IN THE SPOTLIGHT: Who Has Time To Be Still?

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"In the age of constant movement, nothing is so urgent as sitting still" – Pico Ayer

Turn on the TV or radio, open any book or magazine and you are bound to come across something on the benefits of meditation. From reducing stress levels and blood pressure, to better sleep, to improved focus, the benefits are seemingly endless. I have tried several times to make meditation a part of my routine. It usually lasts about a week, before those 20 minutes in the morning get re-allotted to another task or "just trying to get out the door crisis". Also short lived were the attempts to meditate before bed and the middle of the day while I was at work, also known as one of the worst thought out plans ever.

I was recently in Seattle for a meeting. Since I had never been there and it takes an entire day on planes and in airports to get there from Cincinnati, I took a couple of days to play tourist. My hotel was located a short walk from the Bellevue Botanical Gardens. My knowledge around horticulture is pretty basic, but who doesn't like pretty plants and flowers? The gardens were lovely, but the walking trails into the forest around the garden were breathtaking. There were very few people out that morning, so was able to really experience and enjoy the quiet and solitude. After a couple of miles, I stopped to catch my breath and a bench. Then the strangest thing happened, stillness. No people, sunshine streaming thru the treetops, soft hum of nature and me on the bench. For those 30 minutes, I stepped off the hamster wheel I have spent most of my adult life running on. I found myself reflecting on the journey that has been the last few years, highs and lows, victories and failures, loss and joy. I even took a little bit of time to think about how those experiences shaped the person I am today and what my future may hold. It was in that moment I realized, despite my numerous fails at the practice of meditation, sometimes stillness is enough.

So now you are thinking, what the heck does this have to do with transplant? We have all been on the giving and receiving end of the self-care lecture. We hear it from each other and preach it to our patients and their families. In today's world, we are all trying so hard to be in three places at the same time, live up to extraordinary expectations, take care of our patients and our own families, climb the proverbial ladder and leave our mark. Thanks to technology, we are accessible anywhere, anytime and are rarely able to truly unplug and step off the hamster wheel. The inevitable reality is we spend most of our lives running at least 20 minutes late to our life. I think it is important we all try to find a little bit of stillness in our lives, even if it is in your car in the parking garage at work.

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STRATEGIC PLANNING UPDATE

During July and August, the Scientific Councils collected input from their members regarding their needs and their thoughts about the future strategic direction of ISHLT. A big THANK YOU to all of you who contributed to this information-gathering process. The next step is for the Council Chairs to meet with the Strategic Planning Task Force on September 17 to share the feedback they have received with the other Council Chairs and with the Task Force members. For the remainder of September, we will be conducting phone interviews of some key ISHLT leaders, as well as junior faculty members and non-members, and we plan to collect information as well from members and non-members in countries where transplantation is less well developed. After that, our strategic planning consultant will collate all of this information into a Findings Report which will be reviewed and discussed at the Board's October meeting.

As you can see, this process involves a lot of people doing a lot of hard work to help develop a framework for the Society's future. We are all looking forward to learning what the Findings Report has to say about what you, ISHLT's members, want and need and what aspirations for future directions you share in common.

Thank you again for all of your input. We will keep you updated through the LINKS on the progress of this important process.

ISHLT Board of Directors Call for Nominations

Dear Colleagues:

I am writing to you in my capacity as Chair of the ISHLT Nominating Committee to solicit nominations for the ISHLT Board of Directors. We are seeking nominations for three (3) Director positions. Any current regular member (not a student/resident or emeritus member) may be nominated to serve as a Director. All terms are for 3 years.

ISHLT is currently engaging in a Strategic Planning process that will help define the Society's course and identify key goals and objectives for the next 3-5 years. Helping the Society follow this course and achieve these goals and objectives will require the effort of Board members who are dedicated to the Society, who have time to devote to Society work, and who possess the appropriate skill set to lead the members and key volunteer leaders in these new directions. It is therefore important that all ISHLT members give consideration to the nomination process and participate in the election process during the Annual Business Meeting. The Board of Directors is eager to involve more of the members in the workings of the Society, thus your participation in the selection of the future leadership of the Society is both important and desired.

The nomination process is designed to gather information about the background and skill set of potential nominees and has been modified this year to reflect an increased focus on choosing Board members with strong leadership abilities and experience. I wholeheartedly encourage you to take a few minutes to consider whether any of your ISHLT colleagues should be nominated for the ISHLT Board of Directors. Please see the Call for Nominations (hyperlink) for criteria and instructions. The Nomination Packet must be completed and submitted with all required attachments no later than September 30, 2015. The Nomination Packet consists of an Application Form (hyperlink) that must be completed by the nominee, and two letters of reference.

The Directors whose terms on the Board expire in April 2016 are as follows:

Myung Park, MD, USA
Andrew Fisher, FRCP, UK
Daniel R. Goldstein, MD, USA

The individuals who will continue to serve on the Board are as follows:

Carla Baan, PhD, Netherlands
Christian Benden, MD, Switzerland
Lara Danziger-Isakov, MD, MPH, USA
Duane Davis, MD, MBA, USA
Tobias Deuse, MD, PhD, Germany
Danny Goldstein, MD, USA
Peter Hopkins, FRACP, Australia

Maryl Johnson, MD, USA
Jeff Teuteberg, MD, USA
Michael Petty, PhD, RN, CNS, USA

Thank you for your participation in this very important process.

With best wishes,

Hermann Reichenspurner, MD, PhD
Immediate Past President, ISHLT
Chair, ISHLT Nominating Committee

Call for Abstracts: ISHLT 36th Annual Meeting and Scientific Sessions

The Abstract Submission System is now live on the ISHLT website at http://ishlt.org/meetings/abstracts.asp. The deadline for receipt of abstracts is **November 3, 2015 at 11:59 PM EST**.

NEW THIS YEAR: the Main Menu page of the Abstract Submission Site offers three different link options for submitting an abstract:

1. **New Abstract Submission**
   Use this link to submit an abstract in one of the following 12 main categories:

   - Basic Science (BSI)
   - Economics, Ethics, Public Policy (EEP)
   - Heart Failure – Adult (HF)
   - Heart Transplantation – Adult (HTX)
   - Infectious Diseases (ID)
   - Lung Transplantation – Adult (LTX)
   - Mechanical Circulatory Support – Adult (MCS)
   - Nursing, Health Science, Allied Health (NHSAH)
   - Pathology (PATH)
   - Pediatrics (PEDS)
   - Pharmacy & Pharmacology (PHARM)
   - Pulmonary Hypertension (PH)

2. **New Junior Faculty Clinical Case Reports (JFCCR) Submission** (for Junior Faculty <7 years out of training only)
   Use this link to submit an abstract in one of the following 6 CASE sub-categories:

   - Infectious Diseases
   - Heart Failure/Transplantation
   - Lung Failure/Transplantation
   - Mechanical Circulatory Support
   - Pediatrics
   - Pulmonary Hypertension

3. **New Late Breaking Clinical Science (LBCS) Submission**
   Use this link to submit an abstract in the Late Breaking Clinical Science category.

Detailed instructions for submitting an abstract in any of these categories are available on the submission site and in the 2016 Call for Abstracts brochure which can be downloaded via the following links:

- ISHLT 2016 Call for Abstracts PDF Brochure
- ISHLT 2016 Call for Abstracts Flipbook (great for Android users)

In addition, below are a few helpful pieces of information regarding Abstracts and the Abstract Submission Process:

- An abstract may be submitted in only ONE category.
- The size limit for an abstract is 2,140 characters, including abstract title, body, table(s) and images(s).
- Proofread abstracts carefully to avoid errors before submission. Corrections to the abstract content cannot be made once an abstract has been finalized/submitted.
- All submitted, finalized abstracts will be blindly reviewed by a panel of selected ISHLT members from November 6-17, 2015.
- All primary authors will be notified in January 2016 regarding the acceptance or rejection of their submissions.

We look forward to receiving your best science submissions!

It's "Child's Play"

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Children express themselves through play. Pediatric healthcare professionals know that, but how do we help decrease fear and ease the pain of the technologically advanced therapies (mechanical assist devices/VADs and heart transplantation) we currently have available to treat all ages of children dying of advanced heart failure?

Although the concept of Child Life (CL) has existed for decades, healthcare facilities' perceptions may have been that they were not able to budget yet another service. Presently, this service is considered a vital part of the multidisciplinary care model. In the midst of a potentially devastating part of a child and family's life, in steps the CL specialist, not only to promote emotional stability and healthy growth and development for this child, but also to teach their valuable techniques to the family and staff.

A (CCLS) Certified Child Life Specialist's aim is to decrease the stresses and anxieties related to hospitalizations for both the patients and their families. In order to do this, the top priorities are building rapport in a non-threatening manner and familiarizing them with the environment and equipment. In practice, playing with the various types of medical equipment that the patients will be exposed to, achieves these goals best.

For this patient population, dolls equipped with their own VAD devices allow patients and families to explore the new equipment on their own terms. Once the device is implanted, the role shifts to supporting the patient and family through the daily dressing changes and the emotions involved with this new life style. This new way of living can be especially challenging due to pain, fear of the unknown, anxiety for a variety of reasons and the loss of independence that was previously gained.

For the young/infant population, the CCLS works with the parents/caregivers to model and guide them on how best to support their child through frequent procedures (i.e. dressing changes) including how to handle the stresses of dependence on a machine. One goal for the mechanical device patient is to get them to a point of not needing sedation medications for the frequent dressing changes. This has been an achievable goal for all patients at our institution thus far. Patients have been able to be distracted and supported using developmentally appropriate toys, iPads, music, positive touch, and various other coping tools, as well as providing thorough preparation prior to the initial dressing change. Each child copes in his/her own way and their lead is followed by the CCLS in order to use their preferred coping method, while advocating for this with the medical team and family.

Another tough goal to accomplish during this time is continuing to meet developmental milestones. Child Life works to achieve these goals by providing developmentally appropriate toys that would be found in their normal environments, providing individual play sessions, etc. An example of this is collaboration with the transplant team, infection control, and nursing teams to allow a patient with cumbersome equipment to go to the hospital playroom. This can be a time of fun, developmental growth, and exploring – all age and developmentally appropriate activities for a two year old. For adolescent patients, the developmental milestones are more social and can be difficult to accomplish due to precautions for infectious disease exposure for the waitlisted patient who could get an organ donor offer any moment.

Again, through advocating and collaborating with the teams and the modern marvels of technology and social media, we are usually able to help promote socialization and normalization as much as possible from the confines of the hospital setting using technology. With adolescents especially, the emotional component to coping can be the hardest for staff and family to understand and be able to help because it's the thing one can't easily see. Providing outlets and opportunities for self-expression can be the key to supporting this population through the long hospitalization and the entire process of transplantation. There are many various aspects of the waiting process for patients on the mechanical devices that go far beyond the actual medical equipment. We may find ourselves in this grey area that can sometimes easily get overlooked. The CCLS must strive to find how to best allow patients and families to cope, in order to prevent regression and provide an avenue to have their thoughts, emotions, wants, and needs advocated for and conveyed to the medical team. Facilitating this communication is so integral to them.

Each multidisciplinary team member has a share of responsibility to ensure each patient the intent of improved quality of life. From the talented surgeon who performs delicate anatomical repairs on tiny hearts, to the nursing staff and others who must not only understand the science, but also facilitate the application and humanize the care delivery, the CLS guides a transformation from emotionally traumatized infants or children to healthier well-adjusted kids. An enormous task, even for such competent professionals, this role is a vital component of successful pediatric heart failure support and transplantation.

In the past, some transplant coordinators may have enviously joked that if they had been aware of the Child Life discipline before entering the nursing field, they would have taken that career pathway instead…so they could "play with kids all day." In all sincerity, however, creating a child-friendly environment is a priority for pediatric healthcare facilities. Child Life Specialists decrease the fear and pain of a child during a lengthy hospitalization while educating the family and staff how to do this, as well.

GOAL: Let's ALL go home and PLAY!

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Mentoring: Not Just for Newbie Nurses

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It is unclear when exactly mentoring began within the profession of nursing. According to Hodgson and Scanlan, literature on the subject dates back to the 1980's, but Florence Nightingale could be considered a mentor to others early in the profession, dating back to the Crimean War [1]. Mentoring amongst nurses is described as "a valued relationship, a nurturing process in which a more experienced person supports the professional growth and career development of another" [1]. The success in mentoring new nurses to increase retention has been documented in the literature as well as mentoring seasoned nurses for leadership roles. Literature regarding mentoring of ventricular assist device (VAD) coordinator registered nurses is lacking.

Mentoring continues to be important throughout one's nursing career, especially when changing career paths. Industry has played a role in teaching new VAD coordinators through conferences designed to give them the basic tools needed to coordinate for this patient population. VAD manufacturers have created tool kits to guide new coordinators through the stages of VAD patient management. Other learning tools such as MyLVAD.com and the MCS Collaboration website are also helpful tools for the new coordinator. This author proposes that new VAD Coordinators need a more personal experience in acclimating to their new role.

Mentoring new coordinators can help alleviate the stress of not only being a novice again, but can also help manage the transition from being task driven to seeing the overall big picture when managing a patient population throughout the continuum of VAD support. For example, in bedside nursing, one is concerned with patient care and documentation for the shift with a little education thrown in if there is time. As a VAD coordinator, the nurse must not only be concerned with the medical care of the patient across the entire continuum, but also the well-being of the caregiver(s), ensuring the VAD equipment is in good working order, education of patients, family, staff, and community members, data collection, and meeting all regulatory requirements related to VAD therapy. Additionally, many coordinators are also required to take after hours call for VAD patient needs.

Given the wide variety of duties assigned to a VAD coordinator, mentoring is important to increase retention and provide opportunities for growth. The aging nursing population is another important reason to mentor new coordinators. A survey conducted in 2013 by the National Council of State Boards of Nursing and the Forum of State Nursing Work Force Centers indicated that 55% of registered nurses still working are 50 years old or older [3]. The mentee is not the only one to benefit from this partnership. The mentor should take great pride in helping the new coordinator move from novice to eventually expert in the field of VADs.

In conclusion, expert VAD coordinators should take a more personal approach in growing new coordinators through mentoring. Seasoned VAD coordinators should consider mentoring through International Society for Heart & Lung Transplantation (ISHLT) [4]. Perhaps future mentoring opportunities could be developed through International Consortium of Circulatory Assist Clinicians (ICCAC), the organization dedicated to those that work in the field of mechanical circulatory support [5].

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Selexipag: The Next Major Advance in PAH Pharmacotherapy?

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Selexipag is a first-in-class, orally available, selective agonist of the prostacyclin IP receptor [1]. The IP receptor is one of 4 different types of prostanoid receptors found in the lungs and regulates vascular tone, platelet activation, and immunologic cell responses. The IP receptor is principally expressed in vascular smooth muscle cells (SMCs) and platelets. Activation of the IP receptor triggers SMC vasodilation and inhibition of SMC proliferation and platelet aggregation. These effects are regulated through stimulation of adenylate cyclase and increases in plasma cyclic adenosine monophosphate (cAMP) [1,2]. Despite its similar mode of action to endogenous prostacyclin, selexipag is chemically and pharmacologically considered a non-prostanoid. A summary of its pharmacology and relevant pharmacokinetic properties are highlighted in Table 1 below.

Table 1. Key Pharmacologic and Pharmacokinetic Features of Selexipag [1]

Selectivity for IP Receptor	Orally Active	Tmax	Metabolism	Active metabolite	Half-life (parent/ active metabolite)	Dosing Frequency
Yes	Yes	1.5 hrs	Rapid hydrolysis in liver	Yes; ACT-333679	1-2 hrs/8 hrs	Twice daily

The clinical efficacy and safety of selexipag have been evaluated in both phase II and phase III trials [2,3]. A multicenter, double-blind, placebo-controlled, proof-of-concept study was conducted in 43 patients with symptomatic pulmonary arterial hypertension (PAH) on stable background therapy (endothelin receptor antagonists [ERAs] or phosphodiesterase type-5 inhibitors [PDE-5i]. All patients were required to have a baseline pulmonary vascular resistance (PVR) of > 400 dynes-s/cm^5. Eligible patients were initiated at 200 mcg PO BID and up-titrated to a maximum of 800 mcg PO BID [2]. The primary endpoint was change from baseline in PVR after 17 weeks. In the selexipag group, the PVR decreased significantly by 30.3% ($p = 0.0045$) coupled with an increase in cardiac index and reduction in systemic vascular resistance, without apparent hypotension. The most prevalent adverse events with selexipag were: headache, jaw pain, pain in extremity, nausea, and nasopharyngitis [2].

The landmark phase III trial, GRIPHON (P**G**I2 **R**eceptor agonist **I**n **P**ulmonary arterial **H**ypertensi**ON**) was completed in May 2013 and final results were presented at the ACC.15 meeting in March 2015 [3]. The trial was particularly compelling because it represents the largest randomized, double-blind, controlled study among PAH patients to date. The trial enrolled patients from 181 centers in 39 countries and was an event-driven trial which evaluated morbidity/mortality versus placebo [3]. Approximately 80% of patients received stable background PAH therapy at baseline (ERA, PDE-5i,

or both). Dosing was initiated at 200 mcg PO BID and up-titrated based on patient tolerability to a maximum of 1,600 mcg PO BID. A summary of the key findings is shown in Table 2 below. The mean duration of treatment for selexipag and placebo was 76.4 ± 50.45 and 71.2 ± 48.32 weeks, respectively. The overall treatment effect of selexipag was seen regardless of age, sex, PAH etiology, baseline functional class, and background PAH therapy. In terms of safety, 14% of participants that received selexipag discontinued therapy due to an adverse event compared to 7% of those in the placebo arm. The most frequent adverse events (> 3%) were: headache, diarrhea, nausea, jaw pain, pain in extremity, myalgia, arthralgia, and flushing [3].

Table 2. Summary of Key Findings from the GRIPHON Trial [3]

Study Design	Patient Population	Number of Patients	Primary Endpoint	Results
MC, DB, PC, phase III	PAH, age 18-75 yrs; 20% treatment naïve; 47% monotherapy; 33% combination therapy	1,156	Time to first morbidity/mortality (M/M) event‡	Selexipag decreased time to M/M by 40% (HR 0.60; 99% CI: 0.46, 0.78) vs. placebo (log-rank p < 0.0001)

MC = multicenter; DB= double-blind; PC = placebo-controlled
‡ M/M defined as either disease progression (based on 15% decrease in 6-minute walk distance, and either worsening functional class or need for additional PAH therapy), hospitalization for PAH worsening, PAH worsening (need for atrial septostomy or lung transplant; initiation of parenteral prostanoids or chronic oxygen therapy), or all-cause death

Relative to most prostacyclin (PGI_2) analogues, selexipag exhibits a higher affinity and selectivity for the IP receptor [1]. Consequently, potential pharmacologic advantages of selexipag relative to current prostacyclin-based therapy may be realized with regard to safety and efficacy. The high selectivity of selexipag and its active metabolite for the IP receptor may minimize the frequent gastrointestinal (GI) effects seen with prostacyclin therapy by way of less stimulation of gastric smooth muscle and slowing of gastrointestinal (GI) transport leading to nausea and vomiting. However, it should be noted that similar types of adverse events to prostacyclins have still been observed in both the landmark phase II and III trials of selexipag [2,3]. The most obvious advantage to selexipag may come in the form of dosing convenience by way of oral, twice-daily administration. As an alternative to parenteral prostacyclins, this would negate complications such as catheter-related infections and injection-site pain [4]. Inhaled prostacyclins obviate these complications, but still require more frequent administration and specific delivery systems. Oral treprostinil is also now approved, but is limited by GI adverse effects and lack of clear benefit as part of combination therapy [4]. Beraprost is another oral prostacyclin that has been studied, but it remains unavailable in most countries due to lack of sustained efficacy [4]. Ultimately, the safety and efficacy of selexipag relative to prostacyclin-based therapy remain uncertain at this time and require further study.

In summary, selexipag is a promising treatment which may soon add to the rapidly growing therapeutic advancements seen in PAH management over the past decade. Its novel pharmacologic effects, dosing formulation, and phase III trial results provide optimism for the next major advance in PAH pharmacotherapy. However, key questions remain including the relative effects compared to current prostacyclin formulations. Selexipag (Uptravi®) was submitted for regulatory approval to both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in December 2014. Regulatory review is also underway in other countries, including New Zealand, Canada, and Switzerland.

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Infection, Rejection, and Hypogammaglobulinemia: The Chicken or the Egg?

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Intravenous immune globulin (IVIG) products are derived from pooled human plasma from over tens of thousands of screened donors collected largely by private industry,[1] which contributes to its limited availability and high cost. Nevertheless, demand for IVIG continues to increase, with greatest use in North America, Australia/New Zealand and Europe.[2] Currently, the labelled indications for IVIG include treatment of primary immunodeficiency, acute/chronic immune thrombocytopenia (ITP), prevention of bacterial infection in chronic lymphocytic leukemia (CLL) patients with hypogammaglobulinemia (HGG), and provision of passive immunity for hepatitis A, measles, rubella, and varicella in specific patients.[3] The use of IVIG in the setting of thoracic transplantation, whether for treatment of rejection or provision of passive immunity, remains off-label.

Hypogammaglobulinemia (HGG) is common following transplantation, with a reported incidence of 34-70% for mild HGG (IgG<700mg/dL) and 10-37% for severe HGG (IgG<400mg/dL).[4-7] However, questions remain surrounding the clinical importance of these findings and whether treatment with IVIG will positively impact outcomes. Does HGG independently lead to poor outcomes or do patients with more severe disease have HGG? This question leads us into a "chicken versus the egg" paradox. The volume of evidence that links HGG with significant clinical implications, particularly infection, after transplantation is growing. A large meta-analysis of 1756 solid organ transplant recipients, including heart (OHT) and heart/kidney recipients, reported a 4.8-fold increase in respiratory infections, a 2.4-fold increase in the likelihood of CMV infections, a 8-fold increase in aspergillus infections (3.7-fold increase in other fungal infections), and a shocking 22-fold greater 1-year all-cause mortality rate in those with severe HGG (2.7-fold increase in mortality for those with mild HGG).[4] Two other groups have also reported an increased incidence of opportunistic infections in OHT with HGG, particularly CMV viremia.[8,9]

Many studies of HGG in lung transplant (LTx) have also found an increased incidence of fungal infections.[5,7,10] The incidence of CMV was found to be higher with HGG in two LTx studies,[10,7] but found to be similar in another.[5] Community-acquired respiratory viruses appeared not to be linked to low IGG[6,10] but possibly to low IGA.[10] Studies evaluating severe HGG also reported an increased incidence of bacterial infections, hospitalizations, and increased mortality.[5,7] There have not been any studies to date that link HGG with increased rejection risk or reduced lung function in the LTx population.[5,6,10]

Risk factors for development of severe HGG have currently been identified as OHT recipients with ≥ 3 episodes of rejection or those requiring intravenous methylprednisolone therapy,[8] and LTx recipients with emphysema, female gender, or presence of BOS.[5]

Given the mounting evidence linking morbidity and mortality with HGG, studies evaluating the treatment of HGG with IVIG are beginning to emerge. While one recent retrospective study of 37 SOT recipients did not find a patient or graft survival benefit when targeting IGG >400,[11] two smaller studies from one group found a reduced incidence of infection and mortality in IVIG-treated OHT recipients with infections or CMV disease when targeting IGG>700-750.[12,13] These two studies repleted IVIG at 200-400mg/kg . Published data regarding the benefits of IVIG for HGG in LTx is still materializing, as well. One small cross-over study of 11 patients found no difference in infection rate despite maintaining IGG>700 during the treatment phase.[14] Another recent retrospective found similar 5-year survival and 5-year chronic lung allograft dysfunction-free survival between patients who received IVIG and those who did not. Of note, this study used time-dependent exposure and was thus subject to immortal time bias in favor of treatment.[15] Immortal time bias is a time interval during the follow-up period in which the outcome(s) cannot occur by design. In this study, patients who received IVIG were alive until receiving IVIG; patients who had an event before treatment were automatically in the untreated group.

IVIG remains a costly and limited resource facing increasing demand. While current evidence likely supports a link between HGG, infection, and even mortality, there is much need for further evaluation of the effectiveness and optimal dosing strategy for IVIG repletion in this setting. As we delve deeper into this paradox, perhaps which comes first no longer matters. Whether we begin with HGG, infection or rejection, the result is the same: impaired outcomes. What is important for future pathways is the relationship between these characteristics. We may find that the benefits of IVIG in HGG are linked to target immunoglobulin levels, overall immunosuppression, or other patient-specific characteristics. On the other hand, we may find that HGG is a non-modifiable risk factor for inferior outcomes.

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Clot Through the Heart...And You're to Blame?

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Using heparin for ventricular assist devices (VAD) is like a great song from the 1980's. You're really happy it's on but you know it's going to get a little hairy. Preventing device thrombosis can definitely cause a lot of head banging as well. The risks of bleeding and clotting are both present; however, the need to maintain device patency and prevent embolic sequelae must be tempered by the risks associated with bleeding.

Device thrombosis was previously thought to be of minor concern; however, recent data has shown the rate is increasing. Starling and colleagues reported a significant increase in thromboses from 2.2% - 8.4% in three large U.S. centers [1]. Additionally, data analyzed from INTERMACS highlighted that time to thrombosis, from device implantation, has decreased from 18.6 to 2.7 months [2].

Heparin is considered the treatment of choice in the acute phases of prevention and treatment of device thromboses. However, you know how heparin is...you play your part and it plays its games [10]. One of the biggest challenges we have in utilizing heparin is our inability to fully understand whether or not it is working. Alternative monitoring strategies are available; however, moving away from activated partial thromboplastin time (aPTT) is often a matter of debate.

Heparin is an incredibly complex molecule and management of heparin therapy can be misunderstood. The manufacturers for most devices recommend monitoring aPTTs with a goal of 60-80 seconds. However, that information is misguided. Based on only *one* study, the goals for aPTT were established as 1.5-2.5 times baseline. *In that institution*, this translated to an aPTT goal of 60-85s. Since that time, this has become the "gold standard" for monitoring heparin's anticoagulant effects in *all* populations *everywhere* [3]. PTT can be affected by multiple endogenous factors including antithrombin III, fluctuation in factor levels, and hemolysis - all of which are present during times of stress and inflammation. Lactase dehydrogenase (LDH), which is elevated in the presence of hemolysis, has been shown to prolong aPTT independently of anticoagulation [4,5]. Therefore, aPTT may be an unreliable measure of heparin's activity but remains essential as an overall measure of physiological anticoagulation status.

Approximately ten years ago, some institutions began monitoring heparin with unfractionated heparin activity (UFH) levels. The Antithrombotic Therapy and Prevention of Thrombosis guidelines (CHEST) from 2008 included recommendations to titrate heparin based on UFH levels or to correlate an institution-specific aPTT to an UFH goal range. Many institutions have complied with these recommendations; however, not many institutions have created guidelines based on UFH levels for device anticoagulation. Due to the inflammatory nature created by VAD placement or in post-thrombotic states, the time has come to find a strategy for monitoring patients without solely relying on aPTT.

In all fairness to aPTT, it is important to note that UFH activity levels can be affected by physiological factors present during hemolysis as well. UFH levels are measured spectrophotometrically which means interpretation is determined by color and can be artificially lowered by anything that can change the color of blood (e.g. lipemia or elevated bilirubin). Additionally, UFH activity levels can be artificially lowered in the presence of low antithrombin III levels which are commonly associated with hemolysis [8].

Many of us have been confounded when PTT disagrees with UFH levels and multiple studies have recognized this frustrating discrepancy [5,6,9]. A recent study by Adatya and colleagues, showed that during mechanical circulatory support, aPTT levels and UFH activity levels are most discordant when LDH is >2.5 times baseline or when INR is ≥1.5 both of which can be elevated during times of stress and inflammation [4]. When this occurs, we either ignore the level we don't like or stubbornly rely on aPTT, biting our fingernails, recognizing that aPTTs between 60-80 seconds are probably doing nothing to anticoagulate our patients. In this scenario, would following UFH activity goals while assessing aPTTs independently be better? In most cases, if the overall goal is anticoagulation, I'm just going to say it, yes.

As we know, the first level after instituting this practice will be an UFH level of 0.11units/mL with a PTT>150s. Of course, the patient will be "oozing" but not bleeding and there "might be some concern for a clot". What is the best method for interpretation and clinical application? Other factors must be analyzed to assess overall anticoagulation status.

Why is the aPTT elevated?
• Elevated LDH or INR • Variance in coagulation factors (fibrinogen or antithrombin III) • Acute phase reactants (factor VIII)
Can we believe the UFH activity level?
• Elevated bilirubin • Lipemia • Elevated plasma free hemoglobin
Clinical status?
• Clinically significant bleeding or oozing? • Presence of clot in the device or other known risk factors?
Other thoughts?
• Is the aPTT telling us that the patient is more likely to bleed for a reason unrelated to heparin? • Would a TEG (thromboelastograph) or thrombin time be useful? • Are we adequately anticoagulating the patient and, more importantly, *are we okay with this lower level of anticoagulation?*

By having this (internal or external) discussion, the aPTT becomes a barometer for the patient's risk of clotting versus bleeding which supports more or less aggressive treatment. The UFH activity level, if

valid, remains as a guide for heparin adjustment. With available lab monitoring, there really isn't one "rock star" value for understanding the true anticoagulation status of our patients. By relying on more stable UFH activity goals to direct anticoagulation and using other clinical data, including a classic like aPTT, to guide decision making, we can finally stop giving device anticoagulation such bad name.

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EDITOR'S CORNER: From Old Rough and Ready to the Bachelor and the Tennessee Tailor: Out of Ineptness, Compromises, Know Nothings and Do Nothings comes a Pediatric Handbook and the Great Emancipator

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Zachary Taylor of Montebello, Virginia and born on November 24, 1784 was a lifelong military leader. He joined the Kentucky militia as a teenager and distinguished himself in Indian campaigns as well as the War of 1812 against the British. Because of his military prowess, disheveled appearance and unsophisticated manners he was known as "**Old Rough and Ready**." It was the result of the Mexican War that established him as a national hero in 1848. He had driven the Mexican army from Texas and captured the impregnable city of Monterrey, Mexico in 1846. Although his troops were outnumbered four to one, he defeated Santa Anna at the Battle of Buena Vista in 1847. He was compared to George Washington and Andrew Jackson. When the possibility of presidency came up, Taylor stated, "*such an idea never entered my head nor is it likely to enter the head of any sane person*."

The Whig Party took notice of Zachary Taylor's national attention and using his popularity, he became the 12th President. As a resident of Louisiana, he was the first President elected in 1848 from a state west of the Mississippi River. Tensions between the North and South were intensifying when he took office. The addition of California and New Mexico territories caused the unraveling of the Missouri Compromise. When Taylor opposed extending slavery to these territories, Southern states threatened secession. The President's response was swift – he threatened war, saying he'd lead the Army himself and hang the rebels. His most famous quote, "*For more than half a century…this Union has stood unshaken. The patriots who formed it have long since descended to the grave; yet still it remains, the proudest monument to their memory*." But Taylor's sudden death turned the ensuing crisis over to his Vice-President Millard Fillmore, whose feeble attempt at yet another compromise only delayed the inevitable bloody conflict. Taylor died in Washington, D.C. just 16 months after he took office of either gastroenteritis, cholera or typhoid fever on July 9, 1850. It has been stated that *"William Henry Harrison got too cold and died and Zachary Taylor got too hot and died."*

Millard Fillmore was the first President born in the 19th century on January 7, 1800 in Locke (now Summerhill), Cayuga County, New York. He was raised in extreme poverty, received little education and studied law. In 1846, he founded the University of Buffalo and was named its first chancellor, a position he held until his death. He became the 13th President after the sudden death of Zachary Taylor. Although he personally opposed slavery, Fillmore supported Henry Clay's Compromise of 1850 because he believed it would help preserve the Union. This Compromise allowed California to join the Union as a free state in exchange for Congressional enactment of the Fugitive Slave Act, which helped slaveholders recapture runaway slaves. Abolitionists were outraged, including many

Northern Whigs, and their passions were further stirred by the 1852 publication of Harriet Beecher Stowe's anti-slavery novel, *Uncle Tom's Cabin*.

One of Fillmore's finest achievements was the expansion of commercial activities in the Pacific with Japan. However, he came under increasing attack from both pro- and anti-slavery factions, and his ineptitude at resolving the slavery issue led to his demise. The Whigs nominated another candidate in 1852. The party eventually disintegrated, ruined by the same forces tearing the nation apart. His nickname was "**The American Louis Philippe**," an obscure reference to King Louis Philippe of France who was the last king of France (1830-1848). Fillmore was the last Whig to serve as President. His memorable quote was "*An honorable defeat is better than a dishonorable victory.*" In 1856, Fillmore ran unsuccessfully for President on the xenophobic American (nicknamed "Know-Nothing") party ticket. He died in Buffalo on March 8, 1874 of a stroke.

Franklin Pierce was a direct descendant of a Massachusetts Bay Colony settler in the early 1600's. From a distinguished family, he was born on November 23, 1804 in Hillsborough, New Hampshire. Having been the youngest-ever member of the U.S. Senate in 1837, he became the then-youngest President. He earned the nickname "**Handsome Frank**" because of his charm and good looks. He did serve in the U.S. Army as a brigadier general to fight in the Mexican War. Pierce became the 14th President after winning the 1852 Presidential election against Whig candidate Winfield Scott – a general under whom he served in the Mexican War. The tragic death of Pierce's 11-year-old son in a train wreck darkened his early days as President. National events were no more portentous of a happy tenure in the White House.

Northern opposition forced Pierce to abandon his plans to acquire Hawaii, Alaska and Cuba, although he did manage to buy a large tract from Mexico that is now part of Arizona and New Mexico (the Gadsden Purchase) for a Southern railroad. In 1854, the Kansas-Nebraska Act superseded the Missouri Compromise which enabled residents in all new territories to determine their own slavery policy. Both pro- and anti-slave factions poured into Kansas which lead to rioting and bloodshed, giving Americans a foretaste of the Civil War. The "Bleeding Kansas" ordeal stained his Presidency and lead to the failure of his re-nomination. His famous quote was "*With the Union my best and dearest earthly hopes are entwined*." He died on October 8, 1869 of dropsy related to alcohol, either cirrhosis or congestive heart failure, with gastritis or peptic ulcer disease.

James Buchanan, a career politician, was born on April 23, 1794 in Cove Gap, Pennsylvania. A lawyer, Congressman, Senator and Secretary of State under Polk, James Buchanan was untainted by the fractious domestic politics of the Franklin Pierce Presidency, thanks to his posting overseas as Pierce's Minister to Britain. Chosen as the Democrat's Presidential candidate in 1856 and becoming the 15th President, Buchanan favored popular sovereignty in the territories but he failed to recognize the impact of slavery on the nation. Nicknamed the "**Bachelor President"**, he attempted to compromise and make political deals on the issues of slavery. Harriet Lane, Buchanan's niece served as first lady and became a popular figure. Buchanan was much less popular, just two days after his inauguration in 1857, the Supreme Court announced the Dred Scott decision allowing slavery in all U.S. territories. This led to further divisions of the North and South, thus increasing the looming possibility of a civil war.

Other than the first Southern state seceding from the Union (South Carolina) toward the end of his term, notable events during his presidency included: the Lincoln-Douglas debates in Illinois, the laying of the Atlantic cable for the first telegraphic communication between Europe and North America, the drilling for oil in Pennsylvania and the start of the Pony Express mail service between Missouri and California. His most memorable quote was, "*The ballot box is the surest arbiter of disputes among free men*." Though Buchanan called the secession of South Carolina illegal, he took no action to save the Union as he watched the nation wither with the end of his term. He died on June 1, 1868 of a cold complicated by respiratory failure.

As much as he has been distinguished as the worst President in American History, the polar opposite is true about his niece **Harriet Lane**. As the first non-spousal First Lady, "**Our Democratic Queen**" was as popular in her time as Jacqueline Kennedy as a First Lady. Women dressed like her, songs were written about her and ships were named after her. Among her most enduring legacies, Harriet dedicated a generous sum to endow a home for invalid children at Johns Hopkins Hospital. This renowned pediatric facility continues to serve thousands of children with the widely used manual for pediatric trainees bearing her name, ***The Harriet Lane Handbook***.

Abraham Lincoln, the "**Great Emancipator**" was born on February 12, 1809 in a log cabin near Hodgenville, Kentucky to a penniless frontier family. Despite having only one year of formal schooling, he became the most towering figure in American History. He is best remembered as the President who preserved the United States as one country and ended the slavery of African-Americans. Lincoln was a successful lawyer in Illinois and ran for Senate. He lost, but his brilliant campaign oratory secured him the Republican Presidential nomination in 1860 to become the 16th President of the United States. He was the first President born outside the original 13 colonies, the first Republican President and the first President to be assassinated.

Between Lincoln's election and inauguration, seven Southern states seceded. On April 12 1861, the Confederates attacked Fort Sumter. Nearly two years later with the Civil War raging, Lincoln issued the Emancipation Proclamation (slavery was later banned by the 13th Amendment). In November 1863, Lincoln delivered the Gettysburg Address, vowing "*that these dead shall not have died in vain-that this nation, under God, shall have a new birth of freedom – and that government of the people, by the people, and for the people, shall not perish from the earth*."

The bloodiest conflict in US history, the Civil War cost more American lives than the two World Wars and Vietnam War combined. Re-elected in 1864, Lincoln lived to see the South surrender on April 9, 1865. Five days later, he was assassinated by Southern sympathizer John Wilkes Booth on April 14, 1865, before he could fulfill his pledge to "*bind up the nation's wounds*." He died on April 15, 1865.

Andrew Johnson was born on December 29, 1808 in Raleigh, North Carolina. He never attended school but was apprenticed to be a tailor and later achieved modest success with his own tailor shop in Tennessee. Although nearly illiterate until his wife, Eliza McCardle, began tutoring him, he did manage to champion the cause of the common man. He taught himself the rudiments of law and entered politics as a Democrat. The only Southern Senator who remained loyal to the Union when

the South seceded, Johnson was chosen by the National Union League (a coalition of Republicans and War Democrats to run with Lincoln in 1864.

When Lincoln was assassinated, Vice-President Andrew Johnson, the "**Tennessee Tailor**" took the oath to become the 17th President on April 15, 1865. He tried to restore Southern prosperity and pride, but he profoundly lacked Lincoln's genius and hard-won reputation as a man of his word. As a result, Johnson never had a chance. Sharing Lincoln's desire for reconstruction instead of retribution, President Johnson offered amnesty to those who took the oath of allegiance to the Union. Congress had other ideas. He disputed with Congress and in defiance, Johnson fired Edwin Stanton, the Secretary of War, claiming he was disloyal. This occurred without Senate approval, therefore in 1868 the House initiated impeachment proceedings against him for ousting Stanton, but the Senate fell one vote short of conviction. Notwithstanding these difficulties, the Johnson Administration managed a notable acquisition. Alaska was purchased from Russia for $7.2 million. Following his Presidency, he became the first former President to be elected to the U.S. Senate. He died of a stroke on July 31, 1875 and leaves us with "*Honest conviction is my courage; the Constitution is my guide*." Take note, Andrew Johnson remains the only former President to serve in the Senate while John Quincy Adams is the only one to serve in the House of Representatives.

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