IN THE SPOTLIGHT: Bleaching Organ Procurement Crimes in China

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For the past thirty years China has been practicing the procurement of organs from executed prisoners for the purpose of organ transplantation **[1]**. My own personal involvement with the Chinese organ transplantation system started back in 2005, when a Status 1 candidate for heart transplantation notified me that his medical insurance company had instructed him to travel to China in two weeks' time, as he was scheduled to undergo heart transplantation. I later learned that the patient did, indeed, travel to China where the operation took place on the exact date that had been promised **[2]**.

Enacted in 1984, the *Temporary Rules Concerning the Utilization of Corpses or Organs from the Corpses of Executed Criminals* authorizes the procurement of organs following a criminal's execution if no one claims the body, the prisoner volunteers to have his corpse so used, or if the family consents to such actions **[3]**. These regulations have allowed the emergence of a flourishing organ transplantation industry in China to accept around 10,000 cases each year **[4]**. The term "industry" is not incidental, as credible sources have indicated the illegal and corrupt market for atrocious forced organ procurement, which caters to both national and international organ transplant candidates alike and includes anyone from court bailiffs to prison personnel and even hospital physicians **[5]**.

In the past, Chinese authorities have consistently denied the use of organs from executed prisoners for transplants. It wasn't until 2005 that the practice was brought to light via public admission made by Dr. Jiefu Huang, then Vice Minister of Health of the People's Republic of China, that, apart from a few traffic victims, more than 90% of deceased donor organs in China came from executed prisoners **[6]**. However, even admitting this source of organs cannot explain the large annual number of organ transplants that occur in China as, even without official announcements regarding the numbers of executed prisoners, there is ample indirect evidence that this source has been diminishing over the years **[7]**.

Several independent researchers suggest that specific minority groups in China are being persecuted with the specific intent to facilitate transplantation **[8,9]**. The focus of most comprehensive investigations into alleged forced organ procurement from minority groups has been Falun Gong practitioners. The conclusions of these investigations suggest that a large number of Falun Gong prisoners of conscience have been put to death on the basis of unverifiable offenses. There is also evidence that other minority groups, such as Uighur Muslims, Tibetans and Christians, have suffered a similar fate. However, State Chinese authorities have been unyielding in their denial of this additional source of organs, but have refused to provide verifiable information about officially proclaimed organ sources.

Despite numerous statements over the past years alleging plans to phase out the reliance on organs procured from executed prisoners, no such cessation has occurred. However, international medias have recently reported, based upon statements made during a plenum of the Chinese State Council in October 2014, that, as of January 1, 2015, organs for transplantation will no longer be obtained from executed prisoners **[10,11]**. Even more recently, on December 3, 2014, Dr. Jiefu Huang, now Director of the Chinese National Committee on Organ Donation and Transplantation, announced that after January 1, 2015, only voluntarily donated organs could be used for transplantation **[12,13]**.

Unfortunately, the enthusiasm with which these recent Chinese announcements have been accepted has caused a critical part of the alleged new reform in organ donation to be overlooked **[14]**. Not only has there been no new announcement from China regarding the abrogation of the 1984 rules, but, in repeated interviews, Dr. Huang made it clear that death row prisoners could still donate their organs if they wished to do so **[15,16,17,18]**. This would require that death row prisoners be redefined as "citizens" who have "the right to donate organs", thus rendering organ procurement from executed prisoners "voluntary donations from citizens". The principal change in this new reform, then, would be only that China would begin to integrate this new source of "voluntary organ donation" into its new computerized organ allocation system for such donations, thereby bleaching its unethical source **[18]**. In emphasizing that future organ donations by death row prisoners will require agreement by both the prisoners themselves and by their families, the same as is required of citizens, Dr. Huang inadvertently confirmed that, thus far, organs have been procured from executed prisoners without their explicit consent **[17]**. Moreover, in a recent paper Dr. Huang clearly states that "if we brutally interrupt the source of organs from executed prisoners, it would inevitably lead to loss of lifesaving hope for many of patients with organ failure" **[19]**.

In support of the assumption that Chinese officials do not anticipate any drastic decrease in organ supply for transplantation soon, Dr. Huang recently offered Taiwan the opportunity to establish a cross-strait organ exchange platform that would enable Taiwanese patients to get transplants without having to travel to China **[20]**. This offer is particularly surprising as there are already 300,000 patients in China waiting to be one of the annual 10,000 transplant patients.

Finally, the recent reports from China indicate that the Red Cross Society of China has been officially recognized as the organization that will be in charge of organ donation and allocation. It should be noted that in the first two years of the pilot organ donation system, the majority of ''voluntary'' donations from true citizens were reported to be obtained by the Red Cross Society of China following payments made to the families of a deceased individual. These large sums, some equivalent to twice the annual income of the family, are offered as incentives to ''donate'' their loved one's organs, thus exemplifying a different, but still forbidden and internationally denounced, form of promoting organ donation.

So far only two medical organizations, the Declaration of Istanbul Custodian Group (DICG) and Doctors Against Forced Organ Harvesting, have recognized the pitfalls in the announced Chinese reform and published statements expressing their concerns **[22,23]**. I was happily informed by our President, Prof. Reichenspurner, that, following my proposal, our own ISHLT Board of Directors has

unanimously endorsed the recent DICG statement, which establishes their position that it is obvious that prison inmates condemned to death are not truly free to make an autonomous and informed consent for organ donation and that no legal due process exists to assure such consent.

While we all remain eager to support the Chinese transplant community and their intent to build an infrastructure of donation that complies with the internationally accepted ethical rules, we should continue to be very cautious in prematurely praising the recent announcements from China, as they seem to remain far from the desired goal.

The international community, medical and non-medical alike, needs firm and immediate action by China to abolish the 1984 rules permitting the use of organs from executed prisoners, and ban their use under any condition; to fully and swiftly implement such a ban in all hospitals, including military hospitals, regardless of the burden it will impose on the waiting lists for organ transplantation; to acknowledge that not only executed prisoners, but also prisoners of conscience, are subject to forced organ procurement and ban that practice; to stop promoting transplant tourism, and to facilitate transparency and international monitoring to verify these changes.

It is our moral duty, both as humans and as physicians who practice and promote the most noble of human gestures – voluntary organ donation – to be the leaders of these demands.

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Single Ventricle Babies: The Fontans Have Come of Age

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When earlier literature is compared with the more recent data describing staged surgical palliation for single ventricle infants, skilled surgical technique and precise medical management seem required for better survival. As these children have matured to adolescence, medical experience has revealed improved longevity and quality of life. Over time, these longer term observations have additionally revealed complications possibly associated with the Fontan physiology **[1]**.

With increased access to fetal echocardiography, healthcare providers may now be able to counsel parents of single ventricle infants as early as the defect becomes evident. Treatment choices at time of diagnosis may include three main choices for parents of these children: comfort care, staged surgical palliation, or orthotopic heart transplantation. Depending therapy chosen, patients may be referred to selected experienced, larger volume programs that offer their chosen option and are successful in such interventions **[2]**. Centers skilled in surgical palliation may show preference for that pathway due to concerns related to transplantation such as limited donor availability and desire to avoid immunosuppression **[3]**. However, as Fontan patients age after all surgical palliations have been exhausted, referral for heart transplantation may once again be considered when heart failure or other associated complications demand a different course.

Decreased survival has been reported in heart transplant patients after the Fontan procedure, compared to those with other heart disorders **[4]**. Multiple previous chest surgeries and allo-sensitization may influence transplant candidacy and challenge management **5]**. Other morbidities associated with passive, rather than pulsatile, blood flow of the Fontan circulation over extended time are: ventricular failure, liver disease, plastic bronchitis, protein-losing enteropathy (PLE), thrombosis/stroke, decreased oxygen saturations, and arrhythmias. Ventricular assist device support may not be successful or even offered due to single ventricle anatomical challenges and increased mortality risk.

Considering anatomic and physiologic challenges alone, the medical transplant evaluation for such a referral may prove to be quite complex. Add the nursing assessment and psychosocial preparation piece, and the undertaking becomes colossal.

For the failing Fontan, medical therapy may consist of referral to Transplant, Palliative Care or Both **[6, 7]**. Effective medical, nursing and psychosocial support for the failing palliated single ventricle patient and family must involve collaboration of the multidisciplinary team. Up to this point in their lives, Fontan patients have survived some very extreme life experiences including multiple chest surgeries, lengthy hospitalizations, frequent clinical monitoring and chronic illness states. They may bring a lot more "wounds" to the transplant evaluation than their old surgical incisions.

Transplant Social Worker

During the psychosocial assessment, a multitude of factors must be evaluated within a limited amount of time. These include patient's/family's cognitive understanding of transplant process, emotional readiness and motivation for transplant, adherence to medication regimen and treatment plan, adequate income and access to health care, and reliability of support system. Risk factors such as history of substance abuse, psychiatric illness, maladaptive coping and poor communication with medical team must also be taken into account. In the pediatric setting, it is imperative to consider the developmental stages of the child and provide age appropriate discussions and interventions.

During the evaluation phase, patients and parents are asked to make many important decisions within a short time frame. Parents have little time to process medical information while facing the unknown survival outcome of their child. The Transplant Social Worker and Palliative Care Social Worker can guide families through the decision making process by assisting family in clarifying their goals of care based on the family's values and beliefs. These interventions can be particularly helpful as the disease progresses or complications/risk factors arise.

Many pediatric patients and families will face a prolonged hospitalization following transplant listing. The unfamiliar hospital environment, multiple care providers, and the different routines in the CTICU can increase the patient's and family's anxiety. Supportive interventions for hospitalized children include creating a daily schedule, visits from hospital school teacher, and play therapy through Child Life Services, Music and Art Therapists to assist the child in coping. Social Workers can provide individual counseling to parents, referrals to community support services or parent to parent support networks, and suggest financial assistance programs to meet the short term needs during a lengthy hospitalization. Through frequent visits with the patient and family, social workers gain a clear understanding of the impact of the illness on the patient and family and can relay clinical impressions to the child's medical and nursing providers.

Palliative Care Social Worker

Palliative Care brings a unique perspective to how families cope and make medical decisions. Often mislabeled as the "death team," palliative care as a source of support for families and staff has become integrated into the transplant landscape. How and when they are introduced to the families varies from program to program, depending on many factors. Whether a baby is diagnosed prenatally or postnatally, and how the trajectory of their medical course is presented to the parents at the time of diagnosis, however, is a factor that is out of the control of the transplant team. In an ideal world, the palliative care team would be introduced at the time of diagnosis or soon after, to facilitate

communication with the many teams involved and to assist with medical decision-making and symptom management.

When the palliative care team is introduced when transplantation becomes the treatment option, the palliative care team can be instrumental in providing additional support in ensuring that the family understands the information that has been presented, assessing the patient's and family's goals and hopes in the context of what quality of life means to them, and considering the needs of all family members in light of the changes that will impact each person post-transplantation. When there is seamless collaboration and communication between the transplant and palliative care teams, the potential for holistic care is maximized as patients, family members, and staff receive the tools that they need to cope adaptively through this transitional time.

Summary

It's truly amazing that surgical and medical advances have allowed many single ventricle patients' lifespans to be extended and quality of life to be improved. When referred to the transplant team, medical evaluation includes assessment for prediction of relative success or failure of this potential intervention so that the family and patient are able to make educated decisions. However, we must not be focused only on previous procedural histories and current anatomic and physiologic measurements.

Adolescent and adult congenital single ventricle patients have been coping with illness and advanced medical interventions their entire lives. If a candidate is referred late into the heart failure course, the multidisciplinary transplant team must mobilize and be prepared to intervene very quickly to complete the evaluation before more decompensation occurs. Earlier referral or consultation with Palliative Care prior to end-stage heart failure may allow the family and candidate more time for adjustment and thought, well before a formal transplant evaluation which demands full attention to education and training about transplant lifestyle expectations that ensure acceptable survival.

These patients have probably experienced many different healthcare team members in institutions and have adapted in various individual styles in order to tolerate much of it. Sometimes a professional self-reminder that the focus of healthcare providers' roles must be to ensure that families and patients receive adequate education, so that they may make their own choices, may prove helpful to avoid the pitfalls of complicating their decisions with our own personal views.

In addition to education and valuable supportive counseling for the patient and family, perhaps the busy medical, nursing and ancillary care teams who care for these patients would benefit from regular supportive solution-driven conferences aimed at enhancing their own skills for effectively working with complex patients who may experience emotional crises during the course of continued treatment.

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Sense and Sensibilities: Finding Consensus in Adult Cardiothoracic Transplant Nursing

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In November 2014, a consensus document on nursing practice in Adult Heart and Lung Transplantation was published. This document stems from a global transplant nursing conference convened on April 12, 2011 involving members of the ISHLT Nursing, Health Science and Allied Health Council. This conference, which included nursing representatives from 12 countries and 4 continents, sought to define minimal recommendations for transplant nursing education and role responsibilities while also discussing retention strategies and models of care. Of the 77 attendees, 72% were transplant nurse coordinators, 15% were transplant nurse practitioners, 4% were nurse managers, and 6% were nurse researchers. The size of the transplant programs represented ranged from small to large, as defined by the United Network of Organ Sharing. Attendees completed a survey prior to the consensus conference. The survey centered on staffing levels, minimum core competencies, levels of education, roles and responsibilities, and areas of future research.

While education varies among transplant nursing professionals depending on country of origin, prior to this document, there were no consensus guidelines available on required education level, licensure, or certification for the transplant nursing specialty. Among the transplant nursing experts attending this conference, consensus was reached that a minimum of 2 years clinical nursing experience was required for all transplant coordinators, nurse managers, or advanced practice nurses. A baccalaureate degree in nursing is the minimum education level requirement for a transplant coordinator. Additionally, the attendees reached consensus that transplant coordinator-specific certification is recommended. Such certification does not exist in all countries and could not be mandated. Finally, in the area of education, consensus also agreed that transplant nurse practitioners, clinical nurse specialists, and transplant managers should hold at least a master's degree.

The cardiothoracic transplant coordinator role is critical to the success of transplant programs as well as quality patient outcomes. For this reason, the presence of a transplant nurse coordinator on the transplant team is mandated by the US Centers for Medicare and Medicaid Services. However, recruitment and retention strategies aimed at finding and keeping transplant nurse coordinators with this specialized skill set are lacking. Consensus was reached that strategies to retain transplant nurse coordinators include engaging donor call teams, mentoring programs, flexible hours, and support with career advancement.

While consensus was reached in the above mentioned areas, agreement on appropriate staffing levels for nursing within an adult cardiothoracic transplant program remained elusive. The contingency of experts convened for this task believed too many variables were left unanswered to reach conclusive staffing levels. Models of care vary widely across the continuum and such models affect staffing

needs. No ambulatory care metric exists to gauge staffing levels and all current information is based on inpatient staffing ratios. Although not yet attainable, determining appropriate staffing levels for transplant nursing was deemed high priority by attendees.

Consensus was reached that future research should focus on the relationships between staffing levels, nurse education, and patient outcomes. To this end, a new survey has been developed and will be distributed to the ISHLT Nursing, Health Science and Allied Health Council in hopes of finding a path to consensus on these more difficult issues of staffing levels and models of care. The results of this survey will fuel discussions for future direction at a special Transplant Nursing Forum to be held in Nice, France, in tandem with the ISHLT Annual Meeting and Scientific Sessions.

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Life Is Not Fair

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Life is not fair. The sooner you learn that, the better off you will be.

This was my mom's favorite response to all of her three girls' many "that's not fair" comments over the years. Long gone are the days when life's list of injustices included who got to ride shotgun, who used the last of the hot water or who drank the last of the milk. As a transplant coordinator, watching patients and families who wait for a transplant that never comes is what comes to mind when I think about the word "unfair". While losing a patient is never easy, there is an added sharp edge for me when it is a loss of someone who didn't get their shot at a second chance. It would be so easy to blame the system, the lack of organ donors, or our own inability to get our patients to transplant. The reality is much more difficult to swallow – there is no good answer, no blame to place. The reality is simply that life is not always fair.

When people ask about how I deal with the death of a patient as a pediatric nurse, my answer is always the same. It never gets any easier and the day that it does is the day I know it is time to hang up my scrubs. We all deal with the loss of a patient in different ways. Some people use their natural outlets to work through the grief process - their teams, their family and friends, their pastimes and hobbies. Some people want to talk through their feelings, while others are more private and stoic. There is no right way to move through the process as long as you are dealing with your feelings and moving forward.

Growing up, decorating the Christmas tree was a really, big deal in our house. The day after Thanksgiving, we would pull out all of our decorations, including our family Christmas ornaments consisting of homemade ones we created at school for our parents, those my mom had purchased for us to remember family vacations or milestone events in our lives, and those given by grandparents or other relatives over the years. Each one was special in its own way and held a story or memory. Every patient is like a treasured, precious ornament on my tree. When one of them passes away, it is like watching one of those beautiful, unique ornaments fall off the tree and shatter before my eyes. I mourn the loss of something so special and fragile that can never be replaced, but eventually have to sweep up the pieces and move on. At the same time, I tuck the memories away in a corner of my heart to be cherished and never forgotten. This is the best analogy that I have been able to come up with in trying to put my own process into words.

The great equalizer for the grief is the joy we experience as care team members. There are so many small victories, so many happy endings, so many stories of those who get their second chance and thrive and so – cherish them. George Bernard Shaw had the best advice, "write your sad times in sand, write your good times in stone". There is still much work to be done.

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Pharmacotherapy Considerations for Agents Used in the Treatment of Non-Tuberculosis Mycobacterial Infections in Cardiothoracic Transplant Recipients

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The number of identified non-tuberculosis mycobacteria (NTM) species has increased rapidly over the last decade, and, due to their impaired immunity, cardiothoracic transplant recipients are now at an even greater risk of infection from these organisms **[1,2]**. Recent increases in the incidence/prevalence of NTMs can be attributed to advancements in the techniques for their detection and identification **[1]**. The incidence of NTM infections is greater in lung and heart transplant recipients, with rates up to approximately 8% and 3%, respectively. The most common manifestations of NTM infections are pulmonary and skin, or soft tissue infections, and the frequency and manifestation of NTM diseases are partially determined by the geographic distribution of the different species **[3]**. Worldwide, mycobacterium avium complex (MAC) is the predominant isolate found in most countries, followed by *M. xenopi*, *M. kansasii* and other rapidly growing NTM species, especially *M abscessus* **[4]**. Treatment strategies vary across centers globally in terms of choice of agents, timing of therapy, and treatment duration. The development of drug resistance is a recognized problem, and thus multi-agent therapy is recommended **[5]**. While treatment response isn't necessarily correlated to *in vitro* susceptibilities for all NTMs, susceptibility testing can help direct therapy and monitor for resistance **[5]**. This article aims to discuss pharmacotherapy considerations for agents commonly used in the management of NTM infections in cardiothoracic transplant patients.

Macrolides are recommended for multiple NTM infections, including MAC and *M. abscessus*. Monotherapy with macrolides is not recommended due to the high risk of resistance, and some NTMs (*M. fortuitum* and *M. smegmatis*) have been associated with *in vivo* macrolide resistance despite susceptible MICs **[5]**. Clarithromycin use for NTMs is common; however, due to inhibition of both P-glycoprotien and CYP450 enzymes, it has strong drug interactions with immunosuppressive agents (i.e., calcineurin inhibitors and mTOR inhibtors) used in transplant recipients **[6,7]**. Additionally, clarithromycin is often not well-tolerated due to gastrointestinal side effects **[8]**. Azithromycin is a favorable alternative in transplant patients due to a lesser effect on CNI/mTOR kinetics and better GI tolerability **[3,9]**. Drug levels should be monitored more closely upon initiation of any macrolide therapy and dose reductions of CNIs/mTORs shortly after clarithromycin initiation of at least 50% will likely be necessary **[9]**. Other concerns with macrolide therapies include increased risk of *C. difficile* infection, QTc prolongation, and abnormal liver function tests (LFTs)/hepatitis **[8]**.

Rifamycins are recommended in the treatment of MAC and *M. kansasii*, among other NTMs **[5]**. This drug class has strong drug-drug interactions with CNIs/mTORs due to CYP450 and P-gp induction

[10,11,12]. Concomitant therapy with CNIs and mTORs can result in drastically reduced exposure to the immunosuppressants. Rifabutin is often the preferred rifamycin in transplant patients due to its lesser effect on CNI pharmacokinetics **[3]**. The dose of CNIs/mTORs will likely need to be increased by at least twofold with rifamycin initiation, but it may take anywhere from a few days to weeks before the full effect of the interaction can be seen. Drug levels should be monitored closely during this time **[9]**. For those patients receiving azole antifungals for treatment or prophylaxis, co-administration with rifamycins can result in a significant reduction of systemic exposure to the azole antifungal and increased risk of toxicity form the rifamycin agent **[13]**. Consequently, if possible, concomitant administration of azoles and rifamycins should be avoided. If benefit outweighs risk and both agents are to be administered, therapeutic drug monitoring of the azole and clinical monitoring for rifamycin toxicity is recommended **[14]**. Rifamycin toxicity can also occur when used in combination with clarithromycin **[15]**. Long-term therapy with rifamycins is associated with increased LFTs/hepatotoxicity, anemia, neutropenia, thrombocytopenia and GI side effects **[10,16,17]**. Lastly, rifamycins have numerous interactions with other commonly used drugs **[18]**.

While used in the treatment of multiple NTMs, ethambutol is most notably recommended for the treatment of MAC **[5]**. This antibiotic has no known drug interactions with immunosuppressive agents. However, ethambutol has a unique adverse reaction profile which includes visual changes, red/green color blindness, optic neuritis and peripheral neuropathy. Patients should be questioned regarding visual disturbances, including blurred vision, on a routine basis. Periodical testing of visual acuity and color vision should be performed for patients taking higher doses or receiving the drug for more than 2 months **[19,20]**. A recent study suggests lesser risk of ethambutol toxicity with thrice weekly dosing **[21]**.

For all NTM infections, the treatment duration depends on clinical response, and in many cases, will continue for six to twelve months after resolution of symptoms and/or conversion of sputum cultures. The table below highlights some of the important pharmacotherapy considerations for both the aforementioned agents as well as other commonly used drugs for the treatment of NTMs. The reader is referred to the ATS/IDSA guidelines for a more detailed discussion of diagnosis and treatment of NTMs **[5]**. Also, articles in the *American Journal of Transplantation* by Keating and Trofe-Clarke are recommended for further information on treating NTMs in transplant recipients **[3,9]**.

<table>
<tr><th>Agent</th><th>Monitoring</th><th colspan="2">Adverse Reactions &
Drug Interaction Considerations</th><th>Renal Dose Adjustment[3]</th></tr>
<tr><td>Amikacin</td><td rowspan="2">·Renal function
·Hearing loss [23]
·Amikacin levels [9]</td><td colspan="2" rowspan="2">·Ototoxicity (signs and symptoms - unsteady gait, tinnitus, diminished hearing): question patients regarding these symptoms routinely [5,23]
·Nephrotoxicity (increased risk with simultaneous use with CNIs) [22,23]</td><td>YES
(major)</td></tr>
<tr><td>Streptomycin</td><td>YES
(major)</td></tr>
<tr><td>Azithromycin</td><td rowspan="2">·CNI levels [9]
·mTOR levels [9]
·ECG (QTc)
·LFTs</td><td>·Prolonged QTc [8]
·GI disturbance [8]</td><td>·Preferred agent in transplant Patients [3,9]</td><td>NO</td></tr>
<tr><td>Clarithromycin</td><td>·Contraindicated with everolimus and sirolimus [9]</td><td>YES
(mild)</td></tr>
</table>

		·Increased LFTs **[8]**	·Monitor CNI/mTOR levels closely **[9]** ·Reduction in CNI/mTOR doses necessary **[9]**	
Ethambutol	·Vision changes and impairment **[19,20]**	·Red/green color blindness **[20]** ·Optic neuritis **[20]** ·Peripheral neuropathy **[20]** ·Neutropenia **[20]** ·Thrombocytopenia **[20]** ·Periodical testing of visual acuity and color vision performed for patients taking higher doses or on therapy for more than 2 months **[19,20]**		YES (mild)
Imipenem		·GI disturbance **[28]** ·Increased seizure risk **[28]**		YES (moderate)
Isoniazid	·Frequent LFTs **[16,25]** ·Clinical symptoms of hepatitis (jaundice, nausea, vomiting) **[16,25]**	·Well tolerated, minimal interactions with CNIs **[24]** ·Hepatotoxicity **[25]** ·Alcohol consumption increases the risk of hepatitis while on therapy **[16]** ·Neurotoxicity is dose dependent: co-administration of pyridoxine 50mg daily is utilized to decrease this risk **[5, 16,25]**		NO
Linezolid	·Frequent CBC with differential **[26]**	·Thrombocytopenia **[26]** ·Leukopenia **[26]** ·Lactic acidosis **[26]** ·Simultaneous use with serotonergic agents should be cautioned due to the increased risk of serotonin syndrome **[26,27]**		NO
Ciprofloxacin	·Tendon or joint problems **[29]**	·GI disturbance **[29]** ·Prolonged QTc **[29]** ·Tendon rupture **[29]** ·Administer at least two hours before or two hours after calcium / magnesium containing products (e.g., antacids) **[30]**		YES (moderate)
Levofloxacin				YES (moderate)
Moxifloxacin				NO
Rifabutin	·CNI levels **[9]** ·mTOR levels **[9]** ·CBC with differential **[10]** ·LFTs ·Renal function	·GI disturbance **[10,16,17]** ·Neutropenia **[10,16,17]** ·Thrombocytopenia **[10,16,17]** ·Increased LFT/hepatotoxicity ·Increase in CNI/mTOR dose Necessary **[9]** ·Avoid concomitant use with azole antifungals if possible **[13,14]**	·Preferred agent in transplant patients **[3]** ·Contraindicated with everolimus and sirolimus **[9]**	NO
Rifampin			·Contraindicated with sirolimus **[9]**	NO
Tigecycline	·LFTs[31]	·GI disturbance[31] ·Elevated LFTs/hepatitis[31]		NO

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Antifungal Therapeutic Drug Monitoring: Confessions of a Pharmacist

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The ability to perform therapeutic drug monitoring (TDM) for antifungal therapy has been available for nearly a decade. Initially, there was not a wealth of data on how to adjust doses based on serum drug levels, or what levels should be targeted to maximize efficacy and minimize toxicity. To be fair, I wasn't quite sure of the role of antifungal TDM in our patient population either. Over time, we have gained significant experience with antifungal TDM, and it is now the standard for all of our patients on voriconazole and posaconazole.

The (U.S.) package insert does not recommend TDM for either of these agents; however, voriconazole's product labeling has the following language:

> *"If patient response is inadequate, the oral maintenance dose may be increased from 200mg every 12 hours to 300 mg every 12 hours. For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patient is unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg)."* ***[1]***

When examining the product labeling, one can certainly conclude that there must be a more specific way to optimize voriconazole regimens. Titrating doses based on clinical response, or lack thereof, can place patients at risk for therapeutic failure. Conversely, abandoning therapy due to intolerable adverse effects may eliminate therapeutic options in patients that may achieve therapeutic levels with reduced dosing. Voriconazole and posaconazole are both metabolized through our favorite cytochrome P450 pathway, 3A4 (as well as 2C9 and 2C19), and therefore are subject to the same genetic polymorphisms that impact our calcineurin inhibitor levels. Regardless of whether patients are slow or rapid metabolizers, therapeutic drug monitoring will ensure that our patients are getting the correct dose of posaconazole or voriconazole.

A group in Austria examined voriconazole trough levels in a population of the critically ill and hematological malignancy patients. Their results showed that 56% of voriconazole levels were sub-therapeutic (as defined as <1.5 mg/L) while 8% of levels were found to be supra-therapeutic (> 5.5 mg/L) and associated with hallucinations and encephalopathy. The authors reported that female patients, older patients and patients not on concomitant Proton Pump Inhibitor (PPI) therapy were more likely to have high voriconazole levels. Low body weight, male sex and concomitant PPI therapy were more likely to yield a low voriconazole level **[2]**. A group in Pittsburgh showed that patients

with Cystic Fibrosis had lower voriconazole levels compared to other indications for lung transplant **[3]**.

Posaconazole also has reason to pursue TDM. Patients are instructed to take their posaconazole dose with a high fat meal and acid; the FDA suggests a high fat meal is one in which 500 calories are derived from fat. Many post-transplant diets are limited in calories and fat, making dietary compliance for posaconazole difficult **[4]**. PPI use is almost ubiquitous in lung transplant, thus nullifying the acidic environment needed for optimal absorption. Posaconazole also has saturable absorption, where absorption of the suspension is better with multiple doses over the course of the day, rather than big doses given less often **[5]**. Fortunately, there is little variation between peak concentrations and trough concentrations so timing of blood draws (trough versus random) will not have a significant impact in the resultant blood concentration. The goal that we utilize for monitoring posaconazole levels is > 0.7 mg/L.

Based on the limited data, and clinical experience, I have become a believer in voriconazole and posaconazole TDM. Personally, I have been surprised by a few levels I have received in our patients that I would not have anticipated being "out of range." The dose adjustments that occurred enhanced therapy by maximizing benefit and preventing untoward adverse effects. We have also explained adverse events by having a supra-therapeutic level and patients that better tolerated the medication when the dose was decreased. TDM has had an impact on our patients; it might on yours as well.

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Prothrombin Complex Concentrates to Reverse Warfarin

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If you prick us, do we not bleed? *– William Shakespeare, The Merchant of Venice, Act III, Scene 1*

For decades we have used oral anticoagulants to reduce thrombotic risk. All too familiar with the effects of the vitamin K antagonist (VKA) warfarin in the pre-, peri- and postoperative arenas are the surgeon, anesthesiologist, perfusionist, and allied staff. Center specific protocols and professional guidelines have been developed to contend with the balance between bleeding and clotting risks and anticoagulation management at various times in a patient's surgical care **[1,2,3]**. Warfarin reversal has traditionally been done with intravenous (IV) or oral phytonadione (Vit K) and Fresh Frozen Plasma (FFP) to replete vitamin K dependent clotting factors (II, VII, XI, X). But as Bob Dylan so thoughtfully stated in 1964, "…*times, they are a changin*".

With short ischemic times heart and lung transplantation are ascribed to urgent anticoagulant reversal. Delays due to long anticoagulant duration of warfarin (7 days) and slow international normalized ratio (INR) reversal effects of phytonadione (12-24 hours) alone do not lend themselves to the rapid sequence of events **[4]**. The use of FFP in the reversal strategy is also less than optimal, as multiple plasma units (15 to 20 mL/kg) infused over hours are necessary to correct the INR. FFP has been associated with fluid volume overload, increased risk of transfusion-related acute lung injury (TRALI), necessity of thawing, ABO matching, and infectious risk **[5]**. Transfusions are associated with high rates of morbidity and mortality in critically ill, and worsening outcomes, respiratory, renal, cardiac, and neurologic complications in cardiac surgical patients **[6]**.

Cardiac Surgery has traditionally used high rates of allogeneic blood transfusion **[5]**. Reducing exposure to transfusions reduces HLA sensitization in transplant **[12]**. Centers are adopting *Blood Management* strategies to lessen expense and exposure, creating patient-centered approaches to transfusion **[10]**. One approach at reducing blood exposure is the use of Prothrombin Complex Concentrates (PCCs) to reverse the effects of warfarin. PCCs come from pooled donors and measures 25 times the vitamin K dependent clotting factor concentrations of FFP. They have the advantage of small administration volumes, improved viral inactivation, room-temperature stability, and lack of ABO incompatibility **[7]**. Until recently, off-label use of 3-factor PCC, Profilnine SD (Grifols, Barcelona, Spain), and Bebulin VH (Baxter) (containing factor II, IX, X and very little if any factor VII), and Factor Eight Inhibitor Bypassing Activity (FEBIA), an activated 4-Factor PCC (containing II, IX, X and activated Factor VIIa), were the only options available. These agents are approved for prevention and control of bleeding in patients with hemophilia B. In 2013 the FDA approved a non-activated 4-Factor PCC [Kcentra], CSL Behring, Marburg, Germany) composed of Factors II, IX, X, VII and Protein S and C, and trace amounts of Heparin. While licensed for urgent reversal of warfarin abroad for several years as Beriplex (CSL Behring, King of Prussia, PA, USA) and Octaplex

(Octapharma, Lachen, Switzerland), it was only recently FDA approved for warfarin reversal during acute major bleeding (April 2013) or urgent invasive procedure (December 2013).

4-Factor PCC has not been studied extensively in heart and lung transplant, only in small studies of cardiac surgery patients and massive bleed populations. When compared to FFP in the context of excessive bleed after cardiac surgery, it is superior at correcting the INR and significantly reducing the need for RBC transfusion **[8,9,11,12]**. 4-Factor PCCs rapidly reverse vitamin K dependent factors within 30 minutes of administration (INR < 1.3) when initial INR>2 compared to FFP (12-96 hours) **[8,10,12]**.

There are practical considerations to the 4-Factor PCCs. PCCs and FEBIA are considered fractionated components of blood, accepted by Jehovah's Witness patients along with rFVIIa **[14]**. PCCs are administered along with IV Vitamin K to prevent rebound increase in PT/INR **[12]**. Dosings of 4-Factor PCC are based on current INR and actual body weight. [See Figure 1] **[4]**. Each dose is calculated based on Factor IX activity. There have been reported dosing errors with Kcentra **[15]**. Special attention by the clinician should be placed on adding the units listed on the vial and not the product packaging. Doses are administered within 4 hours of reconstitution. Administration is at room temperature through a separate peripheral infusion line. The infusion rate is listed as 0.12 mL/kg/min up to a max of 8.4 mL/min (210 units/min). Monitoring should consist of baseline INR and repeated INR 30 minutes after administration. INR should be reassessed in 3-6 hours (due to the shorter $t_{1/2}$ of Factor VII and the onset of action of Vit K). Re-dosing 4-Factor PCC is not advised. Additional coagulation factors may be administered if hemostatic goals are not achieved. Observation for hypersensitivity reactions is vital, especially if antithrombin III or human albumin intolerances are known. Because of the small amount of heparin in each dose, caution should be exercised if the patient has known heparin-induced thrombocytopenia **[16]**. Thrombotic complications are possible with the use of 4-Factor PCC, but they are equivalent to FFP (4% vs 3%), and lower than activated Factor VII (5-20%) **[8]**.

Significant bleeding is associated with cardiac surgery. Minimizing contributors to bleeding risk is important, especially in transplant patients. Transfusion sparing strategies, utilizing factor concentrates, present an opportunity to reduce patient sensitization, volume overload, infectious risk, and to minimize infusion reactions. While little data is currently available surrounding the use of 4-Factor PCCs with heart/lung transplants, extrapolation of cardiac surgical bleed information provides us with a working template from which we can start to create warfarin reversal strategies.

Disclosure statement:

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Treatment Updates in Idiopathic Pulmonary Fibrosis and Considerations in Transplant

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease that is characterized by irreversible loss of lung function **[1,2,3]**. IPF remains the most common interstitial lung disease referred for lung transplantation and the second most common disease for which lung transplantation is performed **[4,5]**. Two medications, pirfenidone (Esbriet) and nintedanib (Ofev), appear to slow disease progression in IPF and were recently approved for use in the United States by the Food and Drug Administration (FDA) **[2,3,6,7]**. The approval of these medications signifies a turning point in the management of IPF as pharmacologic options are now available.

Pirfenidone exerts anti-fibrotic and anti-inflammatory by inhibiting the synthesis of transforming growth factor-β and tumor necrosis factor-α **[6, 8]**. Two of three phase 3 studies of pirfenidone in IPF demonstrated a reduction in disease progression, as measured by the decline in forced vital capacity (FVC). These studies included a trial conducted in Japan and two multinational studies, CAPACITY 004 and 006. Of the three studies, CAPACITY 006 did not show a reduction in the decline in FVC when compared to placebo. This prompted the fourth trial, ASCEND, which was designed to clarify the previous results **[2,3]**.

The ASCEND study compared pirfenidone to placebo. The primary endpoint was the change in the percentage of the predicted FVC (%FVC) at week 52. Two secondary endpoints were the change in 6-minute walk distance and progression-free survival at week 52. Treatment with pirfenidone resulted in a significant difference in the predicted %FVC (P<0.001). The pirfenidone group had a 47.9% relative reduction in the proportion of patients who had a decline of 10 percentage points or more in %FVC predicted or who had died, as compared with the placebo group. There was a significant difference in the 6-minute walk test with pirfenidone (P=0.04) and a reduction in the relative risk of death or disease progression by 43%. These findings led to the FDA granting pirfenidone fast track, priority review, orphan product, and breakthrough designations **[2,3]**.

Nintedanib is an intracellular inhibitor that targets multiple tyrosine kinases implicated in fibrogenesis. Two phase 3 trials (INPULSIS-1 and INPULSIS-2) were conducted to evaluate its safety and efficacy. The INPULSIS studies compared nintedanib to placebo for 52 weeks. The primary end point was the annual rate of decline in FVC. Secondary endpoints included time to first acute exacerbation and the change from baseline in total score on the St. George's Respiratory Questionnaire (SGRQ). Nintedanib significantly reduced the decline in FVC compared with placebo in INPULSIS-1 (difference of 125.3 mL, 95% CI 77.7-172.8 mL, P<0.001) and INPULSIS-2 (difference of 93.7 mL, 95% CI 44.8-142.7 mL, P<0.001). In INPULSIS-2, there was a significant increase in the time to first acute exacerbation with nintedanib as compared with placebo (HR, 0.38; 95% 0.19 to 0.77; P=0.005) and a smaller increase in the total SGRQ score (difference -2.69; 95% CI, -4.95

to -0.43; P=0.02), corresponding with less deterioration in health-related quality of life **[3,7]**. Based on these results, the FDA also granted nintedanib fast track, priority review, orphan product, and breakthrough designations.

Fibrosis after lung transplantation can lead to chronic lung allograft dysfunction (CLAD), which is the leading cause of allograft failure, morbidity and mortality. Due to their mechanisms of action and anti-fibrotic properties, pirfenidone and nintedanib may be viable options in the treatment of CLAD as it has a final common pathway leading to organ fibrosis **[8]**. Furthermore there is evidence in animal models that pirfenidone, used in combination with calcineurin inhibitors, results in down-regulation of profibrotic genes **[8,9]**. Current case reports in lung transplant recipients show conflicting experience with use of pirfenidone in CLAD. One report showed radiographic evidence of improvement, as well as a decrease in the decline of FVC with use of pirfenidone **[9]**. However, another report showed improvement on physical exam and computed tomography scan, but no symptomatic improvement in the patient **[10]**.

IPF is a progressive and fatal lung disease. Until recently, treatment options were limited to lung transplantation and supportive care. With the recent approval of pirfenidone and nintedanib as treatment options for IPF, the need for lung transplantation may slowly decline. However, more experience with the use of these new agents is needed to further evaluate their long-term impact on patients with IPF. Additionally, more studies are needed to consider whether pirfenidone and nintedanib have a role for lung transplant recipients suffering with CLAD.

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Tocqueville, Democracy, Involvement and the ISHLT

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"The health of a democratic society may be measured by the quality of functions performed by private citizens." - Alexis de Tocqueville

Alexis de Tocqueville was born of noble descent in Paris on July 29, 1805 and died at age 53 with tuberculosis on April 16, 1859. He got his name from a village near the city of Cherbourg in Normandy. Raised as an aristocrat, he was a liberal who rejected the old French regime of aristocracy. From his father's library he explored and studied the provocative French Enlightenment authors Montesquieu, Voltaire and Rousseau. While studying law, he read the 18th century *philosophes* and concluded that democracy would replace aristocracy everywhere and that America was more advanced in democracy than any other nation on earth. As a result Tocqueville wanted to study America to determine what could be learned about democracy, and possibly be applied to France. Therefore, he and his close friend, who became his alter ego, Gustave de Beaumont, received official permission to study the uncontroversial problem of prison reforms as a pretext to learn about democracy in the United States in order to shape the political future of France.

On April 2, 1831, Tocqueville and Beaumont boarded the American ship *Le Havre*. After enduring four days of seasickness and 38 days at sea, they arrived in New York City. In nine months with sharp-eyes, great listening skills, restlessness, keen awareness, astute powers of observation and reflective insight they traveled from Boston to New Orleans with brief forays west of the Alleghenies. They dined with Charles Carroll, the last surviving signer of the Declaration of Independence, in Baltimore. They rejoiced how aristocrats, unlike European counterparts, accepted the new democracy. They described their time shared with a crowd of Choctaw warriors being forcibly moved west on a Mississippi steamship. They saw the Mohawk River Valley, the setting for James Fenimore Cooper's bestselling novel *The Last of the Mohicans*. They met with President Andrew Jackson and spent time with Senator Daniel Webster, former President John Quincy Adams and Texas adventurer Sam Houston, among many other notable Americans.

Soon after leaving America on February 20, 1832, they began writing the *Système pénitentiaire aux États-Unis et de son application en France* (1833; On the Penitentiary System in the United States and Its Application in France). Although they talked about collaborating on a book about America, their divergent interests resulted in Beaumont's *Marie, ou l'esclavage aux Etats-Unis* (1835; *Marie, or Slavery in the United States*) with his focus on America's race problems and slavery. Tocqueville was more fascinated with American social and political life. The difficulties his own country had developing institutions favorable to liberty resulted in his most enduring works published as two volumes: *De la démocratie en Amérique* (1835/1840; *Democracy in America*). The scholarly works of Harvey Mansfield and his remarkable wife, Delba Winthrop, claimed this as both the best book

ever written about democracy and the best book ever written about America. In Tocqueville's last great work, *L'Ancien Régime et la Révolution* (1856; The Old Regime and the Revolution), he interpreted the French Revolution, which ignited war throughout Europe. Here, by confronting the demon of centralized government, he produced what is, today, regarded a classic study of the French Revolution.

Today, your Chief Editor of the Links is 53-years-old, without tuberculosis and far less accomplished than Tocqueville. We take for granted a trip by air across an ocean within a day, which for Tocqueville required nearly six weeks by sea. At an age where many of us were nearly completing our professional training, he completed the first volume of *Democracy in America* which still greatly influences us nearly 200 years later. The rest of this article will highlight salient features essential for a successful democracy from this prize winning publication and how they apply to us, and the ISHLT, today.

According to Tocqueville, it was not freedom that was the central tenet to democracy, but rather equality of conditions; he stated democracy was not merely a form of government but a way of life in America. A prevailing belief was that wisdom of many was greater than that of one, thus applying theory of equality to the intellect. Progress on equality of conditions in France was evident, but was much farther along in America. However, aristocratic tendencies, such as setting of bail and punishment by fines which favor the wealth and that the South was more aristocratic than the North, still remained in America. He rationalized that equality eliminated barriers across people, but, he prophesized, it was the inequality of conditions experienced by people of African descent in early 19th Century America that would lead to a revolution.

Another point Tocqueville brought up was that equality of conditions could lead to either prosperity or misery. Individuals, who are equal pursue more wealth, a pursuit which severs bonds between individuals but can lead to commerce and industry. Growth of industry leads to inequality, which can become permanent, thus resulting in an aristocracy. Was this inevitable? Did this occur?

Tocqueville viewed equality and freedom differently; where equality can bring pleasure, freedom requires sacrifices. Moreover, equality can exist without freedom; everyone is equal under a despot. Nevertheless, he explained that freedom was necessary for equality of conditions. Freedom of Speech, Freedom of the Press, and Freedom of Assemblies or Associations were essential for a democratic society to flourish. Regarding speech and all the talk Tocqueville had observed during his nine month tour, he discovered less independence of the American mind. The majority who agreed on certain topics created a circle. Those inside the circle, similar interests, had the freedom to think and discuss particular matters. Those with ideas outside the circle kept their privileges, but they were regarded as strangers and their privileges, useless.

Regarding the press, he discovered the press was less powerful in America than in France. The French newspapers delivered news while American papers provided advertisements. In France, there were very few newspapers with a controlling group. In America, nearly every small town had a newspaper. Tocqueville recognized that the way to restrain the influence of the press was to increase the number of newspapers. Newspapers curtailed administrative centralization, such that if administrative

centralization emerged, newspapers would diminish in numbers and censorship would prevail. However, fragmented administration would greatly increase the number of newspapers, and thus decrease censorship.

Another salient feature highlighted was that democracy, "trickles up", rather than "trickles down." He suggested that frequent elections and numerous offices were important and gave society members the opportunity to practice democracy and see results in organizations at the local level. Involvement was, and remains, a much better teacher than just reading about it and served to prepare those who might advance to the state and federal levels of politics. In democracy, popular sovereignty for all citizens became the rule. However, because of the strong conviction for equality in democracy, centralized administration of government could emerge through "majoritarian government," one of the most dangerous threats of a democratic society.

Those with strong opinions who can persuade the masses can create the circle of belief, and those outside the circle who might disagree may find themselves in isolation and despair. It would be difficult to believe what the majority rejects. Moreover, the minority would be persuaded, and not necessarily constrained. In pre-revolutionary France, the king cannot fail. In America, majority cannot fail. Eventually the power of the majority leads to instability and the minorities are tyrannized. As a result, according to Tocqueville, tyranny of the majority and administrative centralization greatly threatens freedom in a democracy or any democratic organization.

The freedom of association and assembly can guard against the tyranny of the majority. Any membership, in any association or organization, can represent a minority and frequently it's a small minority of the population. Such a small organization, such as ISHLT, can have a great deal of influence because of specialized interest and focus. Associations carry out their objectives peaceably by speaking publicly and petitioning openly. Newspapers or newsletters are necessary to unite members consistently and conveniently. Today, we also have blogs, tweets, chat rooms and, for the ISHLT, discussion groups. Take note, individual members or citizens in a democracy are weak. Working together they are stronger. Participation and serving others implies that participants are serving themselves through whatever organization, private or civil association, thus potentially maintaining individual rights.

Finally and most importantly, the longest chapter in *Democracy in America* was devoted to the three distinct races inhabiting America in the 1830's: the American Indians, the whites and the African Americans. Tocqueville piercingly pointed out that the Indians and the blacks suffered the effects of the same tyrant, giving us the two great scars of 19th Century America: the extermination of Indian tribes and the institution of slavery. A couple examples and explanations are in order and the effects of democratic tyranny were witnessed by Tocqueville on America's waterways. Along the Mississippi River in Memphis, he wrote:

There was a general air of ruin and destruction in this sight, something which gave the impression of a final farewell, with no going back; one couldn't witness it without a heavy heart. The Indians were calm but gloomy and taciturn. One of them knew English. I asked him why the Choctaws were leaving their country. 'To be free,' he answered. I couldn't get anything else out of him. Tomorrow

we will set them down in the Arkansas wilderness. I must confess it is an odd coincidence that we should have arrive in Memphis to witness the expulsion, or perhaps the dissolution, of one of the last vestiges of one of the oldest American nations.

Another angry analysis by Tocqueville focused on the subject of slavery. He stated that in America, slavery is racial and attitudes would be difficult to change. He forecasted that slavery would be abolished but it would not eliminate prejudice of the master, prejudice of race or prejudice of the white. It was the "American Syndrome: - morality, independence, enlightenment, industry, commerce, and success, which did not work where slavery existed. When traveling west on the Ohio River he contrasted the "industrious" Ohio (free state) with "idle Kentucky" (slave state).

The State of Ohio is separated from Kentucky just by one river; on either side of it the soil is equally fertile, and the situation equally favorable, and yet everything is different…But Kentucky, because of slavery is inhabited by a people without energy, without ardor, without a spirit of enterprise.

In Ohio, work was honored and there was liberty. The land was cultivated by whites, there was industry, prosperity and improvement. In Kentucky, work was dishonored and there was servitude. The land was not cultivated. Slaves were never remunerated for their toil. They were corrupted by their masters, lost the memory of their origins and language and were separated from their families. Slavery corrupted the masters.

These differences cannot be attributed to any other cause but slavery. It degrades the black population and enervates the white…Slavery threatens the future of those who maintain it, and it ruins the state…Slavery is incompatible with democratic freedom and the enlightenment of the age.

In summary, the ISHLT functions democratically with a variety of councils, workforces and other small work groups that serve our democratic ISHLT which severely limits the likelihood of a tyranny of the majority. There is no subjugation and no extermination. When members get involved with different activities they are practicing what Tocqueville calls "self-interest properly understood". To further guard against despotic behavior frequent elections, changes in our leadership, listening to and working through the many differences, and the preservation of individual rights all can work against uniformity within the ISHLT. The goal is consensus. Our society is quite diverse, with many nations represented. Each member is on equal footing with "equality of conditions." To have your voice heard, get involved!

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