VINCENT’S FLU SENSE:

From about half a millennium to a century to today, we have yet to change our response and preparedness to threatening situations. Consider this –

When in danger, when In doubt - Run in circles, scream and shout.

This month, we reflect on the 20th century anniversary of the 1918 flu pandemic by offering an agitprop that stirs our emotional and physical responses. With contributions from Jaime-Jürgen Eulert-Grehn, Heather T. Henderson and Evgenij Potapov, we are motivated to explore educational and professional opportunities to prepare ourselves for holistic reactions. Nathan Verlinden takes on multiple perspectives in his article, “Generic Medications in Pulmonary Arterial Hypertension – the Good, the Bad, and the Ugly,” and Michael A. McCulloch forecasts the future in his article, “Chronic Lung Disease Associated Pulmonary Hypertension– The Next Epidemic?” Martin Schweiger discusses “Cerebral Strokes in Pediatrics on Intra-Corporeal LAVDs,” as Melissa Smallfield gives us an update on the “Management of Pulmonary Hypertension in LVAD Patients.” Amresh Raina immunizes us with her article, “Pulmonary Veno-Occlusive Disease – From Clinical Ambiguity to Molecular Diagnostics,” while Amy Sherman and Stephanie Pouch help me recap the progression of influenza over the past 100 years. Finally, Becca Holt and yours truly reiterate Shakespeare’s prediction of immoral judgement in society.

We all know ring around the Rosie, how many recall:

There was a little girl, and she had a little bird,  
And she called it by the pretty name of Enza;  
But one day it flew away, but it didn't go to stay,  
For when she raised the window, in-flu-Enza.

Vincent Valentine, MD  
Links Editor-in-Chief

WORD OF THE MONTH:

Agitprop (noun) - Political propaganda delivered through art, music, drama, or literature.
IN THE SPOTLIGHT:

2018 Recipients of the ISHLT Leach-Abramson-Imhoff Links Travel Awards

Over the past year, the ISHLT again had a productive year from over 100 writers contributing to the ISHLT Links Newsletter. To deter us from analysis paralysis, we must decide, sometimes with “Big Decisions” but not always the right decision. From power dynamics and groupthink to group polarization, our decisions are subjected to biases resulting in decisions that could be hazardous to someone’s life. A grid and a checklist will foster collaborative decision making to reduce hazards as we have decided on this year’s Links’ Writers of the Year. Congratulations from such big decisions and with what were you doing in 1996 to Pediatric Cardiac Prehab. Of course, the forever important and necessary discussions of difficult news with our pediatric transplant recipients shed light on our sensibilities about caring and compassion. In the end, simply showing up proves that it is all worthwhile. Here, our Writer of the Year Award goes to none other than Erin Wells. Our First Runner-Up is Martin Schweiger, and Honorable Mention awards go to Adam Cochrane, Pam Combs, Kyle Dawson and Joshua Mooney.

Let's extend a warm ISHLT congratulations to these writers.

Writer of the Year: $2,000

Erin Wells, RN, BSN, CPN
Northwestern Memorial Hospital
Chicago, Illinois, USA

January 2017, Moments in Time
May 2017, Going Back to Cali
June 2017, Back to the Future
September 2017, Leadership in Tough Times

First Runner-Up: $1,000

Martin Schweiger, MD
Children’s Hospital Zurich
Zurich, Switzerland

February 2017, Looking Forward to San Diego: 1st Core Competency Course on Pediatric MCS
Honorable Mention (4 recipients): $500

Adam Cochrane, PharmD, BCPS
Inova Fairfax Hospital
Falls Church, Virginia, USA

June 2017, 2017 Annual Pharmacy Update: Continuing Progress and Forging Ahead

Pamela S. Combs, PhD, RN
University of Chicago
Chicago, Illinois, USA

April 2017, Pam Combs' Musings on the ISHLT Annual Meeting
November 2017, Perspective of the VAD Caregiver: The Transition Home

Kyle Dawson, PharmD, MBA, BCPS
University of Kentucky
Lexington, Kentucky, USA

May 2017, The Highs and Lows of ISHLT Annual Meeting Symposia

Joshua Mooney, MD
Stanford University
Stanford, California, USA

November 2017, Assocao Brasileira de Transplante Orgaos (ABTO)/ISHLT Joint Symposium

History of the Leach-Abramson-Imhoff Links Travel Awards

The ISHLT Leach-Abramson-Imhoff Links Travel Awards, funded in part by the generous support from W.O. and Joan Leach (Gadsden, Alabama, USA), Mrs. Sue Abramson (Birmingham, Alabama, USA) and Mr. Larry Imhoff (La Place, Louisiana, USA), were created to support the growth and development of our future leaders from within our society including physicians, nurses, and other health care professionals. Those motivated enough with investigation, communication, and dissemination of new ideas for the betterment of patients with failing lungs and/or a failing heart including such conditions as pulmonary fibrosis, cystic fibrosis, emphysema, pulmonary hypertension, and from ischemic, nonischemic to congenital heart diseases should be awarded for their efforts.
Eligibility requirements include:

1. Any healthcare professional including but not limited to nurses, nurse coordinators, social workers, pharmacists, therapists, dietitians and early career physicians are eligible and must be a member of the ISHLT regardless of duration in their career.

2. An imposed restriction on physicians is that they must be in their Early Career—within 7 years of training, Assistant Professor equivalent, or junior faculty level with rare exceptions.

3. Individuals must display some form of research interest, basic, clinical, translational or outcomes investigations or at a minimum display some skill in journalism best exemplified by their contributions to the Links Newsletter engendering fresh and creative ideas.

Each year, the winners are selected from a pool of nominees by the ISHLT Links Travel Award Committee (LTAC). This committee includes the following individuals: the Links Editor-in-Chief, ISHLT Executive Director, ISHLT President, ISHLT Program Chair, and the Links Managing Editor.
FOCUSING ON PEDIATRICS:

Chronic Lung Disease Associated Pulmonary Hypertension—The Next Epidemic?

Michael A. McCulloch, MD
University of Virginia Children's Hospital
Charlottesville, VA, USA
Mam3fk@virginia.edu

Advancements in neonatal intensive care unit management have improved average discharge rates to 55% following 24 week gestations and 92% for 28 week gestation [1]. However, as many as 68% of these 'NICU graduates' are diagnosed with bronchopulmonary dysplasia (BPD) and between 18 to 43% of these develop pulmonary hypertension [1,2,3]. This population's vulnerability becomes abundantly clear in mid-term follow up papers demonstrating 2-year mortality rates up to 40% [4,5].

A myriad of reasons exists for this sobering data. Echocardiographic assessments of right ventricular function and pressures are commonly inaccurate, complicating the diagnosis of right ventricular dysfunction and pulmonary hypertension [6]. Aspiration of oral or gastric contents are a frequent source of recurrent lung injury and oftentimes clinically silent [7]. Left ventricular diastolic dysfunction and pulmonary vein stenosis can significantly complicate the care of BPD patients, but are less common and often go unrecognized [8,9]. Most importantly, however, is the incomplete understanding of BPD pathophysiology and a lack of data-driven guidelines on how to care for these patients [10-15].

When pulmonary hypertension complicates BPD, it is tempting to initiate systemic pulmonary vasodilator therapies despite insufficient evidence supporting their use. Mourani, et al. retrospectively evaluated their experience with sildenafil therapy in 25 neonates diagnosed with BPD and pulmonary hypertension [14], and although echocardiographic evaluation suggested improvement in right ventricular systolic pressures, there remained a 20% mortality rate and nearly 10% of patients discontinued therapy due to medication-induced adverse events. Trottier-Boucher, et al. assessed 23 similar neonates receiving sildenafil therapy and also found echocardiographic evidence of decreased right ventricular systolic pressures in nearly ¾ of patients, but 44% experienced systemic hypotension and only 1/3 appreciated 'clinical improvements' [15]. These are the two largest such studies on this patient population and are clearly inadequate to guide therapy.

The World Symposium of Pulmonary Hypertension Classification System clusters different types of pulmonary hypertension expected to have similar pathophysiology and therapeutic responses. Chronic lung disease/ BPD exists within the ‘Developmental Lung Disease’ subgrouping of group 3 pulmonary hypertension which also includes its closest adult correlates of chronic obstructive pulmonary disease and emphysema [16,17]. As these diseases are characterized by a ‘capillary’ level pulmonary hypertension and associated regions of incomplete gas exchange, the most recent guidelines clearly state “there is no specific therapy for (PH) pulmonary hypertension associated with lung diseases” [17] because systemically administered pulmonary vasodilators (i.e. sildenafil and bosentan) have proven to worsen gas exchange in several adult studies [18-20]. Although children
and babies are not small adults, it would be shortsighted to extrapolate adult criteria and treatment regimen for all other types of pulmonary hypertension but not consider them for this group.

At our institution, surveillance echocardiograms start with the diagnosis of BPD or earlier in neonates with birth weight less than 1500 g and/or gestational age less than 34 weeks demonstrating hemodynamic compromise or need for mechanical ventilation/ non-invasive positive airway pressure at 4 weeks of life. Management changes are only suggested in patients who have pulmonary hypertension (greater than ½ systemic right ventricular pressures as suggested by interventricular septal position in systole, TR jet or PDA flow) AND evidence of right ventricular failure (two or more echocardiographic measures of abnormal right ventricular function; BNP greater than 2 times the upper limits of normal; hepatomegaly, hemodynamic instability, failure to thrive or feeding intolerance without other etiology). When applicable, initial recommendations are optimization of respiratory support to obtain a goal pH greater than 7.35, paCO2 less than 60 and paO2 greater than 60 or oxygen saturations greater than 92%. ‘Dry’ lungs are encouraged through the use of diuretics and concentrated formulas are preferably administered through nasoduodenal tubes to minimize micro-aspiration. If right ventricular dysfunction is deemed severe on the initial evaluation or persists after addressing the above issues, a pulmonary vasodilator is typically recommended.

Due to a significant incidence of hepatotoxicity associated with bosentan therapy in a population frequently plagued by hyper-alimentation associated liver disease, sildenafil is our first choice. Goal enteral dosing is the lower of 10 mg q6 or 2 mg/kg/dose q6. Half of the patient’s weight based maximum dose is administered for 8 doses and then increased to the full dose with repeat echocardiogram, BNP and physical assessment performed after at least 8 doses of the ultimate regimen. It is not our goal to normalize right heart pressures but to improve right heart failure; bosentan is added at 2 mg/kg/dose q12 if right heart failure persists, or we recommend a gradual return towards a potentially dischargeable respiratory support and feeding regimen if right heart failure has resolved. Repeat assessments are performed with each significant change.

This relatively conservative approach is predicated on a general lack of data, the inherently resilient neonatal right ventricular myocardium, and the fact that newborns are capable of healthy acinar development until approximately their 4th birthday as long as they receive adequate nutrition and are free of ongoing lung injury [21]. Unadulterated lung development is the ultimate goal for these patients, and it has been our experience that this is achievable without pulmonary vasodilatory medications in the vast majority.

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

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Cerebral Strokes in Pediatrics on Intra-Corporeal LVADs

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There has been a rapid evolution of using adult designed continuous flow VADS (cf-VADs) to support pediatrics even in children with congenital heart disease. This comes with the need for care providers specialized in this field to determine optimal patient and device selection, and to improve outcomes and decrease complication rates for new innovative strategies. The Berlin Heart EXCOR® is and has been the mainstay of long term VAD support for children of all ages but its limitations, especially the risk of thromboembolic events, are well known. Data from adult experience have shown a significant decrease in neurologic dysfunction with cf-VADs compared with pulsatile VADs in adults [1].

There are very few data on outcome especially on cerebral strokes in children supported with adult sized LVADs. One may speculate that in children where flow rates in the VAD might be lower compared to adults, pump thrombosis and thrombo-embolic events might occur more often. The US-only Paediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) database revealed cerebrovascular stroke or hemorrhage in 26%, but without stratification to body weight or BSA [2].

We sought to investigate ischemic and hemorrhagic strokes in children supported with intra-corporeal cf-LVADs depending on BSA using the largest European VAD database (European Registry for Patients with Mechanical Circulatory Support (EUROMACS)).

We identified 51 pediatric patients on cf-LVAD listed in the database. The patients were stratified by body surface area (BSA) (Group 1 < 1.2 m², Group 2: ≥ 1.2 m²). Except age/weight and size, there was no significant difference between groups.

Except 24 patients who did not receive anticoagulation prior to LVAD placement, all others were on anticoagulation (Heparin or antiplatelet treatment or oral anticoagulation). One of the patients died due to cerebral stroke. After LVAD implantation, all the patients either received heparin or an alternative (n: 2). Only 38% received additional antiplatelet therapy including aspirin, clopidogrel, or dipyridamole.

Overall, four cerebral stroke events were observed in the older age group without reaching significance (p = 0.26). Cerebral strokes occurred between 19 and 524 days on support (mean = 244 days). All but one patient died due to this event; one patient underwent HTx.

Taken together, the incidence of cerebral strokes in this paediatric cohort of intra-corporeal VAD patients was low with 0.1 per patient year but when occurred, the event led to death in three-fourths of the patients, thus being the most frequent cause of death (37%) among the whole study population.
Acknowledgements: EUROMACS is an official committee of the European Association for Cardiothoracic Surgery (EACTS). EUROMACS also contributes data to the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS). The study was granted by the Executive and Extended Board of Directors of EUROMACS (Apl.2015). Involved authors of the paper are: Oliver Miera MD.\textsuperscript{2}, Theo M.M.H. de By MBA.\textsuperscript{3}, Michael Hübler MD. Prof.\textsuperscript{1}, Felix Berger MD. Prof.\textsuperscript{2}, Mustafa Özbaran MD, Prof.\textsuperscript{4}, Antonio Loforte MD.\textsuperscript{5} Burkhardt Seifert PhD., Prof.\textsuperscript{5}, Gaetano Gargiulo MD.,PhD, Prof.\textsuperscript{5}, Jan Gummert MD Prof.\textsuperscript{7}, Paul Mohacsi MD. Prof.\textsuperscript{8} on behalf of the EUROMACS members

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

References:
FOCUSING ON PULMONARY HYPERTENSION:

Pulmonary Veno-Occlusive Disease – From Clinical Ambiguity to Molecular Diagnostics

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As pulmonary hypertension (PH) clinicians, we are often faced with diagnostic challenges that force us to re-evaluate the physiology of a patient’s disease. In the clinical realm, outside of randomized clinical trials, a patient’s PH diagnosis can often be painted in shades of gray rather than with the clarity of black and white. Especially when patients do not respond to therapy in an expected manner, we often find ourselves reassessing the diagnosis and questioning common alternative diagnoses: I have often found myself pondering again “is it left heart disease?” “Is it chronic thromboembolic disease?” “Is it smoldering interstitial lung disease?”

Consider the recent case of a 52-year-old man with an 18-month history of progressive dyspnea, extremity edema and presyncope. He admitted to a 30 pack-year smoking history, but had only mild emphysema on CT of the chest and minimal obstructive lung disease on pulmonary function testing, but with profoundly reduced diffusion capacity for carbon monoxide (DLCO). Echocardiogram revealed a markedly dilated and dysfunctional right ventricle with compression on the left ventricle from interventricular septal flattening (Figure 1A). Left atrial size and left ventricular function were normal. Invasive hemodynamics revealed near systemic PH with profoundly reduced cardiac index and PVR of 12 WU (Figure 1B). Pulmonary capillary wedge pressure (PCWP) was normal.

The patient was admitted to the CCU and started on IV prostacyclin under careful hemodynamic monitoring. On day 2 of prostacyclin infusion, CT of the chest was repeated, showing diffuse ground glass opacity and interlobular septal thickening (Figure 2A), while repeat PCWP tracing remained normal (Figure 2B). On the basis of this clinical response, the patient was diagnosed with suspected pulmonary veno—occlusive disease (PVOD) and referred for urgent lung transplant evaluation.

PVOD and the related disorder, pulmonary capillary hemangiomatosis (PCH), are extremely rare clinical entities in the general population and thought to make up 10% of cases initially diagnosed as pulmonary arterial hypertension (PAH), itself a rare disorder [1]. However, in PH referral centers, PVOD is seen with increasing frequency. The pathologic hallmarks of PVOD are a fibrotic thickening of small pulmonary venules, especially in the interlobular septa, typically sparing the larger veins. Patients with PVOD will typically have a normal PCWP as the wedge pressure reflects pressure in the larger pulmonary veins rather than the small veins affected by PVOD and the disease process itself may be patchy.

The diagnosis of PVOD is often entertained due to the development of a pattern of pulmonary edema or diffuse ground glass opacities and interlobular septal thickening on X-ray and/or high resolution
CT of the chest in the setting of normal PCWP and absence of left heart pathology, accompanied by hypoxemia and very low DLCO on pulmonary function testing [2]. In many cases, pulmonary edema may be provoked with the initiation of pulmonary vasodilator therapy. PVOD, like PAH, may be familial or sporadic and is associated with inflammatory disorders such as sarcoidosis and scleroderma, as well as chemotherapeutic agents, radiation and malignancy. PVOD, unlike PAH has a higher male:female preponderance and is associated with cigarette exposure [3].

Definitive diagnosis of PVOD has traditionally required surgical lung biopsy for confirmatory histopathology; however, this is rarely performed pre-mortem due to risks involved in lung biopsy in patients with severe PH, and thus most commonly the diagnosis has been made on clinical grounds alone. This is typically unsatisfying for both patients and clinicians alike; in the best-case scenario, eligible patients are referred for bilateral lung transplantation without a definitive confirmatory test or a pathologic diagnosis, and those who are not candidates are faced with a grim prognosis, with or without a trial of pulmonary vasodilator therapy, again commonly without definitive confirmation of the diagnosis.

However, recently a major step forward in the diagnosis of PVOD was the finding of biallelic mutations in the gene encoding the eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) in both familial (100%) and sporadic (20% to 25%) cases of PVOD/PCH [4, 5]. This strongly suggested an underlying genetic basis for the risk of development of PVOD.

Moreover, a recent study by Hadinnapola et al, demonstrated that in a large cohort of 864 patients with a clinical diagnosis of idiopathic or heritable PAH, 9 patients carried a biallelic mutation in EIF2AK4; these patients had a younger age at presentation, lower DLCO and worse response to therapy and prognosis. However, these patients could not be readily identified by radiographic findings and did not develop pulmonary edema with pulmonary vasodilating therapy. Indeed, many of these patients were on parenteral prostacyclin therapy as they had been classified as having PAH at major European referral centers [6]. In contrast, mutations in EIF2AK4 were almost never identified in patients with idiopathic and familial PAH in a US cohort [7].

Thus, genetic testing for biallelic mutation in EIF2AK4 may provide a means to definitively diagnose patients with PVOD earlier in their clinical course, even in patients without classic radiographic findings and may guide earlier referral for lung transplantation in eligible patients.

Though this may represent a major advance with regards to diagnostic and genetic testing, there unfortunately remains limited therapy for this progressive and fatal disease. Pulmonary vasodilators should be used with caution and with close follow up at expert centers due to risk of worsening hypoxemia and pulmonary edema. With a more detailed understanding of the genetic underpinnings of PVOD may come more specific targeted therapies short of lung transplantation.

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References:
Update on Management of Pulmonary Hypertension in LVAD Patients

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In the United States, there are 5.8 million people with heart failure, a small percentage of them with advanced heart failure requiring therapy with left ventricular assist devices (LVAD) and heart transplantation. A significant number of advanced heart failure patients will have secondary pulmonary hypertension due to the passive congestion of left heart disease. LVAD therapy is effective in decompressing the left ventricle, thus reducing left sided filling pressures and reducing pulmonary pressures. Unfortunately, patients may have combined pre- and post-capillary pulmonary hypertension (CpcPH) for which LVAD therapy does not entirely normalize PA pressures and pulmonary vascular resistance (PVR). CpcPH is defined as a mean pulmonary artery pressures (mPAP) > 25 mmHg, a pulmonary artery wedge pressure (PAWP) > 15 mmHg, a PVR ≥ 3 WU and a diastolic pressure gradient (DPG) ≥ 7 mmHg by hemodynamic testing. These persistently elevated PA pressures can lead to right ventricular dysfunction after LVAD placement and exclude heart transplantation if the PVR does not return to normal.

There has been a growing interest in using pulmonary vasodilators for the treatment of CpcPH after LVAD implantation. The 2013 ISHLT guidelines for mechanical circulatory support recommend using PDE5 inhibitors for the treatment of persistent pulmonary hypertension and right ventricular dysfunction although the benefits of such therapy have not been sufficiently proven. Tedford et al published one of the most cited studies on the use of PDE5 inhibitors to treat CpcPH after LVAD implantation. They evaluated 26 consecutive patients with persistent pulmonary hypertension (defined as PVR > 3) 7 to 14 days after LVAD implantation despite normal PAWP. They were started on sildenafil 20mg three times a day and compared to 32 LVAD control patients. The patients on sildenafil had a decrease in the mPAP and PVR within 2 to 4 weeks of therapy, and these results were maintained though 12 to 15 weeks. There was marked improvement in RV function. Sildenafil was well tolerated and did not elevate PAWP or decrease cardiac output [1].

While there are several studies using PDE5 inhibitors in the treatment of pulmonary hypertension due to left heart disease, the same cannot be said for endothelin receptor antagonists (ERA). Early studies performed with bosentan in patients with systolic dysfunction showed worsening edema and more frequent hospitalizations for heart failure. Macitentan is the newest ERA to be used for the treatment of pulmonary arterial hypertension. The SERAPHIN trial (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinic Outcomes) evaluated two doses of macitentan (3mg and 10mg) versus placebo with the primary endpoint of time from initiation of treatment to a composite endpoint of death, atrial septostomy, lung transplantation, initiation of prostanoids, or worsening PAH. There was significantly reduced morbidity and mortality seen in the macitentan arms with improvements in 6-minute walk distances, WHO functional class, pulmonary vascular resistance and cardiac index. The incidence of edema was similar among all three treatment
groups ranging from 16-18%. Other side effects in the macitentan groups include nasopharyngitis, headache and anemia [2].

The MELODY-1 study (Macitentan in subjects with combined prE- and post-capillary pulmonary hypertension due to left ventricular dysfunction) was the first study to evaluate macitentan for pulmonary hypertension due to left heart disease in patients with CpcPH. Patients were required to have a LVEF > 30% with evidence of CpcPH on RHC. The primary endpoint assessed was a composite of significant fluid retention or a worsening in NYHA functional class. More patients in the macitentan group experienced significant fluid retention or worsening in NYHA functional class. There was no difference in PVR, mRAP, or PAWP after treatment with macitentan. There was a nonsignificant decrease in pro-BNP levels and 6-minute walk distances in the treatment groups. Of note, 76% of the patients had a LVEF ≥ 50% [3].

The SOPRANO trial (Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients with Pulmonary Hypertension after Left Ventricular Assist Device Implantation) is an ongoing study enrolling patients with CpcPH after LVAD implantation. The aim is to assess the effect of macitentan on PVR at week 12 versus baseline. It is the first randomized, placebo-controlled study of ERAs in this patient population. Secondary objectives include effect of macitentan on cardio-pulmonary hemodynamics, disease severity, right ventricular function, renal function, and pro-BNP levels [4].

CpcPH can be common in patients with advanced heart failure and can persist even after LVAD implantation. This can lead to persistently elevated PVRs and RV dysfunction which increases morbidity and mortality after LVAD implantation and heart transplantation. Studies using pulmonary vasodilators for the treatment of CpcPH after LVAD implantation have included short term follow up. More research is needed to understand the long term outcomes of these patients after heart transplantation.

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

References:

4. Clinical trials.gov NCT02554903
Generic Medications in Pulmonary Arterial Hypertension – the Good, the Bad, and the Ugly

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Pulmonary arterial hypertension (PAH) is a rare disease associated with a high burden of healthcare costs. In a recent analysis of costs in the United States, the average per-patient-per-month healthcare costs for patients with PAH were over $9,500 US dollars [1]. The average annual pharmacy costs in this study exceeded $50,000 per patient [1]. For patients requiring oral or parenteral prostacyclin therapy, medication costs can surpass $100,000 annually. The availability of generic medications to treat PAH might be expected to help reduce medication and overall healthcare costs. This article will discuss the current state of generic medications for PAH and some of the challenges for generic availability with a specific focus on issues in the US.

There are currently two Food and Drug Administration (FDA) approved PAH medications with generic availability in the US – sildenafil and non-thermostable epoprostenol (generic for Flolan®). The phosphodiesterase type V inhibitor, sildenafil, remains the only orally available generic medication in the US. Sildenafil is the least expensive medication for PAH and is available for less than $100 for a monthly supply [2]. Non-thermostable epoprostenol is the only available intravenous (IV) medication to treat PAH that is available as a generic.

One of the challenging cases for generic availability of PAH medications in the US has encompassed the endothelin receptor antagonist (ERA) class due to Risk Evaluation and Mitigation Strategies (REMS) regulations. In the case of bosentan, the branded manufacturer, Actelion Pharmaceuticals Ltd., pre-emptively took legal measures against several potential generic manufacturers in 2012 after declining to provide samples of bosentan to those generic companies [3]. Typically, generic manufacturers acquire medication samples from branded manufacturers for bioequivalence testing, which is required for filing abbreviated new drug applications (ANDAs) with the FDA. Actelion cited the REMS regulatory restrictions as justification for not supplying bosentan samples to generic competitors [3]. The generic manufacturers counterclaimed that Actelion’s position violated antitrust laws [3]. During these proceedings, the Federal Trade Commission (FTC) filed an amicus brief regarding this case arguing that a branded manufacturer’s refusal to provide samples to competitors can violate antitrust laws [4]. The FTC enforces antitrust laws and oversees areas of consumer protection. In addition, the FTC’s brief explains that the current federal law framework cannot function as intended if generic manufacturers cannot access branded medication samples, which may threaten pharmaceutical competition and lead to increased drug costs [4]. The suit was eventually settled out of court in 2014 with the details remaining undisclosed to the public [5].

Where does all this legal background lead us now? In response to past court cases involving bosentan and other medications, FDA commissioner Scott Gottlieb announced a series of initiatives to enhance generic availability and lower drug costs in the US. In his June 2017 announcement, the FDA
commissioner mentioned the past practice by branded manufacturers of limiting the availability of medication samples due to REMS program requirements [6]. He additionally discussed branded manufacturers using the requirement of a single, shared REMS system between brand-name and generic manufacturers to hinder generic access [6]. As a part of these initiatives, the FDA released a list of off-patent, off-exclusivity branded medications that do not have approved generics and a new policy to expedite review of generic medications where competition is limited [7]. Notably, bosentan was listed as a branded medication that is off-patent without an approved generic. Finally in November 2017, the FDA published new draft guidance on streamlining the process of a single, shared REMS program between brand-name and generic manufacturers [8].

Despite the challenges of generic availability for PAH medications, the year 2018 is expected to be a banner year for generics in the US. Table 1 lists PAH medications with expected or possible new generic availability in 2018. Currently, generic manufacturers have tentative ANDA approval by the FDA for parenteral treprostinil and tadalafil [9, 10]. As stated previously, bosentan is currently off-patent, but a timeline for generic availability remains uncertain. The patent for ambrisentan is set to expire in July 2018, so a generic may become available in the second half of 2018.

<table>
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<tr>
<th>Medication</th>
<th>Anticipated Availability</th>
<th>Comments</th>
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<tr>
<td>Treprostinil injection</td>
<td>June 2018 [12]</td>
<td></td>
</tr>
<tr>
<td>(Remodulin®)</td>
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<tr>
<td>Bosentan (Tracleer®)</td>
<td>Unknown</td>
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With the upcoming availability of several generic medications to treat PAH, the hope is that drug cost will subsequently decline over time. This is particularly relevant due to recent developments with non-profit assistance funds for patients with PAH in the US. Caring Voice Coalition (CVC) recently had its charity status revoked by the US Department of Health and Human Services [14]. CVC is no longer offering financial assistance for 2018. Several other non-profit organizations are no longer enrolling new patients, but will continue to cover patients already enrolled. In the past, pharmaceutical manufacturers of PAH medications have provided significant patient assistance for patients who have been unable to afford their medications. However, generic manufacturers typically do not have patient assistance programs. Thus, while generic availability may lead to overall lower drug prices from a payer perspective, it remains to be seen if this will translate into greater affordability for certain patients in the short term. In the long-term, generic medications for PAH are a welcome sight to reduce the high cost of these medications.

In conclusion, the road to generic availability for PAH medications has been difficult. Hopefully, with new FDA guidance the accessibility of generic medications with REMS programs will be easier in the future. Several new generic medications are expected to become available in 2018 for patients with
PAH. In the long-term, these generics may help to lower drug costs. In the short term, it remains unclear how generic availability will affect affordability on a patient-specific basis.

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

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FOCUSING ON MECHANICAL CIRCULATORY SUPPORT:

Right is the New Left, Right?

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As a resident in cardiac surgery from a northern European center with a large amount of experience in mechanical circulatory support (MCS), I am especially looking forward to the ISHLT Annual Meeting in Nice and the sessions about MCS.

I attended the Master Class in MCS at the last meeting in San Diego this year, and now I wish to join the ISHLT Academy session on Core Competencies in MCS one day before the annual meeting really gets started. This makes the ISHLT meeting unique for residents interested in MCS: the combination of educational and state-of-the-art scientific sessions.

The next day, after recouping energy at the Junior Faculty Mentor Lunch, the next session for me will be “The devil wears Prada – The role of the RV in advanced heart failure and LVADs.” Our team for implantable electronic cardiac devices faces on a daily basis many questions concerning the management of such devices in LVAD patients, and my next stop, on Thursday at 2 pm, will be “It’s Electric! Electrophysiological management of the LVAD patient.”

Another crucial aspect while caring for the LVAD patient is the right side of the heart: the right ventricle and the pulmonary vascular bed. So definitely on the agenda will be symposium number 29 on the Friday, “Joint ISHLT/ESC Symposium: Pulmonary hypertension due to left heart disease - When RIGHT meets LEFT.” Then, I will be happy to present my own poster on the interaction of aortic regurgitation and right ventricular function before the presidential reception at the famous Negresco Hotel. In no time, it will already be Saturday, the last day of the meeting. When it is all over I shall go directly to the Promenade des Anglais and spend the afternoon relaxing on the beach before returning to Berlin and looking forward to the EUMS meeting to be held there in November. See you soon, ISHLT.

Disclosure statement: The author has no conflicts of interest to disclose.
My Nice 2018

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Our Congress in Nice is fast approaching. My high expectations of the congress have not lessened in the past 20 years, and I have been asking myself why.

For me, the aspect I look forward to most is the opportunity to meet my colleagues and close friends, to chat with them personally and have some beautiful moments under the starry sky of Nice which will remain with me forever. What do I mean?

At the beginning of the congress, participation in the ISHLT Academy as a faculty member is very challenging. It is not easy to squeeze all one’s knowledge about a particular topic into the requisite 15 minutes, but it is even more challenging to make the presentation easily intelligible and to field the questions that follow. This day is full of vibrant presentations, fresh ideas and questions fired by nimble-minded students.

I know that in Nice I will meet my friends and colleagues and be able to discuss at length all the facets of my topics of interest – mechanical circulatory support and heart transplantation. Why is this important? It means that I will acquire personalized information which I would never be able to get from reading abstracts or papers and that I may be able to share in new ideas and thoughts about how to improve my daily work on patients. I hope to bring myself up to date with new ideas and current directions and developments in my field. And I shall be able to refresh my feeling for the needs of young colleagues in terms of education and science, and also to educate myself. Of the greatest importance for me are the abstract sessions and symposia, where I learn from my colleagues and friends and receive community experience, which is of a much higher order than I could ever get from reading journals or working in my institution.

Sometimes I participate in completely different sessions to gain inspiration from other groups outside the MCS field.

Altogether our congress lifts me out of my daily business for 4 days and gives me a perspective on the future regarding medical care, science and new developments.

Communication with the industry can be fun, but apart from small pieces of news and a modest measure of satisfaction, I expect I shall remain mostly frustrated, as usual. I always do expect too much from the MCS industry, it seems. Looking at the leaps and bounds in general technology in the past decade, especially in electronic devices including autopilots, I wonder why developments in the field of MCS are so very slow. Transcutaneous energy and information transfer, better batteries, modular design, smart pumping algorithms using integrated sensors – all these small but extremely important features would definitely improve survival and quality of life on long-term MCS. They would
also increase the acceptance of the devices by our friends, the cardiologists. Maybe we need somebody like Elon Musk or Mark Zuckerberg to further the cause, pluck the obvious solutions out of the air and actually implement them.

In my opinion, because of its varicolored nature the ISHLT meeting is definitely the address for heart failure in spring. However, beautiful Nice, excellent French cuisine and the already warm Mediterranean Sea with its beaches and restaurants on the promenade and boutiques such as Michal Negrin somewhat distract our attention from the congress. In contrast, in autumn, the EUMS meeting, which will be held in Berlin on 1-3 November 2018, will offer comprehensive, pure presentations focused on MCS in a city that is a far cry from sunny beaches and boutiques, but does have its own attractions, among them traditional shopping in KDW and German food accompanied by various German beers.

This has been my very subjective view on Nice. Now I wish you a congress that will not only meet, but exceed, your expectations and where the pleasant surroundings will not distract you too much from the matters at hand.

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

PRE-REGISTRATION DEADLINE

If you are planning to attend the ISHLT 38th Annual Meeting and Scientific Sessions, or one of the 2018 Academies, please keep in mind that the deadline to pre-register is Monday, March 12, at 11:59 PM EDT. Registrations received/postmarked after March 12 will not be processed and such registrants must go to Onsite Registration to register for the meeting. Higher onsite registration fees will apply. Fees for onsite Annual Meeting registration will be $300.00 more than the early bird fees, and fees for onsite Academy registration will be $100.00 more than the early bird fees. Avoid long lines and additional costs by registering NOW.

Register for the Meeting
Annual Meeting Website

Tweeting at #ISHLT2018

Want to get even more out of ISHLT 2018? Twitter can help!

Reading on Twitter about what others are learning in sessions is the easiest way to start. If you’re new to Twitter, CLICK HERE for easy to understand information on how to set up a Twitter account, how to read what others are posting, and how to post your own comments.

If you want to really engage, you can share comments about what YOU are learning. Share your conference experience and use #ISHLT2018 to connect with attendees, build professional relationships, uncover ideas, spark inspiration, and help others!

A #ISHLT2018 Twitter feed will be scrolling across the bottom of the mobile meeting app home page all day every day to provide real-time commentary and information.

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We would like to congratulate the following people on being the recipients of the 2017 ISHLT Grants and Awards:

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2018 Council Meetings and Networking Receptions

**BASIC SCIENCE & TRANSLATIONAL RESEARCH**

**Council Meeting**
Wednesday, April 11 from 7:15 AM – 8:15 AM  
(Clio/Thalie/Erato)

**Council Networking Reception**
Wednesday, April 11 from 6:15 PM – 7:15 PM  
(Agora 2)

**CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION**

**Council Meeting**
Wednesday, April 11 from 7:15 AM – 8:15 AM  
(Athena)

Friday, April 13 from 6:15 PM – 7:15 PM  
(Gallieni 1-2/Mykonos)

**HEART FAILURE & TRANSPLANTATION**

**Council Meeting**
Friday, April 13 from 7:15 AM – 8:15 AM  
(Clio/Thalie/Erato)

**Council Networking Reception**
Thursday, April 12 from 6:15 PM – 7:15 PM  
(Muses)

**INFECTIOUS DISEASES**

**Council Meeting**
Friday, April 13 from 7:15 AM – 8:15 AM  
(Gallieni 5)

**Council Networking Reception**
Thursday, April 12 from 6:15 PM – 7:15 PM  
(Gallieni 1-2/Mykonos)

**JUNIOR FACULTY & TRAINEES**

**Council Meeting**
Friday, April 13 from 7:15 AM – 8:15 AM  
(Uranie/Calliope)

**Council Networking Reception**
Wednesday, April 11 from 6:15 PM – 7:15 PM  
(Agora 3)

**MECHANICAL CIRCULATORY SUPPORT**

**Council Meeting**
Thursday, April 12 from 7:15 AM – 8:15 AM  
(Athena)

**Council Networking Reception**
Wednesday, April 11 from 6:15 PM – 7:15 PM  
(Muses)
NURSING, HEALTH SCIENCES & ALLIED HEALTH
Council Meeting
Wednesday, April 12 from 7:15 AM – 8:15 AM
(Uranie/Calliope)

Council Networking Reception
Wednesday, April 11 from 6:15 PM – 7:15 PM
(Gallieni 1-2/Mykonos)

PATHOLOGY
Council Meeting
Thursday, April 12 from 7:15 AM – 8:15 AM
(Hermes)

Council Networking Reception
Wednesday, April 11 from 6:15 PM – 7:15 PM
(Agora 2)

PEDIATRIC THORACIC TRANSPLANTATION & HEART FAILURE
Council Meeting
Friday, April 13 from 7:15 AM – 8:15 AM
(Hermes)

Council Networking Reception
Thursday, April 12 from 6:15 PM – 7:15 PM
(Agora 3)

PHARMACY & PHARMACOLOGY
Council Meeting
Wednesday, April 11 from 7:15 AM – 8:15 AM
(Hermes)

Council Networking Reception
Wednesday, April 11 from 6:15 PM – 7:15 PM
(Agora 2)

PULMONARY HYPERTENSION
Council Meeting
Thursday, April 12 from 7:15 AM – 8:15 AM
(Uranie/Calliope)

Council Networking Reception
Friday, April 13 from 6:15 PM – 7:15 PM
(Gallieni 1-2/Mykonos)

PULMONARY TRANSPLANTATION
Council Meeting
Thursday, April 12 from 7:15 AM – 8:15 AM
(Clio/Thalie/Erato)

Council Networking Reception
Friday, April 13 from 6:15 PM – 7:15 PM
(Euterpe)
SPECIAL INTEREST:

ISHLT Joint Session at American Heart Association Scientific Sessions

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In October 2014, I wrote of the progress in the field of pediatric heart failure and highlighted the creation of the American Heart Association’s (AHA) Cardiovascular disease in the Young (CVDY) pediatric heart failure subcommittee. As previously stated, the goal of this committee is to support the mission of the CVDY council to "improve the health of children with heart failure or cardiomyopathy through research, education, prevention, advocacy and quality improvement." The committee is supported by members of the CVDY council and from other councils within the American Heart Association, including a liaison with the ISHLT. The committee focuses on education and programming dedicated to pediatric heart failure for AHA scientific sessions and other conferences. The group continues to explore opportunities to develop scientific statements and open the doors for collaboration with other pediatric heart failure groups.

In keeping with the goal to collaborate with other pediatric organizations, this past November at the annual AHA Scientific Sessions in Anaheim, CA, there was a very successful AHA/ISHLT Joint Session entitled Long Term Outlook of Children After Heart Transplant: Do They “Live Happily Ever After” as in Fairy Tales? It was well attended with over 130 of the 150 chairs filled with standing space only in the back of the room! To start the session, Dr. Richard Chinnock (pediatric transplant cardiologist at Loma Linda University) discussed how children differ in their long-term outcomes compared to adults. Dr. Jeffrey Platt (transplant immunology, University of Michigan) then presented on “The Ultimate Matching Game: Cohabiting between the donor heart and recipient”. Following, Dr. Elfriede Pahl (pediatric transplant cardiologist at Lurie Children’s in Chicago) discussed some of the challenges faced in dealing with children and teens after transplant with a talk on “What Aches the Human Heart: Sex, Drugs, Rejection-and-Roll.” Dr. Jonathan Johnson (pediatric transplant cardiologist at Mayo Clinic) then shared his knowledge of coronary artery disease after pediatric heart transplantation. The session talks concluded appropriately with an excellent discussion from adult congenital/heart failure cardiologist, Dr. April Stempien-Otero (University of Washington), on the difficulties with transitions and being a young adult with a heart transplant. The audience members were able to submit questions electronically throughout the session for the moderators to pose to the speakers, and there was positive feedback on the topics and talks from the audience.

Collaboration is a key element in improving the science of pediatric heart failure. The joint session between the AHA and the ISHLT is just one example of how we can work together to expand knowledge of pediatric heart failure and transplantation across both groups.

Disclosure statement: The author has no conflicts of interest to disclose.
Influenza – 100 Years

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1918: Shifts and Drifts in Disease and History

An incomprehensible but important fact about the Spanish flu is it killed over 3% of the world population in less than two years. Nothing; no infection, no war, no famine nor any calamity has killed so many by something so small in so little time. The mortality surpassed the deaths seen in World War I, with an estimated 50-100 million people worldwide and 675,000 in the United States who succumbed to the illness [1]. Deaths were largely due to respiratory complications, such as secondary bacterial pneumonias; however, unlike prior influenza pandemics, the 1918 pandemic presented with more aggressive and fatal complications such as severe bronchopneumonia and progressive cyanosis [2]. Another surprising aspect of this pandemic was the excess mortality in otherwise healthy, young patients between 20-40 years old with a lower than expected mortality among the elderly. It also likely changed the course of history.

Nobody knows precisely where the 1918 influenza pandemic began, but evidence points to Haskell County, Kansas. Local physician, Dr. Loring Miner was seeing many patients stricken by an unusually virulent form of the flu between January and mid-March 1918. It faded away as quickly and as mysteriously as it had appeared. Dr. Miner was so concerned with its intensity that he reported it to the US Public Health Service, who neglected his published cautionary note. There it might have ended, except for one unalterable fact: we were in the midst of “the war to end all wars.”

Some 300 miles from Haskell County was Camp Funston, part of the huge Fort Riley military complex. In early March, soldiers began to report to the infirmary with flu-like symptoms. Within days, several thousand were afflicted and 38 deaths – not enough to quarantine a camp in wartime. Nonetheless, troop movement soon distributed the flu to other army camps. Soldiers from Fort Riley were loaded onto troopships by the thousands. Those lucky enough to disembark soon began to disseminate the illness to healthy troops, prisoners of war and civilians who spread the disease throughout Europe which marked the beginning of the 1918 influenza pandemic.

Apparently, the Spanish flu returned to the United States on August 12, 1918 from passengers on the Norwegian ship, the Bergensfjord. The liner entered New York harbor with 200 people sick and four buried at sea. All sick and exposed were so frightened they hurriedly disembarked and
scattered into the abyss of the New York population. From sailors and soldiers in coastal cities, influenza spread inland by rivers and rail. As many as 500,000 US citizens became infected, and at least 12,000 died. Across America, the fate of the survivors was problematic. Many families were impoverished, with one or more bread winners sick or dead. Influenza also left behind a world filled with widows and orphans, including 21,000 orphans in New York City alone.

As WWI was coming to an end, not unlike the flu, rumors of the armistice were spreading, but President Woodrow Wilson was determined to fight to the death and concede nothing to the aggressors. He met with Lloyd George and Clemenceau in Paris in early 1919 to work out the terms of surrender as the third wave of the virus was hitting Paris and killing thousands. On Thursday, April 3, 1919, Wilson was struck by a coughing spell so severe he had difficulty breathing. The attack was so sudden that Dr. Cary Grayson, Wilson’s White House physician, at first thought that Wilson had been poisoned. He was very ill, with severe diarrhea and a fever over 103 degrees. Although the peacemakers, George and Clemenceau met in Wilson’s room to continue the talks, Wilson’s health deteriorated. Wilson had changed after his illness, becoming stubborn and unwilling to listen to advice; he became paranoid, insisting that his home was filled with French spies as he grew obsessed with trivial details, like who was using what official vehicle. He had a complete change of face, conceding to Clemenceau on virtually every point he had previously fought so hard to make. Later authorities speculated that Wilson had suffered a mild stroke, which is an idea that persists to this day; however, neurological complications were described during the 1918 pandemic, leading some to wonder whether Wilson’s mentation was altered by the influenza virus itself. We may never know whether Wilson’s concessions resulted from his struggle with influenza, but his changes in attitude and behavior helped to create the conditions that ultimately led to the next World War.

At the time, the cause of the 1918 pandemic remained elusive. We later learned, however, that the etiology of the 1918 pandemic was an influenza A virus of the H1N1 subtype. Taubenberger et al have demonstrated links to an avian ancestral source by using techniques of sequence analysis [3]. However, unlike prior pandemics whose strains developed by a re-assortment between circulating human virus and avian influenza strains, the 1918 strain is thought to have arisen by genetic adaptation of an avian virus to a new human host [4,5]. Several authors have proposed that the influenza strain itself was not hypervirulent, but the effects it caused, such as virus-induced aberrant immune responses, were responsible for the high mortality. Based on historical records, patients who were exposed to the 1918 influenza strain likely had dysregulated and pathologic cellular immune responses to infections with the influenza A H1N1 strain [6,7]. It is hypothesized that these effects transiently increased susceptibility to secondary bacterial infections; thus potentially explaining the high mortality rate in otherwise young and healthy individuals. The most common bacteria recovered from the sputum, lungs, and blood of patients (alive and dead) included *Hemophilus influenza*, *Streptococcus pneumoniae*, *S. pyogenes*, and *Staphylococcus aureus* [8]. Taubenberger and Fauci examined 58 slides of lung tissue obtained during autopsy from 58 influenza fatalities in 1918-1919 from various United States military bases. They confirmed that almost all of the histologic evidence showed proof of severe acute bacterial infection; indeed, bacteria were often found in massive amounts in the sections studied. The samples also showed evidence of injury from the influenza virus itself, with features including necrosis and desquamation.
of the respiratory epithelium admixed with dilation of alveolar ducts [9]. Another pathological finding that Taubenberger found in the autopsies was similar to an ARDS-pattern, although it is thought that this represented a rarer cause of fatality related to influenza infection [10].

Treatment options were limited during the 1918 pandemic, as were public health initiatives. Medical treatment consisted mostly of comforting; however, other therapies included bleeding, saline or glucose injections, enemas, alcohol, camphor oil, heroin, morphine, mustard plasters, castor oil, sulfur smoke, lard mixed with camphor and chloroform as well as lard mixed with turpentine. Such interventions will cure you or kill you. Public health responses included fumigating campaigns against spitting and sneezing, warnings about public gatherings and a general prescription of rest, fresh air and reporting cases to the authorities. However, these efforts and basic knowledge about transmission of the virus were likely also hindered during this pandemic, as World War I entangled physicians and medical personnel overseas. In the United States, analyses of mortality data from large cities have shown that public health interventions such as isolation, quarantine, and banning public gatherings were associated with decreased influenza-related mortality rates [11]. However, these interventions likely reduced spread of secondary infections and pneumonia but did not primarily decrease rates of influenza transmission. During this time, folk cures abounded and included stuffing salt up children's noses, magic charms, wearing goose grease poultices, hanging little bags of garlic and onions round your neck and gargling with disinfectants. Charlatans, mountebanks and snake oil salesmen were everywhere.

Unfortunately, this was an era before the development and widespread use of antibiotics, which could have prevented deaths due to secondary bacterial infections. Vaccinations for pneumococcus and *Hemophilus influenza B* also did not yet exist. Interestingly, two vaccines were developed in Minnesota during the 1918 pandemic, one by a bacteriologist at the University of Minnesota that was made to prevent pneumonia, and a second created at the Mayo Clinic that was proposed to prevent pneumonia and influenza [12,13]. Unfortunately, neither of these vaccines contained influenza virus or proteins and were not shown to be effective for protection.

### 2018: The More Things Change, The More They Stay the Same

As compared to the 1918 pandemic, we are much better equipped now to respond to an emerging influenza threat. Public health and knowledge about transmission have improved. Through the Centers for Disease Control and Prevention and the World Health Organization, both national and international influenza surveillance programs are in place. Prevention has also been a main target, with encouraged annual vaccination for influenza. Drug development has also been important. Two classes of antiviral drugs, adamantanes and neuroaminidase inhibitors, are available and have proven effective against most circulating H5N1 viruses. Furthermore, we now have effective antibiotics to treat secondary bacterial complications of influenza that were not available in 1918. Intensive care units that host mechanical ventilation and circulatory support systems are also widespread in the 21st century. Without such modern marvels of medicine in 2018 nearly a quarter of a billion of the world’s population might succumb to a similar deadly influenza strain from 100 years ago, and possibly more given the swifter means of dispersion through our modern networks of highways and air travel. Not to mention our means of less self-reliant behaviors, over reliance on more perishable items and fast food restaurants along with our overcrowded behaviors.
Despite these advances, many challenges remain. Seasonal influenza outbreaks continue to cause substantial disease burden, with an estimated 3-5 million cases of severe illness, and 250,000 to 500,000 deaths worldwide each year [14]. While we do have antiviral medications, there is growing concern for adamantane resistance [15]. The seasonal vaccinations that we use are problematic, since they must be developed and manufactured months before the influenza season is upon us, and there is some degree of guesswork and estimation in predicting which strains will be prevalent for the upcoming season. There is an urgent need to develop a more effective vaccine that does not rely on annual updates, provides broad protection and is durable; i.e., a universal influenza vaccine.

Humans have been on the losing and winning sides of the battle with the microbes. We conquered the germ of laziness (*Necator americanus*, the American hookworm), but we were slaughtered by the 1918 flu. There may be a very good reason why we’ve managed to survive the evolutionary arms race so far: our highly evolved immune system provides us an arsenal to dispose of our unseen or microscopic rivals – unless, of course, our immune system is suppressed. Does a suppressed immune system dampen the cytokine storm, leading to decreased mortality, but prolonged viral shedding and increased transmissibility? On the 100-year anniversary of the 1918 influenza pandemic, we have much to learn, and an improved understanding of the effect of influenza on transplant patients may be the key.

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

References:


Additional Reading:
EDITOR’S CORNER:

The Beetle and the Giant

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CLAUDIO: Death is a fearful thing.
ISABELLA: And shamed life a hateful.
CLAUDIO: Ay, but to die, and go we know not where;
To lie in cold obstruction, and to rot;
This sensible warm motion to become
A kneaded clod; and the delighted spirit
To bathe in fiery floods, or to reside
In thrilling region of thick-ribbed ice;
To be imprisoned in the viewless winds,
And blown with restless violence round about
The pendant world; or to be worst than worst
Of those lawless and uncertain thought
Imagine howling—‘tis too horrible!
The weariest and most loathed worldly life
That age, ache, penury, and imprisonment
Can lay on nature is a paradise
To what we fear of death.
4.2.115-131

Have you ever felt wedged between a rock and a hard place? If you work in healthcare, your answer is likely yes. The adage refers to a situation offering two objectionable outcomes. As clinicians, we are forced into this uncomfortable and distressing environment daily. With arduous patient diagnoses, insurance regulation and universal healthcare, we often fight with a double-edged sword. Among the sea of urgency, the physical and emotional demands are challenging enough. With physicians, patients and families are forced to make tough decisions where results could render both negative outcomes. For patients suffering from disease, it’s either morbidity or mortality. Long after treatment, patients are still dealt the hand of the Joker, and at times, families have to play God.

On both sides of the spectrum, physician and patient, there is a catch-22. Over 400 years ago, Shakespeare provided a quintessential illustration of this wholesale dilemma in his play Measure for Measure. In this early seventeenth century play, the town of Vienna parallels our world of today
with lawless leadership, immoral justice and capital punishment. The antagonist, Angelo, is delegated by the Duke to cleanse the town of all sin and corruption and to achieve “mortality and mercy in Vienna.” He starts by sentencing Isabella’s brother, Claudio, to death for impregnating his future bride out of wedlock. Isabella, a proposed nun, is distraught over the condemnation and pleads to Angelo for her brother’s life. In turn, Angelo offers her a deal: sleep with him then her brother’s life will be spared, otherwise decline and her brother will be hung.

Now, we may not have the hand of virginity, but we can clearly see the hypocrisy and immorality in Angelo’s bargain. Like most of our patients, and us providers, Isabella is forced to choose from two degenerate outcomes. She can either lose her virtue and innocence because of societal demands, or she can remain pure and kill her brother. There is no right choice. Luckily, the Duke disguised as a Friar enters the scene with a more wicked plan to save Claudio. He tells Isabella to agree to submit to Angelo as long as the lights are off and no one speaks of it. Meanwhile, the Duke plots for Angelo’s ex-fiancée, Mariana, to take the place of Isabella in the dark. Now, Angelo will have committed the same “crime” as Claudio, eye for an eye. The only issue is that Angelo never intended to take up his side of the bargain. Instead, he planned to kill Claudio no matter Isabella’s choice (this goes to say for women's rights in Vienna at the time), and he requests for Claudio’s head as confirmation.

In the face of recalcitrance, how does one govern a city, or for that matter, oneself? The title of the play reminds us that judgement does not fall to man, perhaps to nature. In an environment with grotesque extremes (often reflected in the time between World Wars I & II), tensions are heavy as we often experience with patients and ourselves. Like Isabella, we are offered a potentially corrupt bargain with chronic consequences. In healthcare in particular, there is a continuous stream of economic opportunity, harvesting constant apathy and impassivity. This spearheads immoral decisions, ineffective communication and distrust. Whether we realize it or not, we are infinitely bound within borders. So how do we get out from the proverbial rock and “hard place,” if it is our Rock of Gibraltar? Numerous great scientists and writers warned us of humanities' self-destruction, yet here we are with Angelo in the flesh. Perhaps, the solution is to impeach the "hard place."

So, what is Shakespeare trying to say with Angelo’s power over life and death? Is Angelo put in charge as a test for his character, or does the Duke think Angelo’s judgement is genuine? In healthcare, we are often given the role of both Angelo and Isabella. We are expected to enforce and abide by the rules, even if we do not necessarily agree. Many critics argue this in Angelo’s character; he is not merciless or corrupt, but rather a human who can mess up. However, we see the compliance to one viewpoint of justice leads to the abuse of power and failure of equality.

As providers and patients, are we equipped to respond to an emerging threat, whether it be disease or human frailty? On average we retort to shortage of resources, money and manpower, but these issues are urgent crises, not evolving, venal environments. To save Claudio’s life, the Duke dressed as the friar decides to execute another criminal in his place to please Angelo. The prisoner called on, drunken Barnardine, is not too thrilled, and insists he is “not fit” for hanging because he is too hungover. Like Melville’s Bartleby the Scrivener, Barnardine reminds us of the person who constantly “prefers not to.” Shakespeare insinuates that Bernardine is already living in
hell. Barnardine’s blunt and comical refusal to die is the antithesis to Angelo and the Duke’s hypocrisy and morality. Luckily, they were able to substitute another prisoner’s head for Claudio’s.

While there is minimal evidence on healthcare moral judgement, Terry Hill reports on the topic in her article “How Clinicians Make (or Avoid) Moral Judgments of Patients: Implications of the Evidence for Relationships and Research.” Here, Hill explores the contextual dynamics of moral judgement in healthcare including age, race, gender, sexual orientation and economic status. She highlights how clinicians can inadvertently judge patients based of these demographics and place them in moral jeopardy. She mentions that “Carl May and colleagues found that physicians quickly make evaluative judgments of patients’ motives, the legitimacy of their symptoms, and the congruence between the physician's and the patient's conceptual model of illness.”

While Angelo is a barbarous, unethical leader, the Duke is just as errant with his own sanctimonious platitudes. Beyond hiring Angelo, the Duke spies on the town of Vienna while impersonating a friar. Not just imitating, but actually performing confessions and giving advice. When Isabella finally is able to speak justice against Angelo, the Duke arrests her and pretends not to believe her. Only until the Duke is re-disguised as the friar, is he able to confirm Isabella’s story. At the time, a woman publicly speaking about sex was stepping out of society’s social norms and restrictions. It should be remembered that the Duke’s conspiracies and Angelo’s hypocrisy put Isabella in this situation to begin with. Similarly, today we see the economic and social issues regarding governmental regulation on sex and gender.

Shakespeare’s dark comedy illustrates justice in the wake of corrupted power. We all have our Angelos and Dukes. Though at the hands of authority, Isabela is forced between unpleasant alternatives. Despite the Duke’s actions, Isabela still sought justice as Angelo is sent to the guillotine for fornicating (What about Mariana? Left dangling by “Measure”). Though not large, the beetle is able to squeeze through cracks and escape from being smashed by the giant or crushed by the wall. We must choose to not innately be the giant, but rather the beetle.

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

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