

INSIDE FALL 2008

Lung Transplantation

2 Non-heart-beating lung donations may dramatically increase lung transplant pool.

Kidney Transplantation

4 Minimally invasive laparoscopic approach is successfully being applied to renal transplant recipient operations.

RESOURCES FOR PROFESSIONALS

- Webcasts
- CME Activities
- Medical Presentations
- Specialty Briefings
- Newsletters

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Trial Signals Machine Perfusion's Evolution

To James Guarrera, MD, using hypothermic machine perfusion of liver grafts for transplantation is an idea whose time has come—again.

Dr. Guarrera decided to apply the lessons learned from the success of machine perfusion in kidney transplantation to machine preservation of livers.

He and colleagues at NewYork-Presbyterian Hospital/Columbia University Medical Center completed a clinical trial of 20 patients who underwent transplantation with livers preserved through machine perfusion. The control group consisted of 20 patients whose transplanted livers had undergone the standard static cold storage on ice. It was the first clinical study to test the safety of machine preservation in human liver transplants.

The results of the trial are encouraging and demonstrate that the utility of machine perfusion is “something that has swung back,” Dr. Guarrera said. The machine perfusion grafts functioned immediately in all 20 patients, with no episodes of primary nonfunction, early allograft dysfunction, or vascular complications occurring.

Whereas 4 patients (20%) in the control group had a minor biliary complication, this occurred in only 1 perfusion patient. Preservation-associated injury to the organ was significantly less in the perfusion group than for control organs, said Dr. Guarrera.

“It is our hypothesis that the machine perfusion platform developed here will permit ex vivo resuscitation, expanded criteria, and suboptimal liver grafts, thereby expanding the donor pool and improving outcomes,” he said.

According to Dr. Guarrera, the slow progress of clinical use of machine perfusion in liver transplantation is attributed to the difficulty in developing a

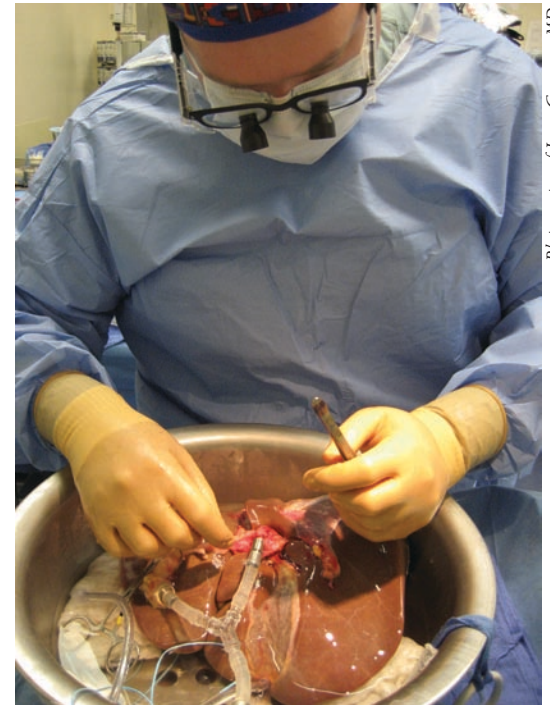


Photo courtesy of James Guarrera, MD.

James Guarrera, MD, performs a liver transplant using a liver that was preserved through machine perfusion.

user-friendly and portable system, the more severe ramifications of primary nonfunction and poor early function in liver transplantation, and the culture of liver transplant surgeons.

The machine perfusion method essentially is a pump device that has been modified for ex vivo perfusion of a single organ, similar to cardiopulmonary bypass.

see **Perfusion**, page 5

Innovative NEAD Chain Approach Makes News

On February 14, 2008, the transplant team at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and The Rogosin Institute successfully performed one of the nation's first never-ending altruistic donor (NEAD) “chain” renal transplants. The chain was continued in 2 sets of procedures—first in May, then this fall. The innovative NEAD approach may forever change the way transplants are performed in the United States.

“In the process of a NEAD-type transplant, an altruistic donor initiates a chain of transplants and the potential donor from the last transplant serves as a bridge donor to initiate another chain of transplants,” said Sandip Kapur, MD, who coordinated the successful triple transplant procedure. “In the case of the first procedure, Gareth Hill, who founded the National Kidney Registry, identified an altruistic donor in California.

see **NEAD**, page 7

continued from *Perfusion*, page 1

Introduced 41 years ago, machine perfusion represented the best way to preserve kidneys for transplant. By the 1980s, it had been supplanted by the cold storage method, which was considered cheaper, easier, more practical, and not as cumbersome because less equipment and fewer technicians were needed.

But when “perfect” kidneys became less available by the early 1990s, age requirements were loosened and “imperfect kidneys” were being transplanted, requiring the reduction of preservation injury to ensure a successful outcome. As a result, the older technique was reconsidered and machine perfusion “came back into vogue in the late 1990s,” said Dr. Guarrera, prompting his team to investigate its application in liver transplants.

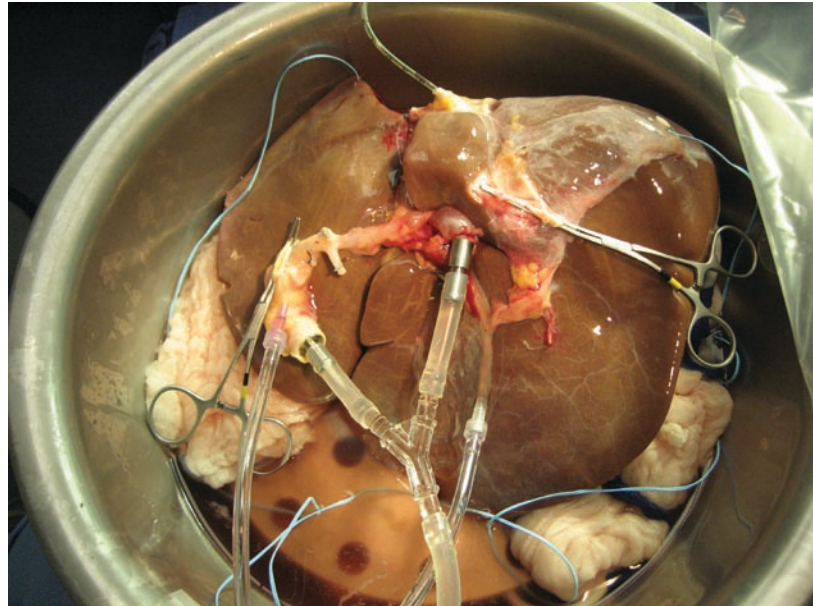
Dr. Guarrera and his study investigators—Jean Emond, MD, Benjamin Samstein, MD, and organ procurement coordinator Ben Arrington—were “always big advocates of the perfusion technique because we saw its success in kidney transplantations,” he explained. “We adapted it and made it applicable for liver transplantations.”

“What we’re doing that’s different is that we’re applying some of the basic principles of kidney perfusion and have pioneered some new techniques for perfusing livers,” said Mr. Arrington. “In the clinical setting, this will allow us to access more organs that are associated with the extended-criteria donor.... This technology, we believe, will help resuscitate these livers, increase the chance of viability for our patients, and improve patient outcomes.”

Despite its effectiveness, the cold storage method sometimes damages the organ by depriving it of continuous circulation of metabolic substrates. Machine perfusion, by comparison, reduces damage to the organ and increases the chance that it will be healthier for transplant.

The clinical trial was designed to prove that machine perfusion in liver transplants is “not inferior to cold storage”—and the result showed that “it’s certainly not inferior,” Dr. Guarrera said.

Since the trial, Dr. Guarrera has fielded inquiries and received many lecture invitations to speak about machine perfusion in liver transplantation. He would like to spread the word: “People are starting to believe that in the next few years, this can change the way we do business—that this will be readily available equipment.”



Photos courtesy of James Guarrera, MD.



Dr. Guarrera recently applied for a U.S. Department of Health and Human Services Health Resources and Services Administration grant for a Phase II trial with 25 patients. The trial will examine the effect of perfusion on the function of high-risk livers, which come from older donors or have a fatty infiltration.

“If you can improve their early function, you can improve their long-term function—and this makes them a viable option to increase the donor pool,” Dr. Guarrera said.

“Our results suggest at least equivalence to cold storage, but likely superiority. With a sample size of 20 patients, it is difficult to prove superiority, but the encouraging, preliminary results motivate us to further

develop and study clinical liver machine perfusion. In the last 20 years, there has been no significant clinical change in liver preservation, which further highlights the need for improvement and development of new techniques.”

As of October 24, 2008, 16,658 people nationally were waiting for a liver transplant, according to the Organ Procurement and Transplantation Network.

“It does give us a reason to keep going and continue to study it,” said Dr. Guarrera. “There hadn’t been a real advance in liver preservation since the University of Wisconsin storage solution was developed [in 1988].”

Contributing faculty for this article:
James V. Guarrera, MD, Ben Arrington

Center Boasts High Survival and Low Waiting-List Rates

Since it was founded, the Center for Liver Disease and Transplantation (CLDT) at NewYork-Presbyterian Hospital/Columbia University Medical Center has been a pioneer in living donor transplant surgery. Although it cannot affect the overall availability of livers, the CLDT carefully considers how it can use the organs that do exist, noted Robert Brown Jr, MD, MPH. “If you can recognize who the patients are who can benefit from expanded-criteria donation, the small risk is more than realized by the huge incremental benefit.

“It’s not just our ability to do the operation, [but to deal with] the organ shortage and with access to treatment,” added Dr. Brown.

The CLDT was one of the first centers in the United States to perform adult living donor transplants, and it has one of the largest and most successful living donor programs. It also successfully performs transplants on small babies with a high risk of adverse outcomes. It can do so, in part, because its team of experienced clinicians in medicine, hepatology, surgery, psychiatry, oncology, radiology, and nursing provide a multidisciplinary approach to adult and pediatric care. Dr. Brown, Dianne LaPointe Rudow, DNP, Patricia Harren, DNP, Steven Lobritto, MD, and Jean Emond, MD, launched the Center in 1998. At many institutions, the medical and surgical components often are separated into pre- and post-transplant care. At the CLDT, the transplant team works as an integrated unit: 6 surgeons, 6 hepatologists, 7 nurse practitioners, and 5 physician assistants. All are full-time employees.

The transplant team at the Center for Liver Disease and Transplantation works as an integrated unit: 6 surgeons, 6 hepatologists, 7 nurse practitioners and 5 physician assistants.

The proof is in the results. The CLDT has the highest patient waiting list survival rate and shortest waiting time in the New York State region.

According to the Scientific Registry for Transplant Recipients, the CLDT’s waiting list mortality rate is 7%, compared with 13% overall at the other 4 transplant centers in its region, all of which are in New York.

From January 2004 to June 2006, the CLDT had a 98% survival rate for the 267 adults and 43 children on whom it performed liver transplants; the national rate was 96%. In that period, the 1-year post-transplant survival rate was 88% for adults (87% nationally) and 94% for children.

“We’re proactive instead of reactive by developing an individualized plan with each patient to maximize access to transplant. This may be with standard criteria livers, expanded criteria livers, and living donors,” said Ms. LaPointe Rudow.

Specialists at the CLDT are experts in determining organ suitability. Surgeons and fellows often will travel out of state to procure livers that will go unused in that area of the country, for patients in whom the organ will be suitable. That affords patients a greater chance of being offered a liver. “We’re a very innovative program when it comes to considering all types of organs that other places may not consider,” added Ms. LaPointe Rudow.

The CLDT offers patients continuity of care not often found elsewhere. As a result, “every time we see our patients, we’re assessing their risks of staying on the waiting list versus the risks of getting a transplant now,” she said. “We call it the ‘early access plan for transplant.’ We teach patients about living donation and ask them to consider expanded-criteria donation. It’s a very active participation by our team.”

“We’ve reduced the pre-transplant chance of dying by far more than any potential small increase in the post-transplant risk of dying,” said Dr. Brown.

Patients and their families are assigned psychiatrists and social workers and attend weekly workshops or support group meetings. Patients are followed every 3 months through a “very active participation” that enables the team to “better predict who’s getting sicker and [who] needs to be prioritized for transplant,” Ms. LaPointe Rudow explained.

Part of the reason for that is location. In a metropolitan area as densely populated as New York City, where there are so many patients waiting for transplants, “we have to be innovative and think outside the box for successful outcomes,” Ms. LaPointe Rudow said.

“It’s not just our ability to do the operation, [but to deal with] the organ shortage and with access to treatment.”

—Robert Brown Jr, MD, MPH

Dr. Brown agreed that the Center’s model was aggressive from the start and that that is a key factor in the CLDT’s success. “Our program was built from the get-go with the multidisciplinary approach. We’ve known for a while that we could lower our mortality on the waiting list with our approach to transplantation, but it was never validated by the government,” he said. “We think that by working together, we’ll deliver superior, better-integrated services to all our patients. That’s a philosophy that isn’t followed all over the country.”

To Dr. Brown, that “seems such an obvious way to do it” because “with a team that’s integrated clinically and financially, you have another set of eyes on the patient and an ongoing discussion that challenges you to do everything better. As a result, we don’t get into any issues of who has ‘ownership’ of the program. We discuss cases twice a week to make sure that everyone is delivering the best care possible.”

The CLDT is the only program in the New York City area in which “the expected rate of death on our waiting list is *higher* than what we actually provide. Our results are better than what would be expected statistically,” Dr. Brown said. That is because “we’re able to take the sickest patients and, through our multidisciplinary approach, transplant them safely and more quickly.

“The better you take care of patients, and the fewer patients there are on your waiting list, the better you’re doing.”

Contributing faculty for this article:
Robert S. Brown Jr, MD, MPH, and
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