When you stand back and view this issue from the outside—or the otherside—it’s all about pills, their successes, their failures, their interactions, their perspectives and when all is said and done, it is as much about the body’s structure as it is its function, including size—tall and small.

Last year, the LINKS e-newsletter published an article on the importance of a Structure-Function Relationship, ISHLT Links, July 2011;3(issue 2):5. This article evoked memories of medical school training and the structure function relationship of the heart and of the lungs. How can there be function without structure? How can there be better function without refinements to structure? How can there be refined structure without constant improvement in function? Deeper thought about these questions leads us to globalize the Structure-Function relationship to everything. Today we easily link the effect of the European financial crisis to America’s economic instability; how about the future of health care and “Obamacare?” So I digress.

To achieve harmony and understanding we need to constantly refine structure and function. Professionals in the ISHLT take on this incessant task every day for the sakes of our heart and lung patients. We unknowingly do this in our daily affairs. Do we take care of ourselves? We believe we have taken care of this newsletter, but we shall not settle on our accomplishments of the past year. We will continue to refine the structure of this newsletter in hopes to continue to optimize its function as the ISHLT continues to refine its structure.

At the same time, we continue to make a plea for ideas, thoughts or any compelling comment, muse, criticism, or whatever to be part of the LINKS e-newsletter. As you consider submitting “whatever,” please review the first three issues from last year ISHLT Links, June 2011;3(issue 1):1, ISHLT Links, July 2011;3(issue 2):5, ISHLT Links, August 2011;3(issue 3):14 and you might have an idea where I am trying to go with all of “Vincent’s Nonsense” or preferably with your own dogs, biases and truths, be brave. Or, on the other hand, I may leave you out of focus and bemused, and you’ll never know exactly where you are. From the Sound of Music, you might solve the problem of Maria. Remember ... unpredictable as weather, she’s as flighty as a feather … gee, that sounds like me. Nevertheless, if I could link an octopus to a barn (so I was told), then you can find a way to link any article you submit for the newsletter to all that we do for our patients and their families, ourselves and our families, and for the ISHLT and our Society. Again my delusive or elusive goal is to compel all of you to share your ideas in the LINKS;
if not, at least see Disney’s most recent animated fantasy adventure film, “Brave,” to feel the full effect of the Will-o’-the Wisps. As a challenge and a bare minimum, you might want to look up the word, “will-o’-the wisp.” If you bother reading this nonsense, kindly send your remarks to vgvalent@utmb.edu or vvbones@gmail.com.

Vincent Valentine, MD  
Links Editor
or embolic diseases, and 5) PH caused by diseases affecting the pulmonary vasculature.

Subsequently, the world symposiums have been held every 5 years. Remarkably, another selective vasodilator, Bosentan, was approved by the FDA in 2001. The 3rd World Symposium in PH was prompted by a remarkable surge in the understanding of the mechanisms involved in the pathogenesis of PH. Held in 2003 in Venice, Italy, it provided the opportunity to assess the impact and the usefulness of the Evian classification and to propose some modifications. Thus, the term “secondary PH” was abandoned because it was found confusing and without value for diagnosis and treatment. The term “primary PH” was replaced with “idiopathic pulmonary arterial hypertension.”

By the time the 4th World Symposium took place in Dana Point, California in 2008, the scientific knowledge about PH was burgeoning. This was a 4-day summit of international experts highlighting the findings of 11 scientific working groups in areas of basic science, clinical science, and future perspectives. The purpose of this symposium was to review the progress made in diagnosing and treating PH and PAH, resulting in a new classification for PH with more etiologies added to WHO group 1 (PAH). Interestingly, more diverse participation occurred at the 4th World Symposium, in contrast with the previous 3rd World Symposium which seemed somewhat more “exclusive,” with a relatively limited number of global experts meeting in small groups. With the advent of widely available, effective therapy for PAH, it was no longer considered a rarefied condition treated in a handful of institutions by high-level experts.

The 5th World Symposium in PH promises to be a historical event. There will be a collective dedication of a group of experts to reach that elusive, yet definite, goal: finding the cure for PAH, a “medical zebra” considered—until recently—uniformly fatal. Thirty years ago, adults diagnosed with PAH could expect to live less than 3 years, with the therapeutic armamentarium limited to nonselective vasodilators. Today, our selection of therapeutic modalities is broader with 8-FDA approved therapies resulting in better outcomes. Yet, there is much more to do and new therapeutic modalities are urgently needed. We expect the upcoming symposium to focus on genetic variations in PAH, RV remodeling and function including understanding fundamental components of the RV-PA coupling, as well as creative, thoughtful approaches targeting novel pathways in PAH. Stay tuned!

Disclosure statement: The author has received research support from Actelion and United Therapeutics and consultant and speaker bureau for Gilead.
Pulmonary arterial hypertension (PAH), is characterised by proliferative and fibrotic changes in the small pulmonary arteries, leading to increased pressure, vessel obstruction, right-sided ventricular failure, and death. Despite recent progress in the treatment of PAH, patient outcomes remain poor. Consequently, improvements in the diagnosis and management of patients with PAH are essential. Interestingly, subtypes of PAH share a similar underlying pathology, suggesting that parameters capable of measuring disease progression might be applicable across PAH subgroups, allowing the development of comprehensive therapeutic tools. Documentation of clinical changes and outcomes associated with PAH permits the development of models that predict disease progression and survival.

The ability to identify and evaluate factors that affect survival in patients with PAH remains of critical interest to clinicians because it facilitates clinical care and directs research. Simply put, the ability to predict a patient's morbidity or imminent mortality prompts the clinician to escalate therapy, or refer for transplant and forewarns the patients and his/her family. Although shown to be a powerful tool for improving our understanding of PAH, interpretations of data from the NIH registry, developed over 30 years ago, have become limited by the era in which these data were collected and prior to the availability of approved pulmonary vascular-targeted therapies. Thus, the survival equation derived from NIH registry data is only applicable to patients who have not yet received treatment. In addition, due to changes in PAH classification since the NIH registry, the NIH prognostic equation may not be applicable to the present classification of group 1 PH as a whole and may not accurately reflect current survival rates. Thus, the PAH community has sought to improve epidemiologic data with newer registries, with the aim of producing a prognostic equation that can be used in all patients with PAH at any time during their disease history.

Among a number of important national PAH registries, four modern registries acquiring data on the management and treatment of patients with PAH have evaluated and developed improved prognostic equations as suggested by the original NIH data. The largest of these modern registries is the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). Analysis of outcome data in REVEAL identified nineteen independent predictors of survival, which were used to generate a prognostic equation based on the Cox proportional hazard multivariable analysis. This equation was then validated and a simplified calculator developed for everyday clinical use (Figure 1). The importance of this calculator is that it is applicable to all forms of PAH and can be used serially to predict on-going survival. Changes in parameters, scores and risk profiles using this calculator also have prognostic importance and were featured presentations at the ISHLT's annual meetings for the last 3 years. In this year's scientific sessions the group from UCSF presented data suggesting this equation and calculator can be utilized with excellent discriminatory ability in other forms of PH and thus may serve as a global predictive equation for most forms of pulmonary hypertension. Importantly, those PH patients with Risk Scores ≥ 10 identifies a subgroup in eminent danger of early death and therefore prime candidates for consideration of lung or combined heart-lung transplantation. Interestingly the REVEAL predictive elements have also been utilized by the United Network for Organ Sharing (UNOS) to reevaluate the lung allocation score (LAS), as it pertains to those PH patients listed for transplant.

It is known that the formula for calculating the LAS, which is used in all diagnoses (COPD, IPF, IPAH, etc) places PH patients at a disadvantage. To address this, UNOS currently employs an expedited appeals process so that patients who meet
certain criteria will be moved to the 90th percentile on the list. To meet these criteria, patients must be deteriorating on optimal medical therapy and have a right atrial pressure greater than 15mmHg or a cardiac index less than 1.8 L/min/m². These factors are reflective of the stability of the right ventricle, which is ultimately tied to prognosis in all PAH patients. Due to the potential for these appeals, it is important for patients to follow up routinely pre-transplant.

Data from REVEAL showed that additional factors, if incorporated into the LAS calculation, would more accurately predict survival and thereby better reflect organ prioritization in patients with PH. These additional factors included estimates of right ventricular function which, as stated earlier, are key in determining survival in PH. The LAS in its current construct, weigh factors reflective of “pure lung dysfunction” like FEV1 (a measure of airway capacity) more heavily since these predict survival better for patients with “lung diseases” like COPD. Although PH does occur in the lung and is hence considered a “lung disease,” these parameters are not useful in predicting survival in PH. This is why it was imperative to have these new “heart-related” parameters added to the LAS. This is currently under review by UNOS, and a revised formula incorporating these changes went out for public vote in April of 2012.

Disclosure statement: Raymond L. Benza has received grant support from Actelion, Bayer, GeNO, Ikaria, Gilead, Lung Rx, Novartis and United Therapeutics. He is on steering committees for Actelion, Ikaria and Bayer. He is on advisory boards for Bayer, Novartis, Gilead, and United Therapeutics.

References:


It is evident from the sessions presented at the 2011 and 2012 ISHLT Meetings that there is great international interest on pulmonary hypertension (PH) associated with left heart (LH) failure. In addition, pulmonary hypertension / right heart failure is an important common theme that brings together the PH, HF, and MCS Councils constituents.

Although the nomenclature, definitions/criteria, pathophysiology, diagnostic approaches and evidence-based therapies are well-delineated for WHO Group 1: Pulmonary Arterial Hypertension, a consensus on these aspects is lacking for Group 2: PH associated with LH Disease. As a result of this lack of standardization in the literature, it is very difficult to compare older studies and design future studies to build a robust evidence-based therapeutic approach.

To rectify this deficiency, an international consensus conference on this topic is being planned as an all-day pre-meeting, joint symposium of the PH, HF, and MCS Councils for the 2013 ISHLT Annual Meeting & Scientific Sessions in Montreal. The aim is to develop a common language by formally defining and classifying this entity and, thereby, making a major contribution to future academic endeavors.

The morning session will be dedicated to presentations geared to literature review. The afternoon session will be designed in a breakout format dedicated to formulating consensus opinions on various topics which will provide the spring board for a consensus manuscript on PH associated with LH failure.

The planning committee is comprised of the conference chairs Teresa De Marco, James Fang and Ray Benza as well as ISHLT leaders and leaders from the PH, HF, and MCS Councils.

More information about this international consensus conference will be available in the coming months, so stay tuned!

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**LINKING AUTOIMMUNITY WITH ALLOIMMUNITY**

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The 8th International Congress on Autoimmunity held in Granada, Spain (9-13 May, 2012) provided physicians, immunologists, rheumatologists, researchers, and clinicians interested in autoimmune diseases a forum where they could present their views on the latest available diagnostic and therapeutic tools.

Alloimmunity and autoimmunity share a number of important afferent, effector, and regulatory immunological pathways. Knowledge of the mechanisms underlying autoimmune diseases may help us to understand alloimmune reactions. Furthermore, recent advances in the control of autoimmune diseases are potentially useful in transplant medicine and vice versa. Here, we provide some examples.

Intravenous immunoglobulin (IVIG) is increasingly used both as substitutive and immunomodulatory therapy in solid organ transplantation; however, uncertainties about its mechanism of action continue to be a barrier. The final
Session of the congress (Dr. De Groot) included an interesting presentation about T regitopes, which are present in both the Fc and Fab fractions of IgG. Knowledge of these highly promiscuous major histocompatibility complex class II T-cell epitopes that are capable of specifically activating CD4(+) CD25(Hi)FoxP3(+) natural regulatory T cells may clarify the immunomodulatory mechanism of action of IVIG.

Rituximab is increasingly used in desensitization protocols in solid organ transplantation. Immune monitoring to identify potential candidates for rituximab from among patients with rheumatoid arthritis who are at risk of developing severe infection is yet another interesting application for transplant medicine. Studies of large cohorts of rheumatoid arthritis patients treated with rituximab have shown that severe IgG hypogammaglobulinemia is a risk factor for severe infection. The indication for rituximab should be carefully balanced in such cases, since IgG hypogammaglobulinemia (sometimes severe) can appear in heart and lung recipients in the first few months after transplantation.

Short courses of anti-CD25 (the alpha-chain of the IL-2 receptor) are increasingly used as induction therapy in solid organ transplantation with good control of alloimmune responses. With regard to manipulation of the IL-2 receptor axis to induce tolerance, Professor Abbul K Abbas suggested that low-dose interleukin-2 had the potential to expand regulatory functions. This immunomodulatory strategy is being tested in cancer therapy, bone marrow transplantation, and autoimmune diseases. Low-dose interleukin-2 has been shown to lead to T regulatory cell recovery and concomitant clinical improvement in patients with HCV-induced vasculitis, an autoimmune condition. A key issue is the definition of a dose of interleukin-2 that is highly selective for human Tregs while avoiding or minimizing stimulatory effects on T effector cell responses. It is interesting that we now consider using a pro-inflammatory cytokine to regulate inflammatory conditions in autoimmune diseases (some years ago this idea would have been considered very risky).

These are excellent examples of the complexity of the immune system and the possibilities to regulate alloimmunity even with seemingly paradoxical interventions.

Disclosure Statement: The author has no relevant financial relationships to disclose.
Invasive fungal infections (IFIs) are common after lung transplantation (15-35% of all infections) with mortality rates up to 60%\(^2\). Antifungal prophylaxis is widely used as a preventive strategy\(^3\), and has reduced the incidence and mortality of IFIs\(^2\). Voriconazole (VOR) is the most commonly prescribed antifungal for prophylaxis worldwide\(^3\), as well as the drug of choice for IFIs caused by Aspergillus spp\(^4\). Patients intolerant to VOR often receive posaconazole (POS) as an alternative\(^3\).

**Point:** Plasma concentrations are important!

An unpredictable drug dose-exposure relationship with significant inter- and intra-patient variability in plasma concentrations, makes therapeutic drug monitoring (TDM) of azole antifungals attractive\(^1\). Drug-drug interactions (VOR & POS), saturable absorption (POS), nonlinear saturable metabolism (VOR), CYP 2C19 isoenzyme genetic polymorphisms (VOR), and physiologic conditions associated with underlying diseases (VOR & POS) further complicate use of these drugs. In addition, lung transplant recipients exhibit reduced bioavailability (24-64%) in comparison to that observed in non-lung transplant patients (96%)\(^6\).

A relationship between plasma concentrations and treatment efficacy has been described; which may substantiate the need for TDM.\(^7\)-\(^16\) Mitsani\(^17\) et al found lung transplant recipients more likely to be colonized or acquire an invasive fungal infection when prophylaxis with VOR resulted in serum levels ≤1.5 μg/ml (p=0.01). Median troughs at the time of positive and negative fungal cultures were 0.92 and 1.72 μg/ml (p=0.07), respectively. Shields et al\(^18\) found cardiothoracic transplant patients receiving POS for both prophylaxis and treatment of IFIs have higher median trough concentrations in those that achieved treatment success than those experiencing failure. Concentrations >0.5 μg/ml were associated with treatment success.

Certain subgroups of patients may have a predilection to both high and low trough values\(^17\). Patients ≥ 60 years old often have VOR troughs >4 μg/ml (p=0.02), while those with cystic fibrosis are more likely to have low trough concentrations <1 μg/ml (p=0.02). Berge et al\(^19\) further characterized VOR plasma concentrations in patients with cystic fibrosis, and determined that <25% of lung transplant recipients achieved therapeutic trough values on standard doses of VOR (200mg PO BID).

Clinical investigations in the area of toxicodynamics have also been performed, and identified associations between VOR pharmacokinetics and toxicity. Although poorly characterized in lung transplant patients, high plasma concentrations of VOR have been associated with photopsia, neurotoxicity, cardiac arrhythmias, and, in some studies, hepatotoxicity\(^20\).

**Counterpoint:** Utility of TDM remains unproven...

This seems to bring about the same questions asked when mycophenolic acid trough monitoring was in-vogue. Consider this scenario: routine cystic fibrosis patient begins VOR for fungal prophylaxis after bilateral lung transplantation and develops photosensitivity and transaminitis; yet, VOR trough is 1.2 μg/ml. One is likely to stop VOR despite so-called sub-therapeutic dosing until the symptoms of toxicity resolve. Alternatively, consider this scenario: routine lung transplant recipient...
begins VOR for *aspergillus niger* identified on multiple fungal growth plates from a recent bronchoalveolar lavage, has nodules on CT, and a 15% decline in forced expiratory volume (FEV₁) in the absence of cellular rejection. Her VOR was dosed appropriately with 4 mg/kg PO BID maintenance and her trough is 5 μg/ml. She is exhibiting no signs or symptoms of any toxicity and her tacrolimus level is at target. Would one consider dose reduction despite impeccable drug tolerance and clear evidence of an IFI?

The data to support or refute the utility of TDM for azole antifungals in lung transplant recipients is sparse and what does exist is of relatively poor quality. While the Mitsani paper describes a reasonable breakpoint for VOR ‘efficacy’, they employ univariate statistical techniques, do not evaluate for other predictors such as preoperative fungal colonization, and poorly characterize the correlation between total dose and trough concentration. After loading, a fixed-dose approach of VOR 200 mg PO BID was used. Though achievement of a trough >1.5 μg/ml was associated with fewer positive fungal cultures, it was not universally protective and IFIs were not stratified by trough concentration. Lastly, toxicities appeared to occur largely in the absence of high VOR trough concentrations. Finally, the definition of IFI used here and in many of these trials was never intended to be applied to, nor has ever been validated in, lung transplant recipients.

**TDM Recommendations:**

1. Early TDM (e.g., after 5 days of treatment) should be performed for patients with an IFI. The role of TDM for prophylaxis in the context of adequate dosing remains unclear.

2. Therapeutic trough concentrations should be targeted for patients with IFIs: VOR >1.5 μg/mL; POS >0.5 μg/mL.

3. Serial TDM in the presence of a previously therapeutic level and in the absence of other drug or diet changes is unwarranted.

4. If plasma concentrations remain low despite dose modification: VOR, consider discontinuing acid-suppression (H₂ blocker; proton pump inhibitor) and/or administer with acidic beverage (e.g., orange juice), POS, divide dose every 6 hours and/or enhance fat consumption upon administration.

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**References:**


COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN THE TRANSPLANT PATIENT

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Complementary and alternative medicine (CAM) can be defined as a “group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.”

This definition encompasses natural health products (NHPs), including herbal medicines, vitamins and minerals, mind and body medicine and manipulative and body-based practices.⁴

The use of CAM is increasing in the general population, and continues to rise. The prevalence of CAM usage reported in the literature ranges between 9-65%.² The prevalence remains high when focusing on the use of NHPs alone. A survey conducted by Health Canada revealed that 71% of Canadians have used a NHP, with 38% using a NHP on a daily basis.³ Results from the United States show that 17.7% of adults use a NHP.¹
Several studies exist that explore the use of CAM in solid organ transplant recipients. These studies suggest that while the use of NHPs is high, most preparations are taken without medical consultation and awareness of their toxicities or drug interactions were low. Therefore, knowledge of patient use and the potential effects on transplant recipients is prudent.

There is little research on the use of NHPs in combination with immunosuppressant medications. As a result, various NHPs are considered contraindicated or to be used with caution due to theoretical drug-disease and drug-drug interactions. Drug-disease interactions occur when the NHP used stimulates the immune system, putting the patient at risk of rejection. NHPs may also contribute to the long term complications of immunosuppressive therapies, such as hypertension and diabetes. Drug-drug interactions can occur when the metabolic enzyme cytochrome P-450 (CYP450) 3A4 or the drug efflux pump, P-glycoprotein (P-GP), are affected. This has important implications on both calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, which are cornerstones in immunosuppressive therapy. Table 1 highlights common agents used by patients and the recommendations for use in a transplant population. This is not an exhaustive list, and readers are encouraged to consult evidence-based resources for further information.

Several case reports of adverse events with NHPs in transplant patients exist in the literature. Acute rejection requiring hospitalization has been reported in two heart transplant recipients after taking St. John's wort (SJW). Other case reports document acute rejection episodes while taking SJW, and therefore this therapy should be considered contraindicated in transplant recipients. There are no published case reports involving SJW and mTOR inhibitors, however this combination should be avoided. Severe acute rejection has also been reported in a renal transplant patient after taking alfalfa and black cohosh therapy for post-menopausal symptoms, despite maintaining therapeutic cyclosporine levels.

It is important to document a history of all NHPs used by transplant patients. Consider questioning the patient on the use of NHPs if a sudden change in drug levels is seen. For those patients who wish to use NHPs, health care providers should encourage open disclosure of therapies. Useful resources for reviewing NHPs and their potential effects on transplant patients include the Natural Medicines Comprehensive Database and Herbs and Natural Supplements: An evidence-based guide. Resources for both health professionals and patients include the NCCAM website and CAMline. Various countries now have regulation and licensing requirements for NHPs, and therefore, encouraging patients to purchase safe therapies from registered brands is important.

NHPs are commonly used in transplant patients and their effects need to be considered when used in conjunction with immunosuppressants and other associated therapies. Health professionals are encouraged to promote an open dialogue with their patients regarding the use of NHPs to ensure safe and effective therapies are utilized.

**Disclosure statement:** The author has no conflicts of interest to disclose.

**References:**


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**Table 1: Commonly used NHPs**

<table>
<thead>
<tr>
<th>NHP</th>
<th>Common Indications</th>
<th>Warnings/Serious Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astragalus</td>
<td>Immunostimulant for treatment of viral infections</td>
<td>Contraindicated in patients on immunosuppressants</td>
</tr>
<tr>
<td>Black Cohosh</td>
<td>Menopausal symptoms, premenstrual discomfort and dysmenorrhea</td>
<td>Hepatotoxicity; Rejection in renal transplant recipient</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immunostimulant for treating various infections</td>
<td>Avoid in patients on immunosuppressants</td>
</tr>
<tr>
<td>Garlic</td>
<td>Hypertension and hyperlipidemia</td>
<td>May increase bleeding or clotting time; May interact with warfarin and antiplatelet drugs; May induce CYP450 3A4, therefore avoid use with CNIs and mTOR inhibitors</td>
</tr>
<tr>
<td>Ginger</td>
<td>Nausea and vomiting</td>
<td>Theoretical interaction with warfarin and antiplatelet drugs increasing bleeding; May increase insulin levels, causing additive effect with OHGs.</td>
</tr>
<tr>
<td>Gingko Biloba</td>
<td>Dementia</td>
<td>May increase bleeding or clotting time; May interact with warfarin and antiplatelet drugs; May effect CYP450 isoenzymes including 3A4, therefore avoid use with CNIs and mTOR inhibitors</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Improving well-being and managing stress</td>
<td>Diabetics should monitor for possible hypoglycemia; May enhance antiplatelet and anticoagulant effects of therapies; Avoid use in patients on immunosuppressants (Panax).</td>
</tr>
<tr>
<td>Kava</td>
<td>Sleep and reduce anxiety</td>
<td>Interacts with sedatives, alcohol, anesthetics, and analgesics. May effect CYP450 isoenzymes and P-GP pump therefore avoid use with CNIs and mTOR inhibitors</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Insomnia</td>
<td>May increase blood pressure, bleeding time, and insulin resistance; Immunostimulant properties therefore avoid in those on immunosuppressants.</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Mild to moderate depression</td>
<td>Interacts with CNI and mTOR inhibitors, warfarin, theophylline, aminophylline, digoxin. Induces CYP3A4 thus lowering drug levels, therefore avoid use.</td>
</tr>
</tbody>
</table>
LIBERATING THE MIND: DEBUNKING TRUTHS OR DESTROYING FALSEHOODS

Vincent G Valentine, MD
Links Editor-in-Chief

You may ask what does Mark Twain have to do with the ISHLT? My answer is everything. The “dead pan” humor mastered by Twain is no different from the manner in which we write and present our rigorous and important scientific information, that is in an indifferent manner, emotionless. The mere thought or mention of the name, Mark Twain, instantly evokes a smile, maybe a chuckle and readies us for laughter. But ponder this, his teaching and preaching are not uplifting like that of a revivalist (the very person he constantly and consistently defrocks); rather, his humoristic teaching and preaching work by tearing down or “cracking up” if you will. He notes, “against the assault of laughter nothing can stand.” Obviously the central theme of his career was humor and he took this very seriously. Yet at the same time, his career troubled him throughout his life. He knew his wife thought “a humorist is something awful and not respectable.” Nevertheless, in his end, he was loved as a humorist, admired as a man of honor and character, and respected as a writer.

Our goal within the ISHLT for the sakes of our patients is to be revered one day with just a fraction of the amount of veneration poured out to Mark Twain. To William Dean Howells, (Dean of American Letters) and first president of the American Academy of Arts and Letters, Twain was “the Lincoln of our literature.” To Ernest Hemingway, Twain was “the father of all modern American literature.” For generations since his death and up until today, Twain’s image is as familiar as the most recent pop celebrities. A close examination of his short stories, his books, his lectures and his most recent work, Autobiography of Mark Twain, Volume 1, published 100 years after his death shows that he was also a genius with words.

One lesson Twain teaches us about telling a humorous story is that it must be told gravely. The teller does his best to conceal the fact that there is anything dimly funny, “dead-pan humor.” The face of the teller remains dead. He mastered this technique of irony at an early age from the founder of dead-pan humor, Artemus Ward (which is actually the pen name of Charles Farrar Browne). Another lesson, and probably the easiest way to get people to laugh, is to make them uncomfortable. There are several unmentionables used by today’s comics that work effectively, especially if used in a self-deprecating fashion (Rodney Dangerfield quickly comes to mind). I’m sure you can provide your own examples here.

"You can scratch your back when the war is over!"

Probably the most important lesson Twain teaches us about the technique of humor is to set up an outrageous contraindication—so-called burlesque humor. However, this requires a deep understanding of well-established or accepted “facts” or conventions. Pause and think about the many strategies we use in managing our patients before and after heart or lung transplantation. With burlesque humor, Twain mastered the technique of making fun by
imitating, exposing or exaggerating a pretext or some earlier work. I recommend carefully reading the following short stories (the titles say it all): The Story of the Bad Little Boy who Didn’t Come to Grief and The Story of the Good Little Boy who Did not Prosper. In the 19th century America, virtue is always rewarded and vice is always punished. Twain made a ridiculous departure from these conventions.

Another example comes from his book, A Connecticut Yankee in King Arthur's Court. Take the knight in shining armor and all he represents. This knight sits nobly on top of his horse. Mark Twain then gives this knight a head cold. How can the knight blow his nose? What sleeve will the knight use to wipe its nose? Or he gives the knight an itch that cannot be scratched. Twain is literally pulling the knight down to the lower aspects of human life. He shortens the distance between common men and heroic figures. Not only is Twain making us laugh, he is teaching and preaching. He was a realist writer staged with burlesque exaggeration. His listeners and readers are brought closer to reality by exposing the gap of what actually happens in the world instead of what we learned or read elsewhere.

What chance do the oppressed races and the impoverished have against a colossal humbug? Over centuries, power, money, persuasion, supplication and persecution may lift it and push it a little, but Twain points out that only laughter can obliterate it. The most powerful and effective weapon that race and poverty have is laughter against which nothing can stand. If everything is funny, what do we have left to take seriously? Twain exposes the frauds and the shams to free the human mind.

BRIEF OVERVIEW OF RENAL SPARING IMMUNOSUPPRESSIVE REGIMENS POST-HEART TRANSPLANTATION

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Chronic kidney disease (CKD) is a common complication after heart transplantation increasing in incidence with time after transplant to 10.9% at 5 years. A number of risk factors have been identified, these include use of calcineurin inhibitors, increasing recipient age, female gender, diabetes mellitus, hypertension, positive hepatitis C virus, need for renal replacement therapy post-operatively, renal function pre-transplant and deteriorating renal function within the first 3 months post-transplantation. CKD is associated with increased mortality and morbidity with a relative risk for death with CKD of 4.55. A recent UK survey reported the highest mortality risk was associated with a CKD stage 5 without dialysis compared to patients receiving dialysis (RR 8.54 vs 4.07).

Calcineurin inhibitors (CNIs) form the cornerstone of immunosuppressant regimens after heart transplantation; however, they are associated with nephrotoxicity. The use of the newer ‘non-nephrotoxic’ immunosuppressants such as the proliferation signal inhibitors (sirolimus and everolimus), mycophenolate mofetil and the anti-CD25 (interleukin-2 receptor) monoclonal antibodies (basiliximab and dacluzimab) have allowed for a number of strategies which have shown potential to improve renal function in heart transplant recipients by allowing for CNI minimisation and even elimination - not all of which will be discussed here. The ultimate goal for such non-CNI based immunosuppression (or CNI minimisation) is to minimise or reverse renal damage but not at a price of increased acute rejection episodes or reduced patient survival.

Mycophenolate mofetil (MMF) inhibits purine synthesis in both T and B cells and is often used together with a CNI and corticosteroids post-transplantation. A number of studies...
including the IMPROVED trial have shown that switching from azathioprine to MMF followed by a reduction in ciclosporin levels in long-term cardiac transplant recipients could be achieved safely and lead to significantly lower serum creatinine\textsuperscript{11-13}. While Hamour et al showed that it is possible to utilise MMF to decrease ‘early’ ciclosporin exposure safely, and hence the incidence of CKD stage 3a or worse was reduced\textsuperscript{14}.

There are two proliferation signal inhibitors (PSI) or mammalian target of rapamycin (mTOR) inhibitors: sirolimus and everolimus, these inhibit T cell activation at a later stage to the CNIs. Sirolimus was the first available; everolimus has a much shorter half-life of 28 hours (vs 62 hours) allowing steady-state to be achieved earlier but is as yet not available commercially worldwide (e.g. in the UK it is available only on a ‘named-patient’ basis).

Early studies using the PSIs with full dose CNI have shown that although the PSIs were not thought to be inherently nephrotoxic, they will exacerbate CNI-induced renal dysfunction\textsuperscript{15,16}. Subsequent studies have since used sirolimus or everolimus with ‘low dose’ ciclosporin or tacrolimus with some benefit\textsuperscript{17-20}.

The Save The Nephron (STN) cardiac study looking at early post-transplant CNI elimination (at 12 weeks) with sirolimus and MMF was terminated prematurely due to an unexpectedly high incidence of grade IIIa biopsy proven acute rejection\textsuperscript{21}. However, ‘late’ CNI elimination with the use of a PSI together with MMF shows more promise\textsuperscript{22-27}, but the reports are somewhat variable. One study of five patients with severe renal impairment late after heart transplantation demonstrated accelerated renal failure\textsuperscript{28}. Alternatively, Gustafsson et al demonstrated that renal recovery from CNI CKD with sirolimus based immune-suppression correlated with shorter duration of CNI exposure and renal dysfunction\textsuperscript{29}. This has been confirmed in other studies, hence timing of the switch is important, and it is likely that residual renal dysfunction relates to irreversible structural kidney damage.

So when using a PSI do we minimise or eliminate the CNI in stable heart transplant patients with CKD? Gleissner et al compared low dose CNI with CNI-free sirolimus based immunosuppression and found that successful CNI elimination was more effective in improving renal function (in terms of estimated glomerular filtration rate) than CNI minimisation\textsuperscript{30}.

Unfortunately, sirolimus is often not well tolerated, often necessitating withdrawal due to its adverse effect profile which includes severe acne, mouth ulcers, myelosuppression, dyslipidaemia, infection as well as oedema, pneumonitis, impaired wound healing and increased proteinuria. Caution should be exercised with the use of sirolimus in patients with significant pre-existing proteinuria, the mechanism for this adverse effect is still not understood\textsuperscript{31}.

The interesting concept of a temporary ‘CNI holiday’ was reported in a small single centre study in patients with acute renal dysfunction. Basiliximab or dacluzimab temporarily replaced CNI therapy; basiliximab was given on days 1, 4 and then every 20 days, while dacluzimab was given every 7 days. Serum creatinine decreased significantly and was maintained at 3 months after re-introduction of the CNI. There were no acute rejection episodes, but, a number of patients required a further CNI holiday due to a new episode of acute renal dysfunction\textsuperscript{32}. However, prospective randomised clinical trials are required to confirm these preliminary findings.

There is no ‘one size fits all’ strategy for managing CNI-induced renal dysfunction, but these agents have given us new tools in our drug armamentarium to potentially improve patient morbidity and outcome.

**Disclosure statement:** The author has no conflicts of interest to disclose.

**References:**

27. Snell GI, Levvey BJ, Chin W, et al. Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. J Heart Lung Transplant

**DRUG INTERACTIONS WITH ENDOTHELIN RECEPTOR ANTAGONISTS IN PULMONARY ARTERIAL HYPERTENSION**

**Steve Ivulich, BScPharm**
Alfred Hospital, Melbourne, Australia

The endothelin receptor antagonists (ERA's), bosentan and ambrisentan are two novel pharmacologic agents indicated for the treatment of pulmonary arterial hypertension (PAH). PAH is characterised by elevated plasma and tissue levels of endothelin, causing vasoconstriction and induction of smooth muscle proliferation. ERA's have proven beneficial effects on exercise capacity, haemodynamics and time to clinical worsening.

Bosentan and to lesser extent ambrisentan are implicated in a number of drug-drug interactions. Identification of these interactions allows clinicians to prevent avoidable harm to patients, as well as optimise efficacy. Some important interactions will be discussed here, in particular interactions with agents that are frequently prescribed to patients with PAH.

The cytochrome P450 (CYP450) enzyme system, particularly the CYP3A4 and CYP2C9 isoenzyme, is responsible for the oxidative metabolism of the ERA's. Concomitant use of CYP450 inhibitors, such as theazole antifungals (e.g. voriconazole, posaconazole, fluconazole, ketoconazole), macrolides (e.g. clarithromycin), protease inhibitors (e.g. ritonavir) and amiodarone results in increased plasma concentrations of the ERA's. Co-administration with CYP450 inducers (e.g. rifampicin, phenytoin, carbamazepine) will result in decreased plasma concentrations.

Treatment of PAH also targets nitric oxide and prostacyclin pathways and combinations with ERA's are utilised to provide possible synergistic benefits. Although no known interactions with ERA's and prostanoids have been reported, high doses of sildenafil increase peak plasma bosentan concentration by 42%. Sildenafil reduces the hepatic uptake and elimination of bosentan via inhibition of the organic anion-transporting polypeptides (OATP). In contrast, bosentan has been reported to reduce sildenafil plasma levels by up to 50%, via induction of CYP3A4. When sildenafil is prescribed at the usual recommended dose of 20mg three times daily, plasma concentrations are expected to be too low to elicit an effect on the pharmacokinetics of bosentan. The combination is therefore well tolerated in clinical practice and appears to be effective. Ambrisentan has no reported effect on CYP450 isoenzymes, but appears to be a substrate of OATP, although the clinical significance of this has yet to be determined.

Anticoagulation with warfarin is commonly administered to
patients with PAH to reduce the risk of thromboembolism.\textsuperscript{16} Warfarin is metabolised by the CYP450 and bosentan mediated induction of CYP2C9 up-regulates warfarin’s metabolism, necessitating higher doses to maintain target INR.\textsuperscript{17,18} Ambrisentan has no clinically relevant effect on the pharmacokinetics of warfarin.

ERA’s are potent teratogens, therefore women of child bearing potential require contraception.\textsuperscript{19} Bosentan, but not ambrisentan may reduce the systemic levels and efficacy of hormonal contraceptives via induction of CYP3A4/5, potentially resulting in contraceptive failure.\textsuperscript{20,21} Ambrisentan may be prescribed as a safe alternative.

Infrequently cyclosporine may be prescribed to patients with PAH associated connective tissue disease or PAH patients undergoing a solid organ transplant.\textsuperscript{22} The co-administration of cyclosporine and bosentan is contraindicated as increases of up to 40 fold in bosentan trough levels and up to 50% reduction in cyclosporine levels have been reported.\textsuperscript{9} The interaction is mediated through OATP inhibition by cyclosporine and CYP3A4 induction by bosentan.\textsuperscript{9} Ambrisentan may be prescribed at a reduced dose of 5mg daily as only a two fold increase in cyclosporine concentration has been reported.\textsuperscript{20}

PAH can occur in up to 0.5% of patients with HIV and bosentan has demonstrated efficacy in HIV associated PAH.\textsuperscript{23-25} There are however a number of clinically significant interactions with anti-retroviral therapy. Boosted protease inhibitor (PI), lopinavir/ritonavir has been reported to increase bosentan concentrations by up to 48 fold primarily via inhibition of OATP.\textsuperscript{26} Bosentan, via induction of CYP3A4/5 can decrease lopinavir and ropinavir concentrations, but this is not clinically significant.\textsuperscript{26} The co-administration of a boosted PI with bosentan requires temporary cessation of bosentan and reintroduction at half the recommended dose.\textsuperscript{25} Close monitoring of bosentan tolerability, clinical symptoms and haemodynamics of PAH and HIV viral load is required.\textsuperscript{5} Unboosted atazanavir is also reduced by bosentan’s induction of CYP3A4/5, contraindicating co-administration.\textsuperscript{28} There are no reported interactions with ambrisentan and anti-retroviral therapy.

ERA’s are an established class of therapeutic agents for the treatment of PAH. As treatment shifts towards combination therapy and more treatment options emerge, careful consideration of potential drug interactions is required to ensure maximum clinical benefit and to avoid risk of harm to patients. Ambrisentan offers some pharmacokinetic advantages compared to bosentan, with only one known clinically relevant drug-drug interaction.

Disclosure statement: The author has no conflicts of interest to disclose.

References:

ORAL RIBAVIRIN FOR PARAMYXOVIRUS INFECTIONS IN LUNG TRANSPLANT RECIPIENTS?

Macé M Schuurmans, MD

Infectious Diseases Council Communications Co-Liaison

Some members of the paromyxoviridae (PV) family, such as respiratory syncytial virus (RSV), parainfluenza virus (PIV) and human metapneumovirus (hMPV), are increasingly being recognized as pathogenic to lung transplant recipients. The spectrum of disease may vary from mild upper respiratory tract infection to severe pneumonia requiring mechanical ventilation. Some of these infections have been implicated in allograft rejection. Diagnosis may be performed by rapid antigen testing and PCR, which for RSV has a sensitivity and specificity > 90%.

Few systematic studies are available for treatment of PV infections in lung transplant recipients and published case series are limited to small numbers. The limited evidence supports the use of ribavirin; however, the most appropriate route of administration and dose is not

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clearly established. Oral, intravenous and inhalation routes have been used with variable success.

Fuehner and colleagues from Hannover (Germany) recently published their single center experience using oral ribavirin in lung and lung-heart transplant recipients with PV infections. The primary clinical endpoint was new onset of bronchiolitis obliterans syndrome (BOS) within 6 months of PV infection. Secondary endpoints were time to recovery of FEV1, incidence of acute rejection, BOS progression, and survival or graft loss after 6 months. Viral detection was performed from nasopharyngeal swabs by PCR only if bronchoalveolar lavage (BAL) was not feasible or isolated symptoms of upper respiratory tract infections were present. Direct immunofluorescence antigen testing was the primary detection method for BAL samples followed by PCR testing for negative samples from patients with a clinical history suggestive of infection. A total of 38 patients were treated with ribavirin (15-20mg/kg/day in two divided doses for 14 days) and increased prednisolone (ribavirin (R) group), whilst 29 patients with contraindications for ribavirin treatment (i.e. renal failure, anemia, leucopenia or known intolerance to ribavirin) received supportive treatment including increased prednisolone (0.5mg/kg/day) if symptomatic (non-ribavirin (NR) group). RSV was the most common PV detected (>63%) followed by PIV (>25%) and hMPV. In 10 patients ribavirin was stopped after 6-10 days due to hemolysis (n=5), renal failure (n=4) and nausea (n=1. Median FEV1 dropped by 20% and 18% from baseline for the R and NR groups, respectively. In 84% of the R group and 59% of the NR group graft function recovered within 30 days (P= 0.02). New onset BOS developed within 6 months in 5% of the R group versus 24% of the NR group (P=0.02). The authors conclude that treatment with oral ribavirin seems to be associated with earlier recovery of graft function and prevention of BOS.

To date, this is the largest prospective study of oral ribavirin published for lung-/heart transplant recipients using a comparison group without ribavirin. Both groups also received an increased prednisolone dose. The selection criteria for inclusion into the ribavirin group were lack of contra-indications for ribavirin rather than a random allocation of subjects potentially eligible for such a treatment. This allocation may have introduced a selection bias, which somewhat limits the conclusions that can be drawn from the study. Nevertheless, this prospective trial provides the strongest evidence thus far supporting the use of oral ribavirin in PV infections and suggests beneficial effects concerning lung function recovery and a reduced incidence of BOS. It also provides some indication regarding dose and duration and draws attention to known adverse events. Close monitoring is advisable to allow for drug discontinuation to prevent hemolytic anemia or kidney failure. Oral ribavirin is considerably less expensive and easier to use than the aerosolized form, which factors may be decisive in case of equal efficacy. Randomized studies comparing various application routes are needed to clarify this question.

**Disclosure statement:** The author has no conflict of interest to disclose.

**References:**


Many years ago, I wrote a paper about recipient/donor size mismatch and downsizing lungs to “fit” small patients with cystic fibrosis (CF).¹ We showed that our surgeons were correcting for differences in predicted Total Lung Capacity (TLC).

When I chaired the OPTN’s lung allocation subcommittee, I tried (unsuccessfully) to get listings based on % predicted TLC, instead of listing with a weight or height range. Some committee members understood that the concept was correct, but thought it would be difficult for physicians and lay people to understand. Eurotransplant physicians have been using TLC to list patients since 1990 (personal communication, Patrick Evrard).

In normal humans, lung size is a function of height, sex, race and age.²-⁴ Each lung fills a pyramidal box with a height and radius. Height is the distance from base (diaphragm) to apex of the box. Because of racial differences in limb:trunk length ratios, there is a racial correction for height. A 6-foot tall Caucasian has shorter legs (and therefore a longer trunk) than a 6-foot tall African American. A 6-foot tall North American Indian or Hispanic has even shorter legs (and therefore a longer trunk), than a Caucasian. So for the same height, different races have different lung volumes (lung sizes). African Americans have 10% less TLC than Caucasians for the same height, and Hispanics about 10% more.

As an aside, this racial difference in limb:trunk ratio may explain the racial mix in the NBA. For the same height, African Americans have longer limbs, meaning a longer arm reach, and longer legs, which means they have a mechanical advantage over Caucasians in the jumping department. Although there are some Hispanics in the NBA, there aren’t as many in proportion to the U.S. population.

Radius of the box is related to sex. Women are smaller around for the same height as men, so their radius is less for the same height. The volume of the thorax is related to the square of the radius, so females have much smaller lungs than men for the same height. Just look at % predicted TLC on a set of PFTs from men and women. Also, look at lung size on a CT scan. Tall people have more slices (height), and women have smaller lungs. Weight is related to the soft tissue around the lungs, but only adds a “restrictive component” because it’s harder to contract the diaphragm against all that abdominal content. Age is the least important predictor, but relates to the height of the box. As we age, our thoracic spines “shrink”. So a 6-foot tall 70-year old male has smaller lungs than a 6-foot tall 25-year old male. Chances are when the 70-year old was 25, he was taller.
What happens with disease? Patients with obstructive lung diseases (COPD and CF), develop larger sized boxes, due in part to flattened diaphragms and increased AP diameters. After lung transplant, the flattened diaphragm corrects right away, but the increased AP diameter may persist for a long time. For that reason, our CF patients sometimes have >100% predicted FVCs 1 year after lung transplant. Conversely, patients with restrictive lung diseases have reduced thoracic volumes. Their AP diameter (radius) is less than normal, and may not completely correct. So, you can undersize patients with restrictive disease to some extent. If you undersize patients with obstructive lung disease, you may pay a price.

What’s the bottom line? Calculate % predicted TLC of your recipient - if they were healthy - and the donor, based on their height, sex, race, and age. Then decide how much mismatch you will tolerate. DO NOT waste your time measuring lung height on a chest X-ray. Want more height? Increase the tidal volume (VT). Want less? Decrease TV. Also beware whether the film was shot during full inspiration or expiration. That’s all the measurement tells you. Now with “protective” ventilation strategies in ICUs, lungs are often small on CXR because of low VT ventilation. Some centers make coordinators waste time with a tape measure. There are reliable equations for predicted TLC with correction for race. The equations are different for adults and children, and may not be reliable for adolescents during a growth spurt (particularly males), because of limb:trunk length ratio discrepancies.

When I posted some of this information in the lung transplant forum in response to a question about donor/recipient lung size matching, someone wrote that older donors often have larger lungs, especially when they have a smoking history. If the lungs look large, it's because the donor has emphysema or COPD, not because they grow with age.

Finally, beware of the indeflatable donor lung upon disconnecting the ventilator. We once transplanted a CF patient who had a previous right lower lobectomy, so the right hemithorax was quite small. Our plan was to place a right lower lobe in the right chest, then go on bypass to replace the left lung. The donor lobe did not deflate when we opened the bronchus, and the implant was difficult. We had the same problem on the left side. The recipient always had poor FEV-1 post-transplant. He later met his donor’s mother, and learned that the donor was being treated for asthma, but in her grief at the time of his death, she forgot to mention this. Although some centers claim that asthmatic lungs are safe to transplant, we routinely turn them down. Sadly, our recipient died of BOS after 2.5 years. Poor deflation was missed by the retrieving surgeon.

You can always make a big lung smaller.¹ You can’t do the reverse.

Disclosure statement: Dr. Egan served on the OPTN Thoracic Organ Committee and the Lung Allocation Subcommittee from 1998-2005. He chaired the Lung Allocation Subcommittee from 1999-2005. He has no financial disclosures relevant to this article.

References:


The ISHLT International Travelling Scholarship Award was established to facilitate the exchange of knowledge and techniques regarding heart and lung transplantation and the treatment of end stage heart and lung failure and to build relationships between individuals, institutions, and countries. The Scholarships may be used to learn new techniques in the clinic, operating room, or laboratory or just to experience first-hand how others deal with challenging problems. These awards are open to any member of the Society, in any country. They represent a unique opportunity for garnering fresh ideas and collaborative work across the globe.

The ISHLT will fund a minimum of ten scholarships per year. Each award will be in an amount of . ALL members of the Society are eligible to apply for a Scholarship. Applications for the next round close on August 1st.

For more information and application instructions/eligibility requirements, visit the International Traveling Scholarship webpage at http://www.ishlt.org/awards/awardIntlTravelScholar.asp.

Congratulations to our 2011 International Traveling Scholarship recipients:

**August 2011**

**Stephanie T. Yerkovich, PhD**
The Prince Charles Hospital
Brisbane, Queensland, AUSTRALIA

**Host Institution:**
Toronto General Hospital
Ontario, CANADA

**Sarah E. Gilpin, PhD**
University of Toronto
Ontario, CANADA

**Host Institution:**
The Prince Charles Hospital
Queensland Centre for Pulmonary Transplantation and Pulmonary Disease, Chermside, AUSTRALIA

**December 2011**

**Kimberly M. Derkatz, BNSc**
University of Alberta, Pediatrics
Edmonton, Alberta, CANADA

**Host Institution:**
Stanford University
Microbiology & Immunology
Stanford, California, USA

**Jennifer Conway, MD, FRCPC**
The Hospital for Sick Children
Toronto, Ontario, CANADA

**Host Institution:**
University of Louisville
Louisville, Kentucky, USA
FEATURED PAPERS IN JHLT JULY 2012

This month, JHLT features incisive editorials on 2 issues of cardinal clinical importance. Sharon Hunt, the 2012 ISHLT Lifetime Achievement Awardee, provides a poignant reflection on the notion of age thresholds for cardiac transplantation (link to article). Drs. Abdallah G. Kfoury and Jon Kobashigawa react to the recently implemented high priority allocation system in Canada for the sensitized candidate (link to article).

Featured Papers:

- **Outcomes of cardiac transplantation in septuagenarians** (Goldstein)
  
  Link to Article
  
  Selected septuagenarians with advanced heart failure can derive great benefit from cardiac transplantation, although survival is inferior to that of an immediately younger sexagenarian cohort. Most of the mortality risk is seen in the first year after transplantation.

- **Voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients** (Singer)
  
  Link to Article
  
  These authors suggest that caution should be taken when using voriconazole in lung transplantation because this drug increases the already high risk for squamous cell cancer in this population.

- **Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: A preliminary randomized controlled trial** (Hayes)
  
  Link to Article
  
  In a randomized comparison, the authors find that exercise training is feasible and safe in patients with a durable left ventricular assist device. Trends toward greater improvement in exercise capacity and quality of life after exercise training point to need for further investigation in a larger trial.

- **Long-term treatment, tolerability, and survival with subcutaneous treprostinil for severe pulmonary hypertension** (Sadushi-Koliçi)
  
  Link to Article
  
  A DRAMATIC RISE IN 2012 IMPACT!

I am very pleased to report that the JHLT now boasts a 1 year Impact Factor of 4.332 (last year 3.426) and a 5 year Impact Factor of 3.521 (last year 3.096).

The 2011 journal citation reports were released on June 28th 2012 and now rank the JHLT:

- 1st among all Solid Organ Specific transplant Journals
- 3rd among all Transplantation Journals
- 6th among all Respiratory Disease Journals
- 8th among all Surgical Specialty Journals
- 22nd among all Cardiovascular and Circulatory Disease journals

These rankings reflect a significant increase from last year. As an example, the JHLT was ranked 7th in the Transplantation category and 34th in the Cardiovascular and Circulatory disease category in the 2010 Citation Report.

The Impact Factor is one way of adjudicating journal ranking and prestige - While imperfect in its methodology and subject to year by year shifts, this metric does allow for a comparison across a “level” playing field in comparison with other journals in various disease and category specific areas. On all counts of modern metrics such as the Eigen Factor, the H-Index, the Article Influence Score and Immediacy Index, the JHLT has demonstrated superlative gains this year.

These rankings are a credit to the confidence placed by the ISHLT fraternity of colleagues in the editorial team, the hardworking group of diligent editorial consultants, reviewers and authors who chose to publish in our journal. This performance amplifies our relentless focus on scientific rigor, quality as well as intended journal diversity beyond transplantation into areas such as Mechanical Circulatory Support and Pulmonary Hypertension have yielded these outcomes.

Sincerely yours,

Mandeep

Mandeep R. Mehra, MD
JHLT Editor-in-Chief
First-line treatment of severe pre-capillary pulmonary hypertension with sub-cutaneous treprostinil is safe and efficacious over many years. If up-titration beyond 6 months is tolerated, effective doses are reached and outcomes are good.

- **Highly sensitized patients in cardiac transplantation: Early outcomes from the Canadian Prioritized Organ Sharing Program (Chih)**
  [Link to Article](#)

This preliminary review demonstrates satisfactory short-term outcomes from the new Canadian 4S-prioritized national organ sharing program. Long waiting times and significant mortality persists for sensitized patients. Without the current system, however, many may not have received a transplant, as suggested by the two-thirds of transplanted patients who received a non-local donor organ.

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**RATTLING LINKS**

**NEW LINKS IN THE LINKS!**

"A Future CNN Correspondent"

Please join us in congratulating Stephen and Selenia Chavez on the birth of their son, Aarón Jesse, born a healthy 6 lbs. 9 oz. and 20 inches long on May 25, 2012 in San Antonio, Texas, USA. This is the couple’s first child and first grandchild for their families so everyone is very excited!

Stephen is the Director of Public Relations and Account Services at Proterra Advertising and served as the Media Relations Manager for the 2012 ISHLT Annual Meeting in Prague, Czech Republic. Stephen wrote and distributed six press releases for the 2012 meeting and helped ISHLT earn over 38 million media impressions. He also managed the onsite press room in Prague and you probably met him as he handed out copies of the Daily Links newsletter in the Congress Centre.


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**JULY IN HISTORY ...**

**July 1st - CANADA DAY**

**July 4th - Independence Day in the United States.**

**July 10, 1871 -** French author Marcel Proust (1871-1922) was born near Paris. "Happiness," he wrote in The Past Recaptured, “is beneficial for the body but it is grief that develops the powers of the mind.”

**July 14th - Bastille Day (French National Day), formally La Fête Nationale**

**July 15, 1606 -** Dutch painter Rembrandt van Rijn (1606-1669) was born in Leiden, Holland. Best known for The Night Watch and many portraits and self portraits.

**July 20, 1969 -** A global audience watched on television as Apollo 11 Astronaut Neil Armstrong became the first Man on the Moon 🚀. As he stepped onto the moon’s surface he proclaimed, “That’s one small step for man, one giant leap for mankind.”

**July 27, 1953 -** The Korean War ended with the signing of an armistice by U.S. and North Korean delegates at Panmunjom, Korea. The war had lasted just over three years.
This month, all eyes are on CANADA … so naturally, we decided to poke a little fun at our Canadian friends! Here’s what comedian Jeff Foxworthy says about Canucks:

You might live in Canada if:
- You’ve worn shorts and a parka at the same time
- Your local Dairy Queen is closed from September through May
- Someone in a Home Depot offers you assistance … and they don’t work there
- You’ve had a lengthy telephone conversation with someone who dialed the wrong number
- “Vacation” means going anywhere south of Muncie for the weekend
- You measure distance in hours
- You know several people who have hit a deer more than once
- You have switched from “heat” to “A/C” in the same day and back again
- You can drive 90 km/hr through 2 feet of snow during a raging blizzard without flinching
- You install security lights on your house and garage, but leave both unlocked
- You carry jumpers in your car and your wife knows how to use them
- You design your kid’s Halloween costume to fit over a snowsuit
- The speed limit on the highway is 80 km, you’re going 90, and everybody is passing you
- Driving is better in the winter because the potholes are filled with snow
- You know all 4 seasons: almost winter, winter, still winter and road construction
- You have more miles on your snow blower than your car
- You find 2 degrees “a little” chilly

From Canadian Jokes to Canadian Sarcasm:
When Vancouver hosted the 2010 Winter Olympics, some silly questions about Canada asked by people from all over the world were posted on an International Tourism Web site. Obviously the answers are not to be taken seriously, but the questions were indeed asked and are now another addition to the collection of Canadian jokes!

Q: I have never seen it warm on Canadian TV, so how do the plants grow? (England)
A: We import all plants fully grown and then just sit around and watch them die.

Q: Will I be able to see Polar Bears in the street? (USA)
A: Depends on how much you’ve been drinking.

Q: I want to walk from Vancouver to Toronto. Can I follow the Railroad tracks? (Sweden)
A: Sure, it’s only 4,000 miles, take lots of water.

Q: Can you give me some information about hippo racing in Canada? (USA)
A: A-fri-ca is the big triangle shaped continent south of Europe. Ca-na-da is that big country to your North… oh forget it. Sure, the hippo racing is every Tuesday night in Calgary. Come naked.

Q: Which direction is North in Canada? (USA)
A: Face south and then turn 180 degrees. Contact us when you get here and we’ll send the rest of the directions.

Q: Can I bring cutlery into Canada? (England)
A: Why? Just use your fingers like we do.

Q: Can you send me the Vienna Boys’ Choir schedule?
(USA)
A: Aus-tri-a is that quaint little country bordering Ger-ma-ny, which is... oh forget it. Sure, the Vienna Boys Choir plays every Tuesday night in Vancouver and in Calgary, straight after the hippo races. Come naked.

Q: Do you have perfume in Canada? (Germany)
A: No, WE don’t stink.

Q: I have developed a new product that is the fountain of youth. Where can I sell it in Canada? (USA)
A: Anywhere significant numbers of Americans gather.

Q: Do you celebrate Thanksgiving in Canada? (USA)
A: Only at Thanksgiving.

Q: Are there supermarkets in Toronto and is milk available all year round? (Germany)
A: No, we are a peaceful civilization of Vegan hunter/gathers. Milk is illegal.

Q: I have a question about a famous animal in Canada, but I forget its name. It’s a kind of big horse with horns. (USA)
A: It’s called a Moose. They are tall and very violent, eating the brains of anyone walking close to them. You can scare them off by spraying yourself with human urine before you go out walking.

Q: Will I be able to speak English most places I go? (USA)
A: Yes, but you will have to learn it first.

WHO’S READING THE LINKS?

Who is reading the Links Newsletter? Where is our audience? What information are they accessing? You may be surprised by the results!

Our readers span the globe, reaching 35 countries and 5 continents. 62% of our readers are from the United States, and the rest (listed by greatest percentage of readers) are from Australia, Canada, Sweden, Germany, United Kingdom, Ireland, The Netherlands, Spain, Italy, Japan, New Zealand, France, Switzerland, Turkey, South Africa, Belgium, Brazil, Denmark, Greece, Israel, India, Saudi Arabia, Singapore, China, Columbia, Czech Republic, Hungary, Nigeria, Norway, Poland, Portugal, Romania, Russia and Taiwan.

In the June issue of the Links Newsletter, the popular pages included content related to Mechanical Circulatory Support (topping the list), Heart Failure & Transplant Medicine, Pulmonary Transplantation, the featured articles in the Journal for Heart and Lung Transplantation, Pediatrics, and the 2013 Annual Meeting in Montreal. Every single page of the Newsletter was accessed multiple unique times, showing us that the content we are providing is relevant and of interest to our members.

Thanks to everyone involved in contributing to the ISHLT Links Newsletter. We appreciate your efforts and are grateful for your support. We are always looking for ways to improve the newsletter, so please do not hesitate to share your ideas with us.

We look forward to hearing from you. In the meantime, happy reading!

Susie Newton
susie.newton@ishlt.org
Links Managing Editor
**PRO**

I am a cardiologist practicing at an institution experienced in heart transplantation. We recently started a VAD program which we are really excited about. Given this bias, I believe that VAD implants should be handled by transplant centers and not by standard cardiothoracic surgery centers. Indeed, transplant is still the first option for advanced heart failure. Although the most foreseeable scenario may be that VAD therapy will be for patients with failing hearts as what dialysis is for patients with failed kidneys. VADs are implanted either to bridge a patient until an organ is available, or to restore as a surrogate survival option for those with absolute contraindications for transplant. These indications can be appropriately managed only by a transplant center, or by a center strictly connected with a transplant center. Thus, in the context of a public healthcare system, health authorities should regulate VAD implants by allowing only selected centers with periodic auditing of indications and outcomes similar to transplant.

The compelling issues of costs, possible restrictions, and over/under treatment, are very difficult to regulate and the decision-making system should be responsibly driven by physicians and surgeons. I think that a very effective tool is to institute a registry similar to INTERMACS in the US. Healthcare authorities, inspired by scientific societies, may then provide national guidelines, tailored by the local system, to identify indications and age limits, to be periodically revised based on meaningful data from the registries. It is only by revising expected outcomes that it would be possible to regulate implants effectively, avoiding dangerous liberalization. Of course, to support these concepts in a rational manner, national healthcare systems need money—not cuts—like we are now facing in southern Europe, thus forecasting a downgrade of our expectation for cutting-edge therapies. In my country, for instance, 70% of the national budget for transplants and organ procurement activities was cut by the Health ministry, leaving the costs mostly on the shoulders of the local governments. In this scenario, it is quite unlikely that money will be allocated for the burgeoning VAD programs. This will induce transplant centers towards a policy of “responsible restriction” thereby limiting the bridge to transplant indication to very selected patients. The efforts of the ISHLT in supporting an international registry and developing MCS guidelines, will be indispensable and akin to helping the performer “teeter-totter on a tight rope with a glass of battery acid on his forehead”.

Dr Seymour Moni

Anyone interested in battling the CON side? If so, please submit your opinion to Susie Newton (susie.newton@ishlt.org) no later than Wed, July 25th, for publication in the August 2012 Links issue.
My beautiful, talented, gifted sister lost the battle of her life on April 24 of 2012.

We were pals growing up; playing games, sharing secrets, attending afternoon movies in the 1930’s, listening to Saturday morning radio shows for children, helping with limited household chores and swimming in the local city pool. In our young life, growing up in Kansas, we had wide open spaces to play hide and seek and occasionally find a burrow full of baby rabbits in the farmer’s field next door. We attended the same schools at the same time through our college years.

Betty was not only my older sibling (by eighteen months), she was one of the greatest influences in my life. She served as my mentor and counselor as well as for other family members, giving generously of her time and knowledge. She had a wonderful dry sense of humor and adventurous ways that were with her to the end.

I admired Betty’s ability to set goals, successfully reaching them one by one. I have tried to pattern my life after hers, falling far short of her intellect and strength.

I love and miss her however I know she is with me in spirit. The following poem speaks for my sister Betty.

AFTERGLOW
by Helen Lowrie Marshall

I’d like the memory of me
To be a happy one.
I’d like to leave an afterglow
Of smiles when day is done.

I’d like to leave an echo
Whispering softly down the ways,
Of happy times, and laughing times
And bright and sunny days.

I’d like the tears of those who grieve
To dry before the sun
Of happy memories I leave
Behind—When day is done.
Mariell Jessup, MD
Penn Medicine Cardiologist Named President-Elect of the American Heart Association
http://www.upenn.edu/pennnews/news/penn-medicines-mariell-jessup-named-president-elect-american-heart-association
26 June, 2012, Penn Medicine News
“My involvement with the American Heart Association has spanned more than 20 years and I am honored to be so engaged with the nation’s leading health organization dedicated to the treatment and prevention of cardiovascular disease and stroke,” said Dr. Jessup, who is also a member of the Penn Medicine Cardiovascular Institute.

Raymond L. Benza, MD
AGH Cardiologist Named Physician of the Year by Pulmonary Hypertension Association
21 June, 2012, Allegheny General Hospital News
22 June, 2012, digitaljournal.com
Considered one of the country’s foremost experts on pulmonary vascular diseases and cardiac transplantation, Dr. Benza has played a major role over the past two decades in advancing the study and treatment of pulmonary hypertension, a progressive and often fatal cardiovascular disease. Dr. Benza accepted his award at the annual PHA scientific meeting in Orlando on June 24, 2012.

Nicholas Cavarocchi, MD
Monitoring Complete Cardiac Function at the Bedside
25 June, 2012, Jefferson University Hospital News
Cardiac function and fluid volume status are essential components in the care and management of critically ill patients. A new device is allowing surgeons at Thomas Jefferson University Hospital to monitor patients’ complete cardiac function at the bedside for the first time.

David P. Jenkins, FRCS
Milestone for Heart Centre
21 June, 2012, Papworth Hospital NHS News
Doctors at Papworth Hospital in Cambridge have announced that they have undertaken a record number of the highly complex Pulmonary Endarterectomy (PEA) operations.

Luca A. Vricella, MD
Baby’s Heart Surgery Becomes Part of Hopkins History
The first surgery to take place in Johns Hopkins Hospital’s brand new, dedicated pediatric cardiac surgery operating room.

David Rosenthal, MD
Olaf Reinhartz, MD
Daniel Bernstein, MD
Three Heart Transplants in about 72 Hours at Packard
Children’s
http://med.stanford.edu/ism/2012/june/heart-transplant-0611.html
11 June, 2012: Stanford School of Medicine News
In an extremely rare series of transplants spanning about 72 hours, three young adults received new hearts at Lucile Packard Children’s Hospital, including an extraordinarily uncommon double-organ heart and liver transplant.

Andrew J. Fisher, FRCP, PhD
Lung Transplant Trial Could Save Lives
30 May, 2012: The Newcastle upon Tyne Hospitals NHS Foundation Trust News
A pioneering technique which breathes new life into previously unusable donor lungs could save the lives of many patients on the lung transplant waiting list.

Margarita T. Camacho, MD and Mark Zucker, MD
Region’s First Successful “Beating” Donor Heart Transport Performed at Newark Beth Israel Medical Center
http://www.barnabashealth.org/services/cardiac/forefront/OCS-device.html
22 May, 2012: Barnabas Health News
The Heart Failure Treatment and Transplant Program at Newark Beth Israel Medical Center, NJ, performed the region’s first successful heart transplant with a donor heart that was transported in a warm and beating state.

John Wallwork, FRCS
Professor John Wallwork receives CBE
17 May, 2012: Papworth Hospital NHS News
Pioneering transplant surgeon, Professor John Wallwork, who was recognised in Her Majesty The Queen’s New Year Honours List attended the investiture ceremony at Buckingham Palace on Tuesday 15 May 2012, where he was presented with his CBE by HRH The Prince of Wales.

Robert E. Michler, MD
New Heath Rules: The Latest Medical and Health Wisdom
http://www.pageturnpro.com/MSP-Communications/37348-Health-Rules/index.html#/1
April 2012: Delta Sky Magazine
Robert Michler, MD, Surgeon-in-Chief and Chairman of Cardiovascular and Thoracic Surgery at the Montefiore Einstein Center for Heart & Vascular Care, discusses lifestyle changes to avoid heart disease and the effectiveness of coronary bypass surgery in preventing the recurrence of coronary artery disease.

Rene J. Alvarez Jr., MD
Temple welcomes Rene J. Alvarez Jr., MD, Vice Chief of Cardiology, Medical Director of the Heart Failure/Cardiac Transplantation Program
http://www.templehealth.org/content/newsroom.htm?page_id=11&minor=1&inCtx5pg=0&inCtx5news_id=182&inCtx5news=3&site_id=1&inCtx5order_by=[start_date]%20desc&major=4&inCtx5view=36
April 2012: Temple Health News
Rene J. Alvarez Jr., MD, has joined Temple University Hospital as Vice Chief of Cardiology and Medical Director of the Heart Failure/Cardiac Transplantation Program and Professor of Medicine and Assistant Dean for Minority Faculty at Temple University School of Medicine, effective April 1, 2012.

Daniel Goldstein, MD
Is 70 the New 60 for Heart Transplants?
http://www.montefiore.org/heart-center-news
27 March, 2012: Associated Press
Daniel Goldstein, MD, Vice Chairman, Cardiovascular and Thoracic Surgery at the Montefiore Einstein Center for Heart & Vascular Care, is interviewed and filmed performing a heart transplant on a 71-year old patient.
**ISHLT Links**

**LINKS AROUND THE WORLD**

**INTERESTING, INSPIRING, AND INTRIGUING LINKS ACROSS THE GLOBE**

**Mending Broken Hearts**


July 2012 National Geographic Magazine

Follow photographer Robert Clark into the battle to save lives—and hearts—from studies that encourage healthy habits to innovative surgical procedures. Featuring photographs taken at the Berlin Heart Center and the Jackson Heart Study.

**Brown and Goldstein**

http://www.utsouthwestern.edu/ life-at/video/index.html

June, 2012: Life@ Videos

Forty years ago, two young UT Southwestern physician/scientists began groundbreaking work that would ultimately lead to lifesaving drugs for heart disease and earn the pair the Nobel Prize. Follow the story from Dallas to Stockholm ... and back to UTSW.

**Facebook’s organ donation drive success spills into Canada**


25 June, 2012: CBC News Canada

Facebook’s recent push to promote organ donation in the United States caused registrations to soar; a similar social media initiative could soon be launched in Canada.

**Risk of cytomegalovirus infection following lung transplant now more measurable**


25 June, 2012: medicalxpress.com

Researchers in the Department of Virology and the Clinical Department of Thoracic Surgery at the Medical University of Vienna have demonstrated that the risk of cytomegalovirus infection following lung transplant can now be determined more effectively by measuring the immune response.

**Exercise helps lung transplant patients**

http://www.upi.com/Health-News/2012/06/24/Exercise-helps-lung-transplant-patients/UPI-32791340518099/

24 June, 2012: UPI.com Health News

Lung transplant patients who participated in a structured exercise program had lower risk factors for cardiovascular problems, says Dr. Daniel Langer from University Hospitals, Leuven, Belgium.

**Cedars-Sinai Heart Institute’s Barbra Streisand Women’s Heart Center**


15 June, 2012: Cedars-Sinai News

The Barbra Streisand Women’s Heart Center in Cedars-Sinai’s Heart Institute will be named for the famed entertainer in recognition of her philanthropic commitment and it will be directed by C. Noel Bairey Merz, MD, a cardiologist and nationally respected expert on women’s cardiovascular disease. The gift will boost crucial research, education to combat growing, lethal incidence of women’s heart disease.

**New action for ancient heart drug**...
An ancient heart drug that’s inspired the work of herbalists and poets for centuries may treat a condition that plagues millions of overstressed and overweight Americans today.

Pride of Australia Medal 2012
03 June, 2012: couriermail.com.au
Inspiring, determined, brave - these are just some of the words that have been used to describe 14-year-old Queenslander Coen Ashton. A worthy and popular recipient of the 2011 Pride of Australia Medal, the young cystic fibrosis sufferer continues to wait for a double-lung transplant and, when well enough, continues to talk about the importance of organ donation.

College freshman at age 9, medical degree at 21
03 June, 2012: the Chicago Tribune
Sho Yano has become the youngest student to get an M.D. from the University of Chicago. Yano was reading at age 2, writing by 3 and composing music by his 5th birthday. He graduated from Loyola University in three years—summa cum laude, no less.

Ellen DeGeneres earns 2012 Mark Twain Prize for American Humor
http://latimesblogs.latimes.com/showtracker/2012/05/ellen-degeneres-mark-twain-prize-for-american-humor.html
15 May, 2012: Los Angeles Times
This fall, Ellen DeGeneres will join Richard Pryor, Steve Martin, Whoopi Goldberg, Tina Fey, George Carlin and Will Ferrell in a very exclusive comedy club: recipients of the Mark Twain Prize for American Humor. DeGeneres will receive her award during a ceremony at the Kennedy Center in Washington, D.C., on Oct. 22.

Is 70 the New 60 for Heart Transplants?
http://www.montefiore.org/heart-center-news
27 March, 2012: Associated Press
Daniel Goldstein, MD, Vice Chairman, Cardiovascular and Thoracic Surgery, is interviewed and filmed performing a heart transplant on a 71-year old patient.
A Taste of Montréal!

Montréal Tourism:
http://www.tourisme-montreal.org

Gibby’s Restaurant in Old Montréal:
http://www.gibbys.com/montreal.php
(Recommended by our very own Prague Tour Guide and ISHLT member, Tereza Martinu, MD)

(this looks sinful)

The Montréal terrasse is the urban hang-out of choice for Montrealers from the advent of warm spring sunshine to the first frosty snowfall; of course the beverages change with the seasons, but the atmosphere stays the same.

WHERE’S MY COFFEE?

Tim Hortons has you covered in Montreal!

Canada’s Top 10 Comedians:

Topping the list:
Jim Carrey
Top female entertainer:
Celine Dion
Top male entertainer:
Justin Bieber

Photo Credit: © Tourisme Montréal, Stéphan Poulin, Place Jacques-Cartier/Terrace

Photo Credit: © Tourisme Montréal, Stéphan Poulin, Terrace on Saint-Denis Street