Vincent’s Hot Summer Sense

The Heat is On (Beverly Hills Cop, 1984, oh and George Orwell comes to mind), for the summer is here in the Northern hemisphere. It is Aric Gregson from near Beverly Hills who explains the role on how the immune system polices the lung allograft milieu with every breath they take. Oveimar De La Cruz worries us more as we age and undergo immunosenescence. From bench to bedside, Pranava Sinha gives us insights on Fontan physiology from animal VAD models. Angela Lorts informs us that MCS in Pediatric Heart Failure is gaining momentum, and Janet Scheel provides an update from the PumpKIN patch. While Joanna Schaeenman tears out a page not from the football or soccer playbook on how to tackle ESBL related infection, the world cup captivates us with many nations traveling afar. Kevin Carney recaps his travel to down under in Melbourne thanks to the Traveling Scholarship from the ISHLT. From the Editor’s Corner, we plant the seeds of the pediatric years of France’s most notable champion of reason who erupted on the scene in a France which by today’s standards was brutal in the extreme with oppressive religious intolerance. Voltaire will enlighten France by pulling her out of ignorance, myth and superstition while summarizing the scientific method with one mere example on inoculation. Finally, a welcome relief to the heat of a huge work load has been delivered to the ISHLT with the addition of Megan Barrett native of Santa Ana, CA (yes the origin of the famous Santa Ana winds). She was blown in and hired on with the rest of the Administration of the ISHLT. She spent most of her life in McKinney, TX and recently graduated with honors with a degree in Liberal Studies from Oklahoma State University. Let’s give Megan a warm ISHLT welcome as she assists us with communications in the ISHLT Headquarter Office as her first article debuts In the Spotlight asking the question with a breath of fresh air, “Is it nice in Nice?”

Vincent Valentine, MD
Links Editor-in-Chief
IN THE SPOTLIGHT: Is it nice in Nice?

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Is it nice in Nice? This particular question can be answered with a resounding YES!! With sunny skies and gorgeous ocean views, it’s no wonder that this particular stretch of French coastline has become one of the top five vacation spots for the rich and famous.

While I personally find the April highs of around 65°F to be a little chilly for beach-going and water sports, don’t let that discourage you! The mild temperatures make the weather perfect for most outdoor activities and the seaside city has much more to offer than the mere opportunity to soak up the sunshine.

The beach, shopping and typical tourist traps aside, Nice has its fair share of unique architectural and cultural gems. Walk, bike or rollerblade your way down La Promenade des Anglais, or climb the steps to the top of Colline du Chateau for exquisite panoramic views of the city, seas and countryside. There are also numerous parks throughout the city that are known for their beautiful plants and design, making them seem more like an arboretum than a public park. If you’re more interested in “inner beauty”, check out the multitude of museums and churches, some of which are just around the corner. See some of the finest displays of Chagall or Matisse, or visit some of the smaller galleries which feature the more local talent.

But more important than these sights, let’s talk about the fragrances and tastes of Nice. Featuring traditional Mediterranean flavors, Nice is known for its unique cuisine, labeled “Cuisine Nissarde”. This particular label is only awarded to the restaurants serving certain local recipes using raw ingredients making them a necessary stop on any Nice visit.

Despite all the fun in and out of the sun, remember not to enjoy the scenery too much and to stop by the conference center from time to time to learn a thing or two. Afterwards? Take a stroll, take a tour, take in some of that incredible food and take away all the niceties that Nice has to offer.

ISHLT 2015 Annual Meeting & Scientific Sessions
April 15-18, 2015
The Acropolis
Nice, France
http://www.ishlt.org/meetings/annualMeeting.asp

Disclosure statement: the author has no conflicts of interest to report.
2014 Historical Interviews

In 2009, the ISHLT embarked on a history project to collect reminiscences and thoughts from leaders and pioneers in the field of heart transplantation to enrich the educational content of the Society. The project has continued each year with more interviews, including six that took place in April 2014 at the 34th Annual Meeting and Scientific Sessions in San Diego.

Click on any of the links below to watch these engaging and captivating conversations! To view interviews of many other transplant greats from past years, please visit:

www.ishlt.org/historyandArchives/videoInterviews.asp

A conversation with Leslie L Brent, PhD
April 12, 2014

A conversation with John H Dark, MB, FRCS
April 12, 2014

A conversation with Mandeep R Mehra, MBBS, FACC, FACP
April 12, 2014

A conversation with Hermann Reichenspurner, MD, PhD
April 12, 2014

A conversation with Amanda W Rowe
April 12, 2014

A conversation with Stephan Schueler, MD, PhD, FRCS
April 12, 2014
How to Tackle ESBL-related Infections: A Page from the Infectious Diseases Playbook

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Your patient, Mr. E., is a 68-year-old man with ischemic cardiomyopathy who underwent mechanical circulatory support device (MCSD) implantation and was doing well until fever and leukocytosis developed on post-op day 3. Prior to surgery he had been hospitalized for several weeks in an attempt at medical stabilization, complicated by a catheter-associated urinary tract infection requiring antibiotic treatment. After obtaining blood cultures, you begin to administer empiric vancomycin and piperacillin-tazobactam. On post-op day 5 the nurse notifies you that the microbiology lab called to report identification of an “ESBL-producing organism.” What should you do now, and could you have predicted this development?

“Extended Spectrum Beta-Lactamase” or “ESBL” is an enzyme produced by some Gram-negative bacilli that confers resistance to many commonly used antibiotics [1]. The Gram-negative organisms that can commonly develop this drug resistance are Klebsiella pneumoniae, Klebsiella oxytoca, and Eschericia coli; however, there have been cases reported involving other Enterobacteriaceae, including Enterobacter, Morganella, and Proteus [2].

The rise of ESBL-producing organisms is generally attributed to the increased use of third-generation cephalosporins during the 1980’s in an attempt to attack resistant Gram-negative bacteria expressing the more narrow-spectrum beta-lactamases prevalent at that time [1]. Widespread use of these antibiotics led to the evolution of “extended” beta-lactamase resistance such as SHV, CTX-M, and OXA. These extended spectrum enzymes are generally defined as beta-lactamases that confer bacterial resistance to penicillins, first-, second-, and third-generation cephalosporins and to aztreonam, but not the carbapenems [1]. These resistance genes are present on transmissible plasmids, which can be easily shared amongst bacteria. There are over 200 known ESBL enzymes, a list of which is maintained in an online database by the Lahey Medical Group [3].

Risk factors for development of infections due to ESBL-producing-organisms include increased patient age, hospitalization or residence in a long-term care facility, and previous antibiotic use [4]. Studies in kidney transplant recipients have also identified positive status for hepatitis C and the need for post-transplant surgery as potential risk factors [5]. Although ICU-related outbreaks are well-described, one study suggests that patients infected with ESBL-expressing organisms can lead to infection in subsequent occupants of the same room [6]. It is now also apparent that ESBL-producing Gram negative bacteria are a problem in thoracic organ transplant and MCSD recipients [7-9]. Significantly, these resistant bacteria are associated with increased mortality compared to non-ESBL organisms, with a relative risk of 1.85 for mortality in a meta-analysis of patients with
bacteremia [10]. The main driver of this increased mortality is likely due to delay in administration of effective antibiotic therapy.

Although quinolones may be used to treat simple urinary tract infections caused by ESBL-producing organisms, the mainstay of antibiotic therapy is the carbapenem class of drugs including meropenem, imipenem, and the relatively new antibiotic doripenem. Although beta-lactam/beta-lactamase combinations, such as piperacillin-tazobactam, may exhibit in vitro activity against these bacteria, it is hypothesized that with the increasing bacterial concentrations likely to be present in a naturally occurring infection, a rise in the MIC will make these drugs ineffective and they are therefore not recommended [1]. Ertapenem is a carbapenem with in vitro activity against most ESBL-producing organism and the convenience of once-daily administration; however, the lack of clinical data for use of this drug makes it suitable only for outpatient use in the setting of a clinically mild infection.

In a review of 1065 patients at the UCLA Medical Center who had undergone heart or lung transplantation, or MCSD implantation between 1996 and 2010, the incidence of ESBL-related infections in these groups was observed to be 2.2%, 5.5% and 10.7% of patients, respectively, with a mortality rate of 8.3% [9]. Surprisingly, the majority of these infections were due to *E. coli*, rather than *Klebsiella pneumoniae* as has been commonly described in the non-transplant literature, and many infections were recurrent, especially in the setting of pneumonia in lung transplant recipients. Risk factors for ESBL-related infection included increased duration of ICU stay, presence of nasogastric tubes and arterial lines, and recent surgery [9].

In conclusion, our patient Mr. E. was at increased risk of ESBL-related infection due to his age, hospitalization, and previous receipt of antibiotics. In order to combat these risks he should be switched to a carbapenem without delay, and catheters should be changed as possible. Defensive measures should be taken, in addition to the offensive measures to decrease the time to start of effective treatment, in an effort to prevent hospital outbreaks. The adoption of increased vigilance in patients with risk factors for infection is also suggested as a means of decreasing the clinical effect of these bacteria.

Although much attention has focused on resistant Gram-positive species, it is now also recognized that resistant Gram-negative bacteria pose a significant threat to survival in thoracic organ transplant recipients and after MCSD implantation. Future challenges will include facing the growing scourge of these ESBL-producing organisms, as well as other highly resistant bacteria such as *Acinetobacter* and the carbapenem-resistant *Klebsiella pneumoniae*.

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References:


Lung Allograft Injury: Need for Different Police for Every Breath They Take

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Because the lung allograft is continuously exposed to the external environment, it is uniquely susceptible to insults that do not plague most other solid organ transplants. The upper respiratory and gastrointestinal tracts provide a conduit by which both environmental and commensal microbes can enter the lung allograft. Under non-transplant settings such incursions rarely result in significant sequelae, like pneumonia. The lung transplant recipient is, however, in a disadvantageous position to adequately respond to microbial advance into the allograft due to both reduced mucociliary clearance and impaired immunologic responses. This increases the probability that non-commensal microbes, such as pseudomonas and aspergillus, can establish chronic colonization within the lung allograft. Chronic residence by pseudomonas results in an inflammatory allograft milieu that promotes fibrosis and angiogenesis, hastening the development and progression of chronic lung allograft dysfunction.

Given the fact that the lung allograft is exposed to the external environment, lacks some of the bacterial clearance mechanisms present in normal hosts and is within an immunocompromised host, it is not surprising that pulmonary infections are a frequent complication after lung transplantation. In fact, at our center, aspergillus and pseudomonas isolation occurs in approximately 35% of recipients. Bacterial infections constitute the vast majority of these post-transplant pulmonary infections [1–3]. Gram negative bacteria make up the majority of bacterial infections, with Pseudomonas aeruginosa being the most frequently isolated, occurring between 25% and 58% of the time [4–7]. At our center, like others, Staphylococcus aureus is the most frequent gram positive bacteria isolated in 14 to 30% of cases (15% of our recipients have had isolation of S. aureus) (ibid). It is no wonder that gram positive and negative bacteria have been widely studied and shown to increase the risk for BOS [5,7,8].

What plausible mechanism is there for this? Pseudomonas within the lung allograft is associated with both increased concentrations of interleukin 8 (IL-8), an ELR+ CXC chemokine, and decreased concentrations of IL-10 [9]. As expected, bacterial pneumonia causes BALF neutrophilia, but only gram negative bacterial infections lead to increased BALF IL-8 and subsequent decline in FEV1 [10]. The ELR+ CXC chemokines are critical chemotaxins for neutrophils, but also recruit T cells expressing their receptor CXCR1. These T cells are more frequent in the blood of cystic fibrosis patients colonized with pseudomonas, suggesting that chronic pseudomonal colonization does influence the adaptive immune system [11]. Furthermore, alveolar epithelial cells (AEC) may express both HLA class I and II during epithelial injury, such as occurs during acute cellular rejection [12,13]. Could it be that such inflammation leads to expansion of a pool of alloreactive lymphocytes?
Ps. aeruginosa increases AEC ELR+ CXC chemokine production, resulting in lymphocyte recruitment to the allograft. This potentially drives alloreactivity associated with airway fibrosis, suggesting an important role for pseudomonas in allograft outcomes. Vos [14], Botha [15] and Hachem [16] all showed that pseudomonas was an important risk factor for BOS, but none accounted for the allograft milieu. Clearly the milieu of the allograft must be considered when assessing the effect of pseudomonas on transplant outcomes. We recently investigated lung transplant outcomes and the interaction between pseudomonas and the allograft milieu as determined by BALF concentrations of the ELR+ CXC chemokines [17]. By using a multistate Cox Semi-Markov model we were able to separate the effect of pseudomonas at different stages post-lung transplantation. For example, in patients who had not yet developed BOS, pseudomonas infection, not colonization, increased both the risk of death and of subsequent BOS development. Elevated BALF levels of ELR+ CXC chemokines further increased the risk of developing BOS and of death after BOS. The chemokine CXCL5 was alone sufficient to increase both the risk of BOS and of death after BOS, while CXCL1 acted in conjunction with pseudomonas infection to increase the risk of BOS. Interestingly, pseudomonas colonization pre-transplantation was an insufficient stimulus to drive the development of BOS, but after BOS developed such colonization via an interaction with CXCL5 did elevate the risk of death after BOS, suggesting a heightened inflammatory milieu in the post-BOS allograft.

Single massive insults to the lung allograft appear to be important risks for subsequent CLAD, with community acquired respiratory infections and severe PGD being prime examples [18,19]. Repeated insults may be even more important, as increasing numbers of episodes of either pseudomonas pneumonia or acute cellular rejection carry greater risk than do single or fewer episodes [17]. Much like repeated insults, organisms that are able to create a chronic niche within the allograft may yet have the greatest impact upon the allograft state. Also, although we tend not to see frequent massive insults or infections with aspergillus, it remains a risk for the development of BOS [20]. Alteration of the allograft environment toward an inflammatory state should show a greater effect on allograft outcome if that influence persists over time, which both pseudomonas and aspergillus colonization tend to do. These organisms dwell within the lung to first create and then maintain an inflammatory milieu promoting angiogenesis and fibrosis. Markers for such conditions are likely to include lymphocytic bronchitis, BALF neutrophilia, and the ELR+ CXC chemokines and CXCR3 ligands, but these are markers of ongoing inflammation, acting as messengers, and of dubious importance in their own right. However, the effect of azithromycin in improving outcomes may be, in part, due to attenuation of lung epithelial cell ELR+ CXC chemokine production, arguing that the ELR+ CXC chemokines such as CXCL5 may have important downstream effects of their own [21]. Additional support for an increased inflammatory environment after the development of BOS comes from our finding that minor graft insults are more influential on outcomes post BOS than prior to BOS. Suddenly, events that could not influence graft outcomes before BOS such as pseudomonas colonization rather than infection, are now a viable risk. Efforts to reduce chronic carriage of either aspergillus or pseudomonas, particularly after the development of BOS, may offer one pathway to improve outcomes for selected lung transplant recipients.

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Immunosenescence and Lung Transplantation—What Does It Mean to Be Old?

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“Anyone who stops learning is old, whether at twenty or eighty. Anyone who keeps learning stays young. The greatest thing in life is to keep your mind young”. Henry Ford

Functional changes in the immune system associated with aging are collectively referred to as immunosenescence. This phenomenon correlates with fatal infections, increased risk of cancer, high levels of autoantibodies, decreased response to vaccines and, in transplant recipients, lower rates of rejection [1,2,3]. Phenotypically, a constellation of modifications occurs at different levels:

- **Cellular Immunity:**
  - Thymic involution with decreased numbers of naïve T cells
  - Increase of memory T cells and cytokines
  - Repeated antigen stimulation and homeostatic replenish (clonal) of T cell compartment
    - T cell depleting agents can precipitate the last phenomena
  - Limited T cell repertoire and dysfunctional activation of effector cells
  - Decreased capacity of immune reconstitution

- **Humoral immunity:**
  - Decreased naïve B cell output
  - Decreased somatic hypermutation => decrease of germinal centers?

- **Innate immunity:**
  - Reduced neutrophil chemotaxis and phagocytosis
  - Increased number of NK (Natural killers) cells, although with reduced cytotoxicity-cytokine and chemokine release

Ultimately, immunosenescence occurs due to a dysregulation of the intracellular pathway transduction and interaction among different cell lines (neutrophils, mononuclear cells, dendritic cells, macrophages, NKs). As the nature of the immune system is to dynamically “learn” and defend against different noxious challenges, its senescence equates to the inability to keep up with the plasticity of younger times.

Immunosenescence is especially relevant to transplantation. The number of solid organ transplant (SOT) recipients older than 65 years has increased consistently in the last 2 decades, with outcomes that are acceptable when compared to younger patients. Nevertheless, infection remains the number one cause of morbidity and mortality among elderly SOT recipients.
The 2006 ISHLT Pulmonary Scientific Council Consensus Report suggests a cutoff age of 65 for lung transplantation. This has been the practice at many institutions, mainly due to reported poor outcomes in an earlier era of lung transplantation [4]. Since implementation of LAS (Lung Allocation Score) in 2005, data has collectively demonstrated that appropriate candidate selection leads to favorable post-transplant outcomes in elderly recipients [5,6]. Vadnekar et al showed that although the >65 years lung transplant population had fewer rates of rejection, they tended to suffer from an increased proportion of infectious complications and malignancy [7]. These observations suggest that a complex influence of anti-rejection regimens on the senescent immune system of older recipients exist [1]. In fact, the intricate balance of anti-rejection drugs and the immune system is one of the greatest challenges in transplantation medicine, a challenge that is even more important in the elderly since immunosuppressant regimens are not adjusted based on age.

In addition, during the early post transplant period, morbidity and mortality from bacterial infections suggests that there are functional gaps related to the innate immune system. The key role of this compartment is also a focus of attention in lung allografts. Lung allografts are exposed directly to the environment and as such they face continuous non-specific antigenic challenges ranging from containment of the normal microbial flora to ischemic reperfusion injury. Its implication on chronic lung allograft rejection and tolerance is being increasingly discussed as well [8]. Clinical biomarkers are not available to elucidate these conundrums.

In this sense, a critical barrier keeping clinicians from preventing infections, malignancy and allograft rejection in older lung transplant recipients is the scarce information on underlying immune dysfunction related to age. We also lack the knowledge of how different compartments of the immune system and cytokine dynamics are modeled by antirejection medications and its variation through different ages. The role of specific infections by immunomodulating viruses that are prevalent in lung transplant recipients, such as CMV, EBV and other herpes viruses, complicates this puzzling picture even more.

Lung transplantation at extremes of age is becoming a common scenario with exciting clinical and research challenges. Development of novel diagnostic tests to assess infection risk, and of therapies to bolster the immune system, is needed if we aim to take better care of this elderly transplant recipient population. Likewise, more accurate bioassays are needed to monitor net state of immune response, to guide clinicians on pharmacologic manipulations, and to help the immune system refresh what it knew well years before.

In summary:

- Lung transplantation in the elderly population is expected to grow
- Aging is accompanied by increased risk of infection, decreased response to vaccine and high levels of autoantibodies
- Standard immunosuppression regimens are likely to exacerbate preexisting immunosenescence
• Bacterial infection is a significant cause of morbidity and mortality in older patients early after SOT
• Identification of patients at risk for infection will likely improve outcomes
• New biomarkers will be valuable to assess the risk for bacterial infections after transplantation

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

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News from the PumpKIN Patch

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In February 2010 NHLBI funded the Pumps for Kids, Infants, and Neonates (PumpKIN) Pre-clinical Program for preclinical testing of mechanical circulatory support devices for infants and children with heart failure. The goal was to support the continued development and necessary FDA testing of promising devices at that time, including some of those from the 2004 NHLBI funded Pediatric Circulatory Support Program. For us in the pediatric community, this was great news. At present, our only option for long term support in our smallest patients is the Berlin Heart EXCOR, initially approved in Europe in 1996, approved in Canada in 2009 and the US in 2011. Prior to approval, it was widely used on a compassionate basis. While the Berlin Heart EXCOR has been a valuable and necessary therapy that has certainly saved many lives, it is paracorporeal and pulsatile. The advantage of intracorporeal, continuous flow devices, such as those developed in the PumpKIN program, has been clearly shown in adults and results in fewer thrombotic complications, increased mobility and the possibility of hospital discharge. It has also been suggested that there is less risk for allosensitization with continuous flow devices. As our waitlist times increase, an intracorporeal pediatric continuous flow device would be a great addition to our growing armamentarium against pediatric heart failure.

This week I had the opportunity to attend The Annual Meeting of the American Society for Artificial Internal Organs here in Washington, D.C. An update on the PumpKIN trial was given by the director of the program, Tim Baldwin, PhD, The Deputy Chief of The Advanced Technologies and Surgery Branch in the Division of Cardiovascular Sciences at NHLBI.

The trial is getting ready to enter its clinical phase. In 2013, the protocol was reviewed by the NHLBI PRC and by the FDA (through a pre-IDE meeting), and clinical sites were selected. The IDE was submitted to the FDA in late April 2014 and an amended IDE, containing additional test results, justifications, and documentation to address FDA’s feedback, will be submitted in this July. Central training has begun, starting with a session completed at the Duke Medical Center and another scheduled for the last week of June at Texas Children’s Hospital. Initially two advanced compact ECMO devices, the Infant Jarvik 2000, and another continuous flow miniature VAD were funded through the PumpKIN program. At present the Infant Jarvik 2000 is the only device left as part of the PumpKIN trial. Roughly the length of a paper clip, this device features a new type of miniature blood immersed ceramic bearing called the cone bearing, which has decreased the thrombosis seen with the previously used pin-in-sleeve bearings. Rather than the single arm study matched with ECMO of the Berlin Heart trial, this study will be a two arm prospective randomized trial with patients randomized 1:1 to receive either the Berlin Heart EXCOR or the Infant Jarvik 2000. The goal sample size is a total of 88 patients with 44 receiving each device, an increase from the 24 patient enrolled in the Berlin Heart Study. Patients will need to be 4-15 kgs or have a BSA < 0.6 M2. While the Berlin Heart Study targeted patients 3.6-13.6 kgs or <0.7 M2.
Twenty-two centers will be participating in the trial. The end point of the trial will be survival of anesthesia for transplant, survival at 180 days or survival until explant for recovery as opposed to the Berlin Heart Study where the outcome was death. All enrolled patients must be eligible for transplant. The clinical phase is expected to start later this year and run through 2018 with data analysis beginning the same year.

Challenges have plagued this trial in the past and as it proceeds, it will continue to face a variety of obstacles. With the Berlin Heart now being used in many centers, the Infant Jarvik 2000 will be competing against a device that is FDA approved and has a proven track record. The number of clinical centers participating in the study and submitting data will present its own challenges. In addition, the limited patient population requires the participation of a larger number of centers than the original 22 involved if the target enrollment is to become a reality.

Despite these obstacles, it remains very important for the field of pediatric heart failure that the trial move forward. The portability and risk profile of continuous flow devices have become clearly preferable to paracorpeal pulsatile devices for use in adults and larger children. As our use of devices grows, so does our transplant list and waiting times. Our patients' quality of life would be significantly improved if they could wait in the comfort of their own home. It is also within the realm of possibilities that the future generation of devices will have better survival curves than those of transplantation. As a pediatric community, we are very anxious to see what we will learn from the PumpKIN trial—we just wish we did not have to wait so long....

Special Thanks to Tim Baldwin PhD for his help with this article.

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MCS in Pediatric Heart Failure Continues to Gain Momentum

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The pediatric heart failure community continues to build momentum with robust data collection and clinical trials. Pedimacs is gaining acceptance with over 30 centers now enrolling their patients in the national database. With higher levels of enrollment, the database has collected data on more than 125 children. These data are similar to that of INTERMACS and will be formatted the same, with the new version of INTERMACS/PEDIMACS 4.0. The online data entry is currently under revision but will be back up for online data entry soon.

Many institutions have recently gained IRB approval to waive consent for Pedimacs data collection, which may further increase enrollment. At this time, entering data into this pediatric registry is free of charge. With the completion of the Berlin EXCOR, post approval study data on Berlin heart patients can also be entered into Pedimacs. We anticipate the data on the first 100 pediatric VAD patients entered into Pedimacs to be presented at an upcoming meeting this Fall.

In addition, the Pedimacs steering committee is starting a Web-based VAD conference to share experiences across the various VAD centers. There is a strong commitment to collaborating across centers in order to better the care for children with end stage heart disease. With the small numbers of patients that each center cares for, we must continue to learn from each other.

The PumpKIN trial has completed phase 1 of the training for the VAD trial. The trial will compare the FDA approved, pulsatile, Berlin EXCOR to the continuous flow, Pediatric Jarvik 2000. Children included in this study must be >4kg and <15 kg and have 2 ventricle anatomy. The study should start late 2014 and high volume VAD centers will be the first to be randomized to the new device. One of the inclusion criteria for use of this device is that the child should be transplant eligible. (For more details on the PumpKIN trial, see the article by Janet Scheel.)

Planning for the Syncardia 50 cc Total Artificial Heart trial is underway and the study will have both a pediatric and adult arm. Meetings with the FDA have occurred and the HDE arm for pediatric patients is expected to start enrollment in October 2014. The trial design will be available in July and negotiation of clinical trial sites will begin at that time.

The next meeting that will have a strong VAD focus is the Pediatric Heart Failure Summit. This meeting is co-sponsored by Cincinnati Children’s Hospital Medical Center, Texas Children’s Hospital and Toronto Sick Kids. This year the meeting will be held in Cincinnati from September 11-13, 2014. There will be a pre-meeting symposium with hands on VAD training and an introduction to using simulation to educate staff and families about VAD troubleshooting.

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Insights into Fontan Physiology from Animal VAD Models

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While the focus of most research on mechanical assistance of failing Fontan circulation is based on providing a subpulmonary pump (artificial RV) to push blood through the passive Fontan circuit, researchers at Children’s National Medical Center have proposed a novel concept of pulling blood through the Fontan circuit by using a standard left (systemic) ventricular assist device.

This concept was proven in a large animal Fontan model through the restoration of cardiac output to almost baseline biventricular levels using an atrial inflow and ventricular outflow configuration.

What was more interesting is that the augmentation in the cardiac output was even greater in partial (Bidirectional Glenn) rather than total cavopulmonary connection (Fontan) circuits. This significant increase in total flows resulted in increased oxygen delivery to the tissues despite more desaturation in the assisted Glenn.

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International Traveling Scholarship Report from Down Under

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The impetus for my trip to The Alfred started in 2007 while researching the clinical management of a potential lung donor. During my literature search, three names kept on repeating; Snell, Levvey and Oto, from The Alfred Hospital. At the 2008 ISHLT meeting in Boston, I attended a symposium on donor management that was chaired by Greg Snell. At the conclusion, I introduced myself to Greg, and was subsequently introduced to Bronwyn Levvey. Both Greg and Bronwyn took the time to answer my questions and offered their clinical expertise, both on donor management and on recipient selection.

Over the years I have had multiple opportunities to interact with Bronwyn during our work with the ISHLT Nursing, Health Science, and Allied Health Council (NHSAH). During the 2011 ISHLT meeting in San Diego, there was an announcement that the ISHLT would be awarding travel scholarships to members that were interested in expanding their knowledge base. While myself and several other NHSAH members discussed potential international visits, I didn’t formally apply until the August 2012 submission period, and was notified in October 2012 of my acceptance.

The purpose of my trip was to work closely with Greg and Bronwyn to learn their donor management strategy, recipient selection, postoperative recipient management and outpatient recipient follow-up. Also, because The Alfred has been at the forefront in the use of lung donors after cardiac death (DCD), I wanted to obtain the national and regional policies towards DCD management to develop a policy at my local hospital. Finally, I hoped to meet with the local organ procurement organization, Donate Life, to understand local and national organ donation protocols and policies, and to follow how they interact with The Alfred Lung Transplant Service.

After spending three weeks with the Lung Transplant Team at The Alfred, I believe the key to their success to be their multi-disciplinary collaboration, their commitment to clinical research and evidence based practices. Detailed algorithms for hemodynamic, respiratory and pain management were developed by the Intensivists with feedback from the bedside nurses and AIR1 consultants, with clear instructions when to call for Senior help, while outcomes research demonstrating the ideal route of calcineurin Inhibitor administration or the ideal length of outpatient physiotherapy after lung transplant is the norm.

I would like to thank everyone who made my visit to The Alfred so successful. Without the support from Greg, Bronwyn and the rest of the Alfred Lung Transplant team, my wife and children, and The Hospital of The University of Pennsylvania’s Lung Transplant team, this trip would not have
been possible. Lastly, I would like to thank the ISHLT Board of Directors for encouraging their members to pursue the exchange of knowledge not only in spirit, but by financially supporting these endeavors. Thanks again!

Disclosure statement: the author has no conflicts of interest to report.
2014 Annual Meeting and Academy Content Now Available!

The ISHLT 34th Annual Meeting and Scientific Sessions was conducted April 10-13, 2014 in San Diego, CA, USA before 3200 attendees, our largest ever audience. The content of the meeting covered a broad, multidisciplinary range of topics of interest for our members and professionals who manage and treat patients with end stage heart and lung disease, including those engaged in transplantation, pulmonary hypertension, mechanical circulatory support, heart failure, infectious disease, pathology, pharmacy, basic science, nursing and social science.

To enhance the value and distribution of the content presented at the meeting, we have digitally captured all 29 symposia, all 48 oral abstract sessions, and all 3 Plenary Sessions, and we are offering them via online access for a little as $10/$13 (member/non-member) per 90-120 minute session. You can purchase online access to the entire conference, or you can purchase a package of sessions based on specialty topic.

Three one-day ISHLT Academies are also available on-line: 1) Core Competencies in Heart Failure and Transplant Medicine, 2) Core Competencies in Basic and Translational Science in Thoracic Transplantation, and 3) Core Competencies in Nursing, Health Science, and Allied Health in Thoracic Transplantation.

To purchase the meeting content, visit www.ProLibraries.com/ISHLT. Your purchases will be stored in a library on the ProLibraries site and will be available for unlimited access through March 31, 2015. We hope you enjoy this service and take advantage of the wealth of information now being offered in digital format. We welcome and encourage your feedback on how we can improve this service going forward.

If you purchased access on-site at the meeting, you should have received an email with a code providing you with access to the sessions you purchased. If you did not receive this email, please access the online content site and click on the customer support link for assistance.

6 FREE SESSIONS NOW AVAILABLE!

We are very pleased to announce that the 3 Plenary Sessions as well as 3 of the concurrent sessions are being offered free to all, members and non-members. Simply visit the ProLibraries site and click on "Browse Presentations" to find these sessions, then click on the "Play Session" link. Or click on the links below to go directly to each session.

- PS01 - Opening Plenary Session
- PS02 - Plenary Session - Saturday
- PS03 - Plenary Session - Sunday
- CS11 - Clinical Case Dilemmas in Thoracic Transplantation: The Best of the Best
- CCSY28 - JHLT at ISHLT: The Year in a Capsule
- CS30 - Philip K. Caves Candidate Presentation Session
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Voltaire, Jesuit Education, Philosophe, and Inoculation

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The most widely quoted statement misattributed to Voltaire, “Although I disapprove of what you say, I will defend to the death your right to say it,” (on the principle of freedom of speech) written by English biographer, Evelyn Beatrice Hall who wrote under the pseudonym S.G. Tallentyre in her book, *The Friends of Voltaire*, 1906. A witty description of the salonnières (to WIT, see Salonnieres (fl. 17th and 18th c.)) and the mind of France can be found in her other book, *The Women of the Salons, and Other French Portraits*, 1901. With this and the last issue of the ISHLT Links Newsletter, she describes how women shaped the life and afterlife of Voltaire. In this issue we will turn to Voltaire’s pediatric years.

Voltaire was fortunate to be deeply immersed in the custom and thinking of early 18th century France. This was the time where the French word for a philosopher of the Enlightenment philosophe, emerged. Recall René Descartes, the Father of modern philosophy and analytical geometry, who laid the foundation of rationalism and is best known for “Je pense, donc je suis; I think, therefore I am.” Then it was Jean-Paul Sartre, a 20th century French philosopher, probably influenced by Voltaire who, through his doctrine of existentialism and human emotions, restated Descartes’ famous quote, “I am. I am, I exist, I think, therefore I am.” Then consider this, I am that I am, therefore I think. All of this thinking may lead us to Shooting Rubberbands at the Stars, an album produced by Edie Brickell and New Bohemians which debuted their 1988 hit, *What I Am*. On the B side is “I do.” Edie Brickell is married to Paul Simon, but enough on this already. A philosophe is not a systematic formal philosopher, but someone who examines critically and analytically important problems of their time without prejudice.

To better appreciate the France that educated Voltaire one has to study the reign of Louis XIV, the Sun King – le Roi-Soleil, who held the longest reign of any monarch in European history, from age 4 until his death in 1715 at age 76. Louis XIV’s rule culminated in stifling orthodox and censorship that yoked and choked the dynamism of 17th century French intellectual life. The last two decades of the Sun King’s reign leading into the 18th century were a period of unprecedented suffering in modern France with unbearable taxation and widespread famines. This led to intense moral and political criticisms. These criticisms from literary works and great works of art indirectly criticized Louis XIV’s leadership through idealized portraits of great rulers of the past. The descriptions of the medieval monarchy depicted a King as a father who would nurture his country in harmony. Voltaire in his criticism did not use the past as a model, but instead made appeals to the future as a contemporary practice or he would directly criticize the abuse around him. France was not the only country stifled by the increasingly stringent censorship. Many works by radicals with philosophical and heterodox thoughts of moral and political criticisms circulated throughout France and Europe. Many of these thoughts were published in learned journals from Holland where there was no
censorship. The world of letters became an international republic in response to orthodox and censorship. These letters were smuggled into France then studied and discussed. Eventually the Jesuits would create their own learned journals primarily out of demand from the highly educated citizens of Paris and France. The Jesuits wanted to be part of these erudite and highly critical appraisals to familiarize everyone about the debates across Europe. Finally, France experiences the Cultural Revolution, known as the regency. In 1715, Louis XIV dies. Louis XV, the heir apparent, is a child therefore his uncle Philippe d’Orleans serves as Regent of the Kingdom from 1715-1723.

Philippe d’Orleans, a libertine or a free-thinker, was interested in the New Philosophy. He was full of deistic ideas and some of the works of the most heterodox minds and poets. Censorship was nearly abolished, resulting in a great outpouring of critical reviews that circulated in the circles where Voltaire was learning. The vitality of the Jesuit education played a major role in shaping the thought of the enlightenment in general, and Voltaire in particular. But Voltaire describes his own education at the hand of the Jesuits as a period of just Latin and bad poetry. Ironically the Jesuits, who run the best secondary schools in France, educate the minds of those who created the enlightenment culture. How is it that all these great heterodox, innovative and enlightened thinkers are educated by the Jesuits in France who received no striking education? How is it that these philosophes emerged as open-minded critical thinkers and are remarkably attuned to a world of ideas? What did the pediatric population learn from a late 17th and early 18th century Jesuit education?

From childhood to adolescence, Voltaire’s education was focused on logic, disputation and rhetoric. The categories of logic and analysis of argument were learned by studying debates where the actual points of contention were reviewed. What would it take to win the argument of pro or the argument of con? One had to always confront all the strongest objections of what one is setting out to prove or demonstrate to overcome these objections. These Jesuit students learned to look for possible objections as a logical exercise not an end of itself but as a habit of their minds.

From childhood to adolescence, Voltaire’s education from the Jesuits included a profound study of the classics in literature and a modern analysis of these classics. Among the classics studied were those authored by the pre-Christian romans including Horace, Cicero and Lucretius. Studying Horace provided an arsenal of witty satires on religion and society and studying Cicero and Lucretius offered an arsenal of anti-religious arguments, ironically from the Jesuits of orthodox Paris.

From childhood to adolescence, Voltaire and his fellow students were learning and were encouraged to write in Latin and in French as Voltaire evolved into a poet and a writer.

The Jesuits educate the uppermost strata of French society which established Voltaire, who himself was of “low birth,” a bourgeois and not a “blue-blood” aristocrat, with important social connections or links. These links gave him lifetime patronage, protection, support and influence in important circles. Voltaire further profits by attending Lycée Louis-le-Grand, the most prestigious college in France with the finest teachers of the Jesuit order and the crème de la crème of the aristocratic society among its students. Some notable alumni from Louis-le-Grand include, among others:
Marquis de La Fayette, Robespierre, Jacques Chirac, Molière, Diderot, Victor Hugo, and the aforementioned Jean-Paul Sartre.

When the regencies lifted the censorship, many political satires against the regents came from literary circles that included Voltaire. Where were his aristocratic friends and protectors when he was accused of a couple of political satires against the regents? He was sent to the Bastille for the first time for nearly a year, not the dreary place depicted in Dickens’ Tale of Two Cities; if you did anything serious in France you were killed, maimed or sent to the galleys to row in the Mediterranean. Voltaire, with some connections, was able to dine with the Governor of the prison and began working on some of his most celebrated works. Upon his release from the Bastille, he enjoyed more literary success and entered the world of philosophical and literary courts in Paris where he became part of the La Société du Temple, Voltaire’s intellectual home until 1723. This was a gathering of heterodox and free-thinking men and women of letters that had been previously bullied by Louis XIV reign but had become prominent during the Regency. He becomes a courtier in Versailles but experienced ridicule because many of the aristocrats know he was from low birth, however he spoke and wrote well at a time when the aristocrats and royal power wanted to be associated with the world of thought and letters. He enjoyed meteoric success beginning with the retelling of Sophocles tragedy, Oedipus. He wrote an epic poem about Henry IV, La Henriade, and along with his tragedies, he was celebrated on the Parisian stage. His reputation soared to a height where he was lauded as the highly sought after Poet and Playwright of France and was considered the first Great French Epic Poet. His early works for the French stage and theater were influenced by a great deal of new philosophical input with themes on religious toleration, abuses of power and the need for aligning justice and power as well as the dangers of fanaticism. What goes up must come down.

He met Chevalier de Rohan, an heir of an aristocratic family, who, among many other insults, ridiculed Voltaire on social pretentions, for example “how convenient is it to give oneself a new name.” Voltaire, never at a loss for wit, replied, “better to give oneself a new name than to disgrace an old one.” Because he was a commoner, neither Voltaire’s aristocratic friends nor the justice system offered any help after the retaliation from Rohan’s thugs who beat Voltaire up in the street. Again, he was imprisoned in the Bastille but negotiated an exile to England from 1726 – 1729. He knew France was a country with aristocratic and royal abuses of power. He knew life was unpredictable under a system of arbitrary wills and he believed he was leaving a country that lacked respect for men of letters, science and learning. France did not appreciate the effect philosophes had on a nation or on mankind. Voltaire would discover a different model of the world in England with a variety of new ideas. One thought in particular he published upon his return to France in the Philosophical Letters, Letter XI – On Inoculation – a seed or germ of an idea for Edward Jenner (see What Would Edward Jenner Say? by Stanley Martin, MD, ISHLT 2011 Volume 3, Issue 4, Page 10) on vaccinations in children. From this Voltaire taught us to judge results by their usefulness and consequences, and through reason and experience to reduce the suffering of the human condition. In this letter, he described the practice of variolation brought back from Turkey to England by Lady Mary Wortley Montague. The Circassian population had found that they could sell their daughters unmarked by smallpox for a higher price to the Ottoman Sultans and seraglios. Voltaire reasoned that exposure to a benign case of smallpox conferred immunity,
avoided disfigurement and saved lives, thus increasing the value of the young women sold into slavery. Voltaire provided this example of English empiricism, which is learning about nature inductively from the particulars of experience to generalizations derived from these particulars which can be tested. He summarized that knowledge can move us from helplessness to understanding and happiness. However, inoculation in France was resisted by religious and medical authorities. Theology argued that this was human intervention against divine providence, and medicine argued that this violated the Hippocratic Oath which begins with "do no harm". Inoculation with smallpox gave a disease to someone and by tradition doctors could not do this.

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