Vincent's Super, Olympic Valentine's Sense

For the month of February 2014, we have what might be the most expensive television program in America, Super Bowl XLVIII; the 22nd Winter Olympics on the World's stage; Valentine's Day and President's Day, mostly commemorating George Washington and Abraham Lincoln. Because of this sports-filled February and in keeping with our focus on improving communication, the Editor's Corner will provide you some everyday language derived from the vocabulary of sports, but I will punt on this for now.

In this issue of the ISHLT Links for the month of February 2014, we focus on lung transplantation and infectious diseases. **Keith Meyer** from the University of Wisconsin School of Medicine refines and defines our classification of BOS. The unchanging outcomes over the years have kept lung transplant specialists whittling away at the various expressions of allograft dysfunction. With clearer definitions of what has been observed over the years by splitting the old lump of BOS into seemingly more meaningful parts may actually allow us to lump our findings into the split categories of phenotypic expressions of allograft injury leading to more suitable and future investigations. Nevertheless, most lung recipients will have architecturally distorted airways down to the bronchioles in their allografts rendering them all the more vulnerable to infection along with their chronic immunosuppression.

Dana Willner and **Dan Chambers** from the University of Queensland in Australia explore the respiratory mycobiome of lung recipients and shed potential bright, shining or twinkling concepts before our very eyes through these fungal communities. These concepts may be the diamonds in the rough that will lead us to the golden fleece of our understanding. **Eileen Marziaz** of Duke University provides a treatise on whether we should treat or not treat nontuberculous mycobacteria isolated from surveillance examinations of the airways of lung recipients. Of course, another means to perhaps maintain microbiota diversity of the respiratory tract and other systems of lung recipients is through prevention by vaccines. **Deepali Kumar** of University Health Network in Toronto summarizes the importance of pre-transplant vaccination for optimal patient care. Other prevention strategies include universal prophylaxis or pre-emptive therapy. **Luciano Potena** from the University of Bologna shares with us the equalities and inequalities of CMV prevention strategies. During this review he conjures up the "iron curtain" originally described by Winston Churchill that had descended across Europe dividing the Soviet Union and her satellites from the democratic nations of western Europe at the end of World War II in 1945. For more on CMV and Winston Churchill the ISHLT Links refers you to the Glen Westall's summary in the June 2011, volume 3, issue 1, page 6, CMV – The Gathering Storm.

If not prevented by vaccines or prophylactic strategies then infections occur, most frequently respiratory infections in lung recipients. Most assuredly antibiotics are prescribed and more than likely too long and too frequently. The result is a change in the microbiota not only in the respiratory tract but the gastrointestinal tract as well. Then waiting in the wings, not Cupid's wings, but is the nightmare of Clostridium difficile. **Cameron Wolfe** of Duke University summarizes the emerging success of fecal microbiota transplant for recurrent C diff infection and what lies ahead in

the revolt of bringing back the homeostatic diversity of lower intestinal microbial communities. Revolting! Repulsive! Yet successful. But I leave you with this, for Valentine's Day, you've got to love a species who shares its species. And there are published reports that poop-throwing may be a sign of intelligence, at least in chimpanzees.

Don't forget those chocolates!

Vincent Valentine, MD
Editor-in-Chief, ISHLT Links Newsletter

In the Spotlight: ISHLT 2014 in *Sun*sational San Diego!

Featuring Meeting Highlights in Pulmonary Transplantation and Infectious Diseases

At ISHLT 2014, there will be a number of symposia with primary content of interest for any lung transplant or infectious diseases healthcare professional, as well as many addressing basic science, nursing, pharmacy, pediatrics and pulmonary hypertension, which will have content of interest to the lung transplant and infectious diseases specialists. Find out which sessions will be of most interest to you, and plan your trip to San Diego TODAY!

Thursday, April 10, 2014:

PRE-MEETING SYMPOSIUM 4: Lung Transplant Candidate Selection: Have We Pushed the Envelope Too Far?

Existing selection criteria aim to discriminate those expected to thrive from those anticipated to do poorly following lung transplantation. The last 5 years has witnessed an explosion in lung transplantation for older and sicker candidates who fall outside of selection guidelines. Since these criteria were developed through consensus expert opinion and established, epidemiological studies have confirmed increased mortality for certain criteria including age above 55, extremes of weight, and, possibly, frailty. The common thread underpinning these observations is body composition derived inflammation. This symposium aims to reevaluate key selection criteria through the lens of body composition and inflammation. It will also explore intervention strategies that may be applicable to all lung transplant candidates.

PRE-MEETING SYMPOSIUM 5: Lung Transplantation: Decoding Early Engraftment Events That Control Survival

It is becoming clear that many significant risk factors for lung transplant rejection occur within the early engraftment period. Also, it is apparent that the current immunosuppression strategies have not significantly improved patient survival in the last decade. Recent developments in experimental lung transplantation have helped uncover novel mechanisms that link innate and acquired immunity following engraftment. In this session, we propose to present new insights into ischemia reperfusion injury, T cell activation, and humoral immunity that impact the maintenance of allograft tolerance as well as long-term survival, using a clinical case to guide the presentations. The goal of these presentations is to educate the wider transplant community of potential new therapeutic targets and translational opportunities for the development of novel immunosuppression approaches for lung transplant recipients.

PRE-MEETING SYMPOSIUM 9: Invasive Fungal Infections Among Cardiothoracic Transplant Recipients: Consensus Guidelines and Recommendations from the ISHLT Fungal Expert Panel

Learn more about the fungus among us in this session. A consensus and guidelines for invasive fungal infection developed by the ISHLT fungal expert panel will present a review of the literature and recommendations regarding the epidemiology, diagnostics, therapeutics and prophylaxis of fungal infections among cardiothoracic transplant recipients.

PRE-MEETING SYMPOSIUM 10: The Many Faces of Chronic Lung Allograft Dysfunction
Lung allograft dysfunction occurs in many different ways. These present and progress in differing fashions; treatment, although not well developed, could be different between different types. This session will address these issues.

PRE-MEETING SYMPOSIUM 15: Bad Bugs? Optimize the Drugs! combines brief illustrative case presentations followed by state-of-the-art lectures reviewing issues and controversies in antiviral, antibacterial, antifungal and antimycobacterial therapeutic drug monitoring (TDM). Although there is a small amount of published information on TDM and azole antifungal agents in heart lung transplantation, the antibacterial and antiviral drugs have been very neglected. Inappropriate dosing may lead to treatment failure, toxicity and the development of resistant organisms, both of which can be catastrophic in the transplant setting.

PRE-MEETING SYMPOSIUM 16: Ex-Vivo Lung Perfusion (EVLP): Evolving Strategy For Improved Donor Lung Management
The last 5 years have witnessed an exponential rise in the use of ex-vivo lung perfusion (EVLP) for both basic scientific research and clinical practice. Various ex-vivo devices are now available for supporting donor lungs. This symposium aims to provide a timely update on the following aspects of EVLP: Expanding the donor organ pool; Cold storage with subsequent functional assessment versus primary physiological support; Limiting cold ischaemia; Sanguinous versus asanguinous perfusion; Repair and reconditioning of poor donor organs; Improving functional assessment of donor organs; Supporting lungs from DCD; and Clinical trials. The symposium also aims to meet the significant educational need of fully appreciating the principles and practice of EVLP. An additional benefit from this educational session is to stimulate wider evidence-based clinical adoption of this technology to expand the donor pool, improve donor organ function, and potentially extend graft and recipient survival.

PRE-MEETING SYMPOSIUM 22: Global Perspectives on Donation after Circulatory Determination of Death in Lung Transplantation
It remains true that most donor lungs offered for transplant are discarded with substantial patient numbers dying on the waiting list. DCD has become widely accepted now in lung transplantation with increased experience. EVLP as a new method of treating and evaluating marginal lungs is being used effectively as well and will be more widely adopted. However, the increased complexity and cost of EVLP is one reality that may limit clinical adoption. What is the best way forward to join these practices and employ EVLP most effectively to quickly impact lungs transplanted? Are these technologies additive, competing, should they be combined international perspective? This symposium will explore these issues.

PRE-MEETING SYMPOSIUM 23: State of the Art Update on Infectious Disease Issues in Pediatric Thoracic Transplantation
The infectious disease sessions at ISHLT traditionally have focused on adults rather than children. Some of the pediatric responses to infections are quite disparate from those of adults. This session will provide a state of the art update based on the latest data in pediatrics.

Friday, April 11, 2014:

SUNRISE SYMPOSIUM 4: Controversies in Lung Transplantation
For the coffee-fueled early birds, this symposium will address some controversial areas in lung transplantation in the form of Pro and Con debates. This is a very popular format and stimulates great discussions.

SUNRISE SYMPOSIUM 5: What You Always Wanted to Know About LISH (Laboratory Tests, Infectious Agents, Special Situations, Hidden Infections) but Were Afraid to Ask
In the field of infectious diseases there are many accepted standards for treatment and diagnoses. However we do not always know the real explanation for them nor do we question them. This symposium will attempt to clarify several main topics in ID from laboratory to therapy.

CONCURRENT SYMPOSIUM 26: Infections in Mechanical Circulatory Support Devices – Understanding and Conquering the Beast
This symposium will focus on pathogenesis, recent guidelines on diagnosis, as well as medical and surgical approaches for the management and prevention of Mechanical Circulatory Support Device-associated infections.

Saturday, April 12, 2014:

SUNRISE SYMPOSIUM 9: CMV Infection in Lung Transplant Recipients: Are We Ready for Personalized Medicine?
CMV infection continues to be a clinical challenge in select lung transplant recipients (LTRs) despite advancements in prevention and treatment strategies. Identifying LTRs at risk for recurrent viral replication and/or allograft injury is essential for adjusting antiviral therapies and improving long-term outcomes. In this session, the latest in translational bench-to-bedside approaches used to evaluate those at risk for active CMV infection and its sequelae will be discussed. By the completion of this session, attendees will be familiar with measurements of CMV-specific immunity to monitor and predict CMV outcomes in higher-risk LTRs, promising new therapies to treat emerging CMV resistance, and pro/con viewpoints for correlating CMV replication in the lung allograft and the risk of BOS.

12:05-12:55 PM INFECTIOUS DISEASES SCIENTIFIC COUNCIL MEETING
1:00-1:55 PM PULMONARY TRANSPLANTATION SCIENTIFIC COUNCIL MEETING

Sunday, April 13, 2014:

SUNRISE SYMPOSIUM 15: High-Risk Donor: Extending our Criteria in Times of Organ Shortage
Transmission of viral infections through solid organ transplantation can lead to adverse outcomes for recipients. Despite the use of highly sensitive serologic tests for most common infections, the use of organs from high-risk donors remains controversial. Understanding the risk of transplanting the organ of a high-risk donor on the post-transplant outcome is important to judiciously advice candidates on the waiting list and to provide appropriate post-transplant care.

BOS Phenotypes and Classification

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When I took on the position of medical director for our University of Wisconsin lung transplant program as it started up in 1988, I faced a steep learning curve. Not only could a host of things go awry up front for lung transplant recipients in the peri-operative period, but the successfully transplanted patient could subsequently develop a plethora of complications that would threaten their allograft function and their post-transplant survival. As the art and science of lung transplantation evolved, it became clear that many patients would have a chronic decline in their lung function and that lung biopsies frequently showed histopathologic changes of obliterative bronchiolitis (OB). Because transbronchial biopsies were often non-diagnostic and surgical lung biopsy would entail significant risk, significant decline in lung function (FEV1) associated with an obstructive physiologic pattern was adopted as a surrogate marker for allograft dysfunction, and this dysfunction was assumed to be due to the presence of OB; hence this syndrome was dubbed bronchiolitis obliterans syndrome (BOS) when FEV1 fell below the threshold of 80% of the best post-transplant FEV1 value, the FEV1 decline was persistent, and the decline in allograft function could not be explained by other factors such as acute cellular rejection or infection [1,2].

In 2008, Ganesh Raghu (medical director of lung transplantation at the University of Washington) and I proposed a project to the American Thoracic Society to establish guidelines for the management of lung transplant recipients. We then sought and received the partnership of the ISHLT and European Respiratory Society (ERS). Paul Corris, Geert Verleden, Jim Egan, Paul Aurora, and Allan Glanville joined the project as co-chairs. We eventually realized that our project was overly ambitious and decided to narrow the focus to the diagnosis and management of BOS. Thirty-seven additional lung transplant experts from transplant centers worldwide accepted our invitation to join our task force committee, and we then thoroughly searched the literature to gather evidence to update our concepts of what BOS truly represents, how it should be diagnosed, and how it can be managed according to the best available evidence. The result is a joint clinical practice guideline (ATS/ISHLT/ERS) that will soon be published in the European Respiratory Journal.

As our project progressed, it became clear that terminology was somewhat of a problem, especially in the light of new information. Do all patients whose FEV1 falls irreversibly below 80% of their best post-transplant FEV1 value have OB as the cause? Is alloimmune rejection the sole cause of BOS? Is BOS the best term to use for delayed (e.g. ≥3 months post-transplant) allograft function decline? Could other factors be recognized that cause or contribute to delayed lung function decline? Articles that were appearing in the published literature often equated BOS with chronic rejection and used the terms BOS, chronic rejection, and chronic lung allograft dysfunction (CLAD) interchangeably.

Chronic lung allograft dysfunction is a term that was occasionally used in the 1980s, but its definition was not clearly established, and it did not make an appearance in the lung transplant literature until 2010. As our task force discussed terminology and new findings, it became clear that calling all cases of delayed allograft dysfunction "BOS" was a gross lumping of all potential causes and cases of delayed allograft dysfunction into a category that assumed that allograft functional decline was solely due to chronic rejection that caused OB. Observations by the Leuven and Munich transplant groups had identified patients whose allograft function declined and met criteria for BOS but could subsequently respond to azithromycin therapy and improve to the point that they regained enough allograft function to re-enter the BOS 0 category; the term "neutrophilic reversible allograft syndrome (NRAD)" was coined because these patients typically had significant neutrophilia in bronchoalveolar lavage (BAL) fluid, and this tended to predict a positive response to azithromycin. Additionally, the Toronto and Leuven groups had identified a substantial subset of "BOS" patients who had a restrictive pattern on pulmonary function testing, tended to have fibrotic infiltrates on thoracic imaging consistent with pleuro-parenchymal fibrosis, and had lung histopathology that showed inflammatory/fibrotic changes with or without evidence of OB; this entity is now perceived to be a form of CLAD that has significant differences in physiology, histopathology, and clinical course in contrast to the "classical" obstructive (reduced FEV1 and FEV1/FVC) BOS entity that was described by previous society statements on BOS, and it has been dubbed "restrictive allograft syndrome (RAS)." It has also become clear that gastroesophageal reflux (GER) with microaspiration can play a significant role in inducing allograft functional decline, and the Duke transplant group has published data showing that recipients who met BOS criteria and had significant GER may improve significantly following anti-reflux surgery. Some of the other potential etiologies have also been identified that include primary graft dysfunction (PGD), autoimmune reactions to glycoproteins expressed by lung cells and tissues (e.g. collagen V), infections (viral, bacterial, fungal), or exposure to high levels of particulate air pollution.

So how should we use new knowledge to classify BOS subsets, and what can we consider to be BOS phenotypes? Perhaps it would be better to adopt the term "CLAD" to replace BOS as the overarching term for delayed/chronic decline in lung allograft function [see reference 3 for our current classification proposal] yet not discard the term BOS, which would be a specific subset of CLAD (note that CLAD should not be used as a synonym for BOS). Subsets (phenotypes) of CLAD could be designated as ("classic") BOS (obstructive physiology without infiltrates on thoracic imaging), azithromycin-responsive allograft dysfunction (ARAD) that is characterized by airway inflammation and improves when neomacrolide therapy is administered, or RAS (restrictive physiology with parenchymal infiltrates). A fourth category could consist of "other causes" and include extra-allograft causes (e.g. diaphragmatic paralysis, pleural disease, or native lung hyperinflation) as well as allograft abnormalities (e.g. anastomotic dysfunction, infection, or primary disease recurrence).

Of course, it must be recognized that these other causes of chronic dysfunction may coexist with BOS, ARAD, or RAS and contribute to allograft functional decline. As an overarching term, CLAD would include all forms of chronic allograft dysfunction following transplant. Additionally, CLAD could also be applied to a transplanted lung that does not achieve a reasonable degree of function following transplantation (e.g. significantly reduced when measured against predicted normal physiologic indices). However, it should be kept in mind that CLAD should be used as a descriptor for a transplanted lung that is losing function or has sustained lack of normal function and not used as a diagnosis. One must also recognize that some patients will not "fit" cleanly into a CLAD

phenotype (BOS, ARAD, RAS) and that phenotypes may have significant overlap. Finally, a decline of 10-20% in FEV1 or FVC could be considered to represent "suspected" CLAD as was the case for the 0-p stage in the BOS classification system, and the previously adopted BOS staging system (stages 1, 2, and 3) could continue to be used for CLAD, BOS, and RAS.

One must then ask whether additional phenotypes can be identified. Could early onset BOS with rapid and relentless progression to graft failure be considered to represent a specific phenotype versus late-onset BOS? Can BOS associated with a specific risk factor such as GER, the appearance of a *de novo* donor-specific antigen, persistent acute rejection, bronchiectasis with persistent infection, a prominent immune response to collagen V, or a community-acquired viral infection be considered to represent specific phenotypes of BOS? Can thoracic high-resolution computed tomography (HRCT) patterns aid or even play a key role in identifying CLAD phenotypes? Can biomarkers be used to refine the identification and differentiation of phenotypes? Sorting these questions out will require an ongoing discussion and ongoing research by the lung transplant community with the goal of being able to identify specific CLAD and BOS phenotypes for which specific therapies of potential benefit can be given to arrest the progression of the disorder and possibly restore seemingly lost function, sustain quality of life, and optimize survival of the lung transplant recipient.

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

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Exploring the Respiratory Mycobiome

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Fungal infections can lead to serious complications following lung transplantation. Specifically, there is strong evidence that colonization with *Aspergillus* species is a risk factor for chronic rejection and bronchiolitis obliterans syndrome (BOS) [1, 2]. Aspergillosis has been reported as the most common post-transplant invasive fungal infection in lung transplant recipients, but reports of infections with emergent pathogens such as non-albicans *Candida* and zygomycoses are increasing [3]. However, how these infections occur as well as the complex interplay between fungi, bacteria, and viruses resident in the respiratory tract is only just beginning to be elucidated.

There has been a recent explosion in studies of microbial communities associated with the human respiratory tract, which is known as the respiratory microbiome. The majority of these have focused on bacteria, exploring the nature and composition of bacterial communities using molecular techniques which do not require cultivation of individual species. Culturing-based approaches provide characterization of individual microbes, while molecular methods allow for the description of entire communities composed of many different organisms. Culture-independent methods generally rely on DNA sequence-based "barcodes," which are short sequences from conserved genetic regions. For example, the ubiquitous and highly conserved 16S ribosomal RNA (rRNA) gene has often been used to identify and discriminate different bacterial species [4]. Recently, exploration of the microbiome has branched out into the exploration of fungal communities, or the mycobiome, using a similar barcoding approach. For fungi, the nuclear ribosomal internal transcribed spacer region (ITS) has been most commonly used for community characterization, and is suitable for discriminating the majority of organisms at the genus and species level [5]. Using ITS profiling, we can explore the full cohort of fungi associated with the human body, otherwise known as the human mycobiome.

While the majority of fungal community profiles generated using amplicon pyrosequencing have been from environmental systems, this technique has been applied to humans, including the respiratory mycobiome, i.e. fungal communities associated with the respiratory tract. Analysis of sputum samples from individuals with and without cystic fibrosis demonstrated that fungal respiratory communities were much more complex than culturing alone would suggest, as over 60% of organisms identified by sequencing were not indicated by cultivation [6]. Individuals with decreased lung function (as measured by FEV1 and FVC) harbored less diverse fungal and bacterial communities, which tended to be dominated by only a small number of organisms [6]. Interestingly, bacterial communities with high abundances of *Pseudomonas* were more likely to be associated with high abundances of *Candida* species than with *Aspergillus fumigatus* [6]. We

observed a similar phenomenon in a study of lung transplant patients, in which positive *Aspergillus* cultures were never isolated in individuals with bacterial communities dominated by *Pseudomonas* [7].

Charlson et al. performed a similar study simultaneously characterizing bacterial and fungal populations in healthy individuals and transplant recipients, including three individuals who developed BOS [8]. Communities in the upper and lower respiratory tracts were compared by community profiling of oral wash and BAL samples [8]. In the non-transplant population, upper and lower respiratory samples were highly concordant, while some transplant recipients harbored specific lung enriched fungal populations, including *Aspergillus* species [8].

While it would certainly be true to say that exploration of the pulmonary microbiome is in its infancy, our understanding of the pulmonary mycobiome, particularly in the context of solid organ transplantation, is currently only a twinkle in the eye of mycologists and transplant physicians. Nevertheless it seems likely that important information with direct implications for patient care is highly likely to be forthcoming as the field continues to develop.

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

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Who, When, With What and For How Long? Management of Nontuberculous Mycobacteria in Lung Transplantation

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A 68 year-old patient with pulmonary fibrosis, who underwent single lung transplant, is found to have Mycobacterium abscessus isolated (smear negative) from the 1-month surveillance bronchoscopy. Post-transplant course has been without notable complications. He has no symptoms and pulmonary function tests continue to improve. Exam reveals stable dry crackles on examination of native lung, clear examination on the allograft side and a well-healed thoracotomy incision. The remaining pre- and post-transplant respiratory cultures are otherwise negative. No rejection was identified on transbronchial biopsies coincident with M abscessus isolation (AFB special stains were negative) and explant histopathology was consistent with usual interstitial pneumonia (UIP) without evidence of granulomatous inflammation involving the lung or explanted lymph nodes. A chest CT without contrast reveals a small effusion, slightly decreased from prior post-operative films, and a calcified upper lobe nodule on the allograft side; review of the native lung reveals stable diffuse reticular opacities and honeycombing consistent with known UIP.

How would you characterize this patient and how do you proceed? Treat? Monitor closely? Does NTM positivity without symptoms post-transplant merit considerations of treatment earlier than in other scenarios? Does the particular species matter?

Infection remains a leading cause of both early and late morbidity among lung transplant recipients. While bacterial, viral and fungal infections have established associations with allograft dysfunction, the impact of mycobacteria on lung allograft function is less well understood. Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms with variable potential to cause human infection, ranging from asymptomatic colonization to invasive clinical disease. Clinically significant NTM pulmonary disease is mediated by complex interactions between the host and pathogen, including recognized risk factors of structural lung disease and immune dysfunction (both systemic and local). For this reason, lung transplant recipients represent a population at unique risk for NTM infections and complications compared to other solid organ transplant recipients.

There are conflicting data on the outcome of NTM infections among lung transplant recipients, which have important implications for candidate selection and management.

NTMs have been isolated with increased frequency among lung transplant candidates and recipients over recent years, likely reflecting both increased prevalence and improved diagnostic and surveillance techniques [3, 11]. Single center estimates of pre-transplant NTM prevalence vary but

have been reported to be around 3% [7,8], without distinction between colonization and disease. Within certain cohorts, however, NTM prevalence is higher, with up to 19.7% of CF patients awaiting transplantation affected [1,12]. *Mycobacterium avium complex* (MAC) and *Mycobacterium abscessus* are the most commonly isolated species in the US, with other species including *M chelonae, M fortuitum*, and *M kansasii* accounting for other clinically significant isolates [1,3,11]. Compared to MAC, *M abscessus* is more likely to be repeatedly isolated and associated with pulmonary function decline [3].

Among lung transplant recipients, post-transplant NTM infection can be acquired in several ways: contamination at the time of transplantation; reactivation of disease from colonized proximal airways or retained lymphatic reservoirs; donor-derived infection; and late-onset environmental acquisition. NTM prevalence following lung transplantation is highly center-dependent, ranging from 1.4%-22.4% [1,6,7,8]. This variation is likely explained by lack of a clear distinction between colonization and disease, geographic distribution of centers and center-specific surveillance protocols. Estimates of post-transplant NTM disease, however, are considerably lower, ranging from 2.5%-4.4% [1,6,8]. Pre-transplant NTM isolation increases the risk of post-transplant NTM isolation [1,12], but only among patients with *M abscessus* has NTM isolation prior to transplantation been associated with development of post-transplant disease [1,6]. *M abscessus* accounts for a disproportionate amount of post-transplant NTM disease and has a unique predilection for pleural space and soft-tissue infection that is frequently disseminated and extremely challenging to treat [4,6,8,13]; identification of this pathogen post-transplant warrants heightened attention. On average, post-transplant NTM disease is late in onset (~ 9.5 months post-transplant) and is often preceded by a period of asymptomatic colonization [2,6,8,9]. Several centers have reported that episodic isolation of NTMs is common following lung transplantation and is not associated with clinical deterioration or meaningful impact on allograft function or survival [1,7,8,9,12]. In contrast, both NTM colonization and disease were found to be associated with (though not causative of) increased risk of death even after controlling for single lung transplant status and bronchiolitis obliterans syndrome (BOS) in at least one analysis [6]. This group observed a non-significant trend toward increased risk of BOS among the NTM group [6].

A few certainties exist in the murky waters of NTM infection following lung transplantation. While the ATS/IDSA guidelines provide a framework for management, there are unique aspects to consider in this population [5]. First, the required treatment involves multiple agents for a prolonged duration (i.e 6-9 months), with well-recognized drug interactions with immunosuppressive agents, and issues of tolerance and long-term toxicities of therapy must be balanced with anticipated benefits [4,9]. In the case of rapid growers such as *M abscessus* and *M chelonae*, in vitro susceptibility should be performed to guide therapy. Second, careful surveillance of patients both prior to and following transplant can help identify at-risk patients and allow for close monitoring and aggressive up-front therapy in high-risk patients, when warranted. Management decisions for patients colonized with NTMs prior to transplant require close collaboration between experts in pulmonary, surgery and infectious diseases to optimize approach and timing/decision for treatment. Not every patient with NTMs isolated following lung transplantation requires treatment and careful surveillance can allow for unnecessary antibiotic

exposure without untoward effects [8,9]. Finally, treatment of concomitant pathogens is important given the recognition of non-NTM infection as a frequent cause of death in these patients [6].

A number of unanswered questions remain, however. There is no consensus on the optimal management of patients colonized with NTMs prior to transplant and many experts consider a course of therapy prior to and through transplantation in most cases, particularly for MAC and *M abscessus*. Whether or not to treat the asymptomatic patient with repeated isolation of the same NTM species following lung transplant is an area of uncertainty as well. Isolation of *M abscessus* and other rapid growers should prompt a directed evaluation inclusive of high-resolution chest CT and evaluation for skin and soft-tissue infection when deciding on an optimal management strategy. Finally, management of the colonized patient undergoing augmented immune suppression for treatment of rejection has not been rigorously evaluated. Ultimately a multicenter approach to understanding the impact of and optimal approach to NTM infections in lung transplantation can best answer these very important questions.

The patient's M abscessus isolate was sent for in vitro susceptibility testing and plans were made for repeat bronchoscopy and bronchoalveolar lavage (BAL) from both native lung and allograft to assess for repeated growth. Course was complicated by Klebsiella pneumoniae surgical site infection requiring operative debridement (AFB cultures negative). Repeat imaging revealed increase in the size of pleural effusion and basilar tree-in-bud opacities on allograft side. A chest tube was placed and the patient was placed on therapy with inhaled Amikacin, Azithromycin, Imipenem, and Tigecycline based on results of susceptibility testing, pending results of pleural fluid and repeat BAL studies, which again demonstrated growth of M abscessus, as did AFB blood cultures. Following drainage of pleural effusion and initiation of directed therapy, blood and BAL cultures remain negative at 16 months follow up. The patient completed a 6-month course of mycobacterial therapy and has had no further infectious complications.

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

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Pre-transplant Vaccination: a Model for Optimal Patient Care

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Vaccines have been the single most important public health intervention in the last century. Vaccination of transplant candidates and recipients is sometimes given little thought especially when the urgency of transplant and the transplant workup takes precedence. However, immunization is a very simple way to prevent hospitalization and mortality in transplant recipients and should be a routine part of our pre-transplant evaluation. The benefits of immunization can start immediately. Consider the relatively common scenario of a donor with previous Hepatitis B infection (anti-HBc positive and anti-HBs positive). A Hepatitis B immune transplant candidate has a significantly lower risk of HBV transmission than someone who is unimmunized.

What immunizations are important? When should they be given? And do they work in the setting of immunosuppression?

Invasive Pneumococcal disease in organ transplant patients occurs at a rate 25 times greater than in the general population. Pneumococcal polysaccharide vaccine (PPV23) has long been considered the mainstay of disease prevention; however, the literature is controversial as to the effectiveness of this vaccine. More recent studies show that the pneumococcal conjugate vaccine (PCV13 originally licensed for infants and children) is immunogenic in transplant patients. Therefore, many public health authorities worldwide (including the U.S. Advisory Committee on Immunization Practices and the Public Health Agency of Canada) have recommended a dose of PCV13 followed by PPV23 at least 8 weeks later. The PPV23 will cover the additional common serotypes of pneumococcus that are not in PCV13. For those who have received PPV23 in the past, there needs to be a one year interval before the PCV13 dose.

Probably the most discussed vaccine is the influenza vaccine, perhaps because it is the only vaccine given every year. Influenza can lead to viral pneumonia, bacterial superinfection, and potentially chronic lung allograft dysfunction. There are now several forms of influenza vaccine (inactivated, live, adjuvanted, high-dose, intradermal) and various vaccine strategies have been studied. Several studies in transplant patients, done by our group and others show that intradermal vaccine, adjuvanted vaccine or booster doses do not offer more benefit with regards to immunogenicity than a standard dose of inactivated influenza vaccine. Studies done in the lung transplant population or larger studies with subgroups of lung transplant patients consistently show that this group has the lowest humoral responses to vaccine compared with other transplant patients. Therefore, in addition to immunizing transplant recipients, it is of utmost importance that health care workers and close contacts of these patients be immunized to prevent transmission to this vulnerable group. Due to the short-lived immunity provided by current influenza vaccines and

the annual variation in strains, this vaccine is given yearly. Quadrivalent formulations (containing two A strains and two B strains of influenza) will likely replace the current trivalent formulations in the near future but will still need to be given yearly. Several studies have shown that influenza vaccination is safe post-transplant and does not induce alloreactivity.

Shingles (herpes zoster) is also more common after transplant and has a cumulative incidence of up to 20% at 5 years after lung transplant. A live-attenuated shingles vaccine was licensed in 2008 and can be given to those 50 years of age or older. However, the vaccine is contraindicated post-transplant because it is a live-attenuated vaccine. Pre-transplant administration could theoretically provide benefit post-transplant, but studies evaluating this are lacking; nevertheless, some centers recommend pre-transplant shingles immunization for the 50+ age group. Inactivated forms of herpes zoster vaccine are under development and may be an option for post-transplant patients.

HPV-related anogenital disease occurs at a higher frequency after transplant and can be very difficult to treat. Human papillomavirus (HPV) vaccines are effective in preventing cervical cancer and anogenital lesions in the general population. Although the age indications vary, HPV vaccine should be considered for pre-transplant patients that meet the age indication (generally age 9-45 in girls/women and 9-26 year old boys/men). The quadrivalent vaccine has been studied in a small cohort of young adult post-transplant recipients; only 55% of lung transplant patients had an antibody response to vaccine compared to 95% of kidney transplant patients. Although this vaccine covers the most prevalent types of HPV, other HPV types may also cause disease. Therefore, a 9-valent vaccine is under development and may be an option for transplant candidates and recipients.

In addition to these specific vaccines, it is important to ensure that routine immunizations for transplant patients are up-to-date prior to transplant. These include live virus vaccines (MMR, Varicella) if needed and other inactivated vaccines (Hepatitis B, tetanus, acellular pertussis, meningococcal etc. if indicated). Vaccine formulations vary from country to country so it is important to consult national guidelines.

Timing of immunization is also an important concept to understand. In general, vaccines given pre-transplant are more effective. Although diminished, any immunity generated pre-transplant is usually retained post-transplant. Immunizations given after transplant usually will be less effective. The use of induction immunotherapy with polyclonal antibody significantly reduces immunogenicity of vaccines for a period of several months. Therefore, it is recommended to wait 3-6 months after transplant to resume immunization. Similarly, the response to vaccines will be reduced after therapy for a rejection episode and significantly reduced with anti-CD20 monoclonal antibody (rituximab) therapy.

Although some vaccines such as Hepatitis B and HPV are given as multiple doses over a period of 6 months, transplant should not be delayed in order to complete the 6 month course. In general, the series can be started prior to transplant and completed post-transplant. As an alternative, Hepatitis B specifically can be given using accelerated schedules.

How can we incorporate this into practice? Setting up a pre-transplant clinic visit that allows for general infectious disease screening and vaccination can optimize pre-transplant care. A checklist of vaccines the patient needs is a helpful tool as is an immunization card that patients can carry with them. Many patients prefer to keep this information on their mobile phones in immunization 'apps'.

Disclosure statement: the author has received research grants from Roche, Merck, and Astellas; speaker honoraria from Merck, Astellas, and Pfizer; consultancy fees from Oxford Immunotec and Roche.

Cytomegalovirus Prevention Strategies: All Are Not Created Equal, But Some More Unequal Than Others

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Cytomegalovirus (CMV) infection remains a major issue in the management of heart transplant recipients. The availability of highly effective oral antiviral drugs supported a generalized anti-CMV prophylaxis approach [1,2]—with several lines of evidence suggesting a protective effect of prophylaxis against indirect CMV-mediated graft injury [3-5]. However, the onset of under-diagnosed late CMV infection reveals that in some patients an important negative counterbalance to the desired protection of universal prophylaxis [6,7]. Indeed, a careful clinical practice approach highlights wide variability in CMV-related scenarios raising doubts on the real effectiveness of a prolonged "all for all" CMV prophylaxis strategy.

One scenario includes patients developing low white blood cell count while on valganciclovir prophylaxis: reduction of valganciclovir dose is not recommended because sub-therapeutic drug levels may favor ganciclovir-resistance development. On the other hand, reducing or withdrawing the antiproliferative agent (i.e. MMF or mTOR inhibitor) exposes the patient to the risk of rejection. In such situations the physician rarely gets it right.

Another scenario is the young lady on Tac and MMF, experiencing one or two early cellular rejection episodes, on six months prophylaxis, and living far away from the transplant center. After recovering from surgery and rejection she finally can go back to her hometown and returns for the scheduled follow-up visit at month 8 or 9 after transplant. This is when, 8 weeks after stopping prophylaxis, and without any transplant-specific medical contact, she presents with diarrhea, dehydration, kidney failure, high Tac levels and 500,000 CMV DNA copies/ml circulating.

Yet another consideration concerns the real risk of developing infection in the heart transplant population: according to studies on the pre-emptive approach and depending on the immunosuppression strategy, 20 to 50% of CMV seropositive heart recipients never show a single CMV positive blood sample. Thus a universal prophylaxis approach would overtreat a significant proportion of patients. The "prophylaxers" party defense is based on the fact that these are often indistinguishable from those who will indeed reactivate infection. But are they really indistinguishable?

These purposeful simplistic considerations aim to emphasize the highly variable CMV-recipient-graft relationship and support the concept that a "universal" therapeutic approach in disease prevention is not necessarily an effective shortcut, but favors mental laziness in avoiding the quest for

"customized" strategies, based on the actual risk the patient has to develop an event. For example, it would be much easier distributing statin-enriched drinking water to enforce "universal" primary prevention against coronary artery disease than differentiate statin prescription after collecting full history and risk profile in the single patient (i.e. 40y old non-smoker female vs. 40y old smoker, diabetic male with a previous coronary angioplasty).

The main parameters to customize anti-CMV strategies include concomitant immunosuppression, feasibility of accurate CMV DNA monitoring, and the level of anti CMV immunity. Immunosuppression, induction strategy, in particular with thymoglobulin, portends a higher risk of subsequent CMV infection as compared to non-induction, while mTOR inhibitors are associated with a markedly lower risk of CMV infection and disease, as compared to MMF or AZA [8].

The availability of a local laboratory providing timely results of blood CMV PCR, and the compliance of recipients to frequent blood sampling (every 1-2 weeks for the first 3 post transplant months) usually allow prompt detection of viremia and planning of a pre-emptive treatment [9]. When frequent assays are not feasible, viral kinetics not captured may pose a higher risk of CMV syndrome or disease in heart recipients.

Host immune capacity to control and respond to viral replication is a major factor influencing the risk for CMV infection and disease. The basic evidence of this concept is highlighted by the notion that CMV seronegative recipients of a CMV seropositive graft are those at highest risk to develop infection. Recently, assays on T-cell activation in response to CMV antigens pointed out a wide variability in the capacity of seropositive recipients to respond to and control CMV infection.[10] In particular, these data showed that T-cell mediated CMV immunity is progressively recovered after transplant, but with different patterns and timings, exposing the patient to variable risk of CMV infection and disease. In particular, recovery of immunity during the first month after transplant identifies patients who will most likely develop infection [11,12], and assay of immunity during asymptomatic viremia may help to discriminate between patients able to clear spontaneously the infection and those who will develop high-grade infection and disease [13]. Similarly, at the end of the prophylaxis period, assessment of CMV specific immunity can discriminate the risk of recipients to develop subsequent late CMV disease [14].

Although information deriving from immune-function assays is likely to be the most valuable to achieve effective customization of anti-CMV strategy, it must be remembered that studies validating the effectiveness of therapeutic approaches based on immune assay response are still lacking. Nevertheless, full consideration of these CMV risk parameters—immunosuppression, CMV monitoring facilities, and CMV specific immunity—may represent a starting point to overcome the "iron curtain" separating the universal prophylaxis and the pre-emptive parties, and moving towards an approach tailored on the risk estimation in the single patient … while waiting for a CMV vaccine to become clinically available [15].

Disclosure statement: The author received speaker's fees from Novartis Pharma.

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Fecal Transplants in the World of Solid Organ Transplantation: A Revolutionary Treatment for Recurrent C.diff or an Infectious Nightmare Waiting in the Wings?

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At first, it's hard not to be revolted at the idea of a fecal microbiota transplant (FMT). Yet, increasingly robust data suggests it is a remarkably effective treatment for recurrent *Clostridium difficile* colitis. Although there are limited reports of FMT in patients with solid organ transplants [1], the increasing frequency of C.diff infections in the general community [2] and the increased morbidity and mortality in immunosuppressed hosts mandates transplant clinicians familiarize themselves with the technique.

The incidence is highest in the first three months after transplant, and affects 1.5-31% of the transplant population, compared to 1-2 % of the general hospital population [3]. There are likely multiple factors at play, including greater use of antibiotics – especially in thoracic transplantation, significant immune dysregulation, and underlying multi-organ pathology.

The reported efficacy of FMT is striking (even recognizing selection and reporting bias – immunosuppressed patients were frequently excluded). In a systematic review published this year [4], a total of 536 patients were treated over 24 studies; 467 (87%) noted resolution of diarrhea, typically within just 1-2 days. 81% resolved when stool was instilled into the stomach; 86% into the duodenum/jejunum; 93% into the cecum/ascending colon; and 84% into the distal colon. No major side effects—other than aesthetics!—have been observed, although there are case reports of norovirus transmission [5].

To date, FMT does not have a set place in treatment algorithms, but is most frequently employed after multiple relapses. An individualized approach to treatment is prudent, using metronidazole for mild to moderate disease and vancomycin for more severe or recurrent episodes [6]. Tapered or pulsed vancomycin 'anti-germination' strategies are also employed frequently for recurrent disease. Minimizing antibiotic exposure is crucial for all patients with C.diff, given a common underlying causative and perpetuating factor is the imbalance of normal bowel flora.

There are no standardized methods of donor fecal microbiota collection, processing, dosing or administration. Typically, donor stool undergoes a blending process to liquefy the product and strain out solid matter. Administration can be via an naso-gastric or gastro-jejunal (NG/GJ) tube (eg: 80-100mls), via a retention enema, or via colonoscopy (250-300mls). Concerns over donor-derived infections also exist, and without unified FMT methodology and follow up, it is difficult to quantify true risk. Currently, most centers screen donor serum for Hep A, HIV, HBV, HCV and

syphilis. Additionally, stool should be screened for C.diff (PCR), pathogenic bacteria (culture for salmonella, campylobacter etc) and parasites (combination of direct examination and antigen screen for giardia and cryptosporidia). Whether or not centers should screen donor stool for drug resistance, for example, VRE or carbepenemase-resistant Enterobacteriaciae is unclear. Pathogenic viruses such as norovirus can also be difficult to detect for many laboratories, yet they can cause catastrophic illness in SOT recipients. In theory, donors could also be screened for recent travel and even risk factors for window-period infections, in the same way we do for increased-risk organ donors.

We are beginning to understand the interplay between human bacteria and our immune system. In fact, the microbiota may have sustained effects on our physiological, metabolic, and immunologic phenotypes [7]. How this impacts alloimmunity and therefore rates of solid organ rejection remains unknown and is a fertile area for research. These and other important unanswered questions led the U.S. Food and Drug Administration (FDA) to recently request that clinicians apply for an IND prior to treatment with FMT. Although the FDA has since then backed away from this position, many desperate patients (suddenly faced with a treatment delay not to mention dreadful diarrhea) began trying at-home fecal instillations, often with the help of online recipes. No clinician enjoys dealing with the FDA, but the thought of completely unregulated fecal donations in our heavily immunosuppressed population is even more disconcerting.

In summary, fecal transplantation appears likely to increase in popularity over the next few years, even in patients with solid organ transplants. Research should be focused on immunosuppressed populations, particularly with regard to fecal dosing and administration, long-term safety (both for the patient and their graft) and C.diff relapse rate.

Hold onto your hat (and your nose!) – we are about to have a fun ride!

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

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Laughing Links

The Incomparable Bill Cosby

Charlie Chaplin. Groucho Marx. Richard Pryor.

Over the past century, few entertainers have achieved the legendary status of William H. Cosby Jr. His successes span five decades and virtually all media, remarkable accomplishments for a kid who emerged from humble beginnings in a Philly project.

In the 1960s, his stand-up act was a coast-to-coast sensation, spawning a string of hilarious, best-selling comedy albums, which went on to win eight Gold Records, five Platinum records and five Grammy Awards. His role on TV's *I Spy* made him the first African-American to co-star in a dramatic series, breaking television's racial barrier and winning three Emmy Awards.

In the 1980s, he again rocked the television world with the *The Cosby Show*, a gentle, whimsical and hugely successful series that single-handedly revived the family sitcom (and rescued NBC). With hit movies like *Uptown Saturday Night* and best-selling books like *Fatherhood*, Bill Cosby is quite simply a national treasure with the unique ability to touch people's hearts.

Cosby's first TV concert special in 30 years, Far From Finished, debuted on Comedy Central on November 23rd, 2013. Here's an excerpt from his special:

"The game of chess. Supposedly men made it up, and it's about war and men and the savages and the bravery and the genius of commanding and moving pieces and ... No. It's marriage. The Queen moves anywhere she wants. Picking off people."

Watch the hilarious YouTube clip: Chess Is Like...

Editor's Corner: Expressions from the Love of Sports

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There are many words, expressions, analogies and metaphors from the language of sports enmeshed in everyday conversation of English vocabulary that largely go unnoticed. For example, children in the English world experience "time outs" because they are misbehaving or in need of a break from playing, which comes from sports. Also, when involved in a discussion outside your purview, you might consider "sitting on the sidelines" or "sit this one out." In so doing, you position yourself as a spectator or as a substitute currently not playing in this discussion. These expressions come from many sports, including football.

Football is an old sport originally referenced in the *Oxford English Dictionary (OED)* in 1424 as an open-air sport with an inflated ball. The word **football** in most of the world refers to Association Football: a game played by teams of 11 players who kick a ball toward the goals at both ends of the field. Only goalies can touch the ball with their hands or arms. This kind of football is the most popular sport in the world. In America, this sport is known as **soccer** derived from the official name of Association Football, which has been shortened to Assoc. **Assoc**, analogous to the **rugger** in **rugby,** has given us the name **soccer**.

In American football there is the "punt," because that's what a team does when it runs out of good options in a quest to make 10 yards in 3 plays or downs. If unsuccessful, the team has the option to punt or give the ball to the other team. There is the famous "Hail Mary" that came to life in a playoff game between the Dallas Cowboys and Minnesota Vikings in 1975. I witnessed this play when Roger Staubach threw a desperation pass to Drew Pearson, who ran the football in for a score to win the game 17-14. Staubach told the press that he closed his eyes on this play and said a Hail Mary. The Hail Mary is now generalized to not only football passes but also to any kind of desperation move.

Suburban American mothers frequently taxi their children to athletic events or children's activities. In 1996, "soccer mom" was added to the *OED* defining any such woman viewed as a member of a particular and frequently influential class of voters or consumers. These soccer moms are the "swing voters" in election coverage. In 2008, "hockey mom," came to national attention when Sarah Palin described herself as a "hockey mom" that election year when she stated that the only difference between a hockey mom and a pit bull is lipstick.

Tennis is another word from the early 15th century that actually appears in Shakespeare's *Hamlet* and *Henry V* referring to the way fortunes may play us or bat us back and forth. "Tennis arm" and "tennis elbow" were recognized as medical conditions in the 19th century. "Tennis shirt" (T-shirt)

and "tennis shoe" have moved beyond the sport of tennis into our everyday vocabulary. "Ace" is from tennis, but why "Love" for zero? Perhaps it comes from the expression, "I did it for love or for nothing", hence zero in tennis.

The word **boxing** came up in the 16th century referring to fighting with fists, later with boxing gloves and here we have "saved by the bell," and if not "saved by the bell," we could be "down for the count." This means that we're out of the running or not considered. A "knockout blow" from boxing is a "knockout idea, performance, or person" with overwhelming quality. Such performance or an individual might "bowl us over," which could be "bowling us over" which comes from cricket. With such amazement or surprise, we might be "floored" an expression seemingly popularized by boxing when a boxer is floored. When in trouble, we might be "on the ropes"; and when we give up, we "throw in the towel." In boxing, throwing in the towel is when the boxer cannot continue. The towel is thrown in by the coach or trainers from the boxer's corner. We all know and hope that we have good people "in our corner" to support or counsel us. People will say things like, "I'm in your corner," to say, "I want to support you." Also, in boxing, one isn't supposed to "hit below the belt," which has generalized to any unsportsmanlike or unfair conduct, and we "pull our punches," when we don't criticize something or someone as harshly as we could. And of course today some of us wear "boxer shorts," "boxer briefs," "boxers," speedos or thongs.

From basketball we have the "slam dunk" and from golf we have the "gimme" or the "chip shot." But these expressions are not always easy or a guarantee. While all expressions to this point are intuitive to most Americans and less so outside the United States, the situation is reversed with the expressions "hat trick" referring to three successes and a "sticky wicket," referring to a difficult circumstance which come from **cricket**. I am sure there are many others from others sports of which I'm unaware.

Most everyday expressions today actually come from baseball and include: "in the ballpark," "in the same ballpark," a "ballpark figure," "big league," "bush league," to "cover all the bases," to "throw someone a curveball," go into "extra innings," "knock it out of the park," "play hardball," be a "heavy hitter," "go into the ninth inning" (aka "the eleventh hour"), "pinch hit," "rain check," "right off the bat," "step up to the plate," "whole new ballgame," and "designated driver." Designated driver is based on the "designated hitter" in baseball. Running the bases in baseball has resulted in some expressions now used outside of baseball: "Getting to first base," which means you've achieved the first step in a project; or "touching base," or you could be "off base" when you are caught off guard similar to when a baseball player is not paying attention when they're off base trying to steal second.

If too far off base, one might end up in left field. But I really believe in right field is where you don't want to be in baseball. In right field is when you're out of action to the point of boredom, almost uselessness, most of the time. However, the bias against left-handedness is witnessed here in the English language when we refer to someone in left field meaning that they are "disoriented" or "out of contact with reality" but it is the right fielder who may be sort of daydreaming while waiting for someone to hit the ball out that way. But the expression is not "out in right field." Recall

the Latin borrowings, *sinister* means left and *dexterous* means right. The expression when you're not tuned into whatever will put you "out in left field."

The most popular expression from baseball is the "homerun." The final achievement of whatever goal is considered a homerun. Also, the work "balk" means to stop abruptly or pull up when a horse stops at an obstacle or at a ridge or mound in the land referring to the ridge between two furrows. The pitcher on the mound can abruptly pull up and be called for a balk in baseball.

Finally in reference to Valentine's Day, sometimes dating is referred to as a game or a sport which is certainly full of baseball metaphors about bases, a score or scores. Time and decorum prevents us from going there but it is out there. Be sure to read this month's **Laughing Links** where I leave you with the "stalemate" from one of my favorite games, Chess, which is really about marriage. Happy Valentine's Day!

And be sure to check out the difference between football and baseball by George Carlin in his YouTube clip, "Baseball vs Football".

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