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Editor’s Recommended Reading
In December 2010, the ISHLT Board approved the creation of the Pharmacy and Pharmacology Council. It is the hope of this council to join forces with pharmacists and pharmacologists around the world in order to foster collaboration and research in the areas of heart and lung transplantation, heart failure, pulmonary diseases including pulmonary arterial hypertension, and mechanical circulatory support, in order to enhance care of patients. We have several key initiatives for this coming year, including: identifying colleagues and having them join us on our initiatives; developing a core competency position statement for thoracic transplant pharmacy professionals; developing symposia for the ISHLT Annual Meeting; and involving our early career colleagues in research and writing projects.

We currently have over 60 members in our council from the US, Canada, Australia and the UK with experience levels ranging from over 15 years of practice to 1-2 years of working with these complex patients. Like our physician counterparts, many of us expand our roles beyond post-transplant care to include management of primary disease states that lead to thoracic organ transplant. In addition, some clinical pharmacists care for both adult and pediatric patients.

Thoracic transplant programs in the United States are required by UNOS to identify a pharmacist that is involved in the care of patients listed for and after transplantation. During the review process, the program must provide documentation of at least the following duties: presence of a pharmacist during rounds, participation of a pharmacist in post-transplant discharge teaching; evaluation of medical therapy by a pharmacist close to the time of the transplant event; and documentation during evaluation and at the time of listing that there are no pharmacologic contraindications for transplantation. Based upon this, our council felt we should determine what makes a qualified thoracic transplant pharmacist. Therefore, we are developing a core competency position statement for thoracic transplant pharmacy professionals that will include disease states beyond transplantation such as advanced heart failure and lung disease, mechanical circulatory support, pulmonary arterial hypertension and encompass training and practice not only in the US but internationally as well.

This coming year, the Pharmacy and Pharmacology council is very excited to sponsor a symposium at the ISHLT Annual Meeting in Prague. It is an innovative symposium that we hope will be an enduring series at the meeting with this year’s entry entitled, “A Lifecycle Journey in Advanced Heart Failure and Transplantation.” Unlike traditional symposia that are presented either in pure didactic tracks or cases with panel discussions, this series is envisioned as a practical hybrid by depicting an enduring case interspersed with a best practice based discussion at predefined key “journey intervals”. The symposium will be rounded off by a panel assisted and audience supported anchoring discussion. For the 2012 Prague meeting, we have focused on the lifecycle of Advanced Heart Failure and Cardiac Transplantation with special emphasis on 3 “journey points” of Mechanical Circulatory Support and anticoagulation, early graft dysfunction, and late outcomes that demand innovative immunosuppressive strategies. The focus of this series will be on the therapeutic aspects that uniquely involve emerging or established knowledge in the pharmacology and pharmacy aspects of the interval disease states or situations. Future symposia could tackle “A Lifecycle Journey …” in advanced lung disease, destination mechanical circulatory assist, a pediatric patient that transitions into adulthood, or pulmonary arterial hypertension. We hope that this new style of presentation will entice you to attend the session in April.
In closing, it is the council’s hope that in the years to come we continue to grow in membership and especially in the numbers of colleagues from all over the world. We are hopeful that we can work with our colleagues from other disciplines on research projects, patient care guidelines, and writing projects such as state of art reviews for the Journal of Heart and Lung Transplantation.

Crossing International Borders – A Call for All Heart and Lung Transplant Pharmacists

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Over the past three decades, our profession has moved from one whose original focus was that of medication distribution to one that places a more inclusive focus on patient care. The value of the pharmacist on multidisciplinary teams has been well documented in all patient care settings in almost all subspecialties of medicine. In Europe, the United States, and Canada, the addition of a pharmacist to a multidisciplinary team has been associated with reductions in mortality and hospitalizations, minimization of adverse drug reactions, enhanced medication adherence, as well as improved management of chronic disease states such as hypertension, hyperlipidemia, heart failure, and diabetes. This especially holds true in the transplant population, with its multitude of comorbidities and complex pharmacotherapies. In many countries, pharmacists with expertise in transplantation have been included as an essential member of a multidisciplinary team dedicated to the provision of medication therapy management and education for transplant recipients. In the United States, the perception and role of the pharmacist was further justified in 2004 when the United Network of Organ Sharing bylaws and the Centers for Medicare and Medicaid accreditation standards were amended to include a pharmacist or someone with expertise in pharmacology as a necessary member of the transplant team.

Over the last decade, pharmacists have been openly welcome to join and actively participate in many of the large medical organizations such as the American Heart Association, American College of Cardiology, Society of Critical Care Medicine, and the American Society of Transplantation, just to name a few. These organizations have allowed us, as pharmacists, to have an equal voice on committees and writing panels, as well as, provided the opportunity to meet and collaborate in a national forum with other pharmacy practitioners with similar clinical and research interests. Recently, with the insight and guidance of Drs. Patricia Uber and Mandeep Mehra, the International Society of Heart and Lung Transplant (ISHLT) has granted us an excellent opportunity to form our own Council on Pharmacy and Pharmacology within the ISHLT. Unlike many other medical organizations, ISHLT allows us to collaborate internationally—crossing all borders.

As our Council continues to grow and thrive, we wish to document our expertise, value, and training to our mechanical support (MCS), pulmonary arterial hypertension (PAH), and thoracic transplantation colleagues, through the development of a Core Competency Statement for Thoracic Transplant Pharmacy Professionals. Since 2004, several organizations have addressed the role of pharmacists in the management of the transplant recipient which include the American Society of Transplantation, the American College of Clinical Pharmacy, the Heart Failure Society of America, and the American Society of Health System Pharmacists. Unfortunately, many of these position papers exhibit several limitations in that they 1) solely take an American perspective and do not include an international viewpoint, 2) do not provide organ or condition specific competencies (e.g., specially heart or lung transplantation, PAH and MCS) and 3) focus upon the adult while ignoring the pediatric patient. It is our hope to address each of these limitations within our Core Competency Statement. More importantly, we would like to pose and address the following questions:
Which governing/professional/regulatory agencies world-wide have formalized the role of the pharmacist within transplantation or other thoracic disciplines and how do they define this role?

What is the education and training warranted for a thoracic transplant pharmacist?

What are the fundamental core competencies of a pharmacist practicing in thoracic transplant, MCS, or PAH, within a health system from the standpoint of patient care, education, and research?

At this stage, the writing group leads consisting of myself, Drs. Patricia Uber, Michael Shullo, and Chris Ensor have developed a proposal to present to the ISHLT Board and have begun to secure writing members. However, we are specifically looking for potential authors within Australia, Canada, Europe, Japan and South America. If you are interested in participating in the writing group, especially if you are practicing outside of the US, I ask that you email me directly (Robert.Page@ucdenver.edu) at your earliest convenience.

This Core Competency Statement is one of the first key essential steps toward the growth and development of our Council granting us the ability to cross all borders!

ISHLT ALERTS

ISHLT Comments on draft United States Public Health Service Guidelines
As a society committed to safe practices in transplantation, the ISHLT has responded on November 21st with strong concerns to the draft of the PHS Guidelines for Reducing the Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) through Solid Organ Transplantation prepared by the Centers for Disease Control and Prevention in the United States.

While the PHS Guidelines advocate for universal nucleic acid testing (NAT) for HIV and HCV in all deceased donors, ISHLT strongly suggests targeted screening of high-risk donors based for these pathogens. The aim of the ISHLT suggestion is to balance the prevention of potential donor-derived transmissible diseases while maintaining and maximizing access to donor organs for the severely ill patients waiting for transplantation who are at risk for death if appropriate donors cannot be identified in a timely manner.

Read the letter: http://www.ishlt.org/ContentDocuments/ISHLT_Comment_on_PHS_ID_Guidelines.pdf

Individual comments can be submitted by December 23, 2011: www.regulations.gov using the keyword “Organ Transplantation” to locate the document.
Training and Practice of the Thoracic Diseases Pharmacist and Pharmacologist: Perspectives from Europe and the USA

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Many programs throughout the world utilize pharmacists and pharmacologists within their structure and practice to perform a wide variety of functions ranging from direct patient care and education to basic and clinical research. This brief report will describe the training and practice of pharmacists and pharmacologists that work in and care for patients with thoracic diseases.

Training: a United States perspective

Pharmacists in the United States (US) most often have completed PharmD, and pharmacologists PhD, training. PharmD training consists of 4 years of post baccalaureate or post bachelor training. The first three years consist of didactic coursework; the fourth of which consists of experiential clerkship experiences with practicing pharmacists. Post doctoral training is very common amongst pharmacists practicing within thoracic diseases, whether prior to or post transplantation. Post doctoral training may consist of a postgraduate year (PGY) 1 pharmacy practice residency, and various PGY 2 residencies, such as cardiology, critical care, pulmonary and critical care, solid organ transplantation, or pharmacotherapy. Pharmacists completing these training years will have a broad range of experiences and enhanced training within their particular area of focus. Additional training may consist of a post PGY1 two year fellowship in transplantation and research. Multiple pharmacists who have completed fellowship in the US have been recipients of young investigator awards of the American Society of Transplantation.

Pharmacists in the US often sit for the Board Certification in Pharmacotherapy examination, though this is not required for practice. Such credentials may differentiate advanced knowledge amongst pharmacists in this field. Added qualifications in cardiology are also sought, and are granted after successful portfolio review, to the qualified candidate. Experienced pharmacists may also seek fellowship within various organizations germane to their practice, such as the American Heart Association, American College of Cardiology, the American College of Chest Physicians, the Society of Critical Care Medicine, and the American College of Clinical Pharmacy.

Practice: a European perspective

At Great Ormond Street Hospital for Children in London, the clinical team consists of 2.5 consultant paediatric cardiologists, 2 half-time paediatric respiratory consultants, a surgeon, two registrars, 3 clinical nurse specialists, two clinical assistants, a pharmacist, 2 psychologists and an extended team of transplant coordinators who are nurses from the cardiac and intensive care unit. The transplant team also manage the Berlin Heart VAD patients jointly with the intensive care and cardiac team, and heart failure inpatients.
The transplant pharmacist attends the daily ward rounds on the intensive care unit and cardiac ward. The main duties and responsibilities are checking drugs are prescribed according to protocol, appropriate doses are prescribed for paediatric patients, dose advice in renal impairment and renal replacement therapy, monitoring immunosuppression, therapeutic drug monitoring of antibiotics and immunosuppression, drug interactions, and adverse effects monitoring. Overall fluid balance and diuretics are monitored. For the lung transplant children, infusions often need to be concentrated up from standard infusion concentrations in order to be within fluid restriction allowance. In the United Kingdom, there is a national focus on reducing patient harm by reducing prescribing errors. The pharmacist supports doctors prescribing by advising on doses and there is a system for monitoring and feedback of prescribing errors.

The transplant pharmacist attends the weekly team business meeting where both inpatient and clinic patients are discussed. Here the pharmacist has input into the management of late complications such as chronic rejection, post-transplant lymphoproliferative disease, cytomegalovirus infection and renal impairment. Logistic issues such as drug shortages or supply problems for particular patients, as well as new drugs or dosage forms can be raised here. Our microbiology/infectious diseases team join this meeting to discuss specific patients. The transplant pharmacist has input regarding the dose and route of administration for the child and potential drug interactions with the immunosuppression. Our lung transplant program now transplants children with high risk microbiology, such as Mycobacterium abscessus. The respiratory consultants with the microbiologists write a ‘night of transplant’ drug and procedure protocol specific for each of these high risk patients. The protocol is sent to the transplant pharmacist for dosage checking with respect to the organism and the child’s renal function. Any unusual antibiotics are ordered in advance, and stored in the dispensary until needed. The ‘night of transplant’ protocol is saved electronically in a specific pharmacy folder so that the on-call pharmacist can access it and action it easily on the night of transplant. The night of transplant protocols are updated every 6 months based on recent sputum and cultures.

The transplant pharmacist is also involved with protocol development for transplantation (immunosuppression, infection prophylaxis), Berlin Heart VAD programme (anti-coagulation), and heart failure. Drug cost monitoring and analysis, and horizon scanning for new drugs or dosage forms is also part and parcel of the UK pharmacist involvement.

These perspectives should serve to shed light on the background, training, and expertise of the pharmacists and pharmacologists who practice in these fields.

**Quotable Quotes**

*Transplant tolerance is like happiness... not always obvious when you have it, but painfully obvious when it is gone.*
- Sir Roy Calne

*Mozart is sweet sunshine.*
- Antonin Dvorak

*Yesterday is history. Tomorrow is a mystery. And today? Today is a gift. That’s why we call it the present.*
- Babatunde Olatunji

*Little things are big.*
- Yogi Berra

*A hug is a great gift – one size fits all, and it’s easy to exchange.*
- Author Unknown
Inhaled Prostacyclin Therapy for Right Ventricular Failure after Ventricular Assist Device Placement

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Continuous-flow left ventricular assist devices (LVADs) are a viable option for advanced heart failure refractory to medical therapy, irrespective of patients transplant candidacy. These devices have been shown to outperform maximal medical management, but are not without complications; post LVAD infection and cerebrovascular events are directly related to increased mortality [1]. In the perioperative phase, LVAD recipients may experience hemorrhage, dysrhythmia, and right ventricular (RV) failure [2]. Acute RV failure is best prevented by LVAD implantation in patients that are not fluid overloaded, such as CVP/PCWP ratio of < 0.63., as well as prevention of hypoxic pulmonary vasoconstriction [3, 4]. Ultimately, patients in right heart failure may require mechanical assistance. Approximately 6% of patients developed RV failure requiring RVAD implantation in the Heartmate II bridge-to-transplant trial. Patients that required an RVAD had a statistically significant increased risk of mortality compared to those that did not (67% vs. 89%, p<0.001) [4].

Medical therapy to reduce afterload on the failing ventricle is limited in patients with severe right heart failure. Systemic vasodilators, such as milrinone, are likely to be limited by hypotension, with the same being said for 'selective' pulmonary vasodilators such as sildenafil or intravenous prostacyclins. A way to avoid these hemodynamic pitfalls is to administer these selected pulmonary vasodilators via inhalation to act locally on the pulmonary vasculature. The two most popular agents that have been utilized are either inhaled nitric oxide (iNO) or epoprostenol.

Nitric oxide (iNO) is a direct pulmonary vasodilator that diffuses into vascular smooth muscle. This results in increased cyclic guanosine monophosphate (cGMP) through guanylate cyclase activation to produce vasodilation. Nitric oxide is inactivated by hemoglobin binding, resulting in a short half-life, easy titration, and minimal systemic exposure. Inhaled nitric oxide results in a rapid reduction of pulmonary vascular resistance and pulmonary arterial pressure without decreasing systemic resistance. The hemoglobin-mediated elimination can result in the development of methemoglobinemia, potentially leading to hypoxemia. Nitric oxide also combines with oxygen to form the toxic molecule nitrogen dioxide which can cause pulmonary edema and bronchospasm. Other downsides to iNO use are rebound pulmonary hypertension and cost, which can exceed thousands of dollars per day depending on institutional pricing. These issues have resulted in the examination of other inhaled compounds for the management of pulmonary hypertension and RV failure [5].

The primary alternative to iNO is inhaled epoprostenol, which is a potent pulmonary vasodilator that is effective at reducing pulmonary vascular resistance in patients with RV failure after transplantation or RVAD implantation [6-10]. Inhaled epoprostenol (iEPO) is administered via continuous nebulization through a ventilator circuit given its short half-life (5 minutes). One of the primary motivating factors to switch from iNO to inhaled epoprostenol is cost. Comparatively, inhaled EPO is compounded using the injectable form of epoprostenol resulting in a fraction of the drug expenditure relative to iNO. That said, in institutions that currently do not employ iEPO as therapy, several capital expenditures are needed to utilize this therapy.
Inhaled EPO is not compatible with any diluent, except for the manufacturer supplied product. This necessitates the use of a dual-chamber syringe pump to appropriately deliver the medication, with one chamber for iEPO and the other for a nebulization vehicle (sodium chloride). The resulting volume that should be delivered is 8 ml/hr which requires the use of a large volume reservoir in the circuit. The solution is photosensitive requiring the syringes and nebulizer to be wrapped in a light-protective material [11]. Inhaled EPO is dosed to response, with rates ranging from 6.25 to 50 ng/kg/min (based on ideal body weight). While purchasing these supplies represent an initial sunk cost, as well as training respiratory therapists in the set-up and delivery of inhaled EPO, it is largely outweighed by the long term cost savings of utilizing an inexpensive and effective agent. With respect to addressing the other downsides of iNO, iEPO does not have any toxic metabolites requiring additional monitoring.

Inhaled EPO presents an attractive alternative to iNO in the management of RV failure, in both device placement and cardiac transplantation. Inhaled EPO is less costly than iNO despite capital funding needed to purchase equipment and is not associated with the toxic effects that saddle iNO. Of note, there are no clinical trials comparing the efficacy or safety of these agents. Further, the inhalation route is an off-label use of epoprostenol. ■

References

Current pharmacotherapy for pulmonary arterial hypertension (PAH) targets vascular remodeling, vasoconstriction and platelet aggregation.

Oral endothelin (ET) receptor antagonists, target the effects of endothelin-1. There are 2 FDA approved medications available in the US; bosentan and ambrisentan. Bosentan has affinity for both the ET-A (vasoconstriction, cellular proliferation) and ET-B receptors (endothelin-1 clearance, vasodilation, anti-proliferation), while ambrisentan is more selective for ET-A receptors. The clinical importance of receptor selectivity on efficacy and patient morbidity is not known. Potential adverse effects common to both drugs are peripheral edema, headache, nasal congestion, flushing, a decrease in hemoglobin/hematocrit and abdominal pain. Both agents are contraindicated during pregnancy and a monthly pregnancy test is required for females with childbearing potential.

Bosentan is given twice a day due to its 5 hour half-life (t1/2). It is both a substrate and inducer of cytochrome P450 (CYP) 3A4 and 2C9 with an active metabolite. Strong inhibitors or inducers of CYP3A4/2C9 may change bosentan exposure while other medications that are substrates of CYP3A4/2C9 may be affected by concurrent bosentan use. Due to this interaction, concurrent use of cyclosporine (CSA) or glyburide are contraindicated. Other medications may require dose adjustments or are rendered less effective. While no dose adjustment is required for renal insufficiency, Bosentan is not recommended in patients with moderate to severe hepatic impairment. The risk of hepatotoxicity requires monthly liver function test (LFT) monitoring with dosing adjustments or discontinuation based on level of elevation of aminotransferases. Patients with clinical symptoms of liver injury or a total bilirubin ≥ 2 times upper limit of normal should have therapy discontinued.

Ambrisentan has a 9 to 15 hour t1/2 allowing for once daily dosing [1]. Metabolism occurs via CYP, uridine 5’-diphosphate glucuronosyltransferase pathways and it is not an inducer or inhibitor of drug metabolism. CSA does increase exposure of ambrisentan, limiting dosing to 5 mg daily. Dosing adjustments are not needed for creatinine clearance above 20 ml/min, and there is limited data in severe renal impairment or hemodialysis. Use of ambrisentan is not recommended in moderate to severe hepatic impairment, however there is no requirement for LFT monitoring and may be used in patients who had liver function elevations with bosentan [2].

Inhibition of the rapid phosphodiesterase-5 metabolism of cyclic guanosine monophosphate (cGMP) allows the vasodilatory and relaxation effects of nitric oxide (NO) to be prolonged. Currently sildenafil and tadalafil are FDA approved for PAH. Potential adverse effects common to both drugs include headache, flushing, dyspnea, nasopharyngitis, nausea, myalgia, insomnia, hearing changes, risk of non-arteritic ischemic optic neuropathy and prolonged erection. Epistaxis has been noted with sildenafil use in connective tissue disorders and concurrent vitamin K antagonist use. The use of nitrates is contraindicated per labeling however clinical use with sildenafil has been reported [3].

Sildenafil has a short t1/2 of 3 to 4 hours requiring three times a day dosing [4]. An intravenous formulation of 10 mg, equivalent to 20 mg orally, is available. Metabolism via the CYP3A4 system generates an active metabolite, while CYP2C9 is a minor pathway. Concurrent medications that are strong inhibitors or inducers of CYP3A4 are not recommended. Dosing in severe in hepatic impairment is unknown and no adjustment is needed for renal impairment.
Tadalafil's $t\frac{1}{2}$ is 15 hours, allowing once daily dosing [5]. Inactive metabolites are generated via CYP3A metabolism and the concurrent use of strong inhibitors of CYP3A is not recommended. It is not an inducer or inhibitor of CYP. Use in severe renal or hepatic impairment is not advised.

Prostacyclin, a potent vasodilator, anti-proliferative, and inhibitor of platelet aggregation is present in reduced quantities in PAH [6]. Supplemental prostanooid therapy is used to augment prostacyclin and shift the imbalance from vasoconstriction and platelet aggregation to vasodilation and antiaggregatory effects. There are several prostanoids available but licensure varies between countries. Potential adverse effects include flushing, headache, nausea, hypotension, muscle cramps, chest pain, dizziness, along with cough and throat irritation with inhaled formulations. Concurrent therapy with other agents that reduce blood pressure, or antiplatelet agents require patient monitoring for adverse effects of symptomatic hypotension and bleeding.

Intravenous epoprostenol, the only agent with proven survival benefit, is a synthetic prostacyclin that undergoes rapid hydrolysis and enzymatic metabolism resulting in a $t\frac{1}{2}$ of 6 minutes, necessitating continuous infusion via central venous access [7,8]. The dose is titrated to clinical efficacy or intolerable adverse effects. No adjustment is needed for hepatic or renal impairment. Abrupt withdrawal can lead to rebound in pulmonary hypertension symptoms and potentially death.

Other prostanooid analogues improve on the chemical stability of epoprostenol allowing alternate routes of administration and increased time between reservoir changes for continuous infusions. They also have different binding affinities for various prostanoid receptors.

Trepostinil is a tricyclic benzidine analog with a longer $t\frac{1}{2}$ of 4 hours. It can be given as continuous intravenous or subcutaneous infusion or via inhalation [9,10]. Compared to epoprostenol, higher doses are needed for comparable effects [11]. The goal inhalation dose is nine breaths four times a day. Metabolism occurs via CYP2C8 to inactive metabolites, but it is not an inducer or inhibitor of CYP. Clearance is decreased in hepatic and renal impairment, which may increase dose-dependent adverse effects.

Iloprost is a carbocyclin analog available in an inhalation formulation and in some countries intravenously. It has a $t\frac{1}{2}$ of 20 to 30 minutes and is metabolized via β-oxidation to an inactive metabolite [12]. Hepatic or renal impairment prolongs the clearance of iloprost. The goal inhalation dose is 5 mcg six to nine times a day. Dosing for the intravenous formulation is up to 8ng/kg/min as a 6 hour infusion [13].

Lastly, beraprost is an oral prostacyclin analog available in Japan and other Asian countries. Dosing is four times daily for the immediate release product and twice a day for the sustained release product.

Footnotes:

1. Letairis [package insert]. Foster City, CA: Gilead Sciences Inc;2011 July
5. Adcirca [package insert]. Indianapolis, IN: Eli Lilly and Company; 2011 April
A Humble Request for an
International Pulmonary Hypertension Collaboration

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One of the limits of being a specialist in an “orphan” disease is the difficulty in evaluating “enough” patients to formulate definitive conclusions; especially in basic epidemiologic trends. This challenge is both frustrating and satisfying as the ability to make progress is as large as the frustration itself. Billing-code-based research, whether it is in the United States or worldwide is always imperfect, but might be a valid measure of trends in disease prevalence and outcomes for an “orphan” disease. Frequency-based statistics are always more challenging to compute precisely for uncommon diseases as is the confusion created by the language used to categorize, and the lack of fundamental knowledge of a rare condition.

Our advances in the understanding of the pathophysiology of pulmonary arterial hypertension (PAH) have led to targeting pulmonary vascular therapeutics. In addition, quinquennial international congresses have changed the once simple dichotomous characterization of the disease as “primary” versus “secondary” to an elaborate, detailed nomenclature. Data exists in registry format and is often based on national coding systems. Unfortunately, coding has not changed significantly and analyses of mortality and hospital discharge data is limited by the quality of the original data collection.

This is especially true in an “orphan” disease with complex diagnostic criteria, those unfamiliar with the validity of the diagnostics required for proper coding, might tend to over report these conditions, and the physicians reporting the codes may be inexperienced with the disease state. Hospital discharge diagnoses do not reflect true incidence or prevalence as one cannot distinguish the first admission for a single patient from subsequent readmissions. Importantly, the codes do not allow for differentiation of the specific disease entities associated with PAH versus pulmonary hypertension (PH) from other causes (i.e. left heart disease, lung/hypoxic lung disease, thromboembolic disease, or other). We know even less about these groups of PH.

Registries, despite all the inherent bias and problems with interpretation, report similar country specific incidence and prevalence of the disease. Specific estimates initiated with the collaborative European registry in 1996, the International Primary Pulmonary Hypertension Study (IPPHS), which included data from 220 centers in the UK, France, Belgium, and the Netherlands. The estimated incidence was 1.7 cases per million population (95% CI 1.0-2.4) for idiopathic PAH. More recently, The French Network’s national prospective registry estimated the incidence of PAH as 5-25 cases per million adult inhabitants. They calculated that the prevalence in France of PAH was 15.0 cases/1 million adult inhabitants with 5.9 cases/1 million for
IPAH. The annual incidence of PAH in Scotland is estimated to be 7.1-7.6 cases per million population with a prevalence ranged from 26-52 cases per million population. The Scottish group also reported a higher annual incidence of IPAH than previously reported, with 2.5 and 4.0 cases per million population in males and females, respectively. In addition, each of our contemporary registries independently determined that the same risk factors prognosticate the disease. This consistency demonstrates both the validity of the findings and the advanced power that collaboration could provide.

In order to learn from our country, region, and center specific registry experience, the community needs to collaborate to develop registries and category specific research to build on our understanding of the epidemiology. A global response is needed as is smaller collaborative groups to enable enough data to validate potential novel biomarkers to be used in clinical practice and clinical research. This is the humble request.

References:

The Unnatural History of Idiopathic Pulmonary Hypertension
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Idiopathic pulmonary arterial hypertension (iPAH) was once called primary pulmonary hypertension (PPH) which, perhaps for reasons of rarity, excited the imagination of clinicians. Of course pulmonary hypertension (PH) per se is not an uncommon physiological response to hypoxia in so many other lung diseases and diseases of the left heart. So why did PPH (and does iPAH) stimulate so much interest, and how did we arrive at the present situation where a burgeoning industry driven by the demonstrable promise of an effective therapeutic armamentarium offers hope to so many who formerly were resigned to being placed in the Kingdom of the Near Dead?
For so it was. Therapeutic nihilism reigned supreme based on both published case series and anecdotal observations that death was imminent in patients diagnosed with PPH. Hence the clinical approach was polarised between those who felt extreme measures were warranted (desperate diseases demand desperate responses from desperate physicians) and those who reasoned that no therapy worked, the outlook was hopeless, so why waste time and resources.

Then there were the academics (those who sat in ivory towers in grand institutions of learning and pontificated, all the while negotiating market share in the field for the purpose of noble research) and the maverick transplant doctors who saw PPH as an ideal target group for heart-lung and subsequently lung transplantation. Indeed there were some spectacular results from both camps and it is worth recounting the early history which sets the foundation for current practice. It is no coincidence that many of the early patients chosen for heart-lung transplantation had PPH. By and large they were young women in the prime of life, struck down by a devastating fatal disease for which there was no other successful therapy at the time. Most had single system pathology, providing cardiac output and backwards right heart failure was not irrevocably established. Moreover, successful recipients returned to work and family and were good ambassadors for the program exhibiting all of the desirable positive outcomes that could be achieved.

The simple notion that transplantation was always and at any time justifiable in PPH was challenged by the Stanford group who recognised that different phenotypes existed. Many of those who may have achieved a net survival benefit from transplantation in fact died prior to formal referral and many of those who survived to be referred, worked up and listed had chronic slowly progressive disease. Then there was the problem of a long lead time to diagnosis. Symptoms are non-specific and the possibility of pulmonary hypertension is often not considered until a major event occurs or manifest right heart failure develops. Perhaps not much has changed!

At the same time as transplantation was being developed, a group of clinician-scientists recognizing the importance of the power of numbers sought to examine specific questions in a nationwide PPH Registry supported by the NIH. Why focus on an orphan disease? Clearly, PPH was the tip of the iceberg and it was fervently believed that rigorous study into natural history and responsiveness to pulmonary vasodilators would unlock a door to better understanding that would benefit many others. Ultimately it has, but the road was not easy.

Originally, a tissue diagnosis was required for entry into the Registry until it became clear that the mortality rate of open lung biopsy in patients with PPH was unacceptable, especially as there was no therapeutic benefit proposed from the said Registry! Common sense and medical ethics prevailed and the Registry amongst other things provided a formula to predict survival based on hemodynamic measurements.

Of course these parameters change prognosis. More importantly, molecular study paved the way for the generation of a new class of drugs, ‘designer’ drugs, specifically targeting the compounds promoting the generation of the target lesion in PPH, the plexiform lesion. Histopathology of the lung is not specific to cause as the lung has a stereotypic response to injury and repair just as the Wagenvorts described in their seminal post-mortem study; plexiform lesions occur in many forms of severe PH. The availability of these new drug classes and the revelation of the importance of the molecule of the year (NO) have revolutionized contemporary approaches to PH of all forms (except perhaps post-capillary and capillary PH); thus the balance between transplant and medical therapy has been altered forever. However, this is natural selection in progress and being wedded to the past is just as risible as trying to live in the future. Neither works in a contemporary world. Many have achieved benefit from the new therapies; some have avoided an unnecessary transplant and some others without PH have been able to benefit from the availability of those donor organs. For the majority, hope has not been extinguished, which of all that we do, is a commendable outcome.
Of Time, and Where We Choose to Dwell

Robert Frantz

The sun beams from it southering perch as the geese hasten noisily.

Whipping wind and scattering leaves bear wistful witness to the changes that surely follow.

Oh, what a day! On the cusp, looking back, looking forward, in what spirit?

Mixed rememberings transforming to resolve?
Anticipation dancing with anxiety?

Perhaps. Yes. A bit.

Each moment, whispers the wind.
Yet thoughts are unruly, darting here and there,
Forward and back, shimmering minnows in surging tide.

Yesterday dwells in our souls today,
Tomorrow beckons but is not yet seen.

Each moment is the keystone, the crux, the crucible,
The fulcrum upon which life pivots.

The wise dwell here.

*ISHLT member Robert Frantz (Mayo Clinic) is the Vice Chair of the Pulmonary Hypertension Council.*

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**Prague 2012: Pharmacy and Pharmacology Program Highlights**

Members of the new Pharmacy and Pharmacology Council will be featured Thursday morning in the inaugural symposium in a series entitled, *A Lifecycle Journey in Advanced Heart Failure and Transplantation*, sponsored by the ISHLT Pharmacy and Pharmacology Council. This series, focusing on therapeutic aspects that uniquely involve emerging or established knowledge in the pharmacology and pharmacy, envisions using an enduring case to create a panel facilitated and audience supported best practice-based discussion at predefined key “journey intervals.” In this session the focus will be on the life-cycle of Advanced Heart Failure and Cardiac Transplantation with special emphasis on the “journey points” of Mechanical Circulatory Support and anticoagulation, post-transplant development of Antibody Mediated Rejection and late complications that demand innovative immunosuppressive strategies.
Heart-Lung Transplant for IPH
Hari R. Mallidi, MD, FRCSC
Stanford University

Prior to the use of epoprostenol in the treatment of idiopathic pulmonary hypertension (IPH), the only effective treatment shown to improve patient quality of life and increase patient longevity was lung transplantation. In fact, heart-lung transplantation (HLT), which began 30 years ago by Drs. Reitz and Shumway and colleagues at Stanford University Medical Center starting with the first successful patient in 1981, was the first medical intervention of any kind to significantly alter the natural history of IPH.

In fact, over 95% of the patients in the original series of patients treated with HLT were treated for pulmonary hypertension (PH). Until the development of isolated lung transplantation (LT) in the late 1980s, HLT remained the only successful way of transplanting diseased lungs (and in that time period its use expanded to patients with complex congenital heart disease, cystic fibrosis, etc...). It was not until the advent of an effective delivery mechanism for epoprostenol to treat IPH did the role of lung transplantation for this disease lose favor. Currently, nonsurgical therapy has improved to the point where many patients who might have been transplanted in the past are no longer considered for transplantation of any kind.

In the intervening period between the development of isolated LT and effective medical therapy for IPH, the choice of isolated LT (either single or bilateral) became more prevalent. This was primarily the result of no apparent significant differences in either short-term survival or longer-term survival with isolated LT compared to HLT. The availability of donor organs, the relative technical simplicity of isolated LT, and the improved short-term outcomes favoring isolated LT also promoted a shift away from HLT.

Currently, based on several single-center-experience reports with single vs. bilateral LT for PH from the late 1990s, the preference is bilateral LT for patients with (primary or secondary) PH. However, since the introduction of the lung allocation score, survival to transplantation has decreased (wait-list mortality has increased) as IPH patients appear disadvantaged in the allotment of donor organs. Despite these trends, there remains no definitive answer as to which surgical approach is better for IPH.

We have maintained HLT in the armamentarium for the treatment of patients with IPH. Generally, patients who are outpatients with PH tend to be treated with isolated bilateral LT. However, those patients who are ill, with overt right ventricular failure, cor pulmonale, and/or admission to hospital for inotropic therapy for right ventricular dysfunction are preferentially treated with HLT. Our recent experience has shown a greater than 90% one-year survival, with significantly improved three-year survival compared to the cohort of patients with IPH receiving either isolated LT or HLT from the ISHLT and UNOS registries.

In a recent presentation at the American Heart Association meeting in Orlando, FL 2011, the modern (year 2000 – present) UNOS experience with patients listed for transplantation with IPH was reviewed. This study demonstrated that patients who received a HLT had the best survival. Patients listed for a HLT who were not transplanted had the worst survival. In between these two groups were patients listed for isolated LT, and patients who received an isolated LT. The survival advantage of isolated LT, compared to patients who were listed for isolated LT but not transplanted, was marginal. The advantage of HLT for
these sick patients persisted even after propensity adjustment for severity of illness. The advantage of lung transplant, over optimal medical therapy (i.e. those patients listed but not transplanted) was only evident in the higher-risk cohort. In fact, in lower risk groups there was no survival advantage at all. HLT recipients were heavily weighted towards the higher-risk profiles and the survival advantage was present at all risk profiles for HLT in patients with IPH.

Over the course of the past thirty years significant improvements in medical therapy has relegated transplantation to only the most ill patients with IPH. Improvements in medical therapy may mean that these patients do not enjoy a survival benefit with transplantation until the right ventricular function has deteriorated to a “point-of-no-return”. In terms of optimal surgical therapy for IPH we seem to have come full circle. Isolated LT doesn’t appear to confer a significant survival advantage. In these most ill patients, HLT may be the only remaining option.

USA VAD Removal – Changes in Reimbursement

Effective Jan. 1, 2012, the physician payment policy in the United States for Ventricular Assist Device removal procedures will change. Payment values will be reduced and no longer include reimbursement for in-hospital and out-patient evaluation and management services. Payments could be reduced dramatically – up to 30 percent – unless you prepare for this change.

If you do VAD procedures, you are providing a substantial amount of critical care as well as in-patient and out-patient care, which are currently reimbursed automatically. After Jan. 1, 2012, however, those services must be processed in an itemized fashion for each patient. Accurate documentation of services provided requires surgical insight and is the surgeon’s responsibility, and accurate documentation is critical for correct coding and ultimately correct reimbursement. Interested individuals should contact the Society of Thoracic Surgeons for more information about these changes.

ISHLT is planning to conduct an educational session at the Annual Meeting in April in Prague regarding these changes as well as device-related payment issues in other countries. Look for more information on this session in early 2012.

A Coming-of-Age Transplant Story

Johanna Beyers Ross

At 18-years-old, I should have been transitioning from childhood to adulthood in the normal coming-of-age fashion dictated by every novel or movie featuring a boy-crazy, blue-eyed, blonde California girl such as myself. Instead, at 90 pounds, and severely cyanotic, I struggled with a congenital heart defect and pulmonary hypertension. While I remained happily indifferent to coughing up blood, my labored breathing, poor circulation and joint pain made me feel worn-out and elderly at 16. I had to drop all the high school classes I could never make in time and (social death!) become home-schooled while I waited for a new heart and lungs. When my teenage social calendar swelled, thanks in part to only one hour of school daily, and a coveted disabled parking placard, the only threat to my time spent at the mall with friends was facing my own mortality. So I didn’t think about it. By then, the pager the hospital had given me had been quiet for almost two years so I took advantage of the situation and gave my beeper number out to all of my friends.

After all, it was the Nineties.

Albert Einstein called common sense “the collection of prejudices acquired by age 18”. Whatever ordinary intelligence or Holden Caulfield-esque cynicism led me to even consider the life-changing decision of getting a transplant, “common sense” didn’t have
to tell me that such a drastic measure was necessary to improve my quality of life. One night in December, 1993, I got the resulting phone call and found myself driving with my parents to Stanford University Hospital, listening to rap music at volumes much louder than they would have normally tolerated. Straightaway a nurse braided my hair and taped my best-friendship bracelet to my wrist, insuring neither would be cut during the transplant surgery. She was instantly fond of me, a skinny kid in pigtails, and I found this would be the case for everyone involved in my care during my extensive hospital stay. A few months difference and I would have been a patient at the nearby Children's Hospital, not at the age of majority, legally signing my own surgery forms.

I have the bizarre distinction of writing this to celebrate the 18th anniversary of a heart/double-lung transplant that I received when I was 18. Which means that next year I will have lived longer on this planet with someone else's organs than the ones I came here with, making my perspective on something I have experienced in the amount of time it takes most people to get to college sound like a pitch for a science fiction film. While it is a rather strange rite-of-passage, having a transplant meets the three stages that classically define such initiations; separation, transition, and reincorporation. First, one withdraws from their current status (in my case, high school student) in preparation to move to another, and there is a detachment, or “cutting away” of the former self, signified by symbolic action, such as civilians getting their hair cut in the Army (or, for example, major surgery).

Second, there is the transitional time between two states, when one has left one place but has not yet joined the next. I lived for several months in a transitional housing of sorts – an apartment complex within walking distance from the hospital. This median time for me was punctuated by pushing my hunched shoulders up against the walls of the hospital as I went from clinic to lab and back again, retraining myself the way my physical therapist advised on how to not carry myself as if I had to constantly hold all my internal organs inside behind my crossed arms. Soon I could safely stretch without fear of my ribcage popping open. The practicalities of enjoying the apartment complex pool with a PICC line and bandages were simple compared to the rejection, CMV virus infection and lymphoma I developed directly after my transplant. There was no learning curve. It took me several years to realize that impatience and irritability were side effects of immunosuppressant medications. While I was grateful for my life, I was, like any teenager, obsessed with my appearance. Overnight I had thick eyebrows and too much hair, which I suddenly stood to lose with my cancer diagnosis. The physical transformations and behavioral changes, paired with the same exhausting routine of the hospital drove me crazy. After a childhood spent feeling tired and sick, I was sick and tired of being a patient and begged every doctor I saw to let me go home, even just for a weekend.

In stage three, having assumed a new identity, one re-enters society with one’s new status, characterized by ceremonies like Graduation (or Homecoming). I looked different, but I was all pinked-up and healthy. Things had changed. For the first time in my life, I was doing things I had never been able to do before, like walk all the way around the lake with my dog. Forgetting that the dog had also never walked around the lake, I ended up having to carry her. Everything was surreal. In the words of Thomas Carlyle, “He who has health, has hope; and he who has hope, has everything.” Though my sentiments were not as well-expressed, I wrote a letter thanking my donor’s family.

I read a story recently about transplant recipients from Cedars-Sinai playing softball with their doctors, and was reminded of my transplant team and the way they worked together for my welfare, coming by my hospital room to watch television, bringing real food from the cafeteria, keeping up my spirits. They gave me hope. I am reminded of the characters on the television show House, M.D.; a solution-oriented team, brainstorming with each other, provoked by someone that they actually adore. I understand that at times it may seem counterintuitive to offer hope to a patient when their outcome is uncertain, but I often wonder why there is so much reluctance to “getting someone's hopes up”. Martin Luther said that everything that is done in the world is done by hope.
At times my experience has been emotionally and physically excruciating. Chemo comes to mind, and being so sick I couldn’t even eat the pizza that cute guys smuggled into the hospital for me, enduring a lumbar puncture, having both of my lungs collapse, and the time I was not firm enough about the amount of sedation I should get during a biopsy. Simultaneously, I have been given the most amazing opportunities and incredible learning experiences; finally being able to ride roller-coasters, borrowing my doctor’s BMW to go on a date, being the only student enrolled in a Medical Terminology class at the community college that was not a “Rad Tech” or in the nursing program.

Frank Lloyd Wright said, “The present is the ever moving shadow that divides yesterday from tomorrow. In that lies hope.” Today, reflecting on both halves of my 36 years, I am hopeful, as I hope all who are involved in transplantation can be. Over the years, there have been adjustments in my medication, lifestyle, diet and, most notably, my attitude. Through years of drug side-effects, migraines and insomnia, throughout a long-term marriage that ended in divorce, a longstanding job that ended in unemployment, and all the life milestones in between, I embraced any option that offered hope. Prayer, meditation, alternative therapies like acupuncture, a plant-based diet, therapy, and volunteering are the things that help me be more compassionate, happy and thankful. Louise L. Hays said, “Good health begins with loving the self”. I have become the New-Age Northern California hippie-eco-vegan that I used to make fun of.

I was given a second chance at life, and blessed with organs that I need to take care of. I have to continue to treat myself like someone worthy to receive such a gift, a kind of palliative care that I have to give to myself. I was told recently that I was “in dog’s years, one of the very old heart-lung recipients, surviving, thriving and driving others crazy, as you should.” As I celebrate my 18 years post-transplant, I find it entirely appropriate that the Hebrew word for life (chai) has a numerical value of 18. It is a spiritual number in Judaism, and in dog’s years, well, it is amazing.

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**2012 ISHLT Grants and Awards Program**

**GENERAL INFORMATION:**

The 2012 ISHLT Grants and Awards applications are online. For general information, funding stipulations, award policies, grant applications and instructions, please visit us on the web at: [http://www.ishlt.org/awards/applications.asp](http://www.ishlt.org/awards/applications.asp).

**AWARD CATEGORIES AVAILABLE THIS YEAR:**

- **RESEARCH FELLOWSHIP AWARDS** are awarded annually in the amount of $40,000.
- **BRANISLAV RADOVANCEVIC MEMORIAL FELLOWSHIP AWARD**, to encourage scholarly clinical work in mechanical circulatory support in emerging countries, is awarded annually in the amount of $75,000.
- **NORMAN E. SHUMWAY CAREER DEVELOPMENT AWARD** is awarded every other year in the amount of $80,000 (available in 2012).
- **NURSING & SOCIAL SCIENCES RESEARCH GRANT AWARD** is awarded annually in the amount of $12,000.
- **TRANSPLANT REGISTRY EARLY CAREER AWARD** is awarded annually in the amount of $5,000.
- **INTERNATIONAL TRAVELLING SCHOLARSHIP AWARD** has two submission dates annually: August 1 and December 1.

Grants will be awarded at the ISHLT 32nd Annual Meeting and Scientific Sessions

*April 18-21, 2012 in Prague, Czech Republic.*
DOLLARS AND $ENSE
The Use and Abuse of the Term “Cost-Effectiveness”
Roger W. Evans, Ph.D.
The United Network for the Recruitment of Transplantation Professionals
Rochester, Minnesota

Each and every day of our lives we make purchasing decisions based on a simple yet subtle, but very powerful concept – cost-effectiveness. We’re usually shopping for the “best deal” and intent on getting “the most bang for our buck.” Yet, only when we’re pressed to provide the basis for our decisions might we even suggest that cost-effectiveness entered our mind.

It seems strange therefore to argue, as many people do in the United States, that cost-effectiveness shouldn't enter into clinical decision-making. The rationale is straightforward: whatever patient needs dictate, physicians should provide and, oh, by the way, excess resource utilization may be good for the economy, while potentially spurring innovation. Consequently, rarely, if ever, are patients presented with the multiple treatment options available to them, coupled with comparative cost-effectiveness information, and then asked to decide what they think is the best strategy. In effect, clinical benefits are underscored, while costs are ignored.

This approach makes no sense given contemporary concerns about health care spending [1]. Yet, on every occasion when an effort has been made to make cost-effectiveness an explicit consideration in the evaluation and application of medical technology, there has been public outcry [2,3]. The outrage is often directed at insurers during the coverage determination process.

Most recently this debate has engulfed comparative effectiveness research, heretofore known as technology assessment [4,5]. The Affordable Care Act (ACA) explicitly states that cost-effectiveness shall not be a consideration in studies intended to establish the comparative effectiveness of drugs, devices, medical and surgical procedures, or the delivery of health care services. To underscore the significance of this exclusion, the word “clinical” is often juxtaposed with comparative effectiveness terminology.

One readily comes to the conclusion that, while policymakers are expected to address health care costs, they are prohibited from using those methods and the resulting information that is most germane to the issue – cost-effectiveness [6,7]. Consequently, the development of policies concerning comparative benefits must turn a blind eye to economic information, even though that information is directly relevant to the priority-setting process.

Fortunately, there is a means to address this debacle, and it has to do with the way we use the term “cost-effectiveness”.

In 1986, when “cost containment” was as serious an issue as “bending the cost curve” is today, Doubilet and colleagues pointed out that the concept of cost-effectiveness was confusing and prone to misuse, thereby compromising its relevance in policy making [4,8]. Times haven’t changed, nor has education dethroned ignorance.

Doubilet et al. identified four distinct uses of the term cost-effectiveness [8]. It’s noteworthy that two of these uses don’t even simultaneously relate costs to outcomes or benefits. The uses are as follows:
1. Cost-effective = cost saving
2. Cost-effective = effective
3. Cost-effective = cost saving, with an equal (or better) health outcome
4. Cost-effective = having an additional benefit worth the additional cost

When describing something as cost-effective, most people think in terms of the first two uses. In reality, however, relative to contemporary debate, the last two uses are the most relevant, providing considerable latitude in making decisions concerning resource allocation. In fact, the third and fourth uses are consistent with what people generally have in mind when they mention the word “value” [4]. Thus, not surprisingly, something has value if it’s cost-effective. Duh.

Clearly, the negative rhetoric surrounding the linkage of cost-effectiveness analyses to comparative clinical effectiveness research is both unfortunate and counterproductive. Moreover, the argument that cost-effectiveness research will lead to rationing and the implicit valuing of human lives is deceptively silly [9,10].

It’s hard to imagine anyone making prudent and meaningful public policy decisions without considering cost-effectiveness. Health care interventions shouldn’t be exempt, even when the value of a human life is an unavoidable, but seldom discussed consideration [11].

In all spheres of their lives people embrace one or more of the four foregoing uses of the concept of cost-effectiveness. Moreover, with the continued appeal of consumer-directed health care, as well as the growing popularity of catastrophic health insurance plans as a means to contain costs, people, absent government intervention, will make the very decisions that politicians wish to avoid.

Unfortunately, future health policy debates relative to the ACA may become even more volatile as efforts are made to define “essential benefits,” a concept akin to what were formerly referred to as “mandated benefits” [4,12]. It’s impossible to ignore cost-effectiveness information when attempting to decide what health plan benefits are essential, leading to the following disconcerting questions: Are transplant procedures truly essential? At what point are elective procedures essential? Of course, one’s perspective matters.

In conclusion, although the means exist to diffuse the underlying issues, it is clear inept politicians have neither the intelligence nor the will to achieve apolitical closure on how cost-effectiveness information should be used. Undeniably, health care is a critical ingredient in deficit reduction [13]. Yet, as we continue to see, policymakers are unwilling to make budgetary decisions based on cost information, which is patently absurd. As a result, health care policy will remain a serious challenge, largely because politicians have failed to grasp what the majority of their constituents realize – cost-effectiveness is an integral part of everyday decision-making and health care isn’t exempt. This prompts me to offer yet another solution to this dilemma – incorrigible politicians with tunnel vision should be tossed on the burn pile out back.

References:


Heart Failure Society of America (HFSA) 15th Annual Scientific Meeting
September 18-21, Boston, Massachusetts
Summary / Highlights Report
Stavros G Drakos, MD
UTAH Cardiac Transplant Program, Salt Lake City, UT

The 2011 Heart Failure Society of America Meeting (Scientific Program Chairs: Lynne Warner Stevenson, MD, Steve R. Houser, PhD, Barbara J. Riegel, RN, DNSc) was very rich in topics and it is definitely worth highlighting some of the presented information for those who did not get to attend.

In the opening plenary session, Dr. Deepak Chopra (Carlsbad, CA), world renowned internist, neuro-endocrinologist and prolific author, delivered the keynote address titled ‘Mindfulness and the Heart - Brain Connection’. Dr. Chopra pointed out that one of the breakthroughs in the field was the discovery by investigational meditation programs that genes are not ‘deterministic’ – the genes can be turned on and off in response to meditation. He explained that research on meditating subjects revealed that after several weeks of mindfulness meditation the level of telomerase significantly increased by almost one third arguing that the observation that this can happen only through mental activity is extraordinary. He also discussed research findings in various meditation programs which are helping us begin discovering the neural correlates of people’s feelings, emotions and thoughts such as activity and even enlargement of the prefrontal cortex. He called for contemporary medicine to incorporate a new paradigm that looks at human body not as a structure, but a process. He argued that the body’s breathing, digestion, metabolism, processing of thoughts, emotions, and dreams, are all a single process. He pointed out that the western school of thought of reductionist scientists constantly tries to separate these processes, but this is not necessarily the appropriate strategy given that all these processes are actually one. He also argued that there is no mental event that does not have a neural representation and no neural representation that does not have a biologic response. The endocrine system is integrated with the sympathetic and parasympathetic nerves (neuroendocrine axis) affecting the heart and other organs. He advocated that we should look at the body as an integrated, holistic process; our treatments (cardiology and heart failure therapies included) would be much more
effective if we strived to target not only one organ or system, but instead restored homeostasis. Dr. Chopra stated that this way any "healing response is evoked".

Myocardial recovery was the focused topic of a session titled ‘Where Is the Route to Heart Failure Recovery’ which was moderated by Drs. Douglas L. Mann (Washington University, St. Louis, MO) and Hanni N. Sabbah (Henry Ford Health System, Detroit, MI). The session included talks reviewing the emerging role of promising therapeutic options such as stem cell/regenerative therapy (Sussman MA, San Diego, CA and Moldovan NI, Columbus, OH), gene therapy (Hajjar RJ, New York, NY) and ventricular assist device-induced unloading (Birks EJ, Louisville, KY) in promoting myocardial recovery. The session also included a talk delivered by Dr. Scott D. Solomon (Brigham and Women’s Hospital, Boston, MA) titled ‘How Can We Recognize Recovery?’ which helped the audience realize a basic gap in the field. Dr. Solomon initially recognized that the heart has “a greater ability to recover function than we have previously thought given that we now have therapies that don’t just ‘attenuate’ the remodeling process but that actually ‘reverse’ the process” in a variety of clinical conditions associated with clinical heart failure (HF). The presenter emphasized the importance of recognizing and predicting recovery in HF before it is obvious because this will impact both the clinical decisions made for patients (advanced therapeutic options etc.) and the design of clinical research trials. After setting the stage, the presenter systematically addressed the issue of how good our current clinical medicine armamentarium is in predicting recovery of left ventricular (LV) function before it happens. He reviewed data from large myocardial infarction trials and resynchronization trials indicating that baseline LVEF is not helpful in predicting who will recover and that improvements in systolic function may lag behind improvements in diastolic function. After making the point that “if LV function was the best way to predict recovery then we would only predict recovery in patients who have already recovered”, Dr. Solomon suggested that we should look beyond standard LV function assessment techniques and create new windows to the recovery process. He reviewed data showing that such options could be the emerging myocardial deformation and myocardial strain imaging or the detection of ischemia/ viability and contractile reserve by PET, stress echo or MRI. He also reviewed data showing that RV function and left atrial size may be more sensitive to subtle changes in LV function suggesting that they can also be used as early measures of recovery and outcomes in HF, beyond the LV. Finally, both Drs. Solomon and Mann agreed that we need to develop more precise methods to distinguish patients who will recover from those who won’t and given that most prior research has focused on predicting adverse outcomes, we may currently need to shift our focus on determining methods to predict recovery as well.

In the session titled “Fluid and Flow”, moderated by John C. Burnett (Rochester, MN) and Steven R. Goldsmith (Minneapolis, MN), Dr. W. H. Wilson Tang (Cleveland Clinic, Cleveland, OH) delivered a talk titled: “Venous Pressure and Renal Function”. Dr. Tang initially reviewed the classic model of cardiorenal interactions in HF illustrating the role of increased nonosmotic vasopressin release and increased sympathetic nervous system activity and renin-angiotensin-aldosterone system activity in the development of diminished renal hemodynamics and decreased renal sodium and water excretion. Dr. Tang went on to show contemporary data demonstrating the association of venous congestion and impaired renal blood flow with diminished renal function in HF. He also provided both published and unpublished data to explain the multifactorial impact of venous congestion on renal function through the interplay of biomarkers, mean arterial and central venous pressures, intra-abdominal pressure, interstitial renal and renal venous pressures, glomerular filtration and proximal tubular pressures (a review paper by the presenter’s group, Curr Heart Fail Rep 2011; 8: 233-41, cited in the talk’s slides is useful for additional reading). Overall, the talk helped the audience understand that systemic venous congestion is one of the hallmarks of the syndrome of HF that results from activation of different deleterious neurohormonal pathways and apart from contributing to patients’ symptoms, growing evidence suggests that congestion itself also drives the progression of the HF syndrome with detrimental effects on end organs including the kidney. In the same session, Dr. James Januzzi (Massachusetts General Hospital, Boston, MA) gave a talk titled: “Circulating Markers of Renal Function and Injury”. Dr. Januzzi initiated his presentation showing data demonstrating that in acute HF worsening renal function occurs early (within 5 days from hospitalization) and is associated with adverse short- and long-term outcomes. After categorizing the biomarker testing in cardio-renal syndrome (CRS) in measures of renal function and
of renal injury he systematically reviewed the effectiveness of each biomarker either in predicting the onset of CRS or predicting HF outcomes after CRS development. The data reviewed indicated that the renal injury biomarkers Kidney Injury Molecule (KIM-1), N-Acetyl-β-D-Glucosaminidase (NAG) and Neutrophil Gelatinase-associated Lipocalin (NGAL) were effective both in predicting CRS onset and CRS prognosis. The renal function biomarkers cystatin-C and β-trace protein were effective in predicting CRS prognosis while more research is warranted to investigate their role in predicting CRS onset. Ending his presentation, Dr. Januzzi defined as a major future direction for the field the need to investigate and establish meaningful therapeutic implications in the sense that the measurement of these biomarkers (on top of predicting impending adverse renal and clinical outcomes) would hopefully guide specific therapeutic/prophylactic interventions to abrogate these impending consequences.

In the Hyde Park Session, Dr. Matthew A. Movsesian (University of Utah, Salt Lake City, UT) delivered a provocative talk titled: “It’s Time to Examine Intramural Conflicts of Interest”. Dr. Movsesian started his presentation with a quote from the Bible: “Why do you notice the splinter in your neighbor’s eye but not the log in your own?” (Matthew 7:3), and went on to make the point about what he described as “double standards”. He initially stated something familiar to everybody: “Medical school faculty receiving payments from industry have financial incentives for promoting the products of the companies paying them. The belief that these incentives adversely affect educational activities has led medical schools to require disclosure and management of faculty members’ relationships with industry”. “However,” Dr Movsesian continued, “despite their greater prevalence and more profound influence, the financial incentives offered by medical schools themselves have gone unnoticed”. He provided evidence that academic medical centers, like pharmaceutical companies, vie for market share through direct-to-consumer advertising and by marketing to referring providers through free ‘educational activities’. Academic medical centers also assign primacy to revenue-generating activities and when it comes to implantable devices, “manufacturers and medical schools are wholesalers and retailers in the same industry” (Figure 1). Dr. Movsesian contended that if disclosure and management of financial relationships with industry are desirable, “comparable expectations should apply to all sources and mechanisms of compensation, including those from our own institutions”. As an example, he noted that a speaker comparing endomyocardial biopsy and gene-expression profiling to screen for transplant rejection at last year’s HFSA annual meeting disclosed that his institution performed more than 800 biopsies a year, appropriately recognizing that the prospect of forfeiting the revenues from these biopsies provided a strong incentive to promote reliance on endomyocardial biopsy. Dr. Movsesian concluded that “medical schools are big businesses focused on generating revenue from clinical services and grants that pay institutional overhead. The financial incentives they offer are functionally similar to those affecting faculty members lecturing on a product while being paid by its manufacturer, and the breadth of their influence is greater. There is no reason to think that faculty members who can be swayed by relationships with industry are immune to the influence of intramural incentives”. In conclusion, intramural conflicts of interest warrant scrutiny, too!

**Figure legend**

Figure 1: “A hypothetical scenario”. Adapted with permission from Dr. Movsesian’s presentation “It’s Time to Examine Intramural Conflicts of Interest” at Hyde Park Session (2011 HFSA annual scientific meeting).

Part 2 of this report will be published in the January 2012 Links issue.
Prague 2012: Pulmonary Hypertension Program Highlights

Marc De Perrot MD, Reda Girgis MB BCh, and Marion Delcroix MD PhD
Pulmonary Hypertension Program Committee Representatives

Again this year, the members of the Program Committee representing pulmonary hypertension have put together a diverse and exciting series of pre-meeting and concurrent symposia highlighting cutting edge pathophysiology of, and treatment for, advanced pulmonary hypertension. Invited speakers include key members of our society complemented by some of the leading authorities in the world.

The meeting will open with three pre-meeting symposia devoted to aspects of pulmonary hypertension. First, Potpourri of Special Topics in Pulmonary Hypertension will include a series of topics on pulmonary hypertension that are less understood and of interest to cardiologists, pulmonary/critical care specialists, anesthesiologists and surgeons, including a presentation on Schistosomiasis: Possibly the Most Common Worldwide Cause of Pulmonary Hypertension. A state-of-the-art understanding of right ventricular (RV) function in health, exercise, resting pulmonary hypertension and right heart failure will be presented in The Right Ventricle and Pulmonary Vascular Load in Health and Disease. The pre-meeting symposia will close with Congenital Heart Disease: Pulmonary Hypertension Dilemmas in Pediatric and Adult Patients providing useful information the management of patients with pulmonary hypertension associated with congenital systemic to pulmonary shunts, particularly those with un repaired shunts.

Concurrent symposia on Thursday and Friday will open with a worldwide tour of Lung Transplantation for Pulmonary Arterial Hypertension – A Review and Panel Discussion, focusing on the impact that regional variability in listing status, organ allocation and the type of organ transplantation (lung versus heart-lung) have on outcomes. On Friday, Following the RV through Thick and Thin will provide a thorough overview of the problem of RV dysfunction in patients with CHF due to LV diseases, with a pathophysiological overview of PH secondary to LV dysfunction and, finally, Pulmonary Hypertension in Chronic Parenchymal Lung Diseases: Does it Matter? will highlight increasing recognition of pulmonary hypertension as a serious complication of chronic obstructive and interstitial lung diseases.

Sixth Prague Adventure of Mr/s XYZ at ISHLT 2012:

From the Performing Arts to the Holiday Carp

Tereza Martinu, MD
Duke University Medical Center

You are standing on the roof-patio of the National Theater in Prague. On this clear night you can see the streetlights below and the illuminated Prague Castle across the Vltava River. On each side of you stands the imposing Triga statue of a three-horse carriage, and behind you is the theater’s upper roof surrounded in an iconic golden crown. In other circumstances you would find this ornate opulence almost repulsive. But in the case of the Prague National Theater (below), it is endearing. Unlike other old sumptuous buildings throughout Europe that were built by royalty or rich sponsors, this particular one is unique in its kind in that it was built entirely with public money.
In 1845, when Bohemia and Moravia still belonged to the Austro-Hungarian Empire, the idea was born to build a theater dedicated to the promotion of the Czech language and to serve as stage for the Czech opera, ballet, and drama. A national public collection of money ensued, leading to the building of the theater in 1881. However, 2 months after the opening, a large accidental fire destroyed most of the interior. Amazingly, the Czech people rallied again and raised money for a complete reconstruction of the theater, which reopened in 1883. To this date the theater is viewed as a tribute to the nation’s resilience, pride, achievement ... and stubbornness.

Looking at your watch, you realize that it is almost the end of the intermission. As you return to your red velvet seat in the parterre section of the theater, you look up at the enormous chandelier hanging high above you. Neo-renaissance style paintings decorate the ceiling around the chandelier and depict stories from Czech mythology with landscapes inspired from works by the Czech painter Mánes.

The theater (at right) is bustling with activity, as everyone is getting ready for the third act of the opera *Rusalka*. You try to imagine the excitement of the theater's first opening performance and your thoughts wander. The theater opened with the premiere of the opera *Libuše* by Bedřich Smetana (1824-1884). Smetana is thought of as the founding father of Czech music and is credited with creating the Czech musical style. His most important pupil was Antonín Dvořák (1841-1904) who is now arguably the best-known Czech composer. Born in Moravia, Dvořák incorporated themes from Moravian and Bohemian folklore and songs in his late romantic music. He is best known for his *New World Symphony (Number 9)*, the *Slavonic Dances*, and his world-famous opera “*Rusalka*”. Dvořák spent 3 years in New York, learning and immersing himself in American music. He was very intrigued by African-American and Indian-American music, which served as basis for his *New World Symphony*, commissioned by the New York Philharmonic and premiered at Carnegie Hall in 1893. As much as Dvořák was taken with the U.S., the U.S. was taken with him, making him a celebrity and appointing him director of the National Conservatory of Music for 3 years. Now, more than a hundred years later, themes from his *New World Symphony* make up the theme song of Disney’s *Pocahontas*.

You mentally review your coverage of the Prague performing arts scene, to make sure you will be able to give your family an accurate report on your touristic exploits. Besides the National Theater, you have seen a performance at both the recently renovated Theater of the Estates (at left) as well as the Prague State Opera. You are quite happy to be here outside of the summer months since the Prague National Opera and Ballet companies travel in July and August and get replaced by foreign companies, rendering the art scene somewhat less authentic during those months. You also have heard Suk’s *Asrael Symphony in C minor* by the Czech Philharmonia, an internationally known orchestra, in the neo-renaissance Rudolfinum concert hall. In addition, you have seen several organ and choir performances in churches in the old town and have heard Old Prague Songs in various pubs around the city. One other favorite of yours was the show at *Křižíkova fontána* (Krizik’s Fountain): a large fountain where water-streams, illuminated by multi-colored lights, shoot up and dance in coordination with music.

In many ways, you feel like your stay in Prague has been one intense cultural marathon. You find it almost amusing that, back home, you have been to the theater only once in the last year: It was to see the Nutcracker last Holiday Season. Your mental wondering take a new turn: you start imagining what going to the Nutcracker in a winter Prague would be like. You are thinking that maybe you will return next December to experience that winter Prague ... the illuminated tree in center of the Old Square, Bohemian crystal tree decorations in all the stores, the carp ... You can’t hold your smile at the thought of the carp. You made your Czech friend recount to you this national tradition many times.
Apparently, many families have carp fish for dinner on December 24th. Months before the Holidays, the process of carp decontamination begins: After being caught in lakes around the country, carps are placed in rivers within large containers that let water circulate through for several weeks to wash off the mud taste. Only then do the live carps get relocated to large water bins located at every other corner of the city for sale. Around mid-December, Czechs start buying live carps from these large bins … and to continue the process of decontamination, they let the carp swim in the family bath tub for about a week prior to killing it and eating it on the 24th. And the 25th … that’s Turkey day in the Czech Republic.

Happy Holidays!

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Pulmonary Hypertension and ISHLT: Past, Present and Future

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The timeline of events relevant to pulmonary hypertension (PH) has accelerated at a remarkable pace since the first anatomic description by Ernst von Romberg in 1892. This tempo can be grasped simply by cataloguing the dates of the World Health Organization congresses that have met when there appeared to be enough new understanding to warrant such a gathering. Twenty-five years passed between the 1973 Geneva and 1998 Evian meetings, and then just 5 years until Venice in 2003, and Dana Point in 2008. Planning is well underway for the next such meeting to be held in Nice in 2013.

The classification system for PH is increasingly elegant and clear. Guidelines for PH evaluation and therapy are widely promulgated. The Pulmonary Hypertension Association has expanded awareness, advocated for patients and supported research pertaining to pulmonary arterial hypertension (PAH). The Pulmonary Vascular Research Institute is beautifully enhancing the geographic reach of the field. Widespread utilization of Doppler echocardiography has greatly facilitated the diagnostic evaluation of PH, including screening at-risk populations such as those with connective tissue disease. An increasing number of patients are being referred for evaluation of possible PH identified incidentally during echocardiography performed for other reasons. Registries including the French and the North American REVEAL, among others, have enhanced understanding of epidemiology, treatment trends, prognostication and outcome. Prostanoid therapy has expanded to include not only intravenous but also subcutaneous, inhaled and oral forms. Endothelin antagonists and phosphodiesterase-5 inhibitors are in widespread use and are remarkable for their tolerability and ease of use. Agents without vasodilatory effect that specifically target the proliferative backbone of PAH appear poised to create fundamental shifts in therapy, as epitomized by the striking impact of imatinib on pulmonary vascular resistance over the 6 month duration of the randomized study recently reported at the 2011 European Respiratory Society meeting.

In the midst of these developments, interest in PH within the ISHLT is expanding, manifested by excellent attendance at the Scientific Sessions PH symposia, and burgeoning PH publications in the Journal of Heart and Lung Transplantation. How do we explain these trends?

1. PH complicates the outcome of cardiac transplantation.
2. PH portends an adverse prognosis in both left heart disease (WHO Group II PH) and in parenchymal lung disease (WHO Group III PH). Efforts to understand whether there is a potential benefit of directing therapy toward Groups II/III PH are directly relevant to the interests of the ISHLT membership.
3. The advent of mechanical circulatory support (MCS) has created a new PH phenotype: “Group II Unloaded”. These are patients who had Group II PH with elevated left heart filling pressures who have varying degrees of residual PH and
right heart failure following left ventricular assist device (LVAD) implantation. All of us involved in the care of MCS patients are hungry for additional information pertaining to:

a. Criteria to determine whether primary LVAD or bivAD support is indicated
b. Extent to which LVAD support will itself mitigate PH and RV failure
c. Role of PH-specific therapy in "Group II Unloaded"

4. PAH specialists are often also involved in left heart failure management and in heart and lung transplantation. The ISHLT is a natural home for them.

5. Lung transplantation in PAH remains challenging, in terms of achieving transplant at the optimal time, and in achieving good early perioperative outcomes. The ISHLT is a great place to pursue dialogue and scientific advances in this regard.

6. MCS in PAH is a quickly developing field.

The future appears bright for an increasingly vibrant presence of PH-related endeavors within ISHLT. I encourage you to join the collegial, energetic and productive group of ISHLT PH aficionados. Together, we can make substantial contributions to the field.

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**Romanticism, Nationalism, and Exoticism**

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The *Time of the Season* is upon us (and for 2011 it seems that Zombies are everywhere—they seem to creep up every time there is a global recession), and with it I hear the sweeping sound of history's pendulum methodically ringing, in one grand extreme after another. Nothing captures the image of this more than the majesty of Charles Dickens. His time-honored classic, *A Christmas Carol*, describes such extremes in the caricature of the merry and the morose, the poor and the rich, and the past, present and future converging to a melodious climatic awakening. Scrooge's past captures his present to reveal his future much the same way Lincoln reveres and remembers the dead to advise the living. The triumph of such bygone lessons is celebrated in song and carols throughout the United States and much of the world for the next month. The splendor of these melodies arises from the pendulum extremes of life that define our romantic era—a time of great thinkers, artists and scientists, and a time of personal self-expression through literary, visual, and musical arts.

Where there's music, there's Beethoven. Despite being regarded as a classicist, Beethoven more than any other composer epitomized the Early Romantic period of classical music. The blending of his intense passion, individualism and fearless self-expression is the central theme of the romantic spirit.

Ushering in the end of the Late Romantic Period, indelibly dotted by Impressionism and the great inventions of the scientific world, was Antonín Dvořák, a Czech composer greatly influenced by the many changes defining the landscape of his formative years. He was surrounded by the specters of past political and social pressures characterized by the Age of Revolution originating with Jean-Jacques Rousseau, followed by the American Revolution, the French Revolution and the Age of Napoleon, ending, finally, with the universal upheaval against the establishment of the Habsburg Empire in 1848. Never before or since has Europe seen such a struggle where Bohemia, among other nations for instance, assumed a position of autonomy within the Habsburg Empire. However, these 1848 revolutions failed giving impetus to the music movement of nationalism for which Dvořák so embraced. With Prague soon upon us, it is fitting we explore this great composer.
A genial family man from peasant stock (and a genius who looked like a tinker given his rustic appearance), Dvořák served as an apprentice in a butcher shop until his talent as a violinist was recognized. He was considered a natural talent with a melodic gift. He wrote with ease music that even today requires an effortless ear. He was grounded in spirit to the beautiful land and simple peasant life of his native Bohemia. His best melodies are based on Bohemia folk models, and all of his music reflects an unself-conscious flair of nationalism. His music swings from dark, sinister, stormy moments (E-minor) to bright, sunny, lyrical and sometimes lively and robust movements (E-major), the effect of which brings us back to that ticking pendulum, marking with short brush strokes the moments of our lives. Such national folk music was incorporated into concert pieces and operas, which stirred ethnic sentiments and feelings giving an artistic independence away from traditional German/Austrian classical music. A great migration of the intellectual class of Hungarian refugees through Hamburg on their way to the New World greatly influenced Johannes Brahms—a friend to Dvořák—bringing us to exoticism.

Musical exoticism is when a composer of one nationality uses the music, rhythm, or ethnic sound of another nationality. A native of Hamburg, Brahms was infatuated with the nationalistic Hungarian fervor of improvisational ethnic dances and songs which inspired his great Hungarian Dances. It was Brahms who made Dvořák a protégé, helping him become known outside his native Bohemia.

In 1892, Philanthropist Jeannette Thurber commissioned Dvořák to become head of the National Conservatory of Music in New York City. By age 50, Dvořák was successful, in demand, admired worldwide and generous to others. His arrival to the United States provoked a media frenzy in September 1892 corresponding with an auspicious occasion—the 400th anniversary of Columbus’ discovery of America. At this time, America did not have its own voice in music. Dvořák's mission was to make Americans aware of their musical culture. He quickly recognized that the soul of American society was its racial, cultural, and ethnic diversity. Upon his arrival in America, he stated:

"I am convinced that the future music of this country must be founded on what are called Negro melodies. These can be the foundation of a serious and original school of composition, to be developed in the United States. These beautiful and varied themes are the product of the soil. They are the folk songs of America and your composers must turn to them."

Dvořák accomplished his mission. His compositional style embodied classicism, romanticism, nationalism and exoticism giving rise to his Symphony No. 9 in E minor, Opus 95, which was later titled the New World Symphony, premiering at Carnegie Hall on December 16, 1893 (how apropos for this issue!). The rising and falling in the first movement is obvious even to the non-listener. Dvořák blended Bohemian, Slavonic and American folk music with the influences of Brahms admixed with Beethoven's motifs and strict adherence to the classical symphonic style amalgamating it all into one of his greatest works. The three main American influences making this symphony principally exotic came from the plantation songs of Stephen Foster, (My Old Kentucky Home and Swanee River); African-American Spirituals (Swing Low, Sweet Chariot, Deep River); and Songs of Native Americans (Songs of Hiawatha) among others.

As with any classical symphony, Dvořák's composition was proportional with the standard four movements. The second movement is made of juxtaposed contrasting themes of confrontation, happiness and sadness, brightness and darkness creating tension and ambiguity. Underneath is simplicity, naturalness, pastoral, and outdoor sounds—all of it creating a truly marvelous blend of expressive and emotional elements. It makes me wonder what Charles Dickens was listening to when he penned his famous prose so rich with themes of similar extremes.

The ISHLT can learn a great deal from composers and writers like Dvořák and Dickens. The four movements in transplantation can be symphonic: the first movement – the evaluation, second movement – listing, third movement – the transplant event, and
the fourth movement – post-transplant care. As in the *New World Symphony*, the symphony of transplantation has a solemn beginning resounding like E-minor. Then there is a struggle with E-minor and E-major, moving from dusk to dawn. As the *New World Symphony* ends in E-major, a new day has awakened and with it comes the view through the eyes of Ebenezer Scrooge gazing upon his second chance for life. So the pendulum remains in full swing welcoming the season once again, with sound assurance, giving our patients hope.

**Editor’s Recommended Reading**

Allan Glanville recommends –
*An Imaginary Life* by David Malouf (novella re: Ovid in exile)
*A Fortunate Life* by A.B Facey (the real Australia)

Amanda Rowe recommends –
*Stumbling on Happiness* by Daniel Gilbert (non-fiction) – good for thinking about how to approach/think about life differently for the coming year

Lori West recommends –
*Shadow of the Wind* by Carlos Ruiz Zafon

Susie Newton recommends –
*Peace is Every Step* by Thich Nhat Hanh – showing us how to make positive use of the very situations that usually cause us stress

Vincent Valentine recommends –
*On The Road* by Jack Kerouac
*Gifts of the Magi* by O. Henry
*A Christmas Carol* by Charles Dickens