VINCENT’S OLYMPIC INNOCENCE

All the world’s a stage. Some have their exits and their entrances; some are larger and some are smaller. Although right now the 30th Olympics in London has the big stage, our time to Come Together in Montreal will be here before we know it. In order to get there we must know where we were and know where we are in order to keep us from scrambling or quivering hither and thither. There was a time in our lives when we all had the slows, but today it seems with our fast-paced lives and the age of the internet, we all have the runs. I’m not talking about Middy Estabrook’s article in this issue; well, maybe I am. To keep us on track we must focus and take aim at this month’s issue, targeting everything from innovative techniques with digital technology and virtual microscopy to simple rationalization and harmony that together will link pathologists globally in helping us move from innocence to experience especially with AMR in lung transplantation. And from this year’s American Transplant Congress, we have many shots from the heart; as far as the lung, from Herman Melville, “thar she blows” or, more appropriately, mastering the skill of obtaining a breath of fresh air.

Regardless, in our quest for optimal performance for our hearts and lungs there are the essentials: preparation, failure, learning, unlearning, agony, and the reality that preconceived notions will be changed. Lest we forget the importance of focus. We must take aim. But what is more important, the journey or the goal? Take archery for instance, it has taken the world by storm thanks to cinematic media displayed in The Hunger Games, Brave and The Avengers. With this weapon of King Arthur’s day when you get to the target, you are better able to see the results of everything you did—the journey. It makes me wonder, how many failures has an archer accumulated before most of their shots consistently hit their goal - the gold? Sometimes you may have to just let the arrow go.

By the way, did you know that the gold medal is 93% silver, 6% copper and 1% gold? And that’s roughing it.
It is appropriate that I sit down to write this report during the running of the XXXth Modern Olympic Games in London. It is also ironic that on the opening weekend of these Olympics, the Program Committee for the 33rd Annual Scientific Sessions of the ISHLT—the Educational Olympics for end stage heart and lung failure—met in Chicago.

What have I discovered during my first 100 days as President? The single most important thing I’ve learned is that other than the Executive Director, only the President gets a complete view of the entire Society’s activities and I AM AMAZED. I have previously served on the Board and was the Program Chair for the Vancouver meeting in 2001 and yet I had NO IDEA of the massive amount of work that the individual ISHLT members and ISHLT administrative staff provide on behalf of the Society.

The motto, ‘Citius, Altius, Fortius’ has been attributed to Baron Pierre de Coubertin, the founder of the modern Olympics, and was based on his belief that that athletes need to be given the ‘freedom of excess’ in order to be able to excel and break records. I would argue that this motto and philosophy equally applies to our Society and its members.

Citius

In keeping with the Olympic theme, in the first 100 days I have found the Society to be Faster than we have ever been. We are providing education to our members and non-members at a greater and more rapid rate than ever before. The time from submission to publication of an article in the Journal of Heart and Lung Transplantation (JHLT) is faster than ever. Due to changes in the annual Program Committee policies and procedures, the time from submission of abstract to decision (and subsequent presentation) is faster than ever. Utilizing the Links, the Journal, our website, Google groups, and the Annual Meeting, the dissemination of new information is faster than ever. As we incorporate other forms of social media over the ensuing years, this transfer of information will be even faster.

Altius

The status of our Society is Higher than ever. The impact factor for the JHLT this year reached an all-time high and under Dr. Mandeep Mehra's stewardship, I'm anticipating a continued climb. Our membership is at an all-time high and given the breadth of our Society's interests, I'm anticipating a continued climb. Our annual meetings continue to attract higher numbers of attendees and the number of abstract submitted for the Prague meeting was the highest ever, having double from 2001 and quadrupled from 1991. Under Dr. Glanville's and Dr. Christie's leadership of the Program Committees for 2013 and 2014, I'm anticipating a continued climb.

Fortius

Finally, I find the Society Stronger than ever. Our numbers are larger, our finances stable (even in the current global financial turmoil), and our foundation solid. The Society stands on a foundation anchored by the JHLT, the Annual Scientific Sessions, the incredible Administrative Team and you, the individual members both directly and through the various Councils and Committees. With this foundation, we will not fall. However, as we have learned throughout history, even the strongest man-made structures can be felled by forces of nature or man, thus we must continue to shore up our Society and prepare for the future. In that regard, we are embarking on another strategic planning
process over the next 9 months to identify areas of strengths and weaknesses and create processes to leverage the former and attenuate the latter.

In closing, I would like to thank you, the members, for the profound privilege of serving as your President this year and am looking forward to a productive year for the Society.

Let the Games Begin And Let’s Break Some Records

I2C2: CAN WE LINK HEART & LUNG PATHOLOGISTS GLOBALLY?
Margaret M Burke, FRCPath
I2C2 Pathology Council Representative

INTRODUCTION
You will have read in the May issue of ISHLT Links that during the 32nd meeting of ISHLT in Prague last April, the Board established a new Outreach Committee – the International and Inter-Societal Co-ordination Committee [known, thankfully, in its abbreviated form as I2C2]. I was honoured to be nominated by the incoming Chair of the Pathology Council, Patrick Bruneval (Paris, FR), as its representative on the I2C2 committee. While emerging international issues are of interest to us all, I consider that my main focus at this stage is on Inter-Societal and International Outreach as it applies to Pathology.

WHY SHOULD THE PATHOLOGY COUNCIL BE INTERESTED IN THIS INITIATIVE?
Cardiothoracic and transplant pathologists are a minority as members of ISHLT and of each country’s community of pathologists. We report allograft biopsies as an extension of our specialty interest, but these form a small part of a large pathology workload for general pathologists who often report allograft biopsies from other organ and tissue recipients. Thus issues of communication, multidisciplinary working, subspecialty training, and reproducibility of biopsy interpretation become important for our “niche” subspecialty. Nowadays progress in digital technology allows us to digitize pathology glass slides and manipulate the images from our desktops in a way that simulates the controls of our microscopes. So, using web-based digital platforms to set up folders of digitized slides, accessible from the desktop globally, overcomes limitations imposed by geography and enables us to promote good practice in cardiothoracic transplant pathology through ongoing education, training, audit and, increasingly, diagnosis and case consultation.

An example of the benefits of this approach is the ISHLT Board-sponsored initiative on cardiac antibody-mediated allograft rejection (AMR) which has evolved over the last three years. This initiative was informed from two sources:

1. In North America, the challenges of biopsy diagnosis of cardiac AMR were addressed in dedicated cardiac allograft sessions, organised by Rene Rodriguez (Cleveland, OH) at several Banff Conferences on Allograft Pathology. Work done at the 2001 session informed the ISHLT 2005 revision of the ISHLT 1990 Cardiac Allograft Biopsy Working Formulation, as part of which criteria for pathologic diagnosis of AMR were proposed. Subsequent transatlantic collaboration identified issues with biopsy detection of C4d, presented at Banff 2009 which was attended by ISHLT Board representative Lori West.

2. In Europe, members of the Association for European Cardiovascular Pathology (AECVP) formed a Transplant Working Group in January 2009 which networked
widely throughout Europe in order to undertake two studies, both of which were presented at ISHLT’s Chicago meeting in 2010. They highlighted concerns around poor reproducibility of biopsy diagnosis of cardiac AMR using the ISHLT 2005 Working Formulation and lack of standardization of C4d paraffin section immunostaining and interpretation.\textsuperscript{6,7}

The data from all this work was fed into discussions at two very successful ISHLT-sponsored workshops held by the Pathology Council prior to the 2010 and 2011 annual meetings of our Society co-chaired by Gerry Berry (Stanford, CA) working with Annalisa Angelini (Padua, IT) and myself (London, UK).\textsuperscript{8} In this issue of Links you will read an update by Patrick Bruneval following a third workshop held prior to this year’s ISHLT meeting in Prague. It is clear to us that the use of web-based digital technology to assess pathology slides was key to the outcome of all this work. So successful were we that the Pathology Council’s remit has now been extended to include pulmonary AMR – an altogether different challenge (!) which Gerry Berry addresses in this issue.

**NETWORKING GLOBALLY?**

Networking between professional societies can bring considerable benefit, as shown by recent collaborative work by the AECVP and the North America-based Society for Cardiovascular Pathology.\textsuperscript{9,10} Both societies hold annual scientific meetings and have strong commitments to education, training and research. Multidisciplinary networking is also encouraged by the American Society of Transplantation (AST) which in 2010 established a Transplant Diagnostics Community of Practice, an educational and training resource open to all AST members of transplant teams who wish to develop best practice in transplant diagnostics. Non-AST members may participate for a one-year trial but thereafter must join the AST if they wish to continue to participate. Links to these societies with details of some of their meetings are given at the end of this article.

We heart and lung transplant pathologists should network globally, even if only informally at this stage. Then we can more easily share access to information about available teaching courses, scientific meetings of relevance and web-based tutorials as well as promoting collaborative research on topics of mutual interest in our “niche” subspecialty. If you, somewhere in the world, wish to link with us please contact me to discuss it (M.Burke@rbht.nhs.uk), especially if you have ideas as to how we can interact and develop as a global heart and lung transplant pathologist community to help keep our skills and knowledge up-to-date. I may not know the answer to any of your queries - but hopefully I will know someone who does!

**LINKS**

- Joint AST and European Society for Transplantation meeting, Nice, France, October 12\textsuperscript{th} – 14\textsuperscript{th} 2012 [http://www.a-s-t.org/events/astesot-joint-meeting](http://www.a-s-t.org/events/astesot-joint-meeting)
- Association for European Cardiovascular Pathology [http://anpat.unipd.it/aecvp](http://anpat.unipd.it/aecvp) [companion society of the European Society of Pathology]. 5th biennial scientific meeting in Cadiz, Spain, October 3\textsuperscript{rd} – 5\textsuperscript{th} 2012. [http://www.5thmeetingaecvp2012cadiz.com](http://www.5thmeetingaecvp2012cadiz.com)
- Banff Conferences on Allograft Pathology [http://cybernephrology.ualberta.ca/banff](http://cybernephrology.ualberta.ca/banff). Next meeting in Comandatuba (Bahia), Brazil, in 2013, details not yet available.
- Society for Cardiovascular Pathology [http://www.scvp.net](http://www.scvp.net) [companion society of the United States and Canadian Academy of Pathology]. Next meeting in Baltimore MD, March 2\textsuperscript{nd} – 8\textsuperscript{th}, 2013, programme not yet available.

**Disclosure Statement:** The author has no relevant financial relationship to declare.

**Reference List:**

The Saga of Antibody-Mediated Rejection: The Pathology Challenge

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Where we were:
Antibody-mediated rejection (AMR) was initially recognized in severe conditions challenging the cardiac graft function and frequently presenting as a life-threatening episode of rejection. Full-blown pathology was described from endomyocardial biopsies and autopsies, including some myocyte necrosis, interstitial edema, plump endothelial cells and microthrombi in capillaries. Rapidly, the deposits of the complement fraction C4d on the capillary walls supplanted any other immunofluorescence tests. Therefore, diffuse and strong deposits of C4d, initially by immunofluorescence on frozen tissues, then by immunohistochemistry on paraffin sections, became the gold standard for the diagnosis of AMR on endomyocardial biopsies (Figure 1).

Meanwhile the presence of intravascular mononuclear cells, so-called “activated macrophages,” “CD68-positive cells” retained the attention and also became a marker of cardiac AMR detectable by plain histology and/or by immunohistochemistry.

ISHLTL and input from its Pathology Council allowed: i) to better characterize cardiac AMR opening this entity to conditions where no cardiac dysfunction was present at the time of biopsy diagnosis; ii) to grade AMR on endomyocardial biopsies as follows:

- **pAMR 0**: both histological and immunopathological studies are negative
- **pAMR 1 (H+)**: histopathological alone
- **pAMR 1 (I+)**: immunopathological alone
- **pAMR 2**: both histological and immunopathological findings are positive
- **pAMR 3**: severe AMR

Figure 1: Diffuse C4d labeling in a case of severe AMR leading to cardiac dysfunction
Where we are:
The 2012 meeting of ISHLT in Prague showed that our knowledge of the pathology of AMR is still progressing, benefited in part from the results of a transatlantic multicenter survey based on the analysis of 25 digitalized endomyocardial biopsies by a panel of 15 skilled pathologists. The results were presented and discussed in a pre-meeting workshop held on April 17th (manuscript under preparation), clearly showing that the 2011 working formulation is still valid and displays pathology-based criteria for the diagnosis of AMR on endomyocardial biopsies. The grading system is correlated to the certainty of AMR. pAMR3 corresponding to severe cases is seldom observed nowadays. The 2012 AMR workshop in Prague pointed at some questions:

- How to consider “focal strong” C4d labeling (Figure 2)? So far the dogma is and remains that positivity requires diffuse labeling i.e. above 50% of capillaries; lower grades labeling, <10% and focal between 10 and 50% are still considered as below the threshold of positivity. However the panel of pathologists recommended to notify when focal labeling is strong and to correlate it with DSA or other biopsy findings such as intravascular macrophages. How to explain that strong focal pattern? Since the panel ruled out technical problems considering that now immunohistochemistry and immunofluorescence are standardized, several speculative explanations were proposed: i) DSA at low levels or DSA species poorly activators of complement; ii) capillary loss due to previous AMR damage to microcirculation.

- What is the threshold for positivity of intravascular macrophages? The panel of pathologists rejected a grading system similar to C4d labeling interpretation and proposed a threshold above 10% for positivity of intravascular macrophages.

- Is still C4d positivity mandatory for the diagnosis of AMR? Most of the pathologists attending the workshop agreed that they have cases of C4d-negative AMR. However it is too early to change the working formulation for diagnosis and grading AMR. Further studies are needed.

Where we’re going:
Finally after the pathologists did their own introspection from 2010—present to characterize the histological and immunohistochemical markers of cardiac AMR, clearly the time is now to correlate our data with those of other specialists dealing with AMR, mainly immunologists. Sophisticated analysis of implicated antibodies [titors of donor specific antibodies (DSA), complement-fixing DSA, non HLA antibodies...] and sequential detection of DSA are mandatory to support new concepts in the pathology of AMR. A multidisciplinary approach is necessary to tackle the following problems:

- C4d-negative biopsies in AMR are challenging the C4d detection as the marker of AMR;
- Subclinical cardiac AMR: We are not often far from the situations of an acute episode of AMR immediately threatening the graft function. Now AMR presents usually as an ongoing phenomenon with fluctuating levels of DSA and variable damages on biopsy.
- Several studies pointed out that subclinical AMR is harmful for the coronary arteries and is an important factor for cardiac allograft vasculopathy (CAV) assessed by coronary angiography or IVUS. A challenge for the pathologist would be to predict the risk of CAV from biopsy analysis considering that a common denominator between coronary arteries and the myocardium sampled by biopsies is the endothelium lining. In this respect looking for markers of endothelial cell activation/damage
on endomyocardial biopsies beyond C4d deposition should draw our attention using transcriptome analysis, immunohistochemical detection (Figure 3).

Characterization of intravascular cells: the dogma that intravascular cells are macrophages is questionable given the frequent inadequacy between the numbers of intravascular cells seen by H&E and those detected by CD68-immunohistochemistry. Phenotype characterization of intravascular cells should provide new insights in the diagnosis and the natural history of AMR.

Many studies remain to be done, some of them should benefit from a multicenter approach and for that the Pathology Council of ISHLT should ease the task.

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**PULMONARY AMR WORKSHOP: WHAT WE LEARNED IN PRAGUE**

**Gerald J Berry, MD**

Immediate Past Chair, ISHLT Pathology Council

There continues to be growing multidisciplinary interest in the problem of antibody-mediated rejection in pulmonary transplant recipients. There are challenges in clinical detection, histopathological manifestations, immunophenotypic profiles, serological characterizations and patient management.

From the pathologist’s perspective, definitions and diagnostic criteria are difficult to extract from the published literature. Most pathologists in busy transplant centers have encountered a few or perhaps a handful of cases that demonstrate either histopathological patterns that resemble previously published cases, nonspecific morphologies but with clinical and/or serological data that support the diagnosis of AMR, or patients with graft dysfunction that responded to AMR-directed therapies such as plasmaphoresis.

With this background of experiences, the Pathology Council initiated a survey of current practices in the diagnosis and reporting of pulmonary AMR. A web-based survey was sent to over 40 centers in North America, Europe and Australia achieving a high rate of response. At a workshop held on April 17, 2012 as part of the 32nd Annual Meeting and Scientific Sessions in Prague, a group of transplant pathologists convened to discuss the results of the survey to develop a consensus approach to histopathological and immunophenotypic criteria for the diagnosis of AMR and the standardization of terminology for the reporting of AMR.

Technical issues that were discussed included the establishment of primary antibody panels for paraffin section immunohistochemistry. Among the interpretative issues that were delineated were the structural components for antibody assessment, thresholds of interpretation of both intensity and distribution of antibody staining and terminology for reporting positive and negative cases. The group affirmed that histopathological patterns previously described in AMR can be observed in a variety of disorders including severe acute cellular rejection, infection, graft preservation injury and drug reactions. A list of histopathological indications for further immunopathological work-up and evaluation was developed.
Most importantly it was also emphasized that the diagnosis of AMR requires a multidisciplinary approach and input including clinical, serological and pathological findings. Pathologists are encouraged to work closely with their clinicians and immunologists to develop protocols to coordinate donor-specific antibody analysis (DSA) with biopsy immunophenotyping. A multidisciplinary protocol approach to the study of AMR will promote future investigations that address issues of time of onset of AMR after transplant, incidence and prevalence, the spectrum of temporal, morphological and immunopathological changes and the clinical outcome and risk for developing chronic allograft dysfunction.

Finally, the Pathology Council seeks to promote educational and collaborative efforts utilizing digital pathology and virtual microscopy as a means to share both classic and diagnostically challenging cases, evaluate and refine diagnostic criteria related to morphological patterns and immunophenotypic staining profiles of established antibodies and the development of potential new markers for the diagnosis of pulmonary AMR.

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SOCIEDAD ESPAÑOLA DE TRASPLANTE KICKS INTO HIGH GEAR

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The 2nd Congress of the Spanish Society of Transplantation (SET-Sociedad Española de Transplante) took place on June 23-26 in Madrid. SET is a young society that provides a scientific and clinical home for Spanish solid organ transplant clinicians and researchers. While this was only the second annual meeting of the Society, the attendance was excellent and the contributions exceptional. A number of sessions addressed important topics in basic, translational and clinical science in the areas of organ donation and organ transplantation. In addition to invited didactic lectures, original science was presented in oral and poster presentations, and roundtable discussions were held to address current topics.

Thoracic transplant was well represented. The heart planning committee included Luis Almenar, Marisa G. Crespo-Leiro, Juan F. Delgado and Nicolás Manito; the lung program committee members were José Mª Borro, Víctor Monforte, Ángel Salvatierra, Piedad Ussetti and Felipe Zurbano.

The following is a sample of the varied topics presented:

- Controversies in immunosuppression after heart transplant were discussed by Finn Gustaffson (Denmark), Marisa Crespo-Leiro (La Coruña) and Jose M Arizon (Cordoba).
- Current knowledge and future directions in stem cell therapies and in rebuilding of autologous organs were presented by Agustin Zapata (Madrid) and Doris Taylor (Texas, USA).
- Fresh advances in heart and lung transplantation were reviewed by James Kirklin (Alabama, USA) and Elbert Trulock.
Global transplantation perspectives were discussed by Jeremy Chapman (Australia), Rafael Matesanz (Madrid) and Francis Delmonico (Massachusetts, USA).

Practical approaches to immunology after heart transplant were reviewed by Jaume Matorell (Barcelona), Josef Stehlik (Utah, USA) and Johan Vanhaecke (Belgium).

An animated roundtable discussion on the present and the future of destination VAD therapy in Spain was led by Luis Pulpon (Madrid), Enrique Perez de la Sota (Madrid), Luis Almenar (Valencia), James Kirklin (Alabama, USA) and other physicians from Spanish hospitals with mechanical assist programs.

It was very timely that right after the conclusion of the SET Congress, a record number of organs—36—were transplanted in Spain in a single day. And, of course, Spain became the UEFA European Soccer League Champion!

Please visit www.setrasplante.org to find out more about the Spanish Society of Transplantation and the 2nd SET Congress. We hope you consider attending the 3rd SET Congress in Spain in 2014.

Disclosure statement: The authors have no conflicts of interest to disclose.

Quotable Quotes

It is curious that physical courage should be so common in the world and moral courage so rare.  -Mark Twain

The important thing in life is not to triumph but to compete. - Pierre de Coubertin

“The Olympics are a wonderful metaphor for world cooperation, the kind of international competition that's wholesome and healthy—an interplay between countries that represents the best in all of us.” - John Williams

I want the privilege of guiding the arrows of my children and giving them the exhortations that can shoot them into the high place. - Laurel Lee

Our present time is indeed a criticizing and critical time, hovering between the wish, and the inability to believe. Our complaints are like arrows shot up into the air at no target: and with no purpose they only fall back upon our own heads and destroy ourselves. - William Temple

Courage is not the absence of fear, but rather the judgment that something else is more important than fear. - Ambrose Redmoon

“The Olympics remain the most compelling search for excellence that exists in sport, and maybe in life itself.” - Dawn Fraser (Australian swimmer, 3-time winner at the Olympics)

“If you don’t try to win you might as well hold the Olympics in somebody's back yard.” - Jesse Owens (American Athlete, 4 time Gold Medalist in Track and Field at the 1936 Olympic Games, 1913-1980)
THE PROBLEM
A 9 year old boy flies through his heart transplant for myocarditis only to be readmitted one week after discharge with fever and diarrhea. The diagnosis is C. difficile infection (CDI). He responds quickly to metronidazole with no further episodes. Another transplant recipient won’t be so lucky and will end up in the ICU with a third recurrence.

C difficile is now the most common cause of healthcare associated, infectious diarrhea. It is also community acquired in 11-28% and rising. Since 2000, the world has also seen the emergence of hyper virulent strains such as BI/NAP1/027 that are associated with increased incidence, severity, and mortality. Virulence factors are likely the production of a binary toxin, increased production of toxins A and B, hyper sporulation, and resistance to fluoroquinolones. CDI is more common in SOT recipients with an incidence up to 31% in lung transplants. To make matters worse, standard antibiotics are ineffective in 8-36%, CDI recurs up to 25% after the first episode, and no antibiotic kills the spores.

THE ANSWERS?
Antibody seems to be important. Adult heart transplant recipients in Spain underwent serial screening of serum IgG post transplant and were given IVIG when the IgG fell below 400 mg/dl or they developed severe infections. Overall, there was a significant decrease in CDI from 20% to 6% and IgG <400 was the only independent risk for CDI by multivariate analysis. In another study, adult patients with CDI on standard treatment of metronidazole or oral vancomycin were given fully human monoclonal antibodies against toxin A and toxin B in a multi center, double blind, RCT that looked at the prevention of recurrence, effect on duration and severity of initial episode of infection and duration of hospitalization. The recurrence rate was significantly reduced in the treatment group from 25% to 7% and the time to recurrence was also significantly longer. There were no differences however, in the duration and severity of the initial episode. There is a vaccine on the horizon. An adjuvanted C. difficile toxoid vaccine was shown to be safe and immunogenic in healthy adult and elderly populations in a Phase I trial. A Phase II trial is underway to look at the primary prevention of the first episode of CDI in high risk adults 40-75 years of age (Clinicaltrials.gov NCT00772343 and NCT 01230957).

Are there any new promising drugs for treatment? Fidaxomicin is a macrocyclic antibiotic that is bactericidal for C. difficile. It has minimal systemic absorption which leads to high fecal concentration and has limited activity against normal gut flora. A Phase 3 prospective, multi center, double-blind, randomized, non inferiority study compared treatment of 596 adults with CDI with either 10 days of fidaxomicin or vancomycin. Endpoints were clinical cure at end of treatment, recurrence within 4 weeks after treatment, and global cure which was resolution without recurrence. There was no difference in clinical cure (fidaxomicin 88% vs. vancomycin 86%) but fidaxomicin had a significantly higher rate of resolution of diarrhea without recurrence (75% vs 64%). Overall, there were fewer recurrences in the fidaxomicin group but this was restricted to those infected with any strain other than BI/NAP1/027. As with any new antibiotic, cost benefit analysis will be important to determine the role of fidaxomicin in the treatment of CDI particularly in the SOT population.

Just a brief note on diagnosis of CDI. Many laboratories use an enzyme immunoassay to detect toxin in stool probably because this method is relatively easy, cheap and fast. EIA can have a poor positive predictive value for true disease however, and is now considered a less optimal tool by some groups. An alternative method for diagnosis that is gaining recognition is an assay that detects glutamate dehydrogenase in stool followed by a second step to detect toxin if the GDH is positive. The sensitivity ranges from 85-95% and specificity from 89-
DYLAN MILLER JOINS PATHOLOGY COUNCIL AS NEW VICE CHAIR

We are pleased to announce that Dylan V Miller, MD, has been selected to serve on the Pathology Council as Vice Chair.

Dr. Miller is Director of the Electron Microscopy and Immunostains Laboratory at Intermountain Central Laboratory in Salt Lake City, Utah. He is also Associate Professor of Pathology at the University of Utah.

He completed medical school in 2000 at the University of Utah and pathology training at the Mayo Clinic in 2005.

His specialty expertise includes cardiovascular and renal pathology, with an interest in cardiac transplantation pathology, vasculitis syndromes, aortopathies, and immune-mediated diseases.

He is also a council member for the Society of Cardiovascular Pathology and Chair of the Autopsy Resource Committee for the College of American Pathologists.

References:


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

CONCLUSIONS

☐ IVIG replacement when serum IgG <400 mg/dl might decrease CDI in SOT
☐ Treatment with human monoclonal antibodies to reduce recurrence appears promising
☐ A vaccine for primary prevention is being studied in humans
☐ Fidaxomicin had a significantly higher rate of resolution of diarrhea without recurrence than vancomycin
☐ EIA for toxin is considered sub optimal for diagnosis by some groups
☐ Consider for diagnosis
    ☐ 2 step assay with initial GDH screen followed by confirmation if positive or
    ☐ Toxin gene amplification methods

99% with a high negative predictive value. Labs that use this type of assay report that up to 80% of stool samples sent for C. difficile testing are negative on the simple GDH screen and need no further work up. Finally, on the horizon are toxin gene detection tests that have outstanding sensitivity and specificity but are still expensive.
Although it was sad to face the fact that not all transplant meetings are held in cities where beer is cheaper than soda or where I can use my Google Translate app to learn how to say "Chci nějaký salám", historic Boston was a perfect venue for the American Transplant Congress (ATC) this past June. As the current chair of the Thoracic and Critical Care Community Practice in the American Society of Transplantation (AST) and member of the ISHLT, I have been asked to share some of ATC highlights for ISHLT members interested in lung transplantation.

In one of the sunrise symposiums, an overview on emerging infectious disease issues in lung transplant patients was presented. One of the studies described included a phase 2 trial designed to evaluate the safety, tolerability, and ability of CMX001 to prevent or control Cytomegalovirus (CMV) disease in CMV seropositive allogeneic stem cell transplant recipients.

CMX001 is a viral DNA polymerase inhibitor that is 400-fold more potent against CMV than Cidofovir. It is orally bioavailable and unlike Cidofovir there is no evidence of nephrotoxicity. Subjects who received 100 mg of CMX001 twice a week met the primary endpoint: a statistically significant reduction in CMV viremia (CMV > 200 copies/mL) or disease at the end of treatment (p<0.001).1

Dr. Mark Nicolls, Chief of Pulmonary and Critical Care Medicine at Stanford University presented his results that were published in the Journal of Clinical Investigation regarding the attenuation of obliterative bronchiolitis in mice using an adenovirus-mediated HIF-1α gene transfer. Nicholls’ team evaluated HIF-1α, a proangiogenic growth factor, in the repair of the damaged microvasculature of orthotopic tracheal transplants in mice. His team found that HIF-1α is required for microvascular repair in transplant rejection and that accentuating HIF-1α promotes airway microvasculature health during rejection and limits acute rejection. He also showed that CD4 T-cells and antibody-dependent complement activation independently mediate ischemia and that CD8 T-cells are required for post-rejection neovascularization. These conclusions suggest that targeted complement inhibitors may help prevent ischemia and limit the development of chronic rejection.2

The group from the University of Pittsburgh brought us one step closer to personalized medicine in transplantation with their presentation regarding the association of different recipient genetic polymorphisms and CMV reactivation and disease. In particular, this study evaluated genetic polymorphisms of proinflammatory cytokines (TNF-α, IFN-γ, IL-6, IL12b), regulatory cytokines (IL-10, CTLA4), growth factors (TGF-β), chemokine/chemokine receptors (CCR5, CCL2). They found that different genetic polymorphisms were associated with an increased risk of CMV reactivation and disease in both CMV recipient positive (R+) and CMV negative recipients who received a lung from a CMV positive donor (R-/D+). They found that R+ patients with TNF-α High, CTLA4-23 AA, and CCR-180 CT/TT had a significantly higher rate of viremic episodes. In R-/D+ patients, a significantly higher rate of virema was associated with people who had IL-6 High while patients with CCL2 TT and IL12b AA had a significantly lower rate of viremia (p<0.01). The authors from this presentation suggest that utilization of these
genetic markers may facilitate an individual prophylaxis management of developing CMV in lung transplant patients.\(^3\)

In a “Hot off the Presses: Late Breaking Science” abstract presentation, the group from Madison Wisconsin showed that skewing of regulatory T-cells towards CD39- subtype promoted Collagen type V (Col V) specific Th17 response in lung transplant patients. Cd39 is an ectonucleotide that hydrolyzes ATP and suppresses pathogenic Th17 immune response by regulatory T cells (Tregs) in lupus and multiple sclerosis. Their results showed that the Col V responsive patients had reduced CD39+ Treg in circulation compared to healthy donors. In addition, they showed that inhibition of CD39 during antigenic stimulation increased the Col V-specific Th17 response and induced a Col V-specific Th17 response in Col V unresponsive patients. They also demonstrated an inhibition of Col V response by blockage of ATP signaling using a trans vivo DTH analysis, while addition of adenosine receptor A2a agonist also suppressed the Col V specific Th17 responses.\(^4\)

In addition to the abundance of immunobiology talks at ATC, ATC is rich with information regarding donor management and allocation. At the ATC, results from the Scientific Registry of Transplant Recipient analysis on the effects of the most recent proposed revisions to the US Lung Allocation Score on Access to Lung Transplantation were released. The LAS is being revised to better reflect the risk of waitlist urgency and post-transplant survival in the post-LAS era. A full description of the proposed revision can be found at [http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_305.pdf](http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_305.pdf).

In this study, the SRTR showed that the revised model changed the LAS < 5 points for 85% of the candidates. The projected LAS in 72.5% of the candidates in group B (pulmonary hypertension group) increased more than 5 points (maximum increase of 26 points). They also showed that on average, candidates in group B decreased ranking on the list (increased priority) by almost 360 counts, while that of all other diagnosis groups increased rank (decreased priority) by less than 15 counts. Despite these changes, there was little change in ranking for the highest priority patients.\(^5\)

SRTR data was used to assess the risk of pre-transplant use of Plavix in kidney transplant recipients. In this study, 3.7% of 46,586 kidney transplant patients had a pharmacy claim that Plavix was used within 90 days of transplantation. Results of this study showed that pre-transplant use of Plavix significantly increased adjusted risk for post-transplant death and graft failure. The use of Plavix within 90 days prior to transplantation was associated with a 47% increased risk of post-transplant death compared to those that did not use Plavix.\(^6\)

Cases of transmission of human immune deficiency syndrome (HIV) and hepatitis C virus (HCV) by organ transplantation have been reported. Serology has been estimated to miss up to 1/11,000 HIV and 1/1000 HCV infections in organ donors. With this concern, an increasing number of OPOs have added nucleic acid testing (NAT) to their screening of deceased organ donors as NAT has a shorter window period and may detect infections earlier than serology. A study of 3 OPO affiliated labs evaluated the discordant serology and nucleic acid testing results for HIV, HBV and HCV in 2010. They found that NAT detected 0.3%, 0.2% and 0.1% additional HIV, HBV and HCV infections in serology referrals. However, many of the HIV NAT+ results were found to be non-reproducible on repeat testing.\(^7\)

Finally, in order to improve donor yield or the number of organs transplanted per donor the Organ Procurement Transplant Network (OPTN) Board of Directors has recently approved monitoring the performance of organ procurement organizations (OPOs) in the US. In order, to predict how many centers will potentially be reviewed, the SRTR performed a retrospective study on patients who were transplanted between July 1, 2007 and June 30, 2011. They calculated observed versus expected organ yield per donor in 2-year cohorts. The authors found that as high as 14% of the 58 OPOs evaluated warranted further review into their performance of donor yield. This suggests that a significant number of programs may be subjected to performance reviews as OPTN initiates monitoring.\(^8\)
Disclosure statement: The author has no conflicts of interest to disclose.

References:


ATC 2012: CARDIAC TRANSPLANTATION HIGHLIGHTS

Jeffrey J Teuteberg, MD

ISHLT MCS Council Chair

After spending a couple of years training in Boston, it is always a pleasure to go back, particularly in the summer. I recently had the opportunity to do just that for the American Transplant Congress from June 2nd through June 6th. Although I had a chance to enjoy the city, there was also a lot to learn at the symposia and abstract sessions. Like most thoracic transplant physicians, I like to take the opportunity to borrow from my below-the-diaphragm colleagues and think about which management strategies or novel immunosuppressives might be integrated into my practice. However, there also is a growing cardiac transplant presence at the meeting which I was asked to summarize for the ISHLT Links. What follows are some highlights from the cardiac sessions as well as a brief overview of what is new in immunosuppression from the remainder of the meeting.

Jon Kobashigawa presented the 24-month results of the A2310 study —an open-label, multicenter, randomized trial of 721 heart transplant recipients to one of three de novo immunosuppression regimens: everolimus 1.5mg plus reduced dose cyclosporine, everolimus 3.0mg plus reduced dose cyclosporine or standard dose cyclosporine with 3gm of mycophenolate. Higher mortality in the everolimus 3mg arm led to discontinuation of that regimen. At 24 months the composite endpoint (biopsy–proven rejection, rejection with hemodynamic compromise, death, graft loss, or retransplant) in the everolimus arm (39.4%) was non-inferior compared to the cyclosporine arm (41.3%). The rates of the individual components of the composite endpoint were similar between groups. The mean difference in renal function as assessed by MDRD was 6.5 mL.min in favor of the standard cyclosporine group, however the achieved cyclosporine levels in the everolimus arm were higher than the target levels, which may have contributed to the lack of a renal benefit in the everolimus group.

There was also a separate report on safety events of interest
in the A2310 study. There were few new adverse events in either the low dose everolimus arm or the standard dose cyclosporine arm after the first post-transplant year. There were few new cases of nonsternal wound dehiscence or pericardial effusions in either arm. Between months 12 and 24, no patient in either group developed new proteinuria, but the rate of new occurrence of hyperlipidemia was higher in the everolimus group than the cyclosporine group, 7.5% v. 4.5% respectively.

The long-term outcomes of the Tacrolimus In Combination, Tacrolimus Alone Compared (TICTAC) trial was presented in which 150 patients from two centers were randomized to tacrolimus monotherapy versus tacrolimus plus mycophenolate. Survival at 1, 3, and 5 years was 97%, 90%, and 81% in the tacrolimus monotherapy group and 99%, 96%, and 91% in the tacrolimus/MMF group, p=0.11. There was also no difference in freedom from vasculopathy in the monotherapy group: 100%, 96%, and 88% versus the tacrolimus/MMF group 100%, 97%, 94%, p=0.18. The four year cancer-free survival after alemtuzumab induction therapy was presented; there was no difference between those who received alemtuzumab 92.1% v. thymoglobulin 92.9% v. no induction 89.5%, p=0.50.

The Cedars group presented data on older donors in older recipients. They reviewed 380 patients who were age 60 or greater at transplant, 327 had donors less than 50 years old and were compared to 53 patients with donors aged 50 or greater. The 5 year actuarial survival was superior for those with younger versus older donors: 85% v. 57%, p<0.001 as was the 5 year freedom from major cardiac events 92% v. 83%, p=0.03. However 1 year freedom from treated rejection did not differ between groups 90% v. 90%, p=0.96. The Eurotransplant donor risk score was applied to patients over 13 years at the University of Vienna. Those with higher scores (≥17 points) had a higher rate of primary graft dysfunction compared to those with lower scores (< 17 points): 37.5% v. 21.9%, p=0.015. Those with higher scores also had worse 30 day (73.5% v. 88%, p=0.004) and 3 year survival (63.3% v. 78.2%, p=0.018). Lastly an analysis of the UNOS database demonstrated worse waitlist survival for Heart/Lung, Heart/Liver, and Heart/Kidney patients, although the survival benefit for Heart/Liver and Heart/Kidney patients was greater than that for Heart-alone patients listed as 1b, but over 80% of the combined organ transplants were listed as status 2. This study questioned whether current status criteria should be amended for those listed for a liver and kidney, in addition to a heart.

The development of DSA was the topic of two abstracts retrospectively analyzing de novo DSA in patients over a 13 year period at Harefield Hospital, exclusive of those who had pretransplant DSA or who did not survive one year. A total of 243 patients were included and 56 developed de novo DSA (using an MFI cutoff of 1000). About 8% of patients developed DSA in the first year post-transplant and about 20% by 3 years. The only multivariate factors predictive of de novo DSA development were having 6 or more HLA mismatches and male recipients who received a male donor. From the date the de novo DSA was detected, the rate of graft loss at 1, 3 and 5 years was 20%, 24%, and 36% respectively. However those with IgG3 isotype DSA had the highest rate of graft loss at those same time periods: 29%, 35%, and 55%. Overall for those who develop any de novo DSA, nearly 40% will have died or developed vasculopathy at 5 years. The Cedars group found no difference in 3 year survival among those with no antibody (n=158) versus those with a positive DSA with an MFI < 5000 (n=18) or DSA with an MFI > 5000 (n=9), 87% v. 78% v. 78%, p=0.43. However, there were significant differences between those with no antibody, low MFI DSA and high MFI DSA with respect to one year freedom from treated cellular
rejection (96% v. 100% v. 78%, p=0.01) and freedom from treated AMR (97% v. 94% v. 78%, p=0.005).

The AST presents a good opportunity to see what is new in noncardiac solid organ transplantation and what drugs are in the pipeline. While an exhaustive survey is beyond the scope of this Links update, I will present a broad overview of a number of presentations on novel immunosuppression. The renal experience with belatacept, which blocks T-cell co-stimulation, in two trials BENEFIT and BENEFIT-EXT was reviewed. All patients received basiliximab induction, mycophenolate, and steroids. Patients were randomized 1:1:1 to receive a more intense or less intense belatacept regimen or cyclosporine. Maintenance therapy with belatacept was given by monthly infusions. Overall results demonstrated that the belatacept groups had similar patient and graft survival and better renal function, despite having a higher early incidence of acute rejection. There were also metabolic advantages to the belatacept regimen with better blood pressure and lipid control. Interestingly there was also less de novo antibody formation, whether this was due to the inhibition of the production of antibody or patients receiving more consistent immunosuppression, given that they had to have supervised monthly infusions, is unclear. Other than a higher incidence of early rejection in the belatacept group there was more PTLD, particularly in the EBV(R-/D+) patients, however there was no differences in the rates of CMV or BK. Additionally, there are issues of logistics, cost, and regulatory burdens with belatacept due to the requirement for intermittent intravenous dosing.

The JAK3 inhibitor, tofacitinib, is being investigated in solid organ transplant as well as rheumatoid arthritis, psoriasis, and Crohn’s disease. In a phase IIb trial of a higher and lower intensity tofacitinib versus cyclosporine on a background of basiliximab induction, mycophenolate, and steroids found similar rates of BPAR, superior GFR, and less chronic allograft nephropathy in the tofacitinib groups. This study also demonstrated a greater incidence of infection, including CMV and BK as well as numerically more cases of PTLD with tofacitinib. However, those who had tofacitinib exposure below the median had similar rates of infection, CMV, and PTLD with comparable BPAR rates to the cyclosporine group.12 Sotrastaurin is a protein kinase C inhibitor which results in a calcineurin-independent blockade of T-cell activation. On a background of basiliximab induction, mycophenolate, and steroids patients were randomized 1:2 to tacrolimus or sotrastaurin. The study was terminated early because the sotrastaurin group had a higher incidence of the primary endpoint of BPAR, graft loss, death or lost to follow-up at 3 months (25.7% v. 4.5%, p=0.001), mostly due to a higher rates of BPAR. However, eGFR was better in the sotrastaurin compared to tacrolimus.13

Other novel agents in development include Diannexin, a recombinant form of human Annexin V, which was developed to prevent ischemia-reperfusion injury. In preliminary studies of marginal kidney transplants the early GFR was better in the Diannexin group. The hypoxia and oxidative stress of reperfusion induces p53 expression which results in apoptosis, the drug QPI-1002 is a synthetic RNA which temporarily inhibits p53 expression. There is not yet human data for QPI-1002. Another drug, ASKP1240, a human monoclonal antibody to CD40 is being assessed in nonhuman primate studies. Lastly, TOL101 is a murine monoclonal antibody to the αβ receptor of CD3+ T-cells which down regulates the T-cell receptor and is in phase I/II development. Disclosure statement: The author reports no relevant financial relationships to disclose.

References:

3. Baran et al. Long term outcomes of patients in the TICTAC trial: Incidence of allograft vasculopathy and
The big, unavoidable news story just now is the Olympics.

London 2012 has had some great performances, some wonderful moments, but also … media overload, the razzamatazz of the opening ceremony, and tax breaks for multinationals (and I live in the UK!). There’s no question why Coca-Cola is the drink of the Olympics and the burgers come from McDonalds. We can applaud the individual achievements of these champion athletes, but is the whole thing an inspiring metaphor for what we do in heart and lung transplantation, as some suggest? My answer is no!

The name Bradley Wiggins may not mean much in North America or Australia, but in Europe and particularly the UK, he is the hero of the summer. His achievement, and importantly, those of his team—to be the first Brit to win the Tour de France—is a real example for all of us.

The Tour is one of the greatest endurance challenges in sports: not a mere 100 metre dash or even a two-hour plus marathon, but three weeks of almost continuous racing covering hundreds of kilometres every day. There are flat-out speed trials, huge mountain passes, 50 mph crashes and mile after mile of effort in sun, wind and driving rain.

The Tour is won by supreme athletes, but only with the crucial support of a hugely accomplished team, keeping up the effort for weeks on end. To my mind, that’s the right metaphor for the work done by members of the ISHLT. The winner rides with a group of others: pace men to set the rhythm, sprinters to burn off the opposition – and sometimes win stages of their own. They are like surgeons, showing the way but each with specialist skills. Traditionally some just carry the water—domestiques—but all contribute. Behind the riders but equally important are those in support: physiotherapists, dieticians, mechanics, organisers, nurses, coaches, logistics experts.

It’s no surprise that, due to such a superb team, this year’s second place cyclist was from the same outfit.

So as we are looking after our patients, rising to the challenges, going that extra kilometre, being there day after day, we should look to Wiggins and the Sky team as an inspiring example of gruelling preparation, grit and determination. Now that is a metaphor worthy of attention!

NB Since writing this piece, Wiggins added to his summer’s success with a gold (his 7th Olympic medal) in the cycling time trial.

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

METAPHORS FROM SPORT?
John Dark, MB FRCS
Freeman Hospital, Newcastle upon Tyne, UK
The August issue of the JHLT follows on the heels of release of our 2011 Impact Factor Rankings which have increased dramatically. Our Impact Factor is now 4.33 and places the JHLT 1st among all solid organ specific transplant journals, 3rd among all Transplantation Journals, and 6th among all respiratory system journals. In the very competitive landscape of cardiovascular journals, the JHLT moved from 34 to a ranking of 22 out of 117 journals.

**FEATURED PAPERS IN JHLT AUGUST 2012**

In this issue of the journal, the JHLT once again focuses on cutting edge issues related to ABO incompatible heart transplants, outcomes in specific situations after transplantation such as those with a remote cancer history and chemotherapy related heart failure. We also feature an important international randomized control trial in lung transplantation that demonstrates a decrease in BOS in the setting of different calcineurin inhibitors. Pulmonary hypertension and response to therapy is highlighted in a sub-study from the TRIUMPH trial. Finally, we see the impact of modification of currently available risk scores to determine disease prognosis in advanced heart failure and guide decision making.

- **Pushing the boundaries: The current status of ABO-incompatible cardiac transplantation** (Irving et al.)

Newer research is now focusing on longer term outcomes of ABOi transplants - in particular the development of graft accommodation or tolerance. This review assesses the current status of ABO-incompatible cardiac transplantation both in infants and in sensitized and older patients. **Read more...**

- **Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation** (Treede et al.)

In a multicenter, prospective, randomized (1:1) open-label superiority investigation of de novo tacrolimus vs cyclosporine after lung transplantation (stratified at entry for cystic fibrosis) these investigators evaluated the incidence of BOS 3 years after transplant (intention-to-treat analysis). Compared with cyclosporine, de novo tacrolimus use was found to be associated with a significantly reduced risk for BOS Grade ≥1 at 3 years despite a similar rate of acute rejection. However, no survival advantage was detected. **Read more...**

- **Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation** (Oliveira et al.)

In an investigation from the International Society of Heart and Lung Transplantation Registry patients with chemotherapy-induced cardiomyopathy (CCMP) selected for heart transplantation were younger, had less comorbidity, and were more likely to require biventricular mechanical support pre-transplant than other non-ischemic cardiomyopathy. Despite the higher incidence of malignancy and infection in CCMP patients who have received a heart transplant, their survival was comparable to those with a pre-transplant diagnosis of other cardiomyopathies. **Read more...**

- **Baseline NT-proBNP correlates with change in 6-minute walk distance in patients with pulmonary arterial hypertension in the pivotal inhaled treprostinil study TRIUMPH-1** (Frantz et al.)
N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a biomarker of disease severity in pulmonary arterial hypertension (PAH). In this study baseline NT-proBNP levels and improvement in 6-minute walk distance (6MWD) in the pivotal randomized, placebo-controlled, double-blind study of the addition of inhaled treprostinil to oral therapy for PAH, was assessed. Greater improvement in 6MWD in actively treated patients with high levels of NT-proBNP noted helps to enhance understanding of the robustness of clinical response to inhaled treprostinil in more advanced disease. Read more…

• Prognostic impact of the addition of peak oxygen consumption to the Seattle Heart Failure Model in a transplant referral population (Levy et al.)

In this study the addition of peak oxygen consumption (VO₂) was found to add prognostic information across the spectrum of the SHFM, but changes in decision regarding transplant listing occurred mainly in moderate-risk patients. Read more…

Disclosure Statement: Dr. Mehra has consultant relationships with the following companies: St. Jude’s Inc, Johnson & Johnson, Medtronic, and Abbott Vascular.

Dear Colleagues:
I am writing you in my capacity as Chair of the ISHLT Nominating Committee to solicit nominations for the ISHLT Board of Directors. We are seeking nominations for seven (7) Director positions. Any current member may be nominated to serve as a Director. All terms are for 3 years.

Over the past couple of years, ISHLT has begun to engage in a number of new initiatives in recent years (practice guidelines, scientific monographs, Academy courses, expanded Annual Meeting, new governance structure, international advocacy, junior faculty outreach, historical archives, to name a few). Helping the Society pursue these new initiatives and lead our many volunteers to achieve these goals requires the effort of Board members who are dedicated to the Society, who have time to devote to the Society, and who possess the appropriate skill set to lead the Society in these new directions. It is therefore important that all ISHLT members give some consideration to the nomination process and participate in the election process during the Annual Business Meeting. The Board of Directors is eager to involve more of the members of the Society in the workings of the organization, thus your input regarding the future leadership of the Society is both important and desired.

The nomination process is designed to gather information about the leadership and related skills of the various nominees. I do strongly encourage you to take a few minutes to consider whether any of your ISHLT colleagues should be nominated for the ISHLT Board of Directors. The Nomination Form must be completed and submitted with required attachments for all nominees. Nominations submitted without using this form and the required attachments will not be accepted. The deadline for submission of nominations is September 30, 2012. Individuals are welcome to nominate themselves.

The individuals whose terms on the Board expire in April 2013 are as follows:
Raymond L. Benza, MD, Cardiologist, USA
Marisa Crespo-Leiro, MD, Cardiologist, Spain
Duane Davis, MD, Thoracic Surgeon, USA
James George, PhD, Immunobiologist, USA
Patricia Uber, PharmD, Pharmacist, USA
Geert Verleden, MD, PhD, Pulmonologist, Belgium
Lori West, MD, DPhil, Pediatric Cardiologist, Canada

The individuals who will continue to serve on the Board are as follows:
Allan Glanville, MBBS, MD, FRACP, Pulmonologist, Australia
If the 2013 Annual Meeting Program Committee members have anything to say about it, the 33rd Annual Meeting and Scientific Sessions in Montréal (April 24-27, 2013) promises to be an exciting meeting with very interesting and well-integrated sessions that will have something for everyone.

Members from this year’s Program Committee met in Chicago, Illinois, over the weekend of July 28-29 to plan the invited content for Montréal. Leading the meeting was our 2013 Program Chair, Prof. Allan Glanville, from St. Vincent's Hospital in Sydney, Australia. Committee members spent a great deal of time in advance of the meeting pouring over the multitude of symposium proposals submitted by the membership at large, so that by the time they convened in Chicago, much of the work had already been done.

As a result we were able to plan 24 pre-meeting 2-hour Symposia, 13 1-hour Sunrise symposia, 3 plenary symposia including the opening and closing sessions and 4 special symposia within the meeting proper. Don’t think this is enough content? Do not despair as there are 44 90-minute sessions left for oral scientific presentations as well as 12 mini-oral sessions, and ample time and space for … wait for it … Moderated Poster Sessions. Yes, that’s right—the ISHLT will be moving with the times and reintroducing Moderators for posters, coupling senior and junior members in teams to lead discussion. The aim is to provide a better forum for discussion of work presented in the poster format.

Well by now you must be wondering exactly what is in the program? That is not a secret but is still undergoing some last minute fine-tuning. Suffice it to say that each Council is well represented in the meeting content and there has been a spirit of cooperation between committee co-chairs to deliver Symposia which reflect the diversity and cross linkages
between groups. As well, the rules of engagement have been followed with affirmative action to ensure speakers and chairs are evenly distributed geographically and from a gender and seniority perspective.

Space has been left for some industry-sponsored Lunch Symposia and importantly, time for Council meetings will be quarantined to provide the optimum opportunity for each member to attend at least one Council meeting. This then forms the basis for the Council Reports to the Board on the closing day so broad representation is desirable.

For the first time we will present a focused symposium on the *JHLT at the ISHLT* to discuss recent literature and how to optimize the chance to achieve publication in our prestigious *Journal*. We will also have 2 back-to-back sessions entitled, *AST at the ISHLT*, which will demonstrate some of the steps taken to achieve intersociety growth and development. We trust and hope you will all come and enjoy the program.

By the way, in case you were wondering if all work and no play makes for a dull meeting, fear not! There will be ample time and opportunity for exciting social and cultural events including a special Gala at which our own *Marginal Donors* will perform fronted by the inimitable Heather Ross! See you there!

For more information on the members of our 2013 Program Committee, visit [ISHLT Annual Meeting Program Committee](#).

For more information on the 2013 Annual Meeting, visit [ISHLT Annual Meeting](#).

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**RATTLLING LINKS**

**NEW LINKS IN THE LINKS!**

**FUTURE HEART TRANSPLANT NURSE**

Please join us in congratulating Emily and Matthew Stimpson on the birth of their daughter, *Ivy Elisabeth Stimpson*, who was born on Friday, July 27th at 8:38 AM weighing 6 lbs 10 oz and 19” long. This is their second child – son Jack is 19 months old.

Emily is a Heart Transplant Coordinator at Cedars Sinai Medical Center. She has been an ISHLT member since 2010 and is the current Communications Liaison for the [Scientific Council on Nursing, Health Sciences and Allied Health](#).

Emily reports that both mother and baby are doing great! She says that so far, Ivy is a very mellow baby, and she feels so blessed.

*Congratulations and Welcome, Ivy!*
By perusing through all of Mark Twain’s works, I am convinced of his genius (as if I am really qualified to make this bold statement) such that the more I read his material the smarter he gets (validates my ignorance). The word peruse gives us an example of the ambiguities and potential ridiculousness Twain uses as tools to teach and preach, well at least me. Let’s carefully examine the word **peruse**, its first definition is to examine or consider with attention and in detail, and its second definition is to look over or through in a casual or cursory manner. Can we get any more ambiguous here? How would a medical student or resident respond to us when we ask them to peruse the electronic medical record of a particular patient? Anyway, Mark Twain secured immediate success with his book *Innocents Abroad* or *The New Pilgrims’ Progress* published in 1869 by selling close to 100,000 copies in its first year. Today, allow me to bring to your attention a chronology of his important works in hopes that you will gain more motivation to peruse and be entertained and educated by some if not all of his works with a side effect of becoming a wordsmith.

Examining carefully or perusing his books show that he was a writer of nonfiction and fiction. His nonfiction works had their roots from his days as a newspaper correspondence to primarily as a travel writer. Among his travelogues; *Innocents Abroad* (1869), *Roughing It* (1872), *A Tramp Abroad* (1880), *Life on the Mississippi* (1883), and *Following the Equator – A journey around the world* (1897). *Innocents Abroad* was the best-selling of all his writings during his lifetime, and it became the standard by which all his books were measured. When comparing it to John Bunyan’s Pilgrims Progress, it seems Twain developed a deliberate plan with his published works. *Innocents Abroad* is a prospectively written travel diary of his trip to Europe and the Holy Land in 1867. Interestingly, while this book is about traveling east to culture Americans, *Roughing It* originally to be published as *Innocents at Home*, is about traveling west into the American frontier. *Roughing It* is more autobiographical and retrospective. With age, Twain further regresses in time in his book and expands his imagination. By the time he publishes *Life on the Mississippi* where his best writing can be found, he is approaching 50 years of age. He is a more seasoned writer. *The Gilded Age* (1873), *The Adventures of Tom Sawyer* (1876), and *The Prince and the Pauper* (1882) were all published before *Life on the Mississippi*. *Life on the Mississippi*, as with most of his books, is written as a first person narrative, but now he recounts his days learning the river day and night as a “cub pilot” for the steamboats on the Mississippi River ten years before he set sail for Europe on the Quaker City. It should be noted that the book *Tom Sawyer* was an adult narrating his childhood and his penultimate book, *Huck Finn*, was the innocent or ignorant boy narrating his childhood as it occurred. Taken to an extreme consider reading *A Connecticut Yankee in King Arthur’s Court*. Twain transports the Yankee back in time and space to the “old world” of King Arthur.

By traveling to the Old World in *Innocents Abroad*, Twain helps American readers develop a cultural identity through the depiction of the first packaged tour group to see Europe in the mid-late 19th century. The “Pilgrims” journey across the Atlantic was comprised mostly of wealthy, respectable, churchgoing, genteel and affluent New Englanders, joined by the unrefined Mark Twain who was considerably younger than the pilgrims, hailed from middle America and the Western frontier and whose trip was paid for by a San Francisco Newspaper. The idea of a tour group traveling east back to the old world had taken hold of America’s sensibilities of the well-to-do and upper crust believing that in order to complete a cultural education, a post-high school American must come face to face with the cultural movements of the old world.
Twain gives us the moral that “Travel is fatal to prejudice.” It is not prejudice against but is prejudice about the old world. He dramatizes misunderstandings and misadventures of preconceived notions, biases, or assumptions with a series of new circumstances, unfamiliar realities realized on the journey. In the first person narrative, Twain uses the hapless innocent or ignorant as himself where his discomfiture becomes the basis of the readers entertainment. As a result, American readers were able to look down and laugh at the old inflated idea of Europe. An idea that by going there you were going to find more spectacular, more beautiful and more wonderful forms of life than anything the new world could offer. It was Henry James who used the genre of tragedy instead of comedy and made Americans feel inferior in Europe. Twain makes exaggerated expectations live hardly up to their promises and encourages readers to feel superior. The renaissance paintings by the old masters may have been fine once they were new, but they are not new now and no amount of his imagination can make them beautiful. To gain the “correct understanding” he “must studiously and faithfully unlearn a great many things I have somehow absorbed.” Consider our biases and countless unanswered questions in the management of patients.

The proverbial advice from Horace Greeley, “go west young man and grow up with the country,” is the main theme of Roughing It. In this story, Twain hits the mother lode of humor as a writer after repeated failures in the western frontier. He sets out west to “strike it rich” and learns how little he really knows. He fails miserably as a miner and learns not only that all that glitters is not gold, but also nothing that glitters when prospecting for ore is gold. Through a series of misunderstandings and poor judgments this “tenderfoot” stays just as broke as he’s ever been until he becomes a journalist.

Mark Twain’s deepest source of power comes from the Mississippi River. Because of Life on the Mississippi his image with a steamboat is akin to Ernest Hemingway’s image with outdoor sports such as fishing and big game hunting. He brilliantly describes the sunset as the passenger. Then, he rewrites his own text and is able to describe the river as an experienced steamboat pilot. He wonders how doctors learn to read the faces of beautiful people and wonders if they can ever really admire beauty as they don’t see it once mastering their profession. Experienced physicians view a series of signs that indicate much the same thing as the river indicates when technically viewed from a steamboat pilot. In time it is the inevitability of decay and death that emerges. The dangers and uncertainties that we come to know the world is full of result from the passage of time. What it tells us is that with sophistication, inside knowledge, and time pleasures vary when read interpretatively, intellectually, and critically.

Now, here’s the hidden genius of Twain in Life on the Mississippi. It is not what he writes, it is what he doesn’t write about and I contend, deliberately. He wrote this book after the American Civil War about when he was becoming a riverboat pilot before the Civil War. The enormous financial success of steamboating North and South on the mighty Mississippi stem from the sweat of slavery, Europe’s craving for and the transportation of cotton. And he barely acknowledges the presence of black slaves except for the most important call out by the boat’s leadsman’s cry of “mark twain.” For the record, Mark Twain was an ardent abolitionist, supporter of emancipation and an advocate of women’s rights. Also, I refer you to this article: Freed slave who penned sarcastic letter to old master after he was asked back to farm pictured for first time. Through these travels east, west and journeying north and south on the Mississippi River from his earlier days as a more innocent or ignorant with a creative imagination in full gear, we can feel Twain moving to fiction and better understanding his quote, “Truth is stranger than fiction, but it is because fiction is obliged to stick to possibilities; Truth isn’t.” Mark Twain is truly the first American author whose writings covered transcontinental America and quite possibly the entire globe ahead of any other writer by the time of his death. Can we recount with such grace, Olympic skill, and humor of our travels to keeps us updated with the fast pace of progress in the ISHLT and our lives?
H Todd Massey, MD
University of Rochester Medical Center, Rochester, NY, USA

URMC Transplant Surgeons Give Horseheads Man New Heart
July 23, 2012, URMC News

Retired Elmira school bus driver Wayne Hart recently returned to his Horseheads home after receiving a life-saving heart transplant at the University of Rochester Medical Center. Transplant surgeon H. Todd Massey, MD, performed the five-hour surgery on June 19. Read more...

Donald E Jansen, MD
St. Joseph’s Hospital, Atlanta, Georgia, USA

Atlanta Heart Transplant Recipient ‘Very Exceptional’
July 20, 2012, knoxnews.com

Jeff Wierenga, 55, is one of the longest-living heart transplant patients in the U.S. “Jeff is a very rare individual,” said Dr. Donald Jansen, who has cared for Wierenga for 15 years as director of the heart transplant program at St. Joseph’s Hospital. Read more...

Francis Fynn-Thompson, MD
Boston Children’s Hospital, Boston, MA, USA

1 Family, 5 Heart Transplants
July 19, 2012, ABC News, Medical Unit

Longer survival on the waiting list and a better prognosis post-transplant are some reasons why many children can expect to be treated successfully, according to Dr. Francis Fynn-Thompson, surgical director of the heart transplant program at Boston Children’s Hospital (who is not affiliated in the family’s care). Read more...

Hartmuth Bittner, MD and Andres Palaez, MD
Florida Hospital Transplant Center, Orlando, Florida, USA

Florida Hospital Establishes Only Lung Transplant Program in Central Florida
July 16, 2012, Florida Hospital Media Relations

The addition of two world class physicians to the Florida Hospital team and the
listing of the first patient to the lung transplant waiting list signals the first lung transplant in Central Florida is rapidly approaching. Read more.

Charles E Canter, MD
Washington University School of Medicine, St. Louis, Missouri, USA

Pediatric Heart Transplant Patients May Benefit From Noninvasive Imaging Technique
July 16, 2012, Medical News Today

Cardiologists at Washington University School of Medicine in St. Louis have developed a noninvasive imaging technique that may help determine whether children who have had heart transplants are showing early signs of rejection. The technique could reduce the need for these patients to undergo invasive imaging tests every one to two years. The new method is described online in the Journal of Heart and Lung Transplantation. Read more.

Arman Kilic, MD
Johns Hopkins University, Baltimore, Maryland, USA

Important Heart Transplant News From Johns Hopkins University
July 15, 2012, My Heart Transplant

According to a March 2, 2012 report from Johns Hopkins University, persons receiving a heart transplant before age 55 and from a center that performs at least 9 heart transplants per year are more likely to survive 10 years after the transplant. Dr. Arman Kilic, a surgical resident at Johns Hopkins, led the study. Read more.

Richard Kirk, MA FRCP FRCPCH
 Freeman Hospital, Newcastle Upon Tyne, UNITED KINGDOM

Freeman Hospital to Continue Performing Child Heart Surgeries

July 04, 2012, BBC News

The Freeman Hospital in Newcastle was one of six hospitals in England under threat after an NHS review claimed expertise was being spread too thinly. Read more.

Frank D'Ovidio, MD, PhD
New York-Presbyterian/Columbia University, New York, NY, USA

Breathing New Life into Lung Transplants
July 04, 2012, NewsChannel5.com

We breathe 17,000 times a day, but for more than 1,600 people waiting for a lung transplant, each breath is a struggle. Now, there’s new hope for patients waiting to inhale easier. “The ex-vivo is an opportunity to test lungs we would be turning down otherwise,” Frank D'Ovidio, MD, PhD, an associate surgical director of the lung transplant program director of the ex vivo lung perfusion program at New York-Presbyterian/Columbia, said. Read more.

William E Stansfield, MD
University of North Carolina Hospital, Chapel Hill, North Carolina, USA

Dr. Stansfield Joins UNC Cardiothoracic Surgery
July 01, 2012, UNC School of Medicine

William E. Stansfield, MD, joined the UNC faculty on July 1st as assistant professor of surgery in the UNC Division of Cardiothoracic Surgery. Dr. Stansfield, who specializes in heart surgery for adults, practices as a cardiothoracic surgeon at UNC Hospitals. Read more.
Abbas Ardehali, MD and Mario C Deng, MD
UCLA, Los Angeles, California, USA

2,000 Transplants And Counting: UCLA's Heart Transplant Program Reaches Major Milestone
June 28, 2012, PR Newswire

The UCLA Heart Transplant Program performed its 2,000th heart transplant surgery earlier in Jun 2012, becoming the first program in the western United States and only the second in the world to achieve this remarkable milestone. [Read more.]

Prof Roland Hetzer, MD, PhD
German Heart Institute, Berlin, Germany
Fastest CT Scanner in the World – and the Lowest Radiation Levels
May 2012, DHZB News

The CT scanner “Somatom Definition Flash” scans extremely rapidly, with a rate of 43 cm per second, which means that even with a very large patient full-body images may be acquired in less than 5 seconds. The heart can also be imaged in its entirety in a quarter of a second by two X-ray tubes that rotate around the body. [Read more.]

Marie M Budev, DO, MPH
The Cleveland Clinic, Cleveland, Ohio

ANY NEWS ON LUNGS?
May 29, 2012: NPR.org

Ashley Dias, 26, has cystic fibrosis and needs a lung transplant to survive. Ashley’s doctor, Marie Budev, has 124 patients on the waiting list for a lung transplant. Dr. Budev desperately wants all of them to get transplants, but there aren’t enough lungs to go around. [Read more.]
As a surgeon practicing in a cardiothoracic center with a large experience in MCS implant and management, I would like to raise some concerns regarding the opinions posted in the July issue of the *Links Newsletter* advocating strict rules to regulate MCS use.

The major point we should take into consideration is that these devices truly represent a revolutionary technology that is going to re-shape the way we think about heart failure. As healthcare professionals, we cannot accept that third parties or governments may limit and/or prioritize the access to this therapeutic option, based on criteria other than rigorous clinical judgment. This would represent an unacceptable limitation to the individual’s rights to receive the best therapeutic treatment available.

While no western country government would restrict transplants because of economical reasons, we are facing a spontaneous restriction of transplant availability. Thus, VAD implantation rapidly is becoming our first and only option to save the lives of patients with heart failure. Nevertheless, we should strive to refine indications, improve techniques and managements, and produce robust evidences to have this therapy offered to all who can gain benefit. We cannot limit innovation fearing lack of resources. To have “VAD therapy become for heart failure what dialysis is for kidney failure,” as forecasted in last month’s letter, it cannot be restricted to transplant centers only. Is dialysis restricted only to kidney transplant centers?

All experienced cardiothoracic centers should have the possibility to implant VAD: increasing numbers will be accompanied by lowering costs. Of course, as for any surgical procedure, training, communication with more experienced centers, and auditing of the results will be a key factor that will help to improve results and accessibility of this procedure.

ISHLT cannot lose the chance to be active part in this revolution and I do believe that our Society has the scientific and organizational resources to be the educational hub through which experienced and naïve centers can collaborate to improve VAD therapy; the international registry that was announced a few months ago is an important step towards this direction.

Respectfully,
Dr. Gino Pultz

If you are interested in submitting a PRO or CON opinion of this debate topic, or proposing a new topic for debate, please submit your opinions to Susie Newton at susie.newton@ishlt.org.

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**CON**

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How is Bradley Wiggins different from the average man?
July 25, 2012: Keith Moore, BBC News

The two main physiological differences between an elite endurance athlete like Wiggins and the average person are a bigger heart - which allows more oxygen-rich blood to be pumped to the muscles - and the muscles’ capability to use that oxygen. Read more...

Get To Know Linda Onderdonk, Lung Transplant Recipient
July 23, 2012: al.com

MOBILE, Alabama: On Oct. 9, 2008, Linda Onderdonk, then 64 and suffering from chronic obstructive pulmonary disease, became the recipient of a healthy transplanted lung. At the death of another person—an 18-year-old boy—she was given a second chance at life. Read more...

1 Family, 5 Heart Transplants
July 19, 2012: ABC News, Medical Unit

HAINES, Oregon: One family with five children, all diagnosed with genetic heart abnormalities, may undergo the most heart transplants ever performed for a single family. Read more...

Double-lung transplant recipient Helene Campbell gets a big welcome home
July 17, 2012: Global News - Global Winnipeg

OTTAWA, Canada: She’s writing a book, wants to continue learning Spanish and plans to once again dance with Ellen DeGeneres. But for now, celebrity organ-donation ambassador Helene Campbell is just happy to be home, surrounded by family and friends. Read more...
A race for life: Double lung transplant woman sails Atlantic
July 11, 2012: CNN.com

LONDON, England: Eight years ago Justine Laymond was told by doctors to say a final goodbye to her family -- she had, they said, only hours left to live before her lungs would stop working and her body shut down. But this July Laymond defied her medical fate and made history by becoming the first double lung transplant survivor ever to have raced across an ocean. [Read more...]

The doctor will see you now, for $5
July 2, 2012: The DAILY NIGHTLY on msnbc.com

RUSHVILLE, Illinois: While we all struggle with the evils of time management, reimbursement, insurance companies, and documentation in our clinics, we can be warmed with a story about a simpler way of doing things. [Read more...]

Who Decides Whether This 26-Year-Old Woman Gets A Lung Transplant?
May 29, 2012: NPR.org

CLEVELAND, Ohio: When doctors come to see Ashley in her hospital room at the Cleveland Clinic, she has only one question. She pulls out a marker and writes in enormous capital letters, as if it’s the only thing she’s ever wanted a voice to say: “ANY NEWS ON LUNG?” So far, there is no news on lungs. Ashley’s still waiting. [Read more...]
A heart transplant gold medalist says she feels honoured to have been an Olympic torchbearer.

Jade Carr, aged 18, from Runcorn, carried the flame along Edge Lane in Liverpool on June 1st. She had a heart transplant when she was three and has won more than 40 medals at table tennis, badminton and athletics at British and World Transplant Games.

She said: “To carry the Olympic flame was a huge honour and being part of the Olympics in this way is a privilege and an opportunity to promote organ donation to the country as this is something very important to me and the reason I am here today.

“I hope to continue to promote organ donation through competing at the British European and World Transplant Games showing that it is possible to live a normal life to the full after transplantation.”

Check out this link for some ‘Tid Bits’ about London.

Without an organ donor, Richard Burbedge would not be alive today.

The 32-year-old from Tilehurst, who has cystic fibrosis, underwent a double lung transplant in June 2010. Doctors said he was told he would be dead within two years otherwise.

Mr Burbedge has gone on to become a top athlete for Team GB, winning two gold medals at the recent European Heart and Lung Transplant Games, and was also one of Reading’s Olympic torchbearers last Wednesday.

“Waiting for a donor was a very uncertain time but luckily after 18 months someone was found and I was able to have the transplant,” said Mr Burbedge, who as part of National Transplant Week last week was keen to emphasize the importance of organ donors not just in his life, but for those in Britain needing a transplant today.

“You can genuinely transform a life and there aren’t the words to express my gratitude to say thank you to my donor. It shows people need to embrace life, and what can be achieved.”

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