A Focus on Infectious Diseases

Vincent’s Fall Sense

If you think we can’t link Mark Twain to the microbial world, think again! You need only to read 3000 Years Among the Microbes, Twain’s originally unpublished autobiography of a microbe that was once a man who was transformed into a cholera germ. If you doubt his genius, Twain foreshadowed our modern understanding of the microbial ecosystem and its critical role on our body. He describes different microbial communities and the various roles they play in maintaining harmony and balance of man, society and the world. It was in this part of his career that Twain reduces man to a germ. “I think we are only the microscopic trichina concealed in the blood of some vast creature’s veins.” Now some believe these were some of Twain’s darkest writings representing a fall from his grace as a prominent citizen of the world. Or was he foreshadowing the fall of man with his brewing cynicism? Anyway, fast-forward a century later and we have Dana Willner’s article on Unlocking Microbial Diversity with Metagenomics.

The focus of this autumnal issue is on the microbial world in thoracic transplantation and how we can best combat this unseen enemy. Going back a few millennia we have Sun Tzu’s Art of War advising us to avoid massacres and atrocities because this can provoke resistance and possibly allow our unseen microbial enemy to gain an upper hand. Also, we must have detailed knowledge of this foe and appreciate its strengths and weaknesses recognizing that the real triumph comes before the enemy’s threat becomes real. Amparo Solé, provides sage advice against the development of resistance. Stan Martin, Fernanda Silveira, and Christian Benden et al, emphasize the importance of prevention. Peter Hopkins gives the scoop on nucleic warfare in the airways of our lung recipients. Shahid Husain prepares us for the emerging threats and Denis Hadjiliadis advises us to proceed with caution with lung transplantation in patients with bronchiectasis. Lastly, Mark Twain remains with us today: our world traveler and gifted lecturer who has entertained us for the last quarter century is no other than our 2013 Program Chair for Montréal, Allan Glanville.

Vincent Valentine, MD
Links Editor
The ID Council continues to be extremely active and productive. Special thanks for preparation of outstanding content for the 2013 Annual Meeting in Montreal on behalf of the ID Council goes to Erik Verschuuren (University Medical Centre Groningen, Netherlands) and Stan Martin (Ohio State University), program representatives, and to Fernanda Silveira (University of Pittsburgh), Amparo Solé (Univ Hospital la Fe Valencia), and Tina Stosor (Northwestern Memorial Hospital) who coordinated submissions on behalf of the ID Council. Also, thank you to Michele Estabrook (Washington University School of Medicine) and Macé Schuurmans (University Hospital Zurich) and all of the contributors to this month’s LINKS.

Watch for these opportunities to “spread” Infectious Diseases:

A survey of MCS infection prevention practices will soon hit your in-boxes. Led by member Shimon Kusne of Mayo Clinic, Arizona, this survey will address issues related to prevention of early infection after implantation of MSC devices. Please respond when you receive this email!

The first-ever Pre-meeting Symposium on Transplant ID at ICAAC will be co-sponsored by the ISHLT ID Council with Dr. Shahid Husain and myself as invited speakers. Come join us is you are in San Francisco (September 8, 2012) for this exciting program!

Drs. Amparo Solé and Fernanda Silveira have created an exciting proposal for a “What to do if” clinical scenario publication that could be distributed to clinicians working in cardiothoracic transplantation. Look for more opportunities as this is reviewed by the Education Committee.

Other ongoing projects “catching” in Infectious Diseases:

Dr. Shahid Husain is spearheading the fungal prophylaxis workgroup that will perform an in-depth analysis of literature to help establish consensus on this very important, yet heterogeneous, topic. Read announcement!

The ID Council is working with IMACS, the ISHLT sponsored device registry, to develop infection related variables. Dr. Margaret Hannan is leading this collaboration. Read article!

Disclosure statement: The author has no conflicts of interest to disclose.
In April 2011 the ISHLT agreed to fund a new International Mechanically Assisted Circulatory Support (IMACS) registry (committee leadership) with a major emphasis on quality data collection that will build on the experiences gained from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). INTERMACS was created in 2006 to develop, manage and guide scientific investigations from a registry dedicated to durable MCS devices. At the time, there was less focus on infection and more focus on surgical parameters. INTERMACS was funded by the National Heart, Lung and Blood Institute (NHBLI) and was contracted to a group of investigators within ISHLT. This database has grown to more than 4,000 devices implanted since 2006.

With the ISHLT commitment on nurturing a multidisciplinary approach to improve the care of patients with MCS devices, the ID council of ISHLT has recently been invited to collaborate with the IMACS committee to create infection variables for the new IMACS database. This is an exciting new collaboration for the ID Council to be involved at the beginning of this major project with the selection of key variables, which will provide insightful data on an international platform of VAD infection in the future.

From an infectious disease perspective, the major limitations to data collected in the INTERMACS registry was the absence of data on causative organisms. The INTERMACS registry also could not discriminate between recurrent infection and new infection or provide details regarding the surgical management of such infections. As a consequence, some of the published studies have not been able to directly link percutaneous driveline infection (FDI) with septic death and morbidity. This information will be collected by all centers enrolled in the new IMACS registry and will provide an opportunity for international ID authors to collaborate in IMACS data analysis for future studies. In addition, the incorporation of ISHLT standardized definitions of infection into IMACS will allow better characterization of these infection events and will provide detailed epidemiological analysis in the future.

In particular, the new IMACS database will involve all international VAD programs large and small and will capture not only types of infection but also specific organisms, antibiotic prophylaxis, recurrent infection, surgical management and antibiotic treatment of infection. The standardized infection data captured in IMACS will allow meaningful statistical analysis on prospectively collected VAD-specific infection, VAD-related infection and non VAD-related infection. This type of standardized, well collected infection data embedded within a detailed international surgical network is an exciting project for the future but will depend on the quality of data entry world-wide. These prospective studies will focus primarily on bloodstream infections and surgical site infection (SSI) in the setting of VAD implant surgery, and the analysis will inform future SSI preventive strategies for VAD implant surgery and patient management. Further collaborative clinical trials, translational research, and interventional studies will be fostered in the areas of VAD infection as the IMACS registry grows and develops and will contribute greatly to the understanding of the pathogenesis of these complex and life-threatening infections over time.

Preventing these infections is a major paradigm for surgeons, cardiologists, and infectious diseases experts as our VAD patients live longer and more independent lives with these highly sophisticated devices. A challenge for the ID council now will be to develop and maintain good quality data collection of these new ID variables through not just the ISHLT network but through other internationally established ID platforms and VAD co-ordinator networks across the world under the steerage of the IMACS committee.

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Come to Montréal and **discover magic**. It’s more than alliteration, it’s more than Gallic savoir faire, it’s more than indigenous culture. It is fusion, the sum of the parts overlaid by the charm of history blended with science and technology rather than subservient to it. So we chose Montréal for the 33rd ISHLT and are exceedingly pleased.

Whether the promise is realised depends on you! For it is, as it always has been, the people of this grand Society who make the meeting and make it work.

We all need to be enticed however and Montréal offers much of excitement, even outside the Program! Of course I jest, but the Program is looking good. Your chosen team has been working hard to follow the broad theme of integrating science and practice and thereby expose us all to the origins and outcomes of or particular niche. The main themes have been maintained; device technology and management, the cutting edge of advanced heart and lung disease care including pulmonary hypertension, heart transplantation, and lung transplantation with an emphasis on children, infectious diseases and pharmacology woven throughout. So there is something for everyone!

Moreover, the accommodating floor plan of the Palais de Congrès allows an economy of transit between rooms. Meetings will all be on the same level and as far as possible each room will have a major theme from Sunrise Symposia through Scientific Sessions. We are trying to move the mountain! Sessions themselves will display a bed to bedside approach as exemplified in the Closing Plenary.

Next month I will let you know more detail about individual Symposia and Sessions. Many of you will be asked to assist this year. We are changing the poster sessions to moderated sessions to allow better appreciation of the hours of work involved. Also, some abstracts are best presented in this format and some actually prefer the intimacy of one-on-one scientific discussion. So, we will need a small army of poster mentors comprising senior and junior faculty to provide expert feedback to poster presenters. This is an important task and often the mentors learn more than the casual audience! So please vote to attend and participate. We depend on each other.

Plan early to come to Montréal. We trust the meeting will meet your expectations and more. Send in your best work and remember the value of congress within our Society is not to be undervalued!

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

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**ISHLT 2013 Exposed!**
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The human body houses a vast consortium of micro-organisms, with microbial cells estimated to outnumber human cells ten to one. Traditional microbiology has relied on cultivation for characterization of the human microbiome and pathogen discovery. The advent of culture-independent techniques coupled with advanced DNA sequencing technologies and bioinformatics have allowed unprecedented insight into the structure of microbial communities, demonstrating that the full extent of microbial diversity in any given ecosystem is rarely described by culturing alone.

Two culture-independent techniques are widely used to describe microbial populations: shotgun metagenomics and community profiling. Shotgun metagenomics involves the wholesale extraction and sequencing of total microbial DNA in an environment, while community profiling relies on the amplification and sequencing of the highly conserved 16S ribosomal RNA (rRNA) gene. Shotgun studies provide insight into microbial taxonomy (who is there?), diversity (how many are there?), and function (what are they doing?), but can be difficult to conduct on a large scale due to informatic and sequencing limitations. Community profiling describes taxonomy and diversity only, but can be easily applied to hundreds of samples, enabling clinical studies of sizeable patient cohorts.

Using a community profiling approach based on 454 pyrosequencing of the 16S rRNA gene, we investigated the microbial communities of bronchoalveolar lavage (BAL) samples from lung transplant patients with and without bronchiolitis obliterans syndrome (BOS) as well as healthy controls. A total of 132 samples from 57 transplant patients (27 female, 29 cystic fibrosis, 22 BOS) and 8 controls were sequenced including longitudinal samples from 16 cystic fibrosis (CF) patients at up to 6 time points ranging from 2 months to over 3 years post-transplant. Microbial community composition was compared between samples using the weighted Unifrac distance which accounts for both community membership and relative abundance. Principal components analysis based on weighted Unifrac distance demonstrated two major microbial community types: one dominated by Pseudomonas and one dominated by Streptococcus and Veillonella. Most cystic fibrosis patients were colonized with Pseudomonas and an inverse relationship was noted between the relative abundance of Pseudomonas and Streptococcus. Nearly all CF patients with BOS had microbial communities dominated by organisms not considered typical pathogens in CF adults including Streptococcus, Lactobacillus, Enterococcus, Neisseria, and Haemophilus, while those with high abundances of Pseudomonas, Burkholderia, and Staphylococcus were more likely to be BOS-free. A stratified exact logistic regression analysis controlling for time post-transplant demonstrated that in CF individuals, the odds of BOS were reduced by more than half when Pseudomonas was the dominant organism in the microbial community (OR=0.37 (0.11,0.83). p=0.009). This observed effect was not due to confounding by history of rejection (p=0.94), or antibiotic treatment (p=0.32). Examination of temporal changes in individual patients demonstrated that stable, high-abundance colonization with Pseudomonas was associated with an absence of BOS. These data suggest that in CF patients, BOS is accompanied by pronounced and sometimes predictable changes in the transplant lung microbiome that could inform therapeutic regimens.

Previous studies have implicated Pseudomonas colonization in the development of BOS in CF individuals; however, this was based exclusively on cultivation. Our results suggest that it is not the presence of Pseudomonas, but its relative abundance in the context of the microbial community as a whole that may be correlated with transplant outcomes. All but one of the CF patients in this study cultured Pseudomonas at all-time points, but its representation in the microbiome was highly variable, ranging from less than 5% to over 95%, with lower relative abundances occurring in individuals with BOS. As opposed to culture-based studies which provide semi-quantitative or qualitative information on a subset of microbial populations, community profiling allows for characterization of all microbes and their relative abundances simultaneously, adding a previously unexplored dimension to the characterization of the respiratory microbiome.

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Multiresistant Gram-negative (MRGN) infections are an increasing worldwide concern, contributing to significant nosocomial morbidity and mortality (up to 50%). These infections are produced mainly by Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., all of them very familiar in our field. Over the last several years, a growing number of Enterobacteriaceae resistant to all of our antibiotics—including carbapenems—have emerged. Historically, carbapenemases have been our last line of defense in treating Enterobacteriaceae; therefore, the development of resistance to these last-line agents has been a significant concern in healthcare. To protect patients and prevent transmission, healthcare professionals need to take specific steps.

The overuse of antimicrobial agents has led to the development of different resistance mechanisms that can be shared easily with other Gram-negative species. In the area of globalization, bacteria can spread rapidly, passing quickly through geographic barriers. Therefore, we need aggressive infection control measures and prevention efforts when resistant-epidemic clones are detected. Clinicians should be aware of this rising problem and practice/maintain a rational use of current drugs.

The terms “multidrug-resistant” (MDR), “extensively drug-resistant” (XDR), and “pan-drug resistant” (PDR) gram-negative bacilli infections are used with different meanings. People frequently confuse these terms and use them inappropriately. The correct terminology is as follows:

Multidrug-resistant (MDR): defined as a pathogen that is resistant to at least 3 antimicrobial classes of agents to which it could have been susceptible.

Extensively drug-resistant (XDR): resistant to 1 or 2 antimicrobial options.

Pan-drug resistant (PDR): term implies resistance to all commercially available antimicrobial agents.

Currently, the most important resistance mechanism is beta-lactamase production. Extended-spectrum β-lactamases (ESBLs) are most often found in E. coli and K. pneumoniae; however, other Gram-negative bacilli, including Enterobacter spp., Proteus mirabilis, Citrobacter freundii, Morganella morganii, Serratia marcescens, and to lesser extent P. aeruginosa, have also been found to produce these enzymes. Some of these bacilli can also produce other β-lactamases, including chromosomal or plasmid mediated AmpC-type enzymes, metallo-lactamase or other carbapenemases, so they can also be resistant to the β-lactams, β-lactamase inhibitors combinations, antipseudomonal cephalosporins, and carbapenemases.

We have very limited options of treatment (Table 1). These include Carbapenems, Aztrentam, beta-lactamics, Polymyxins, Tigecycline, and Fosfomycin. All of these drugs may be used alone or in combination. In the pipeline there are few options in early phase: ACHN-490 neoglycoside, CXA 101, Ceftazidime/NXL104, Ceftalarine. In addition, we can use other routes of antimicrobial therapy as inhaled therapy for respiratory infections. Nebulized therapy with colistin or...
Aztreonam lysine is an attractive option in these cases. A high concentration of antibiotic can be achieved in the infection’s location without systemic side effects. Finally, despite the lack of scientific evidence, combined IV and nebulized therapy is currently a very good option for MRGN respiratory infections. In summary, the limited therapeutic armamentarium has been the reason for the development of novel approaches such as old antibiotics, new routes, doses and combination therapies. A tailored therapeutic approach is recommended in these cases. Since new antibiotics continue to be required, we must avoid returning to the pre-antibiotic era. Bacteria are evolving faster than companies can bring new antibiotics to market. Bacteria are tricky; by changing quickly in response to antibiotics, they can grow resistant, creating even more harmful and life-threatening infections.

Please, when you treat the next nosocomial infection, keep in mind that bacteria are cleverer than us. It is an unequal battle for several reasons. First, bacteria grow faster than human beings, preventing new antibacterial drugs from becoming available in time. Second, bacteria quickly develop resistance mechanisms shared with other Gram-negative species. Finally, they spread easily in this globalized world without effective drugs to combat them.

Meanwhile, strict application of infection control measures is the cornerstone of nosocomial infection prevention. Antibiotic stewardship, exemplified by appropriate duration of therapy and de-escalation policies, is paramount and must not be overlooked.

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Regardless of antiviral drugs availability, cytomegalovirus (CMV) infection is still a major concern in the management of thoracic heart transplantation. Current line of research in CMV field is intensively focused on the understanding of CMV specific immunity.1-3

At the latest ISHLT meeting in Prague, this topic was covered by the invited talk from Martina Sester4 during Wednesday’s pre-meeting symposia, and by Evangelia Petrisli (evipetris@yahoo.gr) who presented the abstract entitled, Reconstitution of CMV-Specific Immunity after Heart Transplantation Is Modulated by mTOR Inhibition, but Not by Antiviral Strategy.5 For this month’s issue which focuses on infectious diseases, I interviewed this young microbiologist who is involved in CMV research at the Clinical Microbiology of the University of Bologna, Italy, to gain more perspective on the research project she presented as well as the current situation of young scientists in southern Europe.

Potena: Evangelia does not sound of Italian origin, though?

Petrisli: Please call me Evi…. Yes, indeed I am from Greece. I was born in Thessaloniki and I moved to Italy in 1997. I then entered the School of Medicine in Bologna, graduating in 2006, followed by four years of Specialization School in Microbiology and Virology linked to Prof. Lazzarotto’s Virology lab. After that I stayed in this lab with a post-doc position.

Have you devoted all these years to CMV?

Yes! Well … mostly but not only. You know, we have two big families of projects involving transplant recipients and pregnant women with primary CMV infection. CMV is not only the leading infection in transplant recipients, but also the leading cause of newborn brain disease in western countries. But our lab is involved also in the diagnostics of other herpes viruses; well, let’s say mostly all viruses except HIV and hepatitis.

Tell us about the research you presented in Prague.

That is a big project we are following with the Cardiovascular Department and has two major goals: investigating the clinical outcome of heart recipients randomized to prophylaxis vs. preemptive approach, and receiving either MMF vs. an mTOR inhibitor, and studying how these therapeutic strategies interact with CMV specific immunity. This project, which is still ongoing, returned very exciting results showing that not only CMV specific immunity is important in controlling the infection, but also it seems that by using different therapeutic strategies we can modulate CMV immunity. On my side, the big challenge has been represented by the set-up of the ELISPOT technique, which I was able to perform thanks to the technical help of all my colleagues biologists working in the lab, of whom I wish to thank in particular Dr. Angela Chiereghin. This approach, although validated in several studies, is very time consuming, with a very long first step of cell recovery, cell count to standardize the count number in each well, etc.

Thus this technique is still far from the clinical applicability?

Well, partially. On one hand it has been validated and clinically applied. On the other hand, it is a really time consuming technique; the results may be influenced by the operator skills, and you need a lot of blood to harvest a sufficient number of cells to incubate in each well. It provides a good balance between feasibility, cost and sensitivity to monitor CMV immunity. CMV Quantiferon techniques, for example, are much easier technically but currently seem less sensitive. You would need dedicated personnel for ELISPOT only if you wish to use it as a diagnostic tool.

Well, you are talking a lot about science, but besides your specific scientific and technical experiences, tell us a bit more about your personal way of feeling your experience as a scientist: are you happy with it? What are the good sides of a job in research?
Well, since I started the school of medicine, I’ve always dreamt of working in laboratory medicine, hopefully microbiology. And I’ve been lucky to have the chance to enter the specialization school immediately after my MD degree. In this lab I found a huge experience in microbiological diagnostics, thus I had the chance to learn the multiple techniques needed in a big academic hospital to diagnose and monitor infectious diseases.

In addition to this I have been involved in several research projects, initially just as a technician; then, in particular with this CMV immunity project, as an investigator. Thus I learned that research never makes one week equal to the other: you are always challenged with new problems, which you are called to solve, and the solutions are just the gateway for new working hypotheses that open up new challenges. And you can really feel the development of knowledge in your hands. I think that the most positive thing in this way of working is that I could couple routine diagnostics for the patients with the excitement of discovery.

But is “that which glitters all gold”? What about the dark sides?

Well, the gold is what we are currently missing! The dark side of research is that your job stability depends on funding. And funding is now lacking. You know what is happening with this crisis. Research and education have been suffering unbelievable cuts in Italy, and even more in my home country, in Greece. And if a faculty or hospital staff position was difficult to achieve few years ago, nowadays is almost impossible in my field. It is frustrating that a lot of the enthusiasm, good ideas, and development we can generate are impeded by the muddy ponds of bureaucracy and funding policies. These are strange times; it seems that following your dreams cannot provide you with a vision or at least a hope for the future. You cannot live forever with permanent uncertainties.

Are you regretting your choices? Would you be happier if you were holding a permanent staff position in the diagnostic lab of a small countryside hospital?

This is the “billion euros” question. On one side you have safety and stability, on the other excitement and discoveries. Anyway I am not regretting anything. I am happy to be a clinical microbiologist even though, I must admit, keeping clinical practice could have helped in looking for a stable job. Or even for moonlighting and being a bit more stable financially. I think that my ideal job would have been one that gave me the possibility of wet lab working associated with clinical practice.

Have you ever thought of going back to find a job in Greece?

When I graduated I entered a deep crisis: either going back to get specialty there and live there, or staying in Italy, mostly abandoning hopes to get a future job in Greece. This is how it worked. I chose to stay, and I must admit that “unfortunately” it was the right choice. Now, from one day to another Greeks suddenly woke up in a nightmare. Few years ago this current situation was unpredictable. Now it is really dramatic: no real hope for the future, in particular for young people. Nobody really has the feeling of what is going to happen one week to the other, or even the feeling of what is reality and what is just a media-driven scenario. People are shocked, as if during a war. Talking about choices—what is happening now in my home country, however, proves that once you have to make a choice for your future, there are so many unpredictable variables to take into consideration that any forecast is irrational.

In the end I’ve always followed my dreams and my gut feeling, instinctively throwing myself into a roadmap still to be drawn. It has always been like this in the last 15 years and I must admit that I have been lucky because things always turned out to be as I wanted them. It could have been better, maybe. But it could for sure have been much worse.

And how about moving away from Italy?

Well, my postdoc here is expiring. And I cannot exclude anything now. It would be another new challenge to face!

ELISPOT technique: http://www.youtube.com/watch?v=tXet7c0mLLA
Economic crisis explained: http://www.youtube.com/watch?v=N-krRLX8dTg
Greek riots: http://www.youtube.com/watch?v=rshdJZruH_0

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References:


In December of 2011, the United States Food and Drug Administration (FDA) approved the use of the pneumococcal 13-valent conjugate vaccine (Prevnar 13®, Pfizer, Inc.) for adults 50 years of age and older. This approval was based on the measured immune responses and observed safety profile of the vaccine and not on controlled trials in adults actually demonstrating a decrease in pneumococcal invasive disease. Those trials are ongoing currently and so a recommendation that it be given to all adults 50 or over has yet to be made.

In the world of immunocompromised transplant patients, the use of a conjugate pneumococcal vaccine is somewhat intriguing. The vaccine includes the most common serotypes to cause disease: 4, 6B, 9V, 14, 18C, 19F, and 23F (similar to the previously recommended 7-valent conjugate pneumococcal vaccine in children), as well as six new additional serotypes: 1, 3, 5, 6A, 7F and 19A. Although this may not be as many as the currently widely used 23-valent polysaccharide pneumococcal vaccine (Pneumovax®, Merck, Inc.), the mechanism of immune stimulation is different and has potential benefits. Since polysaccharides from bacterial capsids are not always immunogenic, the conjugate vaccines utilize an inactivated Diphtheria protein coupled to the pneumococcal polysaccharide subunit in order to activate helper T cells and produce more high affinity antibodies against the polysaccharides. Memory B cells made from this process then, in theory, could be boosted by subsequent polysaccharide antigen vaccination. In normal adult populations, use of the conjugate vaccine appears to stimulate levels of antibody that are at least equal to or higher than the polysaccharide vaccine.

In June of this year, a U.S. Centers for Disease Control and Prevention (CDC) advisory panel recommended that adults (19 years or older) with compromised immune systems be routinely administered the conjugate vaccine.1 Because of the potential “boosting phenomena”, it was still recommended that they receive the 23-valent pneumococcal polysaccharide vaccine as well. This recommendation was primarily based on a randomized control trial of the 7-valent conjugate vaccine in HIV-infected patients which seemed to be beneficial.2

There are several reasons to consider using the 13-valent conjugate vaccine in immunocompromised transplant recipients. Primary among them is the very high incidence of invasive pneumococcal disease in adults with immunocompromising conditions. Transplant patients in general have an incidence of pneumococcal pneumonia, bacteremia and meningitis over 10 times that of the normal population.3 Other reasons include the safety profile of the vaccine to date and the potential theoretical immunogenic benefits.

Unfortunately, there is not much information in actual solid organ transplant recipients currently. A study in renal transplant patients comparing the 7-valent vaccine to the 23-valent pneumococcal polysaccharide vaccine showed higher titers for some serotypes, though functional antibodies were thought to be no different.4 It is also unclear if the boosting phenomenon of administering the polysaccharide vaccine actually translates into any benefit for transplant patients. In a small retrospective study of the 7-valent vaccine given to heart or lung transplant recipients followed by the 23-valent polysaccharide vaccine, no clear benefit was seen in increasing pneumococcal titers.5 Similar results were seen in a study of liver transplant recipients in Canada.6

Although there is a lack of information to date on optimal vaccination strategies, it is clear that any kind of strategy is still better than none. Despite extensive guidelines for immunizations of solid organ transplant recipients, vaccines are routinely underutilized in our susceptible heart and lung transplant recipients.7 It is hoped that further clinical trials will help us understand ideal dosing and intervals of administration for pneumococcal vaccines as well as others. In the meantime, though, the adequate attempt to immunize these patients should be a primary goal for all of us caring for them.

Disclosure statement: The author has no conflicts of interest to disclose.
Thoracic transplant recipients have the highest incidence of varicella zoster virus (VZV) infection among all transplant recipients. Primary VZV infection causes varicella, also known as chickenpox, and reactivation of VZV causes herpes zoster (HZ), which can be complicated by post-herpetic neuralgia, a significant cause of morbidity. Less common but severe complications include disseminated cutaneous disease and visceral involvement, such as pneumonitis.

Almost all adults in Europe and North America have evidence of prior VZV infection, so adult transplant recipients are generally at risk for HZ. In a study of adult lung transplant recipients, HZ occurred in 12.1% of the recipients. Well established risk factors for HZ following transplantation are not known. As seen in the general population, older age increases the risk. Transmission of VZV occurs from individuals with active infection through aerosol particles and direct skin contact.

Prevention of VZV infection post-transplant starts in the pre-transplant evaluation. VZV serology must be checked and susceptible individuals should be given the live attenuated Oka strain vaccine (Varilrix®, GlaxoSmithKline, Belgium or Varivax®, Merck & Co., Inc., USA). The standard two doses should be given prior to transplantation with a minimal interval of 6 weeks. Vaccination should occur at least 2-4 weeks prior to transplantation. Some small studies have shown that varicella vaccine may be safe post-transplant, particularly in pediatric transplant recipients who are clinically stable and not in the early post-transplant phase; however, until larger and controlled trials are available varicella vaccine is not recommended post-transplant.

A live attenuated zoster vaccine (Zostavax®, Merck & Co., Inc., USA), which contains approximately 15 times more live virus than the varicella vaccine is available for individuals ≥ 50 years old. In a large, randomized trial in adults >60 years old, the vaccine showed a >50% reduction in the incidence of HZ and post-herpetic neuralgia. The vaccine has not been studied in patients with end-organ disease or in pre-transplant patients. Further study is needed to determine if it will be efficacious in preventing post-transplant HZ when administered to VZV seropositive transplant candidates. The zoster vaccine is not recommended for post-transplant patients.

Antiviral therapy used for cytomegalovirus (CMV) prevention will prevent VZV reactivation and additional prophylaxis for VZV is not needed. Short-term herpes simplex prophylaxis with acyclovir or valacyclovir given to transplant recipients who do not receive CMV prophylaxis will be effective against VZV. Because VZV infection can occur at any point after transplantation, long-term VZV prophylaxis is not recommended.

References:

Post-exposure prophylaxis should be offered to every seronegative transplant recipient after a significant exposure, due to the risk of developing varicella. Significant exposure includes household contact; contact in the same room, such as a classroom or a 2- to 4-bed hospital room for a significant period of time (usually 1 hour or more); and face to face contact with an infectious staff member or patient. VZV infection can be spread from a person with varicella or HZ. Passive immunoprophylaxis with varicella zoster immune globulin (VariZIG™, Cangene Corporation, Canada) should be given as soon as possible. VariZIG is available in the United States through an investigational new drug application expanded access protocol.

In May 2011, the US Food and Drug Administration (FDA) approved an extended period for administering VariZIG. VariZIG can now be administered up to 10 days after exposure. It was previously approved for administration only up to 4 days after exposure. FDA's decision was based on limited data showing a comparable incidence of varicella among persons who received varicella zoster immune globulin within 4 days of exposure and those who received it up to 10 days after exposure. Disease attenuation is achieved with administration up to 10 days post-exposure.

Post-exposure prophylaxis with antiviral agents can be given as adjunctive therapy or to transplant recipients who were not able to receive varicella zoster immune globulin within 10 days of exposure. Valacyclovir is preferred over acyclovir due to better bioavailability. Antiviral prophylaxis should be given for 7 days, starting 7-10 days after exposure.

Transplant patients with varicella or HZ who require hospitalization should be placed on airborne and contact isolation until lesions are crusted. Exposed susceptible transplant recipients should be placed on airborne and contact isolation from day 10 to 21 after exposure. Those who received varicella immune globulin should remain in precautions until day 28. HZ lesions should be covered to decrease the risk of transmission.

Lastly, we must create a circle of protection around our transplant patients. Their close contacts and family members 12 months or older should receive the varicella vaccine if they have no history of varicella or HZ, were never immunized and have no contraindications to vaccination. Close contacts and family members 50 years or older may receive the zoster vaccine if they have no contraindications to vaccination.

Disclosure statement: The author has no conflicts of interest related to this topic.

References:
The London Olympic Games have recently ended with a great Closing Ceremony, and while some of us might still be in denial, the Olympic idea lives on. The focus is now on Rio de Janeiro in 2016! The Olympic motto Citius, Altius, Fortius (faster, higher, stronger) remains relevant in a number of spheres. Pierre de Coubertin, the father of the modern Olympic Games, expressed his thoughts in the Olympic creed: “The most important thing in the Olympic Games is not to win but to take part, just as the most important thing in life is not the triumph but the struggle....”

In the field of transplantation, the ongoing struggle is to balance the risks of allograft rejection and infection with the benefits of living a normal life following transplantation, a challenge transplant patients face nearly every day. In particular, infectious complications within the first year after lung transplantation account for significant morbidity and mortality.1,2 A recent pediatric study showed an incidence of respiratory viral infection of 14% in the first year after lung transplantation.3 The incidence of respiratory viral infections in symptomatic adult lung transplant recipients (LTRs) ranges from 35-66%.4 Thus, prevention of viral infections is paramount, and the basis for prevention is adequate vaccination if available.

Following the global 2009 H1N1 influenza virus pandemic, recommendations regarding the diagnosis, prevention and therapy of influenza were issued by the American Society of Transplantation, in view of the risk of severe influenza infection and influenza-related complications in solid organ transplant recipients (SOTRs).5 A specific concern in LTRs is the potential association between respiratory viral infections and acute allograft rejection and the subsequent development of bronchiolitis obliterans syndrome (BOS). A recent literature review by Vu et al investigating the relationship between viral respiratory infection and graft complications in adult LTRs did not conclusively support an association between respiratory viral infection and acute lung rejection and the subsequent development of BOS, mainly due to the heterogeneity and the retrospective design of published studies to date.6 In the pediatric lung transplant population, respiratory viral infection has been associated with a 2.5-fold decrease in 1-year survival but it was not linked with the development of BOS in retrospective studies.7 8 Failure to demonstrate a relationship however should not be misconstrued as evidence of the lack of a causal link. Hence, a National Institutes of Health study in pediatric lung transplantation is currently underway to investigate the potential interaction between respiratory viral infections and BOS utilizing improved molecular diagnostics for respiratory viruses and increased patient surveillance (https://www.ctotc.org/).

Usually, transplant centers recommend LTRs receive vaccination with the annual influenza vaccine from as early as 3-6 months post-transplant; however, there is a lack of data regarding the most suitable time point for vaccine administration and concerns exist about an impaired vaccine response.8 Vaccine antibody response is usually used as a surrogate marker of vaccine efficacy; however, this is not equal with protection. Factors that lead to non-response in LTRs after influenza vaccination have yet to be established. A systemic review and meta-analysis assessing influenza vaccination for immunocompromised patients showed a significant effect in the prevention of an influenza-like illness and no consistent evidence of safety concerns or serious adverse events (AEs) after influenza vaccination.9 A recent observational study from Zurich showed that nearly 50% of LTRs reported no AEs after H1N1 vaccination, with the remaining LTRs mostly having minor/moderate AEs, such as local reactions at the injection site.10 Serious and reportable AEs occurred in 6% of LTRs. The effectiveness of H1N1 vaccination was reported as >90% in the study; however, the effectiveness was only assessed based on
protection from subsequent H1N1 infection and not on vaccine antibody response.

Even though the benefits of immunization have been shown, there is evidence that exposure to influenza antigens after vaccination might directly activate alloreactive T and B cells, an effect labelled “heterologous immunity”. Danziger-Isakov et al investigated effects of influenza immunization on humoral and cellular alloreactivity in healthy controls (N=30) and SOTRs (N=17), demonstrating that influenza vaccination induced virus-specific reactive humoral and cellular responses in both groups. In a recent Swiss study in kidney transplant recipients de novo anti-HLA antibodies were detected using single antigen beads technology following one dose of seasonal influenza and two doses of adjuvanted influenza/ H1N1 vaccines. Antibodies were both donor-specific and non-donor-specific and mainly low level. However, in an accompanying editorial in the same edition of the American Journal of Transplantation, Kumar and Danziger-Isakov rightly point out that increased HLA alloantibody titers could potentially be due to sub-clinical or undiagnosed influenza infection during the H1N1 pandemic, and clinical rejection in two study patients could be explained by other factors. Further, Kumar and Danziger-Isakov recommend that the study results of Katerinis should be interpreted with caution so as to balance any potential vaccination-associated risks with the well described benefits in disease prevention.

In conclusion, the benefits of influenza vaccination and its effectiveness in preventing viral disease seem to clearly outweigh the risks of vaccine-related AEs that are predominantly minor and self-limiting in nature. In view of the emerging evidence of the potential impact of influenza vaccination on recipients’ alloresponse, further research is required to investigate its impact on long-term allograft function and the potential association with the development of BOS. As Pierre de Coubertin said, the essential thing is not to have conquered but to have fought well....

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

References:

Lung transplant recipients have a unique predisposition to infection due to a number of factors including diminished cough reflex, abnormal lymphatic drainage, physical impairment of mucociliary clearance, high levels of immunosuppression and exposure to airborne pathogens. One consequence of this continued environmental exposure is a high incidence of respiratory viral infection (RVI) compared to healthy individuals.

A number of viruses have been associated with acute allograft dysfunction including influenza A and B, adenovirus, parainfluenza, respiratory syncytial virus (RSV), human Metapneumovirus (hMPV) and rhinovirus. Clinical manifestations range from mild self-limiting pharyngitis, to the more severe spectrum of bronchiolitis, progression of BOS, viral pneumonitis and acute lung injury with respiratory failure. Respiratory viral infections have been aetiologically linked to the development of BOS through local immune up-regulation or predisposition to acute graft rejection, although no direct causative link has been established.

During a twelve year prospective evaluation period commencing January 2000, lung transplant recipients at the Prince Charles Hospital, Brisbane Australia, underwent nasopharyngeal aspirates (NPA). Patients with symptoms of influenza-like illness were targeted, defined as any combination of sore throat, nasal irritation, low grade fever, myalgia and arthralgia with or without respiratory tract symptoms of cough, dyspnoea or wheeze. Respiratory NPA specimens were obtained in the outpatient department and screened by indirect fluorescent antibody test and PCR for RSV, hMPV, influenza A and B, parainfluenza 1-3 and adenovirus. Clinical manifestations range from mild self-limiting pharyngitis, to the more severe spectrum of bronchiolitis, progression of BOS, viral pneumonitis and acute lung injury with respiratory failure. Respiratory viral infections have been aetiologically linked to the development of BOS through local immune up-regulation or predisposition to acute graft rejection, although no direct causative link has been established.

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All patients with paramyxoviral infection and graft dysfunction (defined as >10 percent decline in FEV1) were hospitalised and nursed in a single room isolation under infection control precautions for droplet transmission. The mainstay of treatment consisted of intravenous ribavirin at a commencing dose of 33mg/kg/day for the first 24 hours then 20mg/kg/day thereafter, with dosing adjusted for renal function if appropriate. Furthermore, patients received an oral prednisolone pulse at 1mg/kg tapering by 5mg per day to baseline, broad spectrum β-lactam based antibiotic therapy and nebulised bronchodilators. Steroid therapy was implemented to attenuate production of macrophage inflammatory protein-1 alpha and interleukin-8, along with down regulation of lymphocyte alloreactivity. Intragram P (human immunoglobulin, CSL Limited, Victoria) was administered from day 7 if there was no improvement in allograft function, in a dose of 0.4gram/kg/day for 5 days. Such immunotherapy may neutralise super antigens, down regulate T cell immunity, inhibit complement and have anti-cytokine effects. Patients with adenoviral infection and graft dysfunction received intravenous cidofovir pending renal function and those with influenza oral oseltamivir 75mg twice daily orally.

There were 147 episodes of RVI in 85 patients - parainfluenza 42, RSV 37, hMPV 26, influenza A 26, influenza B 10 and adenovirus 6 cases. Cox proportional hazard modelling was used to assess risk factors for RVI, BOS onset and death following RVI, by comparison with 93 lung transplant recipients with no RVI during the study period. On multivariate analysis risk factors for RVI included pre-existing BOS (HR 3.25, CI 1.64-6.42, p=0.01) and serum IgA level (HR 0.796, CI 0.622-1.017, p=0.06). Risk factors for developing BOS grade 1 were single lung transplant (HR 2.01, CI 1.36-6.25, p=0.06), serum IgG (HR 0.827, CI 0.753-0.908, p<0.001) and time to onset post transplant of RSV or hMPV (HR 1.75, CI 1.03-3.00, p=0.04). No other viruses were predictive of BOS onset. Risk factors for death included BOS (HR 51.97, CI 17.94-150.57, p<0.001) and time to RSV or hMPV (HR 2.07, CI 1.17-3.68, p=0.013).

In conclusion, our experience suggests that both RSV and hMPV are predictive of both BOS onset and death post lung transplant despite aggressive treatment protocols. Parainfluenza is less problematic, whilst influenza and adenovirus are relatively benign. Mortality is related to BOS acceleration and a predisposition to invasive fungal infection. Changing epidemiological trends, differing viral phenotypes and patient demographics may account for some geographical differences.

Disclosure Statement: The author has no conflicts of interest to disclose.
A 25-year old male patient with cystic fibrosis has developed progressive disease and his medical team is considering referral for lung transplantation. The patient has a history of pancreatic insufficiency and well controlled diabetes. He has been infected with \textit{Pseudomonas aeruginosa} and \textit{Methicillin Sensitive Staphylococcus aureus}. Some of his recent mycobacterial cultures have had low growth of \textit{Mycobacterium abscessus}. Is this an appropriate candidate for lung transplantation?

In recent years there has been an increase in atypical mycobacterial infections in patients with advanced lung disease, especially in patients with cystic fibrosis and bronchiectasis.\textsuperscript{1,2} In particular, \textit{Mycobacterium abscessus} has been isolated with increasing frequency from patients. \textit{M. abscessus} is inherently resistant to many antibiotics and has a propensity to lead to respiratory and wound infections. Treatment with multiple antibiotics, including but not limited to amikacin, imipenem, cefoxitin, macrolides, quinolones, doxycycline, linezolid and tigecycline, is frequently required.\textsuperscript{2} Toxicities are quite significant. Transplant programs are struggling to decide on whether patients with \textit{M. abscessus} can be transplanted safely.

Studies have attempted to identify risk factors for development of mycobacterial infections after lung transplantation. The only one that was found was the presence of \textit{M. abscessus} prior to lung transplantation.\textsuperscript{3} Regardless, the incidence of \textit{M. abscessus} after lung transplant remains quite low. Non-tuberculous mycobacteria are isolated from 3% to 15% of patients undergoing lung transplantation, depending on the population transplanted. \textit{M. abscessus} is the second most common species isolated (ranging from 10% to 16% of isolates); however it required treatment in most cases reported.\textsuperscript{3}

There are multiple case reports, an international questionnaire and a few case series that attempt to assess outcomes after lung transplantation in patients with post-transplant \textit{M. abscessus} infection.\textsuperscript{3,5,7} Despite the many reports with very poor outcomes (from pulmonary, wound or disseminated infections), it appears the majority of patients with \textit{M. abscessus} survive their infections. However, mortality appears to be high and based on a summation of the case reports as many as 30-35% of patients with \textit{M. abscessus} die.\textsuperscript{3,7} Anecdotal information from our center suggests similar outcomes. Many patients had transient colonization and needed no treatment. Other patients had treatable, but relapsing disease. Others died with an active infection, but some of them did not die from \textit{M. abscessus}. Other comorbidities led to death.

A couple of other interesting case reports show that aggressive treatment before and after lung transplantation might lead to better outcomes\textsuperscript{5} and that transmission from person to person during clinic visits is possible.\textsuperscript{8}

So how is the clinician to go forward? It is difficult to make firm conclusions, but based on all the evidence, careful screening of patients before transplant and if isolated, after transplant is necessary. Prior to transplant, aggressive therapy should be considered for two reasons: control of the disease and decreased disease burden and ability to assess tolerance of the many medications that are needed for therapy. After transplantation, monitoring patients carefully will help identify the ones that require treatment. This is a population of transplant recipients that requires significant expertise in pulmonary, surgical and infectious disease, best done at centers with this expertise. Even though outcomes appear to be better than in lung transplant recipients with other difficult infections like \textit{Burkholderia cepacia}, significant morbidity and mortality can be expected.

\textbf{Disclosure Statement:} Dr. Hadjiliadis is a subinvestigator of a clinical trial (Insmed) of inhaled liposomal amikacin in refractory mycobacterial infection.
Expert Panel for Antifungal Prophylaxis in Lung Transplant Recipients

Lung transplant recipients have the highest incidence of fungal infections among solid organ recipients. In order to prevent fungal infections, various antifungal prophylactic agents and strategies have been developed; however, these strategies have shown inconsistent efficacy and safety results with no consensus on appropriate use of antifungals in lung recipients.

The ISHLT Infectious Diseases Council has taken a lead in convening a fungal expert panel with global representation. The objective of the panel is to assess the current data and recommend the strategies based on the GRADE system (The Grading of Recommendations, Assessment, Development, and Evaluation).

The group will be co-chaired by Shahid Husain from Canada, Orla Morrissey from Australia, and Amparo Solé from Spain.

Members of the expert panel representing North America include:
- Robin Avery
- Lara Danziger-Isakov
- Aric Gregson
- Denis Hadjiliadis
- Me-Linh Luong
- Fernanda Silveira
- Sam Weigt
- Aimee Zaas

Representing South America:
- Alessandro Pasqualotto

Representing Europe:
- Christian Benden
- Eliane Billaud
- Kate Gould
- Paolo Grossi
- Victor Monforte
- Antonio Roman

The panel is scheduled to submit its recommendations to the board in a year’s time.

ISHLT MONOGRAPH SERIES VOLUME 5:
Diagnosis and Management of Infectious Diseases in Cardiothoracic Transplantation and Mechanical Circulatory Support

The 5th Volume in the Monograph Series entitled, Diagnosis and Management of Infectious Diseases in Cardiothoracic Transplantation and Mechanical Circulatory Support, edited by Martha Mooney, Margaret Hannan, Shahid Husain, and James Kirklin, was published in April 2011.

Here is a brief excerpt from the Preface:

“Infections in solid organ transplant recipients in general and in cardiothoracic organ transplantation (CTTX) recipients in particular are a moving target. Advances in immunosuppression and mechanical circulatory support (MCS) have not only resulted in prolonging life but have also caused new infectious syndromes. This monograph was created to provide a practical and concise clinical resource for understanding and controlling infectious diseases in cardiothoracic transplant and mechanical circulatory support recipients. It is intended to serve as a resource for medical professionals involved in CTTX and MCS.”

Click HERE to read the full Preface
Click HERE to order your copy of this Monograph
Introduction

Cystic fibrosis (CF) is a devastating disease that affects young individuals. With advancements in management and the introduction of newer therapies, the average survival in CF patients is around 38 years; however, respiratory failure is a known complication in these individuals often requiring lung transplantation. According to the recent ISHLT registry data, 27% of bilateral lung transplantations across the world are performed in patients with CF. Of these patients, 50% will survive greater than 7.4 years post transplant. Infection following transplantation continues to be a moving target and is complicated by the pre-transplant microbiological profile of patients. *Burkholderia cepacia* complex (BCC) infection is well known to increase mortality after transplantation in these patients and there is new data on this old foe. Recently however, other pathogens have also gained more prominence.

*Burkholderia cepacia* complex (BCC)

Zlonisk et al looked into the correlation of phenotype of the BCC isolated to that of poor outcomes. They noticed that patients infected exclusively with the non-mucoid BCC had more rapid decline in lung function (annual FEV1 -8.51±2.41%) than those infected with mucoid bacteria (-3.01±1.09%; p<0.05). In vitro incubation of BCC with ceftazidime and ciprofloxacin caused conversion of BCC from mucoid to non mucoid type thus increasing the virulence, while use of meropenem did not result in phenotypic switch. Although to date no study has looked into the proportion of mucoid vs. nonmucoid infected patients undergoing lung transplantation, it is plausible that most of the CF patients undergoing lung transplant belong in the non mucoid group.

**IMPLICATIONS FOR LUNG TRANSPLANTATION.** Identification of non mucoid strains in patients prior to transplantation and refraining from the use of certain antibiotics post-transplant may prove helpful.

*Methicillin resistant Staphylococcus aureus* (MRSA)

The prevalence of MRSA in North America among CF patients had risen dramatically. The prevalence rate is around 20%. Persistent colonization with MRSA has been previously reported to be associated with decline in FEV1. The same group has recently reported higher mortality associated with presence of MRSA in the respiratory tract. Among those with MRSA, the attributable risk percentage of death associated with MRSA was 34.0% (95% CI, 26.7-40.4) and adjusted hazard ratio of MRSA associated with death was 1.27 (95% CI, 1.11-1.45).

**IMPLICATIONS FOR LUNG TRANSPLANTATION.** The higher rate of MRSA is the CF population is alarming especially in North America. CF patients with persistent MRSA colonization at the time of transplantation may require empiric therapy with anti-staphylococcal agents. However, it is still unknown whether those patients who had colonization once with MRSA prior to transplantation are at higher risk of developing MRSA pneumonia following transplantation.

**Transmissible strains of Pseudomonas aeruginosa**

*Pseudomonas* is the most common organism infecting CF patients. Recently Shawn and colleagues described two transmissible strains of *P. aeruginosa* infecting patients with CF in Canada and United Kingdom (Liverpool epidemic strain /strain A). The incidence rate of new infections with these strains was low (7.0 per 1000 person-years; 95% confidence interval [CI], 1.8-12.2 per 1000 person-years). The rate of decline of lung function was comparable to unique *Pseudomonas* strains. However, the 3 year death rate or lung transplantation was greater with the Liverpool epidemic strain (18.6%) compared with those infected with unique strains (8.7%) (Adjusted hazard ratio, 3.26 [95% CI, 1.41 to 7.54]; P=.01).

**IMPLICATIONS FOR LUNG TRANSPLANTATION.** These strains should ideally be reported to the transplant team for the application of appropriate infection control measures following lung transplantation.

**Non-Tuberculous Mycobacteria (NTM) and M. abscessus**

Two large epidemiological studies have highlighted the rise in the incidence of NTM over time. Olivier et al initially reported the rate of 12.8% in the late 1990’s. Levy et al from Israel
reported the rate of 22.6%. More astonishing was the fact that a higher rate of M. abscessus was also noted in both studies. M. abscessus constituted 16-31% of NTM isolates. Renna et al in their seminal paper linked this increase to the excessive use of azithromycin in the CF population. They noted that the escalating use of azithromycin over the last 5 years mirrored an increase in patients colonized or infected with NTM in their adult CF center. This was not explicable by changes in sputum sampling or microbial culture methods. In their analysis, long-term azithromycin use was associated with developing infection with NTM, particularly M. abscessus \( (P = 0.0009) \). When adjusted for age, azithromycin use remained significantly associated with NTM disease \( (P=0.00046; \text{odds ratio 9.80, 95\% CI 2.09-45.87}) \). 

**IMPLICATION FOR LUNG TRANSPLANTATION.** M. abscessus is a relative contraindication for lung transplantation in most of the centers across the world while NTM colonization prior to transplantation is not. However, one centre had reported higher mortality in patients colonized with NTM prior to transplantation. This study was not specific for CF patients and the true impact of this remains to be seen.

**Conclusions**

Newer organisms continue to emerge and pose significant challenges in managing CF patients undergoing lung transplantation. These emerging trends need to be monitored systematically and stress should be placed in devising appropriate therapeutic strategies to improve outcome.

**Disclosure statement:** The author receives research grants from Pfizer, Astellas, and Merck.

**References:**


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**WORD OF THE MONTH**

**Metagenomics**

Metagenomics is the study of metagenomes, genetic material recovered directly from environmental samples. The broad field may also be referred to as environmental genomics, ecogenomics or community genomics.

http://en.wikipedia.org/wiki/Metagenomics

Many thanks to Dana Willner for writing about it in her Article this month!

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**RATTLLING LINKS**

**NEW “LINKS” IN THE LINKS!**

Submit your proud photos and announcements to Susie Newton at susie.newton@ishlt.org
According to John Hales, Director of Liberal Studies at the University of Louisville, “rhetoric is as noble an art as exists on this planet; rhetoric is the art of clothing in words and in gestures and in presentation to a group the ideas that you have in the most effective way possible.”

His experience as a lecturer may be unparalleled having given thousands of lectures across the globe from the United States and Canada to Finland, South Africa, Australia and New Zealand. If we measure the success of a lecturer based on the number of different locales a lecturer has delivered and include their income excluding politics, then Mark Twain may be among the most successful lecturers of all times. He was not only a best-selling author but also a very popular live entertainer amassing visits to over 200 American cities and across Great Britain and her colonies of Australia, New Zealand, India, and South Africa at the end of the 19th century. Also, Mark Twain performed hundreds of after dinner speeches to specific audiences on special occasions.

Examining some of the important points gleaned from Mark Twain on how to prepare a presentation may actually improve our skills at mastering the art of lecturing and delivering an outstanding speech. First, as a review, allow me to refer you to the March 2012 Links, Volume 3, Issue 10 article on Procrastination, Preparation, Presentation, Prague. There’s no point to review the points from that article, but it will be worth our while to peruse it as we prepare for abstract season, presentations, and manuscripts while we avoid procrastination and reminisce over Prague.

Now if anyone has read Roughing It, you will find Twain’s first experience as a lecturer. First he set the stage with an advertisement that he used frequently such as: “Doors open at 7 ½. The trouble will begin at 8.” Supposedly, his first lecture was given in San Francisco, October 2, 1866 and by his own account, he was terrified. A few excerpts on his feelings just prior to his first talk... “I thought of suicide, pretended illness, flight... The tumult in my heart and brain and legs continued a full minute before I could gain any command over myself.” So it seems, anxiety is part of any lecture especially anyone’s first. But the following few points gave Twain command and control of his audiences in the palm of his hand that allowed him to tickle them whenever he chose. His success as a humorist comes from his mastery of “the pause” up to a minute or longer before he spoke, which may have actually started from his own fear in his first lecture, had audiences in riotous laughter before he uttered a word. Every lecture, after dinner speech, and introductory remark were carefully written out, rehearsed, memorized such that his presentations seemed spontaneous and conversational. And to intensify his humor, he mastered the “deadpan” technique telling the story gravely without a hint of emotion and again with that all important “pause.” Take note that Mark Twain was not only a best-selling author but also a very popular live entertainer.

It should also be noted that one of his most significant introductions still has tremendous influence on us today. It was December 12, 1900 when he introduced the 26-year-old Lieutenant Winston S. Churchill to speak about his adventures as a war correspondent in South Africa in the Grand Ballroom of the Waldorf-Astoria in New York (those of us fortunate enough to have attended the 16th ISHLT Annual Meeting in 1996 stood in this very ballroom). It should be further noted that Mark Twain and Winston Churchill both celebrated the same birthday, November 30th, both regaled against totalitarian aggressors and both promoted democracy. They differed on the righteousness of the South African War in the late 19th century. Take note of the subtle battle of words from Twain’s introduction of Churchill...

“yet I think England sinned in getting into a war in South Africa which she could have avoided without loss of credit or dignity—just as I think we have sinned in crowding ourselves into a war in the Philippines on the same terms. Mr. Churchill will tell you about the war in South Africa, and he is competent—he fought and wrote through it himself. And he made a record there which would be a proud one for a man twice his age. By his father he is English, by his mother he is American—to my mind the blend which makes the perfect man. We are now on the friendliest terms with England. Mainly through my missionary efforts I suppose; and I am glad. We have always been kin: kin in blood, kin in religion, kin in representative government, kin in ideals, kin in just and lofty purposes; and now we are kin in sin, the harmony is complete, the blend is perfect, like Mr. Churchill himself, whom I now have the honor to present to you.”
Churchill’s response on Twain some time later in the 20th century...

“Throughout my journeys I received the help of eminent Americans and my opening lecture in New York was under the auspices of no less a personage than ‘Mark Twain’ himself. I was thrilled by this famous companion of my youth. He was now very old and snow-white, and combined with a noble air a most delightful style of conversation. Of course we argued about the [Boer] war. After some interchanges I found myself beaten back to the citadel ‘My country right or wrong.’ ‘Ah,’ said the old gentleman, ‘When the poor country is fighting for its life, I agree. But this was not your case.’ I think however I did not displease him; for he was good enough at my request to sign every one of thirty volumes of his works for my benefit; and in the first volume he inscribed the following maxim intended, I daresay, to convey a gentle admonition: ‘To do good is noble; to teach others to do good is nobler, and no trouble.’”

Churchill also said...“There is nothing like oratory, it is a skill that can turn a commoner into a king.” Recall Colin Firth in The King’s Speech (interviewed in this fascinating segment on 60 Minutes). And as in King’s Speech, I give you Beethoven.

Beethoven, Symphony No. 7 in A Major Op 92 Allegretto

Beethoven Piano Concerto No. 5 in E-flat major

Beethoven’s Moonlight Sonata (played so beautifully by Wilhelm Kempff)

A summary on the art of speaking from these polished orators:
• Overcome obstacles
• Practice your delivery

To drill the art of delivering a great lecture down to the core:
• Grab the audience
• Repeat regularly
• Bring language to life – action verbs
• End powerfully
• Use simple gestures
• Use pauses to heighten the sense of drama.

One of the longest pauses ever recorded in a political speech came in an address Churchill made to the Canadian Parliament in 1941. He told the members of parliament that when he had vowed the previous year that Britain would fight on even if France surrendered to the Germans, the French generals told their country’s cabinet that “in three weeks England will have her neck wrung like a chicken. [Pause.] Some chicken. [Very long pause.] Some neck.” Churchill confidently waited for the laughter and applause to end during the pause before uttering the concluding phrase. It’s a classic moment of oratory:

SOME CHICKEN – SOME NECK! MR. CHURCHILL AT OTTAWA

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

ISHLT Call for Clinical Case Submissions
Submit your clinical cases and earn a chance to win complimentary meeting registration in 2014!

Inviting junior faculty and trainees to submit clinical case report abstracts for poster or oral presentation. The top oral presentation—based on novelty, clinical significance, and quality of presentation—will be awarded complimentary registration to the 2014 ISHLT meeting to be held in beautiful San Diego. Please follow the procedure for submitting abstracts to submit your clinical case(s).

Abstract Submission Deadline: November 16, 2012 @ 11:59 PM EST
For more information visit ISHLT Call for Abstracts
2013 Call for Nominations to the ISHLT Board of Directors

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 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, Pharmacists, 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
Richard Kirk, FRCPE, Pediatric Cardiologist, UK
Bronwyn Levey, RN, Nurse, Australia
Frank Pagani, MD, PhD, Cardiothoracic Surgeon, USA
Joseph Rogers, MD, Cardiologist, USA
Martin Strueber, MD, Cardiothoracic Surgeon, Germany
David O. Taylor, MD, Cardiologist, USA
George Wieselthaler, MD (Cardiothoracic Surgeon) USA

Thank you for your participation in this very important process.

Lori J. West, MD, DPhil
Immediate Past President, ISHLT
Chair, ISHLT Nominating Committee
Stuart Russell, MD
Johns Hopkins University School of Medicine, Baltimore, MD, USA
The Johns Hopkins Cardiac Rehabilitation Program At Green Spring Station Achieves National Certification
August 30, 2012, JH News

The certification, which is for three years, followed an intensive process of collecting and analyzing data on a wide range of patient outcomes and demonstrating the program’s adherence to the most current standards and guidelines. Read more...

Richard J Shemin, MD
UCLA Medical Center, Los Angeles, California, USA
UCLA uses new device to replace aortic valve in patients who can’t have open-heart surgery
August 15, 2012, UCLA Health News

UCLA has performed its first transcatheter aortic valve replacement (TAVR), using a new device approved by the U.S. Food and Drug Administration to replace an aortic valve in a patient who was not a candidate for open-heart surgery. Read more...

Abbas Ardehali, MD and David J Ross, MD
UCLA Medical Center, Los Angeles, California, USA
UCLA transplant doctors honored for life-saving work
August 23, 2012, UCLA Health News

State Senator Runner, who suffers from limited scleroderma and underwent a successful double-lung transplant at Ronald Reagan UCLA Medical Center in February, praises doctors’ dedication. Read more...

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Clinical Milestone: Excellence, Strong Research Help UPMC Reach 3,000 Heart, Lung Transplants
August 15, 2012, UPMC News

This month, UPMC became only the second transplant center in the country to have performed 3,000 heart and lung transplants. The 3,000 include patients from 43 states and nine countries and sets UPMC apart as a leader not only in clinical excellence, but also in research. Read more...

Charles E Canter, MD
St Louis Children’s Hospital & Washington Univ in St Louis
St Louis, Missouri, USA
Unprecedented study shows Berlin Heart device provides life-saving “bridge” for young children and babies

August 8, 2012, PR Newswire

A tiny heart pump that maintains blood flow in babies and small children with serious heart failure proved effective and life-saving in a pioneering study involving 17 institutions led by Texas Children’s Hospital and Baylor College of Medicine (BCM). A report on this study appears today in the New England Journal of Medicine. Read more...

Cardiothoracic surgeon Spencer Melby, MD, interventional cardiologist Seun Alli, M.D., interventional cardiologist Massoud Leesar, MD, and cardiothoracic surgeon James Davies, MD, are part of the interdisciplinary surgical team that performed Alabama’s catheter-based aortic valve replacement using Edwards Lifesciences SAPIEN transcatheter heart-valve-replacement system on an 89-year-old man. Read more...
Team NorCal Strikes Gold at 2012 Transplant Games of America
August 31, 2012, Stanford Medicine News
Organ-transplant recipients Jill Nolen, Anna Modlin, Isabel Stenzel Byrnes and Anabel Stenzel won gold in the women’s 4x50 medley relay at the 2012 Transplant Games of America. Read more...

Early Activation of Immune Response Could Lead to Better Vaccines
August 30, 2012, Einstein News
Researchers at Albert Einstein College of Medicine of Yeshiva University have discovered a new “first response” mechanism that the immune system uses to respond to infection. The findings challenge the current understanding of immunity and could lead to new strategies for boosting effectiveness of all vaccines. Read more...

When the Mango Bites Back
Gardiner Harris
August 27, 2012, NYTimes
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5 Questions: Yvonne Maldonado on Whooping Cough
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Viral Paths Toward Cancer Charted By Field Guide To The Epstein-Barr Virus
August 27, 2012, Medical News Today
Researchers from The Wistar Institute and Memorial Sloan-Kettering Cancer Center (MSKCC) have teamed to publish the first annotated atlas of the Epstein-Barr virus genome, creating the most comprehensive study of how the viral genome interacts with its human host during a latent infection. Read more...

U of T and SickKids first to grow lung cells using stem cell technology
August 27, 2012, University of Toronto News
Researchers at the University of Toronto and the Hospital for Sick Children (SickKids) are paving the way towards individualized medicine for patients with cystic fibrosis. Read more...

Q & A on West Nile Virus
Anahad O’Connor
August 23, 2012, NYTimes
What are the symptoms of West Nile infection? When should you see a doctor? Expert answers to questions about the current outbreak. More than 1,100 reported cases of West Nile outbreak have been reported to the C.D.C. Read more...

The Widespread Problem of Doctor Burnout
Pauline W Chen, MD
August 23, 2012, NYTimes
Up to half of practicing doctors say they experience emotional exhaustion, detachment or a low sense of accomplishment, putting patients and doctors at risk, a new study reports. Read more...
A change of heart: Vincent waits, and finally receives his new heart
Lisa Dutton
July 9, 2012, H News (Canada’s Health Care Newsletter)

Since September 4, 2011, Vincent has been kept alive by a mechanical heart—a Berlin heart. He’s celebrated Christmas in hospital; he celebrated New Year’s in hospital; he celebrated his 15th birthday in hospital. Read more...

Diseases From Animals Hit 2 Billion People a Year
Kate Kelland
July 5, 2012, Reuters

LONDON — A global study mapping human diseases that come from animals like tuberculosis, AIDS, bird flu or Rift Valley fever has found that just 13 such diseases are responsible for 2.4 billion cases of human illness and 2.2 million deaths a year. Read more...

Illegal kidney trade booms as new organ is ‘sold every hour’
Denis Campbell and Nicola Davison
May 27, 2012, guardian.co.uk

World Health Organisation estimates 10,000 black market operations involving human organs take place each year. Read more...

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Kidneys for sale: poor Iranians compete to sell their organs
Saeed Kamali Dehghan
May 27, 2012, guardian.co.uk

In the only country where the organ trade is legal, the streets near hospitals have been turned into a ‘kidney eBay’. Read more...
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Lionel Logue: I believe that sucking smoke into your lungs will kill you.
King George VI: My physicians say it relaxes the throat.
Lionel Logue: They’re idiots.
King George VI: They’ve all been knighted.
Lionel Logue: Makes it official then.

Lionel Logue: Do you know The ‘F word’?
George ‘Bertie’ VI: F-F-Fornication?

Lionel Logue: Pauses are fine, it shows solemnity
King George VI: Then I’m the solemnest King in the world!

Lionel Logue: How do you feel?
George ‘Bertie’ VI: Full of hot air.
Lionel Logue: Isn’t that what public speaking is all about?

Lionel Logue: You still stammered on the ‘W’.
King George VI: Well I had to throw in a few so they knew it was me.