

Trends in Transplantation

Editor’s Note:

Welcome to the first edition of “Trends in Transplantation,” a report from the clinical and client services team at LifeTrac, Inc.

“Trends in Transplantation” will provide a look at innovation in the procedures and technology applied to the fields of solid organ or blood and marrow transplantation. It will be issued periodically at a frequency to reflect the pace of change in this clinically and financially critical segment of the healthcare marketplace. “Trends” represents the experience and observations of the clinical and client services staff of LifeTrac, and as such, is not intended to represent an exhaustive report on the topics covered. Instead, it is a snapshot in time of fluctuating developments which, added together with other resources, can help clients recognize and plan for the trends in transplantation.

In This Issue:

- Ex Vivo Lung Perfusion - pages 1-2**
- Organ Transplantation and Sensitized Patients - page 3**
- End Stage Heart Failure: Mechanical Circulatory Support and Heart Transplantation - pages 4-5**

The key trials underway include the HELP trial based in Toronto (sponsor XVIVO Perfusion Systems), the NOVEL trial (USA - sponsor XVIVO Perfusion Systems), the INSPIRE trial (USA and Europe - sponsor Transmedics), the Perfusix trial USA and Europe - sponsor Perfusix). These trials and others will help define the role and clarify the efficacy of EVLP for lung transplantation. Other trials are approved to evaluate the impact of EVLP on donor lung availability and its use in standard criteria donor lungs.

Ex Vivo Lung Perfusion

Brief status report—2014

Key Trials and Development

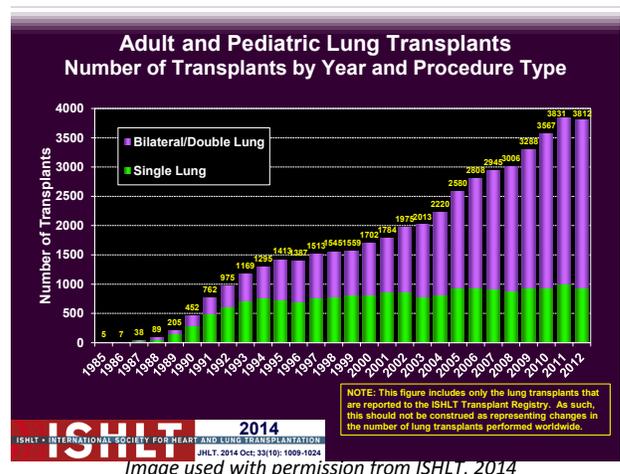
The FDA reported in August, 2014 that it had approved the XVIVO Perfusion System with the Steen Solution for preserving lungs that are determined to be marginal or initially unacceptable for transplantation. This is the culmination of over 14 years of work by Dr. Stig Steen and his colleagues in Sweden. He described the first use of ex-vivo lung perfusion (EVLP) in 2001¹. In 2007, he described the transplantation of an initially rejected donor lung after EVLP reconditioning.² Since then, other groups have demonstrated the safety and feasibility of EVLP for initially rejected and marginally acceptable lungs prior to transplant.^{3,4,5} We think that this is an important development in lung transplantation towards improving the availability of lungs for waiting patients. With this expanding research and favorable outcomes with the use of EVLP, there are at least 4 companies developing devices for lung perfusion. As an additional example of acceptability, Health Canada has approved this approach to lung transplantation and has approved reimbursement to certain hospitals for EVLP costs.

What makes the FDA approval significant is the continued validation of a direction of care for potential lung transplant recipients and an expansion of donor lungs that become usable for patients on the transplant wait list.

Organ supply does not meet transplant demand

The ideal donor lung is from a patient that is less than 55 years old, less than a 20 pack year history of smoking, and no chest trauma or signs of lung infection or excess fluid. In addition, the lung should be able to demonstrate a sufficient oxygenation ratio on a given % of oxygen (FiO2). This combination occurs all too infrequently for patients waiting for donor lungs.

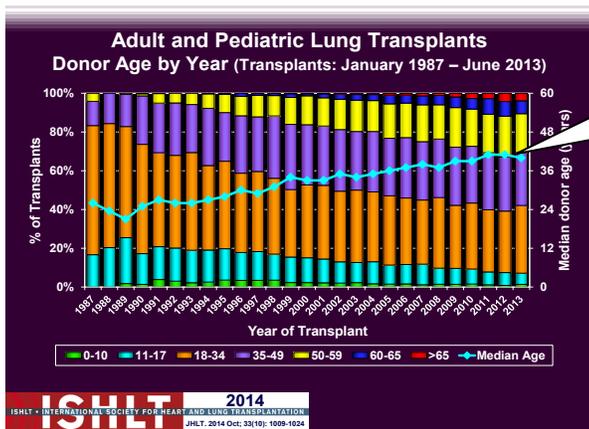
In 2012, the International Society for Heart and Lung Transplantation reported that 3812 lung transplants were reported to their database (mostly from the US, Canada and Europe). Of these, approximately 1700 were performed in the US. However, there were still 1614 potential lung transplants on the US waiting list.



¹ Steen, S., et al. “Transplantation of Lungs from a Non-beating Donor.” *Lancet* (2001) 357: p.825-829.
² Steen, S., et al. First Human Transplantation of a Nonacceptable Donor Lung after Reconditioning ex-vivo.” *Ann. Thorac. Surg.* (2007) 83: p.2191-2195.
³ Ingemansson, R., et al. “Clinical Transplantation of Initially Rejected Donor Lungs after Reconditioning ex vivo.” *Ann. Thorac. Surg.* (2009) 87:1 p.255-260.
⁴ Cypel, M., et al. “Normothermic ex vivo Perfusion Prevents Lung Injury Compared to Extended Cold Preservation for Transplantation.” (2009) *Am. J Transplant.* 9(10): p.226 –2269.
⁵ Cypel, M., et al. “Normothermic ex vivo Lung Perfusion in Clinical Lung Transplantation.” (2011) *N Engl. J Med.* 364(15): p.1431-1440.

Due to improved surgical techniques, better medications for managing rejection and increased focus on donor lung preservation, the average age of donor lungs is increasing. The graph below demonstrates that the average age of donor lungs is increasing (note the yellow, dark blue and red bars representing ages 50 to >65 years old) as well as the median age of donors steadily increasing.

Image used with permission from ISHLT, 2014



Note: increasing average age of donor lungs

What might this mean to insurers?

While under FDA-approved trial phases, the extra cost of the EVLP procedure was approximately \$45,000. Additional data is needed to determine the true costs of the procedure since being recently placed on the market. Not every donor lung will require EVLP, but we anticipate that increased use will occur based on the successful trials demonstrating equivalent survival between initially rejected re-conditioned lungs and the standard transplant process using currently acceptable criteria. In addition, current research is focusing on methods to make lungs physiologically better and reduce primary graft dysfunction, treat specific adverse clinical conditions, and expand the number of hours of acceptable ex vivo perfusion prior to transplantation.⁶

Approximately 80 % of donor lungs become available after major head trauma or a stroke, but even an isolated head trauma has detrimental effects on the donor lungs. Neurogenic pulmonary edema may occur, causing fluid to accumulate in the lungs, even without heart failure. The intensivist team may also use excessive fluids to help preserve the blood flow to the brain. After brain death, the donor is kept on a respirator that may cause additional lung injury due to excessive pressures for ventilation (baro-trauma). In the past, these lungs were deemed unusable because the cold storage and transportation to the transplant hospital did not allow for removal of fluid. The cold temperature slowed down the cell metabolism and shut down any further recovery.

How does EVLP work?

With the advent of EVLP, the lung can be “reconditioned” for the transplant team to further evaluate it for use. EVLP allows for x-ray of the lung over the 4 hour window and even allows for bronchoscopy to look at the bronchial tubes and clear mucous that might have accumulated. The use of warm perfusion temperatures allows the cells to start their own recovery process and help clear out inflammatory mediators and cells. The lung is ventilated which allows for collapsed areas of the lung (atelectasis) to re-expand prior to transplantation. And use of certain osmotic perfusate solutions allows for the “dehydration” or removal of any excess fluid.

As this research is published along with current trials of other EVLP devices, look to the FDA to approve newly developed devices and expand ELVP use to make lung transplantation more available and successful as a treatment for end-stage lung disease, to reduce the transplant waiting list, to increase the percentage of donor lungs used. Also, look for the consideration of organ assessment and repair centers that might be able to regionalize the receipt of organs and better improve their physiology and pre-transplant functioning, as well as better match a donor lung with an appropriate recipient.

⁶ Raemdonck, D., et al. “Ex-vivo Lung Perfusion.” *Transplant International* (2014) published by John Wiley & Sons, Ltd.

Organ Transplantation and Sensitized Patients

What does it mean to be “sensitized”?

To be sensitive or allergic to any material or substance usually requires one’s immune system to identify and recognize something as foreign and potentially dangerous to one’s health. The immune system can differentiate between cells that belong to us and very similar or analogous cells that do not belong to us. This self-identification is the result of specific molecules or markers that exist on the surfaces of all of our cells, sort of acting as a molecular “thumbprint.”

A sensitized patient waiting for transplant is someone who has preexisting antibodies against Human Leukocyte Antigens (HLAs) found on donor tissues; someone who is highly sensitized has a greater amount of these antibodies. In this way, a sensitized patient’s immune system sets up a patient for antibody-mediated rejection (AMR) and prevents that patient from finding a good match. The unfortunate outcome is that highly sensitized patients may spend much more time waiting for an organ offer, all while their disease progresses to a stage that may exacerbate secondary conditions, perhaps preventing them from being transplant candidates altogether. Treatments to prevent disease progression, like dialysis, are costly in the long interim and may result in a higher chance of rejection. In addition, as we age and are exposed to additional antigens (like blood transfusions), we run the risk of becoming more sensitized.

Calculated Panel Reactive Antibodies, or cPRA, is a routine, quantitative method that measures an individual’s percentage of antibodies in the blood that are reactive to HLAs. The measurement is expressed as a percentage between 0% and 99%; the higher the percentage, the more sensitized an individual is to donor cells. A cPRA greater than 20% is qualified as significantly sensitized whereas greater than 50% is considered highly sensitized; the latter has the potential to significantly delay transplantation.

Who is more likely to be highly sensitized?

Some events like pregnancies, blood transfusions, and previous transplants may cause the immune system to build defense mechanisms against “non-self” cells, or cells that do not have an individual’s specific molecular “thumbprint,” through generation of antibodies against HLAs. These individuals are highly sensitized, may be harder to match with a donor, and may experience more severe rejection symptoms. Most patients who receive organ transplants will experience some level of rejection as a result of natural humoral immune responses that exist in everyone, but those who are highly sensitized are expected to have a harder time engrafting. Thus, standard pre- and post-transplant immune suppression protocols may not be enough for those highly sensitized patients. These patients may also become part of a paired donor exchange program in order to broaden match potential.

Paired donor exchange programs match incompatible donor and recipient pairs to other incompatible donor and recipient pairs; then the donor of the first pair gives an organ to the recipient of the second and vice versa.

What can be done for highly sensitized patients?

Facilities and independent infusion clinics that offer desensitization options may differ slightly in their various protocols, but the ideal goal

is consistent amongst them: lowering the calculated Panel Reactive Antibodies/Donor Specific Antibodies ratio (cPRA/DSA ratio) to reduce chances of AMR.

A single protocol may involve several therapies specifically tailored to a patient’s desensitization needs. Some of these protocols may include some combinations of plasmapheresis, prophylactic cytomegalovirus-immune globulin (CMV-Ig), low-dose intravenous immune globulin (IVIg) (or high-dose for those who are very highly sensitized), various immunosuppressive agents (such as Rituximab), and placement in a Paired Exchange (PE) program.¹

Some protocols may also include these therapies post-transplant to ensure that a patient’s cPRA/DSA, as well as any new problematic immune responses, remains low to allow engraftment. For instance, the Johns Hopkins University Hospital’s post-transplant IVIg desensitization protocol lasts up to 10 days to allow the body to accept a new organ. Thereafter, the previously highly sensitized patient receives the same standard anti-rejection medications as any other transplant patient.² Many facilities have looked to Johns Hopkins for the standard in desensitization program development.

What are some outcomes of desensitization therapy?

Highly sensitized patients who receive desensitization therapy may receive benefits such as a shorter time to transplant, less time on dialysis and other expensive disease management treatments, less severe post-transplant rejection symptoms, and greater chances of survival. Additionally, reducing cPRA allows for a patient to reduce AMR, find a better matched organ, and increase graft survival chances. As a result, the patient could require less intense and time-consuming post-transplant immunosuppression therapies that are known for having negative side effects on liver health and for being quite expensive.³

In a desensitization outcomes study that took place from July 2006 to December 2011, the total 3 year cost of desensitization per patient averaged \$219,914, which is net savings of \$18,753 when compared to those patients who received 3 years of dialysis at an average cost of \$238,667. Of the 207 very highly sensitized (cPRA > 80%) ESRD patients who participated in the study, 146 received transplants (71%). The estimated survival at the end of the 3 year study for the desensitization arm was 96.6%, compared with 79.0% of the dialysis arm. Dialysis, which often requires the patient to take medical leave or quit their careers, altogether, is never the answer to ESRD, but rather a disease management tool that slows down the progression of ESRD.

While still relatively new, desensitization therapy is a treatment option that merits consideration by any health plan managing a patient population who are deemed highly sensitized, experiencing prolonged wait time on the UNOS transplant wait lists, or placed in a paired exchange program.

More on Desensitization Therapy

LifeTrac maintains contracts offering substantial discounts on outpatient desensitization therapy through market segment leader, BiologicsTx, Inc. Contact your LifeTrac representative to learn more.

¹ Stanley C. Jordan, M.D. “Desensitization therapy with intravenous Gammaglobulin (IVIg): Applications in solid organ transplantation.” *Transactions of the American Clinical and Climatological Association*: Vol. 117 (2006). Pp 203-205. Used: 12/09/14

² Johns Hopkins Medicine. “Johns Hopkins treatment provides ‘dramatic’ survival benefit for hard-to-match kidney transplant patients.” [www.hopkinsmedicine.org. News and Publications. Release Date: 7/27/11.](http://www.hopkinsmedicine.org/news/media/releases/johns_hopkins_treatment_provides_dramatic_survival_benefit_for_hard_to_match_kidney_transplant_patients) <http://www.hopkinsmedicine.org/news/media/releases/johns_hopkins_treatment_provides_dramatic_survival_benefit_for_hard_to_match_kidney_transplant_patients>. Used: 12/9/14.

³ Stanley C. Jordan, M.D. “Desensitization therapy with intravenous Gammaglobulin (IVIg): Applications in solid organ transplantation.” *Transactions of the American Clinical and Climatological Association*: Vol. 117 (2006). Pp 206. Used: 12/09/14

⁴ Stanley C. Jordan, M.D. “Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab.” www.transplantjournal.com. Clinical and Translation Research. *Transplantation*: Vol. 95 (6). March 27 2013.

End-Stage Heart Failure: Mechanical Circulatory Support and Heart Transplantation

The Reality of Heart Failure and Transplantation

Heart failure is the most prevalent international cause of death in this day and age. Of the 50,000 people who are considered for heart transplantation, only an estimated 5,000 receive that second chance. Many of the patients on the transplant waitlist may be treated with various interventional modalities that go beyond usual medication management to improve their overall medical condition and prolong their chance of survival to transplantation.¹ These interventions that go beyond usual medication management include circulatory support such as intravenous inotropes (medications that strengthen heart function), intra-aortic balloon pumps (assists with left ventricular blood pumping and may improve coronary artery circulation), and left and right ventricular assist devices (assists with heart pumping and may help a heart recover partial function).

Mechanical circulatory support devices, such as left ventricular assist devices (LVAD) have had a significant effect on heart transplant outcomes over the past 10 years. Some thoracic surgeons even consider mechanical circulatory support devices to be the new standard in treating end-stage heart failure.² Due to recent advances in Mechanical Circulatory Support (MCS) therapy, many patients have experienced a better quality of life post implant and choose this option as a bridge to transplant, bridge to candidacy, bridge to recovery or as destination therapy.

Which patients are good candidates for MCS therapy?

Although there are no set universal standards on patient selection for MCS therapy, aggregate historical data on previously implanted patients demonstrates three general categories of patients. These include:

- (1) Individuals who require temporary circulatory support who are expected to recover after a cardiac insult and will not need cardiac transplantation (bridge to recovery);
- (2) Patients awaiting a cardiac transplantation but who would not survive until an organ is available owing to low cardiac output and/or non-cardiac comorbidities (bridge to transplantation); or
- (3) Individuals who need long-term support but who have a relative or absolute contraindication to cardiac transplantation (destination therapy).³

Heart disease patients who are considered for heart transplantation are first evaluated at a transplant center where they receive standard medical interventions to treat their immediate symptoms, as well as manage their long-term heart condition. A selection committee will assess and list the patient on the UNOS list for heart transplantation. During this period, the patient may require MCS to help bridge them to a successful transplantation.

With any medical intervention, the risk versus the benefit is different for every patient. The main risks for MCS devices are related to formation of blood clots in the circulatory system, bleeding from the necessary anti-coagulation, and infections from the circulatory access lines through the skin.

The main benefit is prolonged survival towards the overall goal of the patient (transplantation or as a permanent therapy), as well as improved cardiac functionality and quality of life.

More recently, MCS therapy has been referred to as a “bridge to decision,” which has proven to raise fewer false hopes but also does not ignore improvements in comorbidities and secondary conditions. A patient’s circumstances often changes as a result of the various risk versus benefit outcomes in such a way that changes their prognosis. For instance, complications from MCS implantation or surgery (e.g. infection, sepsis, or stroke) may cause a patient who was originally a bridge to transplantation candidate to become ineligible for transplant. Conversely, some destination therapy patients who receive MCS therapy may become stable enough to be considered for transplant. With that being said, the three aforementioned selection criteria should be considered more of a continuum and be continuously assessed over time.

Numbers on MCS therapy

The U.S. National Institutes of Health maintains a database called INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) which collects data on 164 hospitals throughout the United States who specialize in heart failure management.⁵ From June, 2006 to September, 2014 approximately 12,474 adult implantations occurred. Of these devices, the majority were LVADs. The chart shows the relative volume for the various types of therapies in 2013 and through the third quarter of 2014.

INTERMACS 2014 MCS IMPLANTATION		
	2013	2014 (Q1-Q3)
Destination therapy	1123	780
Bridge to Transplant	640	539
Bridge to Recovery	12	3
Other	17	12

According to the most recent data from the Scientific Registry of Transplant Recipients (SRTR)⁶, the percent of patients with an LVAD on the waiting list for a donor heart has increased from 23.3% (2002) to 41.3% (2012). Similarly, the percent of patients with an LVAD in place at the time of transplantation has increased from 3.4% (2002) to 21.7% (2012). This trend is continuing to increase and the five year survival rates for those patients with an LVAD demonstrate a slight improvement for those with an LVAD as compared to those without an LVAD (75% vs 72%). As additional devices are approved by the FDA and expertise with LVADs grows, one could expect that LVADs will continue to be an attractive option, either as a bridge to decision or as destination therapy for many patients.

^{1,2} Mallidi, Hari R., Jatin Anand, and William E. Cohn. "State of the Art Mechanical Circulatory Support." *Texas Heart Institute Journal* 41.2 (2014): 115-120. MC. Web. 14 Jan. 2015. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004468/>>.

^{3,4} Wilson, Sean R., Gilbert H. Mudge Jr., Garrick C. Stewart, Michal M. Givertz. Cardiovascular Division. Brigham and Women’s Hospital. "Evaluation for a Ventricular Assist Device: Selecting the Appropriate Candidate." *American Heart Association Circulation Journals* (2009): 119; 2225-2232. Web. 14 Jan. 2015. <<http://circ.ahajournals.org/content/119/16/2225.full#cite-by>>.

⁵ National Heart, Lung, and Blood Institute (NHLBI). "Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs)." *ClinicalTrials.gov*. National Institutes of Health. Updated Jan 13. 2015. <<https://clinicaltrials.gov/ct2/show/NCT00119834>>. Web Jan 16. 2015.

⁶ Scientific Registry of Transplant Recipients. "2012 Annual Data Report." Health Resources and Services Administration. U.S. Department of Health & Human Services.

What are the costs and benefits?

The most notable benefit of MCS therapy is almost immediate improvement in quality of life post implantation. The patient may require less costly drug therapies with MCS in place, for example, therapies that damage the kidney and liver over time (i.e. inotropes). Additionally, MCS therapy may reduce severity of comorbidities and secondary conditions, in turn lowering disease management costs and improving quality of life. Aggregate claims data from LifeTrac shows that the average total gross billed charges for implant of an LVAD is around \$801,900. Conversely, acquisition/transplant of a heart averages \$631,000⁷. These numbers do not include pre-transplant care prior to implant/transplant nor do they include post-implant/transplant care. Immunosuppressant therapy is needed after heart transplantation to prevent rejection, while LVAD supplies are needed after implant to maintain the LVAD. Some LVAD programs may bundle the cost of supplies for one year within the implant cost, while other programs may outsource their supplies to vendors. It is important that a care coordinator or case manager continue to follow a patient receiving MCS therapy to ensure adherence to protocol and adequate renewal of supplies.

The future of implantable devices

Implantable mechanical heart devices, such as the LVAD, have evolved over time to become smaller, simpler in design, and more robust. Totally implantable devices are on the horizon of becoming a reality that will decrease risk of drive-line infection, which is the most common complication of LVAD implantation. The HeartWare Miniaturized Ventricular Assist Device (MVAD) is a smaller and simpler version of the Jarvik FlowMaker, which utilizes magnetic levitation and hydrodynamic bearings. Thoratec Corporation's HeartMate III uses similar technology. Both the HeartWare MVAD and HeartMate III have been designed to create less shear contractile force on blood components while still providing proper volume output.

Such developments could potentially reduce embolisms, thrombosis, and overall wear and tear on already compromised vasculature. Implantation surgery will become less invasive as devices become smaller and increasingly self-contained (wire-free). The future of implantable devices may someday replace much of the necessity of heart transplantation and provide the 90% who will not receive heart transplants a comparable tool in combatting end-stage heart failure.⁸

More about LVAD Supplies

LifeTrac can help coordinate vendor connections for LVAD supplies if needed. LifeTrac maintains contracts offering substantial discounts from LVAD suppliers listed below

- Thoratec Continuum
- Orthodynamics, Inc.

Contact your LifeTrac representative to learn more.

⁷ LifeTrac, Inc. Claims Database 2010-2014.

⁸ Mallidi, Hari R., Jatin Anand, and William E. Cohn. "State of the Art Mechanical Circulatory Support." *Texas Heart Institute Journal* 41.2 (2014): 115-120. *MC. Web.* 14 Jan. 2015. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004468/>>.