
University of California, San Francisco Medical Center
Stanford University Medical Center, Stanford, Calif.
UCLA Medical Center, Los Angeles, Calif.

Region 6
Children's Hospital Medical Center, Seattle, Wash.
University of Washington Medical Center, Seattle, Wash.

Region 7
Children's Memorial Hospital, Chicago, Ill.
Northwestern Memorial Hospital, Chicago, Ill.
University of Chicago Medical Center, Chicago, Ill.
University of Minnesota Hospital & Clinics, Minneapolis
University of Wisconsin Hospital & Clinics, Madison

Region 8
University of Iowa Hospitals & Clinics, Iowa City
Barnes-Jewish Hospital, St. Louis, Mo.
St. Louis Children's Hospital, St. Louis, Mo.
Children's Mercy Hospital, Kansas City, Mo.
St. Louis University Medical Center, St. Louis, Mo.
University of Nebraska Medical Center, Omaha

Region 11
Medical University of South Carolina, Charleston