Vincent’s Two Sense

This issue closes out the Summer or Winter of 2016, depending on your point of view. Manreet Kanwar, Claudius Mahr and Evgenij Potapov representing Cardiology and Mechanical Circulatory Support Council along with Ed Horn and Kyle Dawson representing the Pharmacy and Pharmacology Council have compiled an insightful and practical compendium of material the ISHLT and her patients that will arguably set a new standard for the road ahead in the *Links*. These articles stretch the boundaries of our society and provide useful bits of information applicable to everyone. In the spotlight, we are reminded of the importance of hoping for the best and preparing for the best from the outstanding article by Jill Steiner, Jennifer Beckman, Stephanie Cooper, Jason Smith, James Kirkpatrick and Claudius Mahr. This exemplary team of specialists emphasize the imperative of caring for patients requiring mechanical circulatory support who have been simultaneously nearing the brink of death. The early involvement of a palliative care specialist is the “moral imperative” message – these two carefully chosen words were drawn from the 1985 comedic flick *Real Genius* starring Val Kilmer. Other summaries from the Mechanical Circulatory Support Council include: *Wheels of Fortune or Walking Dead?* by Felix Schonrath and Evgenij Potapov, *The Challenges and Early Successes of an MCS Program at The Fortis Memorial Research Institute (Gurgaon, India)* by Sandeep Attawar and *The Art of Decision Making in Patient Selection for Durable MCS: Goldilocks* by Manreet Kanwar. Next from the Pharmacy and Pharmacology Council, we have Laura Lourenco Jenkins and Lisa Potter with *Navigating the Quagmire of Immunosuppressant Drug Coverage and Affordability in the United States*, Jennifer Day with *Meds For My Pump: Common Medication Insurance Encounters in MCS*, and Teshia Sorensen, John Ryan and Erin Michaelis with *Insurance Considerations for Initiating Parenteral or Inhaled Prostacyclins in the Hospital for Pulmonary Arterial Hypertension*. In addition, the PHARM Council further educates us on the *Clinical Considerations for the Use of GLP-1 Agonists Post Lung Transplantation* by Robin Klasak and Kyle Dawson, and *Eight Years Later: How Comfortable Are We Really With Target Specific Oral Anticoagulants (TSOACs) After Cardiothoracic Transplant* by Derek Owen and Kyle Dawson. Also, the ISHLT announces that Monograph Volume 9 is now available as an eBook. As Special Interest pieces, we have Stefania Paolillo’s *Change Your Mind, Think Differently*, a report from an ISHLT International Traveling Scholarship Award Winner, and another poem by Maryanne Chirsant. Finally, you have been spared of Vincent Valentine’s rants and raves usually thrown in the Editor’s Corner. The Valentine Family is in the final stages of “the move” from League City, TX to Birmingham, AL in order to be part of an outstanding Lung Transplantation Team at the University of Alabama at Birmingham.
IN THE SPOTLIGHT: Hope for the Best, Plan for the Worst: Integrating Palliative Care in Mechanical Circulatory Support

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Many patients who have received ventricular assist devices (VAD) will die with their devices. This difficult reality continues to cause distress for patients, families, and care teams. Over a third of patients with destination therapy (DT) VADs will die within three years [1]. To complicate matters further, according to INTERMACS data, 40% of patients cross over between bridge-to-transplant (BTT) and DT strategies. Despite clear improvements in longevity, patients with VADs remain severely, often tenuously, ill and may die unexpectedly, not infrequently as a complication of VAD support. As many as 70% of patients with VADs experience complications ranging from infection and bleeding to device malfunction and stroke [2]. Quality of life is still markedly better than without these devices, [3] but this speaks mostly to the challenges of living with end stage heart failure. As the risks of VAD therapy may not truly be appreciated until they become catastrophic realities, patients and family members may feel ill-prepared to confront the realities of life “on pump.” [4]

Given the complexity of the described patient population, it is imperative that a multidisciplinary approach to care planning take place. VAD implantation will increase blood flow, however non-cardiac comorbidity burden will not magically improve after implantation. As such, it is an inherent responsibility of the mechanical circulatory support (MCS) team to offer ongoing advance care planning, early in the process and guided by the expertise of a palliative care specialist. The mantra of “hope for the best, plan for the worst” encourages disease management and addresses expectations of both the care team and the patient/family cohort alike.
An important consensus is developing surrounding the essential nature of palliative care involvement in the MCS population. ISHLT and ACCF/AHA guidelines recommend the addition of a palliative care specialist to the care team [5,6]. In addition, the Centers for Medicare and Medicaid Services (CMS) and the Joint Commission (JC) have updated their definitions of the core multidisciplinary team to require the inclusion of a palliative care specialist [7,8].

Clinicians who care for patients with advanced heart failure often have a holistic orientation toward patient care. The importance of a palliative care specialist support may be in question: “Why do patients need palliative care consultation, especially early in the disease process?” Contrary to common misperception, palliative care is not the equivalent of hospice and does not mean withdrawal of care. Instead, its focus is on symptom management, advance care planning, easing suffering, and discussions surrounding goals of care. It can and should be instituted alongside life-prolonging interventions [1,9].

Palliative care clinicians expertly facilitate communication between patients, family members, and medical providers, which is particularly important in the setting of psychosocial distress or uncertainty in goals of care [1]. Many barriers to effective advance care planning have been described, including unpredictable disease trajectory, cultural differences, and impaired cognition or decision making due to critical illness and impaired cerebral circulation [10]. These complexities argue for the involvement of palliative care specialists who have a unique skillset to address these problems. Patients may perceive the process of MCS evaluation as rushed, without time to digest the information presented before making a decision [11]. When brought in early in the process of preparedness planning, [1] palliative care specialists can foster communication about alternative therapies and discussion regarding the potential need for other therapies after VAD, such as parenteral nutrition, mechanical ventilation, or dialysis. Characterization of acceptable quality of life and how that may be affected by having a VAD is also explored. In addition, preparedness planning can include discussion of patients’ wishes if the VAD fails or becomes infected, [10] or if the patient wishes for device deactivation, with particular attention toward end of life. Palliative care for patients with VADs, as shown in cancer, may actually prove to prolong life and improve quality of life [9].

MCS team members are well-versed in treating heart failure symptoms such as fatigue and shortness of breath, but they may be less comfortable managing non-cardiac symptoms like chronic pain, anxiety, difficulty sleeping, and loss of appetite. Palliative care specialists provide extensive expertise in symptom management, the need for which increases with disease progression. In fact, they are often more comfortable with focusing on comfort and quality toward the end of life than cardiologists and cardiac surgeons, who are accustomed to providing interventions designed to prolong life. Importantly, palliative care specialists can provide guidance for family members, as well as bereavement and grief counselling after a patient’s death.

In addition to the services made available to patients and their families, palliative care specialists can also provide support to MCS team members. Patients with advanced heart failure are a multi-faceted group, often leading to emotional or moral distress on the part of some clinicians who care for them. MCS teams deal daily with an incredibly sick patient cohort and experience both great
successes as well as gut-wrenching losses. Support and education in self-care for MCS team members is a critical but under-recognized role of the palliative care specialist.

What is intended to be the exact role of palliative care specialists in the care of patients with VADs, at least according to CMS and JC, is vague. Neither CMS nor JC delineates specific credentials or experience required for palliative care specialists. Activities expected of the specialist are not outlined, and the documents do not specify how the specialist should collaborate with other MCS team members. As such, it is left up to individual institutions to interpret needs and create protocols for palliative care involvement [10]. Rapid growth in demand for palliative care consultation has further strained an already substantial workforce shortage in palliative care [10,12]. Some institutions have suggested training in “primary” palliative care for MCS providers. Other centers have suggested the implementation of nurse screening visits to identify the need for formal palliative care consultation. Creative, resource-efficient models like these are necessary to off-set the growing need, [10] particularly since many institutions still lack formal protocols for the inclusion of palliative care services in the process of VAD implantation [12].

The time has come to firmly integrate palliative care clinicians into mechanical circulatory support care teams, and not merely to appease regulatory requirements. Professional societies’ recommendations and those of CMS and the JC formalize this process, but vaguely, and there remains a paucity of information about the effective application of palliative care for patients with VADs [12]. Instead of improvising systems to mark a box on a checklist, we must work to create sustainable, integrated care collaborations upon which patients and their families can depend to improve their lives, and their deaths.

Disclosure statement:

- Ms. Beckman is a consultant for HeartWare, Thoratec-St. Jude, and Abiomed
- Dr. Mahr is a consultant for HeartWare, Thoratec-St. Jude, and Abiomed, as well as an investigator for HeartWare, Thoratec-St. Jude, and Syncardia
- Dr. Smith is a consultant for HeartWare and Thoratec-St. Jude, as well as site PI for the EXPAND trial with Transmedics
- None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the submitted article or other conflicts of interest to disclose

References:

Wheels of Fortune or Walking Dead?

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Is sacubitril valsartan the future of heart failure medicine or simply futile medicine in end-stage heart failure patients?

Since the PARADIGM HF study in 2014 showed remarkable improvements in outcome of heart failure patients with sacubitril valsartan, an angiotensin receptor neprylisin inhibitor (ARNI), this combined drug therapy has been at the center stage of heart failure medicine. Therefore, heart failure guidelines from both the US and from Europe launched in 2016 recommend this drug combination for the treatment of symptomatic heart failure patients.

Many promises and desires were associated with the first new heart failure drug therapy for fifteen years. But is it really possible to improve outcome in such a way that other end-stage heart failure treatment strategies will step back and be useless in comparison?

The PARADIGM HF trial included patients with NYHA class II to IV but only a minority were in class IV (60 patients) and results were not significant for these patients. Beside an overwhelming body of literature addressing ARNI therapy for chronic heart failure that has arisen since 2014, not a single article directly addresses the problem of acute heart failure. Therefore, a statement concerning the patients with most severe, and in many cases acute, heart failure seems to be questionable. But for these patients who are at highest risk and often receive an assist device in an emergency or at least urgent procedure, sophisticated treatment algorithms are needed. In this situation one can assume that trials with therapies that are administered in this setting of acute heart failure, such as dobutamine, milrinone or levosimendan, would gain more insight into necessary treatment strategies in this patient cohort. In view of this further delay in finding a definitive treatment, strategies like VAD surgery or heart transplantation could influence outcome in a negative direction, e.g. if right heart function worsens or end-organ failure arises. Another more practical problem we are facing in this acute and often end-stage heart failure patient cohort nowadays is that with a new drug combination like sacubitril valsartan the lack of awareness of the pharmacological activity on the part of some more general health care providers is a relevant issue. This has led to patients ending up with diuretic therapy only, because sacubitril valsartan was stopped due to worsening of renal function. That this was because of the wanted natriuretic effect and the wanted blood pressure lowering was not taken into account. If this happens, other drugs like diuretics need to be reduced but, as always, the new kid on the block is first blamed for the problems and reluctance toward change may increase. This is different to the situation with well-established therapies with ACE inhibitors or ARBs where everybody is aware of this effect.
But is this enough reason to be hesitant in treating end-stage heart failure patients with ARNIs and is there at least some data tackling this problem?

A post hoc analysis of the Paradigm HF data presented by Scott Salomon in 2016 (Circ Heart Fail, March 2016) showed an effect of sacubitril valsartan on mortality and hospitalization independent of the baseline left ventricular ejection fraction. In this analysis a relevant number of patients (>1200) had a most severely impaired left ventricular ejection fraction (less than 22.5%).

Another analysis by Milton Packer published in 2015 in Circulation tackled concerns that are important in acute heart failure. He showed shorter ICU stays (-18%) and less use of positive inotropic substances (-31%) in patients on sacubitril valsartan. Astonishingly, Kaplan-Maier curves for hospital admission diverged after 5-10 days following randomization and differed significantly after 30 days, supporting the assumption of acute effects of this drug combination.

With this glimpse of data and being aware of the formal contraindication for sacubitril valsartan in patients with acute heart failure, under close monitoring it could become an additional arrow to tackle this disease in selected patients. For example, patients with high systemic vascular resistance in an acute setting or patients with chronic low cardiac output, if the blood pressure allows the treatment, could possibly benefit. At least acute heart failure patients should be included in upcoming trials in efforts to hopefully further decrease the burden of this epidemic disease.

The “heart team” is en vogue and is required for many invasive procedures such as PCI or TAVI. In our opinion, the use of new potent heart failure drugs versus LVAD -Implantation in patients with acute or severe chronic heart failure should also be regularly discussed in a “heart failure team” consisting of a heart failure cardiologist and heart failure cardiac surgeon. At the least, the treatment with those drugs should be initiated and monitored in centers running a VAD or HTx program.

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The Challenges and Early Successes of an MCS Program at The Fortis Memorial Research Institute (Gurgaon, India)

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I was a late adopter of mechanical assist devices as far as heart failure or thoracic organ transplantation was concerned. Given the available modalities of practicing cardiac surgery in India, I have felt a longstanding, personal frustration at the inability to support failing hearts, both post-cardiotomy and following acute heart failure. I do not believe I am alone as this has been a source of contention for my contemporaries across India.

The origin of this issue may stem from out-of-pocket payor system. Our nation’s private healthcare infrastructure presents patients with a host of obstacles, most notably that patients must pay (mostly) upfront money for all major surgeries and hospitalizations. Private medical expenses are a source of financial ruin to individuals in middle- and lower-income groups, especially given the patchy coverage and inconsistent quality of the nationalized health service.

In late 2011, the relocation of my practice to Chennai with the Global Hospitals group coincided with a sudden and fortuitous surge in organ donations in the state of Tamil Nadu. I say fortuitous, because it proved an opportunity to push for solutions that had hitherto been absent from an Indian healthcare context. We made some early inroads, securing promising results with both heart and lung transplantation - our success the result of observing the strength and organizational nous of first-world healthcare systems and strict implementation of fundamentals. Our goal was to isolate lessons that would inform our attempts at setting up a robust program of our own. On the heels of my work in Chennai, I spent three months at a Heart Failure, Transplantation and MCS program at the Allina Health System in Minneapolis - an invaluable experience that has informed my current vision for cardiac care in my home country.

Since relocating to the Fortis Memorial Research Institute in Gurgaon, I have worked in my capacity as Head of Cardiac surgery to set up a robust, quality center for transplantation. Though my location may have changed, I noted that many of the obstacles and issues that I had faced in Chennai remained: stubbornly low rates of organ donation and doubts over advanced therapy for donation. If anything, problems were even more deeply seated. Yet, at the same time, the rising tide of medical tourism to India, especially from the Middle East and Africa, buoyed my long-term vision of mechanically-assisted circulatory support as a viable and reliable, albeit expensive, solution. The existing shortage of available organs coupled with state and national laws effectively blocking access to foreign nationals in need of a transplant meant that prospective patients with terminal and end-stage heart failure were implanted with a HeartMate II ventricular assist devices.

One procedure on an Iraqi male in mid-2014, in particular, was covered extensively by the Iraqi media, and ultimately paved the way for many more patients to come to our center for destination
therapy. Our link with ReliantHeart Inc. enabled us to implant 5 HA5 Axial Pumps successfully. Furthermore, our confidence in carrying out such procedures was shored up by improvements in telemedicine that have allowed for remote monitoring, ensuring that even the delicate health of an LVAD patient can be maintained by his or her heart-failure specialist - In this sense, the HA5 has well and truly lived up to expectations.

Utilizing a 24/7 telemonitoring tool and an INR tracker - which allows the implant team to monitor a patient’s vitals - is a major step in alleviating anxiety for both patients and their relatives, which in and of itself produces improved outcomes. It also helps ensure rigorous patient care and daily reinforcement of caregiver protocol. I anticipate improvements in technology to only diminish the issue of geographical gap further in the coming years.

All in all, it is for a plethora of reasons that I am a strong proponent of the effective and judicious use of MCS, many of which are obvious to the medical community: the limited longevity of transplants, the globally static pool of eligible organs, restricted access to available organs, and the onerous task of postoperative care. With continuous improvements in design and materials, artificial support devices have inched up the performance curve and almost match outcomes and survival rates of post-transplant patients. The accompanying benefits of less medication, less intensive monitoring and consistent blood flow thanks to improved pump designs - not to mention the very real possibility of a TET design - mean that a patient’s prospects of an unencumbered lifestyle are greater than ever.

Though I admit my own professional circumstances have shaped my perception, I likewise implore you all to recall the basic truth of treating our patients, which is to leverage the best science and technology available to us to make medical recommendations that will be of greatest benefit to this complex subset of patients.

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The Art of Decision Making in Patient Selection for Durable MCS: Goldilocks

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With an ever increasing use of durable LVADs in end stage heart failure, the need for appropriate patient selection has never been more critical. The determination of who is an ‘ideal’ candidate remains challenging, given the complexity and multi-dimensional nature of this disease. There are various factors that go into this determination – those related to the disease and its impact on various aspects of the patient’s health, their nutritional, financial and psycho-social status, input from caregivers and ability of their health care team to assess and prioritize these issues. As a result, heart failure physicians are constantly debating the need and timing for durable VADs – with both a VAD done ‘too soon’ or ‘too late’ in the course of disease presenting their unique downfalls.

There has been much written about risk stratification and outcome prediction in this area. There are multiple tools published for predicting the risk of mortality, right ventricular failure, stroke etc. post VAD but their clinical utilization in real life is limited. This is partly because they have been derived from limited patient numbers, focusing on few clinical parameters. Their major setback is that they try to find linear and non-dynamic correlation between a risk factor and outcome – whereas patients requiring MCS support are far too complex for these conclusions. A risk score that predicts that an elderly patient on a ventilator, requiring dialysis and pressor support will have a poor outcome post VAD is hardly enlightening. In the absence of validated, dynamic risk prediction algorithms derived from long term, multi-center experiences, physicians continue to use their clinical gestalt while making candidacy decisions.

Another aspect of defining candidacy is the expanding use of MCS from temporary or bridge support to durable/long term support. Boundaries for patient consideration for both BTT and DT indications are being stretched and redefined. Once considered a fairly absolute contraindication, an increasing number of patients are being maintained on renal replacement therapies while on VAD support. Another example is the increasing number of octogenarians being considered for destination LVADs. Regional and institution specific factors add yet another facet to this decision making. Increasing numbers of young heart failure patients with high BMI and blood group O are receiving a more ‘elective’ LVAD as BTT under the hope and premise that they will lose enough weight to become eligible for cardiac transplantation.

Health care teams try to fulfill these varying demands by extending the team of people involved in decision beyond heart failure cardiologists and surgeons to include social and financial case workers, psychiatrists, palliative care specialists, care coordinators, administrators and caregivers – with the patient in the center of this whirlwind of decision. Increasing emphasis is being placed on informed decision making with focus on trying to get the patient to have a reasonable idea of what to expect. Some programs set up ‘meet and greets’ for those considering a VAD where they mingle
with patients supported by pumps. Various websites are dedicated to learning about the VADs in layman terms. Yet the gap between the information considered delivered to a patient and what they grasp stays wide. The questions still remain - Do these patients really understand what they are signing up for? Do their caregivers grasp the immensity of their role in the long term? Are we putting enough emphasis on quality of life? Probably equally critical, are we putting enough emphasis on quality of dying?

*Good decisions come from experience, and experience comes from bad decisions.* (Anonymous)

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Navigating the Quagmire of Immunosuppressant Drug Coverage and Affordability in the United States

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The Quagmire

Immunosuppressive medications are essential for the prevention of organ transplant rejection. Transplant recipients occasionally encounter barriers in obtaining appropriate insurance coverage. Additionally, even with appropriate insurance that includes coverage for medications, high or unaffordable copays can prevent patients from obtaining their lifesaving medications.

Initial concerns were addressed in 1985 by the Task Force on Organ Transplantation following the approval of cyclosporine in 1983 [1,2]. Subsequently, between 1986 and 2000, changes were made in Medicare coverage and reimbursement policies to enhance access to these life-sustaining therapies [3-8]. Those changes led to immunosuppressive coverage under the Medicare Part B benefit. In 2006, Medicare expanded coverage to include prescription drugs through the Medicare Part D program. Despite these changes in legislation, and regardless of whether a patient carries Medicare or some other type of insurance, many patients remain unable to afford their immunosuppressive medications. Missing these medications can lead to premature and avoidable graft loss [1,2,6,7,9-12].

In 2010, the American Society of Transplantation, in cooperation with the United Network for Organ Sharing (UNOS) and the North American Pediatric Renal Trials and Collaborative Studies, undertook a survey of adult and pediatric transplant centers in an effort to establish the scope and magnitude of immunosuppressive medication cost-related non-adherence [13]. Over 83% of transplant programs reported that patients frequently contact them with concerns about the high cost of their immunosuppressive medications. In fact, 43% of all programs report that more than 10% of their patients are not taking their immunosuppressive drugs as prescribed because of difficulties associated with their ability to pay for them. This nonadherence can have devastating consequences, with 68% of the participating centers reporting deaths and graft losses directly attributable to cost-related immunosuppressive medication nonadherence. As such, it is imperative that we as a multidisciplinary team are equipped to assist our patient population navigate their insurance benefit as well as overcome the variety of financial obstacles that may present post-transplant.

Tips for Securing Drug Coverage
In the United States, insurance coverage may come via private plans provided by employers, private plans that individuals purchase through national exchanges or on their own, public plans for those with low incomes (i.e. Medicaid), or public plans for those who meet certain conditions (i.e. Medicare). All plans use strategies such as provider networks, medication formularies, prior authorization requirements, quantity limits, step therapy, and restricted pharmacy dispensing to control costs. An important part of a transplant evaluation, as well as long-term transplant management, is ensuring patients carry adequate coverage, ensuring they understand how to use their coverage, and helping them navigate plan restrictions.

One current and alarming problem centers around immunosuppressant drug coverage under Medicare Part D plans. Affected transplant recipients are any who received their transplant while covered by insurance other than Medicare, then later become eligible for Medicare. As currently written, the Medicare Part D regulations do not obligate plans to cover any medication unless it is used per FDA-approved labeling or for indications deemed appropriate by the Centers for Medicare and Medicaid Services (CMS)-approved compendia (AHFS-DI® or Drugdex®). Beginning in 2016, some Medicare D plans have begun applying this option and have denied immunosuppressant drug coverage for lung transplant recipients, or everolimus/sirolimus coverage for heart transplant recipients. These denials are allowed, since use is off label and not supported by the compendia, and thus they are upheld through multiple levels of appeal. To address this concern, members of the transplant community are proposing revisions to the CMS-approved compendia, as well as lobbying Congress to enact legislation requiring Part D plans to consider peer reviewed literature when making decisions regarding coverage of off label immunosuppression.

**Tips for Overcoming Financial Hurdles**

When gaps exist between cost and coverage there remains a variety of resources available for transplant centers to offer those who require assistance. A few grants and foundations exist as a resource to patients with insurance that are experiencing coverage gaps, high premiums, and/or high co-payments (see Table 1.). These funds exist through donations and strict criteria may apply. Additionally, programs may close when insufficient funds are available. Manufacturer assistance programs are available to bridge these gaps but have a variety of eligibility requirements (see Table 2). Voucher or sample programs, where available, offer a free short-term supply to serve as a bridge to longer-term assistance. Longer-term assistance may include co-pay cards, which can often be applied retroactively 120 days. These copay card programs exclude patients with publicly funded insurance programs, exclude Massachusetts residents, and require renewal over time. Other forms of long-term assistance include the aforementioned grants, foundations, and manufacturer assistance.

<table>
<thead>
<tr>
<th>Table 1. Grants and Foundations:</th>
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<tr>
<td><strong>American Transplant Foundation</strong></td>
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<td>Insurance</td>
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<tr>
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<tr>
<td>Household Income</td>
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Sample funds:

<table>
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<tr>
<th>Premiums, copays</th>
<th>Maximum Grant:</th>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Gout</td>
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<tr>
<td>Heart failure</td>
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<td>Hepatitis C</td>
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<td>Hyperkalemia</td>
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<td>Pediatric assistance</td>
<td>Maximum Grant:</td>
<td>$5,000 for copays</td>
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<th>immediate-72 hours</th>
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<tr>
<th>Disbursement</th>
<th>Vendor</th>
<th>Pharmacy Card or Patient Reimbursement</th>
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As of August 19, 2016

**Table 2. Manufacturer Patient Assistance:**

<table>
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<tr>
<th>Manufacturer</th>
<th>Copay Cards</th>
<th>Patient Assistance Program</th>
<th>30-Day Voucher</th>
<th>Link to Program</th>
</tr>
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</table>
Additional resources are available to aid in identifying potential assistance programs for patients in need. These include: RxOutreach, NeedyMeds, RxAssist Patient Assistance, Sav-Rx Prescription Services, the Partnership for Prescription Assistance, RxHope, GoodRx, and more. The multidisciplinary transplant team must collaborate in order to optimize each patient’s access to coverage through his or her prescription benefit program, identify resources for coordinators, social workers, and other transplant staff, facilitate patient assistance applications, and work with outpatient pharmacies to utilize vouchers and co-pay programs. The transplant pharmacist might be the most appropriate team member to determine when a formulary alternative is reasonable, frame prior authorization arguments, and triage medication access problems. Collaboration of all members of the interdisciplinary team is essential to ensure the coverage and affordability of these life-sustaining therapies.

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References:
Meds For My Pump: Common Medication Insurance Encounters in MCS

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As insurance companies continue to increase the regulation of health plan formularies, in an attempt to control costs, the use of any ‘off-label’ medication therapies is under scrutiny like never before. As practitioners who care for such a unique patient population, we frequently encounter the use of newly approved or investigational devices. We are familiar with the medical management of complex patients with countless co-morbidities. Not unexpectedly then, we sometimes find it beneficial to use even "old” drugs in new ways or for indications not yet approved by the FDA. I’ll highlight a couple of my favorites from experience in our VAD clinic.

**Dipyridamole** initially received approval by the FDA in 1961 for use in the treatment of angina and later in 1986 as an anti-platelet agent [1]. Although it had largely fallen out of fashion, dipyridamole has found resurgence as part of the anticoagulation regimen recommended for patients implanted with many of the current left ventricular assist devices (LVADs). Though numerous publications now describe and support the use of dipyridamole in this patient population, it continues to require prior authorization and non-formulary exception from numerous health plans for coverage. Thankfully, the process in this instance is usually straightforward and authorization is generally achieved with the first request. Being able to attach device specific literature and clinical guidelines available on the FDA’s website to support the request is of great benefit [2].

Another prior authorization request that keeps popping up (pun intended) on my desk is one for **sildenafil**. As we know, the phosphodiesterase type 5A inhibitors have been shown repeatedly to help decrease pulmonary vascular resistance (PVR) in patients with persistent pulmonary hypertension (PH) following LVAD placement [3]. However, sildenafil is currently only FDA approved for use in the treatment of patients with WHO Group I, to improve exercise ability and delay clinical worsening [4]. Getting insurance authorization for its use in our WHO Group 2 patients (PH due to left heart disease) generally requires more effort. Some insurance plans will require pulmonary pressure readings from cardiac catheterizations while others will accept detailed ECHO transcriptions. Some have hard stops for approval with specified parameters for pulmonary arterial pressures, pulmonary capillary wedge pressures, and pulmonary vascular resistance. Others will not authorize coverage for any indication other than the approved WHO Group I. Often the process entails filing an initial request for authorization of coverage, waiting for a denial, filing for an appeal, waiting for another response, and sometimes then results in a review by a third party or a peer-to-peer request. Any less persistent practitioner might recant at some point during that exhausting process (which may very well be the intent). But when therapy is truly indicated, the process cannot be avoided.
The effort and time spent obtaining necessary authorizations for coverage can be burdensome to an already overworked clinical staff. The process, sometimes unresolved after days of faxes or electronic appeals back and forth, can leave patients to pay out of pocket for new medications in order to avoid lapses in therapy. We can all agree that regulations are absolutely necessary to safeguard against inappropriate medication use. In addition, we must be mindful of drug related costs and choose less expensive alternatives when clinically appropriate. However, our ability to thoughtfully prescribe medications cannot be compromised; even when the proposed indication is ‘off-label’ or there are no large, randomized controlled trials available to support us. Given the processes by which coverage for these medications are obtained, it is imperative that authorization paperwork is started in advance to maximize the access that patients can have to these beneficial therapies. Additionally, being proactive in gathering information that is required upfront by insurance payers can help expedite these issues. Engaging your financial coordinators and case management professionals can assist in this process.

Our unique patient population will continue to challenge conventional medication management and require creative solutions. However, if the innovative use of medicine that has brought us to our present practice becomes stifled by rigid inclusion criteria that disregard clinical reasoning, then hope for future advancements and gains will be lost. We must continue to collaborate as medical professionals practicing in this specialty. We must share information and experiences by contributing to the medical literature in the form of case reports and commentaries, sharing questions and answers on list serves, gathering for formal meetings, and working together to create consensus guidelines for care based on our collective expertise. At the end of the day, no matter how cumbersome, we must continue the task of advocating that our health care industry cover such beneficial and reasonable therapies for our patients. By working together, we can increase the strength of our appeals, decrease denials of coverage, and continue to improve patient access to the cutting edge, life-saving therapies we have to offer.

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Insurance Considerations for Initiating Parenteral or Inhaled Prostacyclins in the Hospital for Pulmonary Arterial Hypertension

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Current pulmonary arterial hypertension (PAH) guidelines recommend parenteral prostacyclins (e.g., epoprostenol, treprostinil) and inhaled prostacyclins (e.g., iloprost, treprostinil) for patients with WHO Group 1 PAH and Functional Class III or IV symptoms. Initiating prostacyclins in an acutely decompensated patient in the hospital requires a substantial amount of effort and coordination from the Pulmonary Hypertension team and pharmacy team to ensure therapy can be continued at home following hospital discharge. Developing an institutional process for initiating prostacyclins can help ensure that a safe and timely discharge is not delayed due to issues with insurance approval for continued outpatient use. Potential obstacles include obtaining insurance approval through prior authorization processes, applying for patient assistance programs for individuals with limited resources, and scheduling comprehensive education and delivery of outpatient medication, equipment, and supplies prior to discharge through the specialty pharmacy. This article will describe some experience with these challenges as well as methods that can be developed to reduce the burden on the Pulmonary Hypertension team, and ultimately, the patient.

Prior Authorization:

Before initiating the prior authorization, the treatment options should be discussed with the patient and their family in a shared decision manner. The medicines available in PAH are complex and expensive, especially the parenteral and inhalation therapies. The regimens can be burdensome, and in some cases, overwhelming from a psychological and practical perspective. A significant limitation is the dexterity and sterility that is required for the parenteral therapies. As infusion therapies and inhaled therapies are presented to patients, it is important to ensure that they will be able to manage the regimen at home. It is also important to discuss a time frame with the patient and their family for obtaining insurance approval for these treatments, as well as an expected time frame for discharge from the hospital.

If prostacyclins are being prescribed for long-term use, the patient’s insurance carrier should be contacted early during the hospitalization so that the prior authorization process can be initiated and the appropriate documentation can be prepared and submitted. Common requirements include
submitting the results of an echocardiogram, the results of the right heart catheterization documenting the hemodynamics, most specifically the pulmonary arterial pressures, pulmonary capillary wedge pressure, pulmonary vascular resistance, and the results of a vasodilator challenge. Oftentimes, the 6-minute walk distance (6MWD) results are submitted. The history and physical and progress notes are required and should detail the onset of symptoms, WHO Functional Class, the speed of disease progression, the presence of poor prognostic factors including right heart failure, and treatment history, including current and discontinued medications for pulmonary hypertension. It is important to document that the diagnosis reflects Group 1 PAH. If the patient has risk factors for Group 2 or 3 pulmonary hypertension, detailed documentation is required to explain whether these risks factors are adequately treated and if the patient’s pulmonary vascular disease is independent of these risk factors. Once all the requested documentation is submitted, the insurance will review and respond with either an approval or denial. If denied, additional documentation may be submitted through a formal appeal process.

**Patient Assistance:**

Once insurance approval is obtained, it is important to assess the patient’s out-of-pocket costs, which can be a significant financial burden on some patients. Patient assistance programs can provide financial grants for co-payments and insurance premiums for qualifying patients. Oftentimes, patients are asked to submit proof of household income in order to qualify for assistance programs. This documentation can be difficult to obtain when the patient is hospitalized.

**Specialty Pharmacy:**

Specialty pharmacies provide the PAH therapy and supplies to the patient at home, and can provide significant assistance to the Pulmonary Hypertension team, patient, and family during the hospitalization. Prior to the patient discharging from the hospital, the specialty pharmacy needs to complete sufficient patient and family education regarding preparation and administration of the prostacyclin and troubleshooting the delivery device (i.e., intravenous pump, subcutaneous pump, inhalation device). The education process can be delayed until the insurance approves the prior authorization. Contacting the specialty pharmacy early in the prior authorization process can expedite the training process. Typically, educational sessions for infusion and inhaled therapies can be held over 2-3 days in order to ensure that the patient and their family are comfortable with their medications and the effort required to adhere to the regimen. The specialty pharmacy can also assist in transitioning the patient from hospital pump to home pump on the day of discharge.

**Additional Considerations:**

With parenteral therapies, patients may need to be changed from intravenous to subcutaneous prostacyclins. This can occur in the setting of a line infection, or it may be a patient preference. Patients may also need to be transitioned from subcutaneous to intravenous prostacyclins in the setting of intolerable infusion site pain. It is important to recognize that transitions between different routes of the same medication requires going through the prior authorization process again to justify the change to the insurance company.
Infusion therapy in the hospital poses additional challenges. The high cost of patient-specific inhalation devices and drug may not be feasible from a formulary standpoint. If inhalation therapy is the preferred treatment, one option is to complete the prior authorization and education while the patient is hospitalized, and initiate therapy within 24 hours of discharge with the specialty pharmacy’s assistance.

Ultimately, these medications and regimens, although arduous, can have a positive impact on people’s lives. And although the approval process and introduction of prostacyclins can be time consuming for both patients and providers, having an institutional process in place can help alleviate the burden of getting these therapies initiated.

Table 1. Institutional Process for Initiating Prostacyclin Therapy

- Verify patient has insurance coverage
- Discuss treatment options with patient and family
- Evaluate patient and family’s ability to manage therapy at home
- Submit documentation for insurance approval of selected therapy
  - History and physical
  - Progress notes
  - Echocardiogram
  - Right heart catheterization
  - Vasodilator challenge
  - 6-minute walk distance
  - Additional documentation if component of Group 2 or 3 PH
- Confirm insurance approval and patient’s out-of-pocket costs
  - Apply for patient assistance if needed
- Contact specialty pharmacy
  - Schedule patient and family education sessions
  - Schedule transition to home equipment on day of discharge

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Clinical Considerations for the Use of GLP-1 Agonists Post Lung Transplantation

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Hyperglycemia post transplantation is a relatively common complication, either due to pre-existing diabetes or new-onset diabetes after transplant (NODAT). The estimated rates of NODAT 12 months post-transplant are 28-30% in heart transplant and 6-45% for lung transplants [1-3]. This article aims to discuss pharmacotherapy considerations for a newer class of incretin mimetics, the glucagon-like peptide-1 (GLP-1) agonists, used in the management of hyperglycemia in thoracic transplant patients with focus on risk vs. benefit in lung transplant recipients.

Exposure to immunosuppressive agents, such as glucocorticoids and calcineurin inhibitors, in combination with other risk factors including older age, obesity (BMI>30), and frequent acute rejection episodes requiring treatment with high-dose steroids further increase the risk of NODAT. NODAT is associated with an increased risk of rejection, infections, and cardiovascular complications [4]. Many patients will require pharmacotherapy to manage hyperglycemia post transplantation, and this often includes insulin. Incretin mimetics, one of the latest additions to the armamentarium for the treatment of hyperglycemia and NODAT, are now available as an addition to insulin therapy to lower insulin requirements or as monotherapy in place of insulin [5]. Currently five agents in the GLP-1 agonist pharmacological class are available worldwide; albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide. All five agents are peptides that need to be administrated by subcutaneous injection in various frequencies ranging from twice daily immediate release exenatide to once weekly albiglutide, dulaglutide and extended release exenatide.

GLP-1 agonists are less likely to cause hypoglycemia as a monotherapy than insulin or sulfonylureas, but they have similar rates of hypoglycemia when combined with these agents. GLP-1 agonists mimic the physiological profile of insulin by enhancing glucose-dependent insulin release and inhibiting secretion of glucagon [6]. GLP-1 agonists reportedly lower A1C levels in non-transplant individuals by up to 2% and promote weight loss of as much as 4 kg in 24-32 week-long trials [7]. In addition to lowering A1C and promoting weight loss, GLP-1 agonists also promote satiety in the central nervous system and slow down gastric emptying by relaxing the proximal stomach and inhibiting both antral and duodenal motility [8-12]. In healthy subjects, GLP-1 agonist use causes increased retention of solids in the distal stomach at 100 minutes from 29% to 58% and frequently produced gastroparesis, without regards to its dose [13].

Gastroparesis is a complication of lung transplantation, with a prevalence of 6-24% [14,15]. It is thought to be attributed to intraoperative vagal nerve damage, pharmacological agents, and
preexisting lung disease [16]. Gastroparesis may play a significant role in Bronchiolitis Obliterans Syndrome (BOS) through an exacerbating effect on gastroesophageal reflux disease (GERD) leading to microaspiration and secondary activation of the innate immune system [17]. Bronchiolitis Obliterans Syndrome is a common cause of mortality and morbidity in lung transplantation, with a five-year patient survival from onset of 30-40% [18].

To our knowledge, no data on the use of GLP-1 agonists and gastroparesis complications in lung transplantation have been published at present. GLP-1 agonists increase the risk of gastroparesis in healthy individuals and we can reasonably expect this to affect some thoracic transplant patients as well. Given the role that gastroparesis may play in the development of serious, long-term sequelae, caution should be exercised with this new class of agents. As these agents gain popularity, prescribers should be aware of the side-effect profile before their initiation in lung transplant recipients and consider possible risks vs. benefits of therapy.

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Eight Years Later: How Comfortable Are We Really With Target Specific Oral Anticoagulants (TSOACs) After Cardiothoracic Transplant

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Following dabigatran’s approval by the European Medicines Agency in 2008 and by the US Food and Drug Administration in 2010, TSOACs are being prescribed with increasing frequency in the general population to reduce the risk of stroke in patients with atrial fibrillation and to treat venous thromboembolism (VTE) [1]. Three other TSOACs have since been approved including rivaroxaban, apixaban, and edoxaban. Without listing all of the potential benefits of these medications, the ease of use around biopsies and procedures due to their rapid onset/elimination may be appealing for clinicians. While these newer agents are now recommended ahead of warfarin for the treatment of VTE in the general population, comfort with their use in solid organ transplant patients is still growing amongst clinicians [2].

There are many reasons for a potential lack of comfort in using these agents in the transplant population. First and foremost, therapeutic drug monitoring recommendations are not available for the TSOACs. While laboratory monitoring tests do exist, there are not universally accepted therapeutic ranges for these assays. Imagine the difficulty of dosing tacrolimus without the ability to monitor or interpret levels. While not as drastic, the TSOACs share many similarities with tacrolimus in terms of factors that impact AUC and clinical effects.

Many of the TSOACs are substrates of the CYP3A4 enzyme and/or the P-glycoprotein (P-gp) transporter and are therefore subject to drug interactions with medications commonly used in transplant patients. Dose reductions for these agents may depend not only the strength of 3A4 inhibition, but also the presence of P-gp inhibition. For instance, the azole antifungals (eg. fluconazole, voriconazole, posaconazole, itraconazole, and isavuconazonium) all have different degrees of 3A4 and P-gp inhibition and could possibly lead to varying dose adjustments. Additionally, the unpredictable nature of episodes of acute renal or hepatic dysfunction provide another instance where therapeutic drug monitoring would be helpful. It is difficult to know exactly how changes in organ function correlate to drug exposure, clinical efficacy, or risk of bleeding.

Lastly, recommendations for the management of bleeding in patients taking TSOACs are lacking, and with the exception of dabigatran, there are no approved reversal agents for the TSOACs. Evidence is available for the use of 4-factor prothrombin complex concentrates for reversal, however this is not an approved indication [3]. A novel agent, andexanet alfa, is currently being
investigated. The combination of these concerns in transplant patients can create a hesitancy to utilize TSOACs that may not be seen in the general population.

Key considerations for the TSCOACs in transplant patients:

- **Dabigatran** does not undergo hepatic metabolism and is renally excreted. The dose used is dependent upon its indication and the patient’s renal function. It is a substrate of P-gp and the manufacturer recommends a dose reduction when used concomitantly with strong P-gp inhibitors (ex. dronedarone or ketoconazole). Dabigatran is not recommended in patients with renal impairment and is associated with increased gastrointestinal bleeds [4]. Dabigatran does have an approved reversal agent, idarucizumab, however its use in clinical practice is nascent [5].

- **Rivaroxaban** is a substrate of both CYP3A4 and P-gp and is partially renally excreted. The dose used is dependent upon its indication and the patient’s renal function. The manufacturer recommends avoiding concomitant strong CYP3A4 inhibitors. The manufacturer does not recommend dose adjustments when used with a P-gp inhibitor and/or moderate CYP3A4 inhibitor (eg. amiodarone, diltiazem, or fluconazole), however caution should be used. Rivaroxaban exposure may be increased up to 160% with these medications and the effect of the increased exposure on the risk of bleeding is unknown [6].

- **Apixaban** is a substrate of both 3A4 and P-gp and is partially renally excreted. The dose used is dependent upon the indication and the patient’s weight, age, and serum creatinine. The manufacturer recommends a dose reduction with the combination of strong CYP3A4 and P-gp inhibitors. However, there are no manufacturer recommendations for dosing with multiple moderate inhibitors (ex. diltiazem, azithromycin, fluconazole, tacrolimus). Apixaban is the only TSOAC with evidence for use in hemodialysis patients, however this is limited to a single-dose, pharmacokinetic study in healthy patients [7,8].

- **Edoxaban** is recommended only in patients with an estimated creatinine clearance 15-90mL/min, does not undergo hepatic metabolism, and is only a minor substrate of P-gp. Clinicians should be cautious because the estimated creatinine clearance does not always accurately reflect renal function in transplant patients. No dose adjustments are recommended when using CYP3A4 inducers or inhibitors or when using P-gp inhibitors [9].

There are many options for anticoagulation in transplant patients, including warfarin, LMWHs, and TSOACs. Regimens should be chosen based on patient specific factors, such as need/availability of therapeutic drug monitoring, drug interactions, and the risk/benefit profile of the individual agents. The TSOACs may not replace warfarin or low molecular weight heparin for all cardiothoracic transplant patients, however for the right patient they may provide a safe and effective mode of anticoagulation.

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NEW & ANNOUNCEMENTS:

Monograph Volume 9 eBook is Now Available

Monograph Volume 9: Pulmonary Hypertension and Right Heart Failure is now available as an eBook for purchase through iBook, Amazon, Barnes & Noble, and many other eBook retailers.

Annual Southeast Pediatric Cardiovascular Society Conference

Please join us for the 49th Annual Southeast Pediatric Cardiovascular Society Conference, sponsored by Joe DiMaggio Children's Hospital and held in Fort Lauderdale, FL on September 15 through 17th. The 49th Annual SEPCS Conference will provide an overview of current practice in the diagnosis and treatment of congenital and acquired heart disease in children and young adults. Discussions will include interactive sessions with both individual speakers and panels. The conference will offer learning opportunities for the entire spectrum of healthcare providers caring for children with acquired and congenital heart diseases. The themes for the meeting are: The Right Ventricle, and The Science of Innovation. Guest Faculty include William Norwood, Ed Bove, Andrew Redington, Beth Kaufman and Gil Wernovsky. Program and registration are available via the following link: www.jdch.com/sepcs.
Change Your Mind, Think Differently

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A brief report on my ISHLT International Traveling Scholarship Award at Brigham and Women’s Hospital and Harvard Medical School

Change your mind, start thinking differently. This the main message instilled in me during my ISHLT International Traveling Scholarship at Brigham and Women’s Hospital (BWH) and Harvard Medical School in Boston, USA. After I completed my Postgraduate Course in Heart Failure and acquired my Certificate in Advanced Studies from the University of Zurich in 2015, I applied for the ISHLT award to further enhance my skills in the management of advanced heart failure (HF) and develop a more comprehensive worldwide view. Two short weeks of a visiting fellowship at the Center for Advanced Heart Disease at BWH with Dr. Mandeep R. Mehra and his outstanding colleagues has been nothing short of an indelible and unique clinical experience.

In observing a seamlessly integrated multidisciplinary team composed of various professional disciplines, I was struck by the essence of collaborative spirit in the perfection of the delivery of healthcare, with a patient centered approach. Strikingly, I observed “tough medicine” practiced with ease in diverse clinical areas of advanced HF, focusing on the management of heart transplantation or the complex handling of patients with durable ventricular assist devices (VADs) or participating in the diagnosis of unexplained dyspnea by performing an invasive cardiopulmonary exercise test.

This incremental experience has helped me learn the importance of a complete clinical overview from the acute setting to the transition to homecare by observing and analyzing an integrated system that helps in reducing errors due to overwork by delegating different responsibilities across professional disciplines and that creates a network between the hospital, the patient and local healthcare system. I have been impressed by the profession of a nurse practitioner, not found in my country of Italy, which contributes to simplify a physicians’ daily work, giving them the time to be involved in other activities and yet provides an unparalleled level of clinical patient centered care. Moreover, I had the opportunity to participate in educational conferences, using clinical cases, on specific HF topics and even was lucky enough to have the unique opportunity of a personal tutorial lecture by Dr. Marc Pfeffer on the evolution, uncertainty, and advances in HF therapy over the years.

This international traveling scholarship also provided me the chance to develop collaborations with Dr. Mehra in scholarly research activities, by starting from an idea in a personal point of view, then reflecting on it, analyzing the topic, examining the literature and finally converting the thoughts to an entirely new way of thinking and approaching the initial hypothesis. At Harvard Medical School, teaching knowledge is approached differently, by giving individuals the time and adequate
resources to tailor their scholarly activity, leading you to start thinking differently, finally evolving your thoughts to develop a novel point of view.

In my opinion, this experience is best directed to those clinicians and researchers with expertise and mature skills on a specific topic that are seeking to extend their mental outlook, to create a connection with a leading research center and to develop a different approach to interweaving research and practice.

I am grateful to ISHLT for providing me with the opportunity to acquire this experience in Boston and hope that this can be shared with colleagues with similar experiences, promoting this ISHLT initiative in order to continuously improve our knowledge. Change your mind, think differently.

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The Weight of Angels

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I walk through the hospital halls
weeping at the dying rows
of hot house children. I call
their names—“Jenny, Sam....” The list grows
each day. In small words I explain
how the body can’t undo the damage
that the illness has done. I watch the pain
become mouth lines, eye lines. This age

is hardest. Letting go the bright years—
There is not enough weight in them. Just
a breeze from the window or open door
will brush their un-tacked souls away like dust.

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