ISHLT2022 Roving Reporters – Reports from Advanced Heart Failure and Transplantation (AHFTX)

- **Wednesday, 27 April, 2022**
  - Featured Abstract 2 at Opening Plenary Session: Using Machine Learning to Develop a Contemporary Primary Graft Dysfunction Prediction Model: The International Consortium on PGD
  - SYMPOSIUM SESSION 02: Shock in a Box: What We Need to Learn About Heart Failure Cardiogenic Shock (HF-CS)
  - SYMPOSIUM SESSION 14: Surviving and Thriving After Heart Transplantation: In it for the Long Run!
  - SYMPOSIUM SESSION 15: Don't Lose Heart, as Better Times Are Ahead: COVID-19 From Bench to Bedside
  - SYMPOSIUM SESSION 21: The Future is Multimodal: Imaging the Transplanted Heart for Rejection, Dysfunction and Vasculopathy
  - ORAL SESSION 01: Early Career and Trainees Clinical Case Dilemmas: The Best of the Best
  - ORAL SESSION 09: Rethinking Biomarkers in Heart Transplantation: From Bench to Bedside

- **Thursday, 28 April, 2022**
  - SUNRISE 06: Pregnancy After Cardiothoracic Transplantation
  - SYMPOSIUM SESSION 27: Pets, Plants, & Palatables: When Living Life After Transplant Comes at a Cost
  - SYMPOSIUM SESSION 34: Real Options in Pediatric Heart Transplant: Small Infants, HLA Sensitization, and Non-invasive Rejection Screening
  - ORAL SESSION 28: The Heart Will Go On: Cold, Warm, or Assisted?
  - ORAL SESSION 37: New Insights in Patients with Advanced Heart Failure and Cardiogenic Shock
  - ORAL SESSION 42: Donor Utilization and Heart Allocation System in the Current Era: For Better or For Worse
  - MINI ORAL 07: What's the Score? Modeling Outcomes in Heart Transplantation

- MINI ORAL 11: Moving in the Right Direction: A Quick Jaunt Through Pediatric Heart Failure and Transplant

- **Friday, 29 April, 2022**
  - SUNRISE 07: DCD Heart Transplantation and Ex Vivo Repair: Gift Box or Pandora's Box?
  - SUNRISE 08: What's New? Updates to the ISHLT Guidelines for the Care of Heart Transplant Recipients
  - SYMPOSIUM SESSION 44: Cancer, Advanced Heart Failure, and Heart Transplant: Do Any of My Cells Work Properly?
  - SYMPOSIUM SESSION 49: It's Complicated! Psychosocial and Ethical Issues in Pediatric MCS and Transplantation
  - SYMPOSIUM SESSION 58: Relative Contraindications to Heart Transplantation: Where is the Line?
  - ORAL SESSION 43: ABC, 123, DCD, NRP: Expanding Donor Availability in Heart Transplantation
  - ORAL SESSION 51: Will You Be Mine? Choosing Donors and Recipients for Heart Transplantation
  - ORAL SESSION 54: A Heart Partnership: When is Two Better Than One?
  - ORAL SESSION 56: Don't Go Breaking My Heart: The Influence of Antibodies, Drugs, and Diagnostics on Pediatric Heart Transplant Outcomes

- **Saturday, 30 April, 2022**
  - Featured Abstract 5 at Closing Plenary Session: The Impact of Evolocumab in Cardiac Transplant Patients with Coronary Allograft Vasculopathy
  - SUNRISE 16: The Human Microbiome: Hopes, Threats and Promises
  - SUNRISE 18: Who's Keeping Score? Risk Scoring Systems and Contemporary Risk Factors for Primary Graft Dysfunction in Heart Transplantation
  - SYMPOSIUM 74: Heart, Liver, MCS, Oh My! Walking Down the Yellow Brick Road With Adult Congenital Heart Disease Patients
  - SESSION 82: Revisiting the Status Quo: Changing Paradigms in Routine Heart Transplant Rejection Surveillance
  - SESSION 76: Everything You Wanted to Know About ddCF-DNA in Heart Transplant Recipients and Never Dared to Ask
  - SESSION 80: More Than Meets the Gut: Nutrition and the Microbiome in Heart Transplantation

Thank you to all of our ISHLT2022 Roving Reporters.

ADVANCED HEART FAILURE AND TRANSPLANTATION (AHFTX)

Anju Bhardwaj, MD, University of Texas / McGovern Medical School / Memorial Hermann Hospital, Houston, TX, USA
Rachna Kataria, MD, Massachusetts General Hospital, Boston, MA, USA
Brian Wayda, MD, Stanford University School of Medicine, Stanford, CA, USA

ADVANCED LUNG FAILURE AND TRANSPLANTATION (ALFTX)

Prangthip Charoenpong, MD, MPH, LSU Health Science Center Shreveport, Shreveport, LA, USA
Grant Turner, MD, MHA, UCLA, Los Angeles, CA, USA

MECHANICAL CIRCULATORY SUPPORT (MCS)

David Bearl, MD, MA, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA
Varinder Randhawa, MD, PhD, Cleveland Clinic / University of Toronto, Toronto, ON, Canada

PULMONARY VASCULAR DISEASE (PVD)

Nicholas Kolaitis, MD, MAS, UCSF, San Francisco, CA, USA

Featured Abstract 2 at Opening Plenary Session: Using Machine Learning to Develop a Contemporary Primary Graft Dysfunction Prediction Model: The International Consortium on PGD

Presenter: ***Yasbanoo Moayedi, MD, MHs****, University Health Network, Toronto, ON Canada*

Flipping coins no longer: a potential "game changer" in PGD prediction

Primary graft dysfunction (PGD) afflicts 10-31% of heart transplant (HT) recipients and is the leading cause of early mortality after HT. Yet when it comes to predicting which patients will develop PGD, prior efforts do only slightly better than flipping a coin—at least that is the conclusion drawn from analyses by **Yasbanoo Moayedi, MD, MHs** and colleagues, who find that prior PGD prediction models (e.g. RADIAL, PREDICTA) had c-statistics of 0.51-0.52 when applied to their *International Consortium of PGD* cohort.

But recent work by this *Consortium*, presented at ISHLT by lead author Dr. Moayedi, might be a "game changer" in PGD prediction. Their cohort included 2,764 patients from 14 centers across North America and Europe—more than three times larger than the (mostly single-center) cohorts used to develop prior PGD models. They applied supervised machine learning (ML) with boosting (see "translation" below) to select, from 106 candidate variables, a subset of 17 which best predicted severe PGD in their cohort. The resulting model achieved a c-statistic of 0.73 when tested in their cohort—needless to say, much better than a coin flip.

A skeptic might point out that PREDICTA and RADIAL performed similarly well initially (on internal validation), and wonder if this new model's performance will translate across contexts and over time. But I would encourage optimism—thanks both to the unprecedented size and scope of their derivation cohort and their use advanced ML methods. For example, where simpler models might label recipients as "old" or "young," theirs captures the non-linear effects of recipient age and other continuous variables. Also critical is their use of "boosting" —translation: the sequential combination of many "weak" models to produce a progressively "stronger" model, with progressively more weight given to instances (i.e. HT recipients) that are hardest to classify (i.e. as "PGD" or "no PGD").

Similar "ensemble" machine learning models proved successful in the "Netflix Prize" competition—and seem to have an uncanny ability to identify which soccer documentary will keep me glued to the sofa when I should be studying for boards. Let's hope they prove just as effective at predicting PGD—for this could enable early interventions to prevent it and thus save many lives after heart transplant.

VIEW FULL ABSTRACT

– Summary by Brian Wayda, MD

SESSION 02: Shock in a Box: What We Need to Learn About Heart Failure Cardiogenic Shock (HF-CS)

Advanced heart failure related cardiogenic shock (HF-CS) is on the rise. Management of heart failure related cardiogenic shock is challenging and evidence-based guidelines are limited. This **symposium** addressed topics of paramount importance such as advanced heart failure cardiogenic shock phenotypes, strategies to improve outcomes, as well as the newly convened ISHLT cardiogenic shock consensus guidelines committee.

The Standard of Care Across HF-CS Continuum: When Time is Myocardium

Maria F. Renedo, MD, Favaloro Foundation University Hospital, Buenos Aires, Argentina

Contemporary standard of care for heart failure includes the four-pillars of guideline directed medical therapy that have proven to improve outcomes. However, there has also been a growth in the relative incidence of HF-CS. There remains an ongoing need for active screening and early identification of patients who may benefit from advanced interventions. "I NEED HELP" is simple yet useful mnemonic to help identify such patients. There is also a need for better understanding of HF-CS, the differences between de-novo and acute on chronic HF-CS, and different HF-CS phenotypes. We need risk assessment scores, device tailoring algorithms, multidisciplinary teams, and evidence-based guidance on shock teams.

Tackling the Shock Circle: Implementing an Algorithm for Mechanical Circulatory Support (MCS) in HF-CS

Daniel Kim, MD, University of Alberta, Edmonton, AB Canada

With the increasing options for temporary mechanical circulatory support devices available to us, it is increasingly important for us to have algorithms to guide us to choose the right device for the right patient, to provide the right amount of flow at the right time. Shock teams must comprise of two overarching components: an acute response team and an in-hospital management team. For a center to be capable of managing shock it must at least have an advanced heart failure multidisciplinary team, access to both temporary and durable MCS, cardiothoracic surgery and cardiac critical care teams. A proposed approach to weaning could include repeated assessments at 1, 2, and 4 hours after temporary MCS and then every 12 hours. In case of no change at 24-48 hours and if the patient is a candidate for advanced therapies, those should be considered. There remains a need for guidance on escalation or de-escalation of temporary MCS.

When Right is Wrong: Right Ventricular Failure Cardiogenic Shock: Tips and Tricks When the Guilty is Not the Left Side

Ioana Preston, MD, Tufts Medical Center, Boston, MA USA

Right ventricular (RV) failure in cardiogenic shock is a conundrum. Ventricular interdependence plays a key role in RV failure. An acute insult can result in RV dilation, increased wall stress and an increase in tricuspid regurgitation and RV end-diastolic volume. Tachycardia, hypotension, interventricular septal displacement, and LV encroachment can all result in a significant decrease in cardiac output, increase in coronary sinus pressure and impaired cardiac contractility, and cardiogenic shock. It is important to identify RV failure and then identify reversible causes,

optimize volume status, restore perfusion pressure.

Best Ways to Monitor HF-CS Patients: Invasive and Non-Invasive Monitoring
Fernando Bacal, MD, PhD, Heart Institute, University of Sao Paulo, Sao Paulo, Brazil
Choice of invasive versus non-invasive monitoring for HF-CS may be guided by our therapeutic goals- clinical, macro-hemodynamic, micro-hemodynamic, or endothelial function. Invasive hemodynamics are helpful in early stages (for risk stratification) and in very sick patients. In all others, a combination of transthoracic echocardiography along with newer non-invasive modalities for hemodynamic monitoring may be helpful (examples include: ClearSight system, CNAP®, Flotrac®).

Rolling in the Deep: A Little Kid Does Not Mean a Little Shock
Michal Odermarsky, MD, Skåne University Hospital, Children Heart Center, Lund, Sweden
Signs and symptoms of cardiogenic shock in children can vary immensely from feeding difficulties and stomach pains to anuria and altered mental status. The general principles of management of shock in children are similar to those in adults. It is extremely important to involve caregivers and have in-depth conversations about severity of illness, expectations and outcomes, MCS and heart transplant options. MCS options include extracorporeal membrane oxygenation as a bridge to durable ventricular assist device or heart transplant.

Working Together to Improve CS Outcome All Around the World: Ongoing Registries, Trials and Future Challenges from an International Perspective
Antonio Loforte, MD, PhD, S. Orsola University Hospital, Bologna, Italy
There is an unmet need for an evidence base to guide early identification, timely intervention, escalation and de-escalation of therapies, and timely initiation of advanced therapy evaluation in HF-CS. HF-CS registries are the need of the hour. The newly convened ISHLT cardiogenic shock consensus guidelines committee will aim to provide guidance on these crucial issues.

VIEW FULL ABSTRACT

– Summary by Rachna Kataria, MD

SESSION 14: Surviving and Thriving After Heart Transplantation: In it for the Long Run!

Survival after heart transplant: a marathon, not a sprint (and several other metaphors)

Median survival after adult heart transplant (HT) has steadily improved over the past few decades, from less than one year in the early 1970s, to 8.6 years in the 1980s, to 12.5 years among those transplanted in the early 2000s. Whether recent HT recipients will continue this encouraging trend remains to be seen. Cautious optimism is warranted, but we must take care to avoid complacency—this was the unifying theme among speakers in Wednesday's symposium **Surviving and Thriving After Heart Transplantation: In It for the Long Run!**

In the opening talk: "***Defining the Goalposts: Threats to Survival and Quality of Life***," **Josef Stehlik, MD** of the University of Utah outlined the key drivers of improved survival over the decades. Obvious and prominent is the impact of technological advances, specifically 1) safer, more effective immunosuppressant medications 2) mechanical circulatory support (*e.g.*, in the setting of primary graft dysfunction) and 3) better tools for the diagnosis of rejection. Yet it's easy to overlook the importance of "organizational" advances—which Dr. Stehlik emphasized. In particular, he credited the development of interdisciplinary teams, standardized protocols (*e.g.*, in rejection surveillance, grading, and management), and regulatory oversight (*e.g.*, of program-level outcomes) as key contributors to improved survival.

His survey of game-changing advances over the years prompted me to wonder: "Have we already picked all the low-hanging fruit?"; in other words, if post-HT survival is to continue its positive decades-long trend, what remaining "threats to survival" are amenable to high-impact intervention?

The second talk of the symposium addressed my question, seemingly on cue. In "***Old Problems, New Solutions: The Potential for New Therapies to Protect Kidneys and Prevent CAV***," **Amanda Vest, MBBS, MPH** of Tufts Medical Center opened with a figure showing 4 post-HT survival curves, each representing a separate era from "1982-1991" to "2009-2016," stacked virtually in parallel from bottom to top. Indeed, "parallel" is the operative word—as Dr. Vest noted, survival gains over time are mainly attributable to improvement in the early post-HT period. It seems we've improved our opening sprint, but our marathon pace is stagnant.

New-onset diabetes mellitus (DM) occurs in 21% of recipients after HT, and is a leading predictor of coronary allograft vasculopathy (CAV). Could agents targeting the cardio-renal-metabolic axis—namely, PCSK9 inhibitors, GLP-1 agonists, and SGLT2 inhibitors—be "low-hanging fruit" for improving late post-HT survival? Dr. Vest presented a compelling case in their favor—citing well-known RCTs from the non-HT population and data from rodent models suggesting 1) SGLT2 inhibitors attenuate tacrolimus-induced DM and 2) GLP-1 agonists attenuate CAV. An RCT of PCSK9 inhibitors in HT recipients is already in progress (EVOLVD)—let's hope that a SGLT2 inhibitor trial soon follows.

Other speakers in the symposium offered equally compelling insights—though I'm running out of space (and metaphors) so cannot do them justice here. In "***Learning from the Kids: What Pediatric HT Can Teach Us About Long-Term Survival***," **Joseph W. Rossano, MD** of the University of Pennsylvania highlighted the importance of cross-institutional collaboration: "(Pediatric centers) work very well together—we've had to because numbers are small." In "***Navigating Crossroads: Managing Critical Transition Points with Focus on Psychosocial Stressors and Quality of Life***," **Mary Amanda Dew, PhD** of the University of Pittsburgh reminded us that depression (OR for post-HT mortality ≈ 1.8 in one study) is a critical hurdle in the post-HT "marathon."

The session concluded with a debate: "***Protocols, Patient Selection or Pure Luck: We Can(?) Predict Long-term Success Post-Transplant***." Representing the "pro" side, my mentor **Kiran Khush, MD, MAS** of Stanford University argued that a heart transplant is like a wedding (as opposed to a football game, fruit tree, or marathon), impressed us with her knowledge of celebrity couples (from "V&A" through "Kim K"), and summarized the extensive set of donor and recipient characteristics that predict post-HT survival. On the "con" side, **Friederike Danne, MD** of Deutsches Herzzentrum (Berlin, Germany) emphasized that "outcome prediction always relies on historical data"—a inherent limitation in the rapidly evolving field of transplant. Both made compelling arguments, but the winner was clear—Jay-Z & Beyonce over Brangelina in a landslide.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 15: Don't Lose Heart, as Better Times Are Ahead: COVID-19 From Bench to Bedside

Heart transplantation during COVID-19: pausing to reflect on life in a "vacuum"

In an era of center-level protocols, international consensus guidelines, and large-scale registry data, few transplant clinicians had ever made heart transplant (HT) decisions in a complete vacuum—lacking any data, expert opinion, or precedent whatsoever to guide us. This changed for many of us in March 2020; already difficult decisions regarding who should get transplanted, when, and using what organs were suddenly complicated by a highly-infectious, life-threatening, and then poorly-understood virus. Today's symposium, titled **Don't Lose Heart, as Better Times are Ahead: COVID-19 from Bench to Bedside** offered an opportunity to reflect on how the collective HT community responded to and emerged from this "vacuum."

Our immediate response varied across countries, as noted by **Kim Anderson, MD** of Dalhousie University (Halifax, NS, Canada) in her presentation "***Deceased Donor and Recipient Selection for Cardiothoracic Transplantation During the COVID-19 Pandemic***." Citing *Ritschl et al* (2020; AJT), Dr. Anderson compared transplant guidelines during the early phase of the pandemic. How much they varied serves as a reminder of how little we knew; nations disagreed regarding whether transplant candidates should be screened for COVID and whether recipients should wear masks. Whether to perform HT involving donors or recipients with resolved COVID infection was an even harder question—14 of 19 countries endorsed no recommendation on either and the remainder disagreed.

Since then, knowledge has grown and practice followed suit. By August 2021, ample case reports had established that *resolved* donor COVID infection (confirmed by negative testing) is unlikely to result in recipient infection or other complications. Less is known regarding donors with *active* COVID—only a few small case series have reported on their use for transplant and associated outcomes. But hundreds of (non-lung) transplants using COVID+ donors have since occurred worldwide—large-scale studies characterizing their outcomes are urgently needed. Until then, Dr. Anderson recommends cautious consideration of COVID+ donors, weighing factors such as infection severity, recipient immunity to COVID, and risk to the procurement/transplant teams.

This early pandemic "vacuum" is also manifest in how much transplant volumes varied across countries, as detailed by **Jignesh Patel, MD, PhD** of Cedars Sinai Heart Institute (Los Angeles, CA, USA). For instance, France and the United Kingdom experienced a near shutdown of their HT programs in mid-2019 and the United States saw a more modest and transient decline. In contrast, transplant volumes remained stable in Germany and actually increased in Australia. Regions within the US also had a variable response, and those with the sharpest drops in transplant volume had a concurrent rise in waitlist mortality. Whether the same association exists across nations may warrant further study.

Other speakers in the symposium offered insights on how to prevent and manage

COVID *after* transplant. **Marta Farrero, MD, PhD** of Hospital Clinic (Barcelona, Spain) discussed "***Risk Factors and Severity of COVID-19, Reducing the Risk of Infection and SARS-CoV-2 Testing***." **Jonathan Hand, MD** of Ochsner Medical Center (New Orleans, LA, USA) discussed "***SARS-CoV-2 Vaccination in Heart Transplantation***." Finally, **Diyar Saeed, MD, PhD** of Leipzig Heart Center (Germany) presented on "***ECMO Support During the COVID-19 Pandemic: Challenges and Recommendations***."

Perhaps most notable: all five presenters were live in person, having traveled from four different countries to Boston, during that precious April-September window when its weather is bearable. "Better times", indeed.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 21: The Future is Multimodal: Imaging the Transplanted Heart for Rejection, Dysfunction and Vasculopathy

Endomyocardial biopsy and coronary angiography are the standard of care for diagnosis and surveillance of cardiac allograft rejection and cardiac allograft vasculopathy (CAV). Both modalities have limitations such as sampling error and interobserver variability. In contrast, multimodality imaging is noninvasive. The ideal noninvasive modality, however, should be highly sensitive and specific, reproducible, and cost efficient. The aim of this symposium was to outline various noninvasive imaging modalities, their pros and cons, and areas of future research.

Niche to Mainstream–Contemporary Strain Imaging and Deformation Analysis in Post-transplant Surveillance

Nadia Fida, MD, Houston Methodist Hospital, Houston, TX USA

Surface echocardiography is a noninvasive, resource efficient modality that can be used in cases of subclinical rejection and to monitor response to treatment for rejection. Dobutamine stress echocardiography is widely used for surveillance in patients after heart transplant. There is limited evidence to suggest that use of global longitudinal strain (GLS) can help diagnose allograft rejection as well as CAV. In fact, one study showed that the degree of reduction in GLS may be related to the severity of CAV. However, use of echocardiography in post cardiac transplant patients may be limited by anatomical and structural changes seen post-transplant such as altered geometry of transplanted heart, tachycardia, presence of pericardial effusion, etc. Moreover, data remains insufficient, and echocardiography cannot be used to guide for-cause biopsies at this time.

Precision and Accuracy of T1 Mapping in Allograft Rejection: Ready for Prime Time?

Shinichi Nunoda, MD, PhD, Tokyo Women's Medical University, Tokyo, Japan

Cardiac magnetic resonance (CMR)-based T1 mapping detects interstitial edema and fibrosis, which are important markers of acute and chronic rejection. Recent evidence suggests that CMR based T1 mapping has a high negative predictive value for allograft rejection and may therefore have a role in helping minimize invasive endomyocardial biopsies. T1 mapping can also be used to monitor response to treatment of such rejection. CAV is the Achilles heel of cardiac transplant. Whole body magnetic resonance coronary angiography (MRCA) has been utilized to detect CAV. However, when compared to standard of care (coronary angiography), MRCA was found to have limited sensitivity. Further research is ongoing.

PET Myocardial Blood Flow: Revolutionizing the Detection and Prognostication of Allograft Vasculopathy

Lisa Mielniczuk, MD, University of Ottawa Heart Institute, Ottawa, ON Canada

A growing body of evidence suggests that multiparametric cardiac PET evaluation including quantification of myocardial blood flow provides improved detection and gradation of CAV severity over standard myocardial perfusion assessment. Recently, measurements of a novel parameter, namely cardiopulmonary transit time, have been shown to provide incremental risk stratification in heart transplant recipients and to enhance the value of multiparametric dynamic

PET imaging, particularly in identifying high-risk patients. Serial measurements of coronary flow reserve have also been shown to predict long-term mortality in heart transplant recipients. However, with the limited evidence and experience thus far, utilization of cardiac PET imaging for detection of CAV remains limited to centers of excellence and in patients who are were transplant more than 5 years ago.

IVUS vs OCT for Allograft Vasculopathy: Which Can Brave the Achilles Heel of Heart Transplant!
Anna Kydd, BMedSci, MBChB, MD, Papworth Hospital, Cambridge, UK
Pathogenesis of CAV involves both immune and non-immune pathways that result in vascular inflammation with smooth muscle cell proliferation and luminal narrowing, intimal hyperplasia, and inflammatory cell infiltrate. Both epicardial and intra myocardial coronaries are affected. Coronary angiography (CA) is the standard of care for diagnosis and surveillance of CAV. However, CA alone lacks sensitivity and specificity. IVUS provides better tissue penetration and plaque volume quantification. Unlike IVUS, OCT has better axial resolution but limited penetrance. While both IVUS and OCT are associated with increased healthcare costs, they may facilitate early detection of angiographically silent CAV and thereby enable timely modification of risk factors as well as optimization of immunosuppression resulting in better post-transplant outcomes. However, evidence remains insufficient and utilization of IVUS and OCT is limited to large volume centers.

Breaking from Tradition: Post-Transplant Surveillance Made Simple with AI (Artificial Intelligence)
W. H. Wilson Tang, MD, Cleveland Clinic Foundation, Cleveland, OH USA
Artificial intelligence has the potential to predict complications and rejection post-heart transplant. Translational projects are underway at large volume centers. Data so far is encouraging. There is more to come in this area.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

SESSION 01: Early Career and Trainees Clinical Case Dilemmas: The Best of the Best

Off label, but on course (to transplant)

"Necessity is the mother of invention." This adage that rings true in the field of heart and lung transplantation, as demonstrated by some of this year's top submissions in the Early Career Case Reports category. This "best of the best" session featured cases from varied disciplines, but the translation of familiar tools to unfamiliar settings was a common theme.

In his presentation "***First US DCD Pediatric Heart Transplant Using Ex-Vivo Perfusion (EVP): Is It Time for a Clinical Trial?***", **Nicholas D. Andersen, MD** presented the case of a 14-year-old girl with a history of 1p36 gene deletion syndrome and dilated cardiomyopathy who underwent successful heart transplant (HT) using the investigational Organ Care System (OCS). As her young age excluded her from the OCS DCD Heart clinical trial, a Compassionate Use exception was obtained for use of OCS in her case. After DCD donor transplant, her early course featured familiar complications including 1) moderate biventricular dysfunction and 2) respiratory failure requiring intermittent ventilatory support. The former resolved by discharge on post-operative day 13, followed by a successful ventilator wean. Now, 9 months after making history as the first US pediatric recipient of DCD EVP heart transplant, the patient is thriving. Dr. Andersen concluded by answering the question in the title of his abstract with a resounding "yes," and expert discussant Dr. Jacob Mathew agreed. But Dr. Andersen's case discussion posed other intriguing, more difficult to answer questions. For example, would miniaturization of the EVP platform—thus allowing its use for even younger recipients and smaller donor hearts (with smaller aortas)—be technically and commercially feasible? If not (or not yet), then normothermic regional perfusion may be the best option for most pediatric DCD heart transplants.

Keeping with the theme of familiar tools in unfamiliar settings, **Krishan Patel, MD** of Emory University presented a case of "***Systemic Right Ventricle Mechanical Support with Impella 5.5 as a Bridge to Cardiac Transplantation***." Technical challenges were perhaps inevitable, due to the differing geometry and orientation of the left and systemic right ventricles, and ultimately the device could not be rotated posteriorly away from the RV free wall. While this positioning was not "ideal," this 39-year-old male with systemic right ventricle failure attained hemodynamic stability, had no arrhythmias, and remained stable for 42 days before undergoing HT without complication. He continues to do well as an outpatient.

In two cases of a more common—but equally challenging—cardiac pathophysiology, **Hyeon-Ju R. Ali, MD** of Houston Methodist Hospital described "***Management of Pulmonary Hypertension (PH) Secondary to Valvular Heart Disease with Angiotensin-Receptor Neprilysin Inhibitor (ARNI)***." Both patients—a 63-year-old woman and 59-year-old man—had refractory NYHA class IIIb symptoms and were treated for 2-3 months with sacubitril/valsartan. Both the woman and man experienced a ~20 mmHg drop in their mean pulmonary pressure and equally impressive decreases in their pulmonary vascular resistance (11.4 -> 6.1 Woods units and 4.3 -> 1.1 Woods units, respectively). Could ARNIs be a powerful new tool in the PH armamentarium? Bring on the prospective clinical

trials!

Finally, **Deepika Razia, MBBS** of Norton Thoracic Institute presented a case of "***Persistent Subclinical SARS-CoV-2 Isolation After Redo Lung Transplant for COVID-19-Induced Lung Injury***." The 48 year-old male patient in this case developed COVID-19 in year 2 following bilateral lung transplant. After nearly 6 months of persistent viral shedding, he had two negative nasopharyngeal swabs and underwent repeat lung transplant (LTx). His course was complicated by critical illness myopathy, but was otherwise unremarkable - that is, until the finding of persistent CoV-2 on surveillance bronchoalveolar lavage studies at day 40 post-LTx. SARS-CoV-2 isolation resolved promptly after monoclonal antibody therapy. At no point post-LTx did the patient have any clinical signs or symptoms of COVID, prompting the question: "How should we deal with subclinical CoV-2 shedding in the pre-LTx context?" Dr. Razia's case suggests that it ought not be an absolute contraindication to LTx.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 09: Rethinking Biomarkers in Heart Transplantation: From Bench to Bedside

This **oral abstract session** focused on standard and novel biomarkers as well as parameters used to assess quality of donor hearts.

Relationship Between Lactate Trend and Cardiac Power Output During Ex Vivo Heart Perfusion

Simon Dang Van, MD MSc, Simon Dang Van, MD MSc, Marie Lannelongue Hospital, Paris Saclay University, Le Plessis Robinson, France

The purpose of this animal study was to examine the relationship between lactate trend and myocardial performance during normothermic ex-vivo perfusion (NEP) in working mode (WM) as opposed to Langendorff mode (LM) since this relationship in LM has been previously studied. Eighteen porcine hearts were divided in 3 groups of 6 hearts each: beating heart (BH) procurement followed by 6-hours of cold storage (CS group); BH procurement followed by 4-hours of hypothermic ex-vivo perfusion (HEP) (HP group); and donation after circulatory death (DCD) followed by HEP (DCD group). All hearts were then cannulated for NEP in LM mode for 30 minutes followed by WM for 2 hours. Mean arterial pressure and cardiac output were continuously measured, lactate was measured every 30 mins in perfusate. The major finding of this study was that myocardial lactate extraction (MLE) was not a reliable predictor of myocardial performance as MLE did not correlate with cardiac power output during WM or LM. The study investigators concluded that new biomarkers that correlated with myocardial viability were warranted.

Transcriptional Changes of Left Ventricle Biopsy During Reperfusion Predict the Outcome of Heart Transplants

Joel Ristikankare, MD, University of Helsinki, Helsinki, Finland

Donor hearts are exposed to extreme stress during brain death, cold and warm ischemic times, and again during reperfusion. Ischemia-reperfusion injury may predispose heart transplant to acute rejection and early mortality and treatment possibilities are limited. The aim of this study was to investigate transcriptomic changes and the underlying biological processes of ischemia-reperfusion injury and to potentially utilize this information to interpret recipient outcome as well as to identify therapeutic targets. RNA was extracted and sequenced from procured hearts immediately preceding and 1-hour after reperfusion. Clustering analysis was performed on the 0- and 1-hour samples. Seventy biopsies were performed at 0- and 1-hour and RNA extraction and sequencing was performed. Gene ontology enrichment analysis was performed on the 0- and 1-hour samples and clusters of genes were identified. Prediction analysis was perfomed to identify genes that predicted primary graft dysfunction (any grade and severe grade), acute rejection, and graft-related mortality. The authors found that at 0-hour, genes that differentiated good from bad clusters were associated with oxidative stress, protein catabolism and translation, and inflammation. At 1-hour, these genes were the ones associated with protein metabolism and modification, and mitochondrial functions. As for their prediction analysis, it identified 3 genes associated with PGD, 15 with acute rejections, 17 with graft-related mortality. These genes were all involved in metabolic, immunologic, and mitochondrial processes.

Lactic Acid and Metabolic Analysis of Human Donor Hearts Preserved with Organ Care System

Prashant N. Mohite, FRCS, Royal Brompton and Harefield NHS Trust, London, UK

Primary graft dysfunction (PGD) is the most common cause of early death in patients of heart transplantation (HTx) and the requirement of ECMO is one of the definitive criteria of PGD. Use of organ care system (OCS) preserved donor heart for HTx depends upon the lactate trend and the ventricular contractility. The authors performed metabolic analysis on OCS perfusate samples of 204 procured hearts of which 53 were declined based on lactate trend and of the remaining 151 hearts, 42 required ECMO after HTx while 109 did not. Major findings of this study were that the rate of fall of arterial lactate offered more valuable information compared to the overall lactate trend and end lactate in the prediction of PGD after HTx. Heart declined based on unfavorable lactate trend did in fact show significantly low CaO2, DO2 and Oxygen return on metabolic analysis. The authors also found that coronary flow was significantly lower in the hearts declined for transplant.

Metabolomic Profiling of Cardiac Allografts After Controlled Circulatory Death

Julien Guihaire, MD PhD, Marie Lannelongue Hospital, Paris Saclay University, Le Plessis-Robinson, France

This study was also aimed at investigating new biomarkers of myocardial viability during ex-situ heart perfusion (ESHP) using metabolomic profiling of hearts donated after circulatory death (DCD). Eighteen piglets were randomly allocated to 3 groups of 6 each: donor hearts procured either after 15 minutes of warm ischemia (DCD group); after brain-stem death (BSD group); or without DCD nor BSD (Control group). Blood normothermic ESHP was then initiated for 240 minutes and Plasma and myocardial samples were procured respectively every 30 and 60 minutes, and analyzed by liquid chromatography coupled to high-resolution mass spectrometry. The authors concluded that plasma levels of inosine and guanosine, nucleotides could be relevant biomarkers for viability assessment of DCD hearts.

Proteomic Profiling of Cold Storage Preservation Solution to Identify Signatures of Primary Graft Dysfunction Following Heart Transplantation

Lauren K. Truby, MD, Duke University Medical Center, Durham, NC USA

The investigators of this study hypothesized that proteomic profiling of cold-storage preservation solution may identify novel biomarkers of post-transplant allograft dysfunction. Using non-targeted proteomic profiling of traditional cold storage preservation solution, the authors identified a set of novel biomarkers that are associated with primary graft dysfunction. Key biologic candidates within this set included MYL4, FMOD, ELOC, and CMA1. Future studies are needed to validate these signals and elucidate their role in clinical care.

Myocardial Work Index Correlates with Cardiac Performance During Ex Vivo Heart Perfusion

Dorothée Brunet, MD MSc, Marie Lannelongue Hospital, Paris Saclay University, Le Plessis Robinson, France

The authors of this study sought to investigate the relationship between echocardiographic myocardial work index (MWI) and cardiac performance during ex-vivo perfusion (EVP).

Eighteen piglets were allocated in three groups of 6 each: cold-storage, hypothermic perfusion,

and donation after circulatory death. After 4 hours of preservation based on the group assigned, the hearts were instrumented for normothermic perfusion in Langendorff mode for 30 minutes then working mode (WM) for 2 hours. Surface echocardiography with calculation of myocardial work index, pressure-volume loops, and cardiac output measures were performed during WM. The authors concluded that noninvasive assessment of MWI was feasible in their preclinical model of EVP and that MWI was strongly correlated with cardiac performance in perfused hearts resuscitated after either prolonged hypothermic preservation or after controlled-circulatory death.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

SUNRISE 06: Pregnancy After Cardiothoracic Transplantation

Among the many markers of progress in our field, facilitating safe and successful pregnancies among an increasing number of heart transplant (HT) recipients may be the most encouraging. As noted in Thursday's session by **Francesca Macera, MD**, of Hôpital Erasme in Brussels, Belgium, the pertinent question is not "whether to encourage or discourage pregnancy" but "what to do if the patient decides to become pregnant" after individualized counseling on the risks involved. She and other presenters in the **Sunrise Session** answered this question along many dimensions—from prenatal counseling through management of perinatal complications—while also highlighting the remaining unknowns.

The complex immunologic changes that occur during pregnancy present an array of potential challenges, as expertly summarized by **Ersilia DeFilippis, MD**, of Columbia University Medical Center in New York, NY USA. Increased complement activation, the induction of a regulatory T cell response, and sensitization to fetal antigens all threaten to disrupt graft tolerance – thus close monitoring for rejection is warranted. In her talk ***Surveillance and Management of Rejection During Pregnancy***, Dr. DeFilippis detailed concrete recommendations, including monthly ECGs and echocardiograms during pregnancy, weekly therapeutic drug monitoring during the first month post-partum, and an assessment for donor specific antibodies shortly thereafter. However, more invasive measures (endomyocardial biopsy, imaging) need only be performed "for cause" given the procedural risks and radiation exposure involved. When it comes to the management of acute rejection, the ongoing consensus is that corticosteroids are the safest option; ATG and IVIG may also prove to be safe, though experience is limited.

Dr. Macera elaborated on the hormonal and metabolic changes during pregnancy that might pose particular risk to the transplant recipient in her talk ***Outcomes of Pregnancies Involving a Solid Organ Recipient***. For instance, upregulation of cortisol, progesterone, and prolactin during pregnancy compound the already elevated risk of new-onset diabetes in the HT recipient and its associated complications (e.g. preeclampsia, preterm birth, macrosomia). Pregnancy-induced hemodilution and changes in intestinal motility and cytochrome P450 activity could reduce the effective dose of immunosuppressants—a point further elaborated on by **Lilibeth Carlos, PharmD**, of St. Vincent's Hospital in Sydney, Australia during her talk ***Pharmacologic Considerations with Pregnancy: Effects on Immunosuppression***.

Exactly how this complex physiology affects broader neonatal and maternal outcomes is not precisely understood—due in part to the absence of pregnancy-related data in large-scale nationwide registries. As summarized by Dr. Macera, the largest case series to date (including 157 pregnancies among 91 heart transplant recipients; *Punnoose et al*, 2020) reports the following:

- Complications during pregnancy included pre-eclampsia (23%) and infections (14%).
- Rejection was reported during 9% of pregnancies and within 3 months postpartum in 7%.
- Livebirths occurred in 69%, miscarriages in 26% (half of which had MPA exposure), with no neonatal deaths.

- At last follow-up, 30 recipients had died, an average of 9.4 ± 6.2 years after pregnancy, most commonly due to allograft vasculopathy and rejection.

Synthesizing this data to enable informed decision making by patients is a key component of pre-natal counseling, as detailed by **Tara Miller, NP**, of Duke University in Durham, NC USA in her talk ***Prenatal Counseling: Aiming for a Successful Pregnancy***; and further illustrated in case presentations by **Patricia Chavez, MD**, of Montefiore Medical Center in New York, NY USA as she discussed case presentations in her talk, ***Evaluating Patients in a Cardio Obstetrics Program***.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 27: Pets, Plants, & Palatables: When Living Life After Transplant Comes at a Cost

Pets, Plants, Palatables, and "People"

"Our transplant recipients don't want to be patients; they want to be people." This simple yet astute observation, by **Cedric Spak, MD**, of Baylor University Medical Center in Dallas, TX USA, was echoed throughout the Thursday morning symposium **Pets, Plants, & Palatables: When Living Life After Transplant Comes at a Cost**.

His observation is best illustrated by the patient cases presented during the session. For instance, in ***Just Fly Away: Management of Bird-Related Pathogens***, Dr. Spak presented the case of a 61-year-old male lung transplant recipient who presented with 30 pound weight loss and other "B symptoms." He was not an owner of exotic pets, a recent world traveler, or a partaker in hobbies involving caves, dense forests, or anything else that might form the stem of a Board exam question. Only after bronchoscopy culture and urine antigen tests was the answer clearly "D. disseminated histoplasmosis." Dr. Spak suspects that bird droppings were the culprit—the patient's work site neighbored a rookery. This detail was apparent only after the fact—but even if bird droppings had been mentioned up front, Dr. Spak admits that it probably would not have prompted azole prophylaxis or major lifestyle changes.

So when the list of environmental, occupational, and dietary exposures that pose potential infectious risk is overwhelmingly long and often unforeseeable, how should we counsel our patients? "Keep it simple," recommends **Nicolas Mueller, MD**, of University Hospital Zurich in Zurich, Switzerland. In ***Forbidden Fruit: Food-Borne Illnesses Following Transplant***, he presented data from a Swiss cohort of 4,405 solid organ recipients. The cumulative incidence of food-borne infection (4% over a median 4.2 years follow-up) was higher than in the general population, but largely unremarkable in its etiology and symptoms (e.g. 88% of cases due to campylobacter, nearly all with typical GI symptoms); "exotic" pathogens were rare. Accordingly, Dr. Mueller focuses patient counseling on the "3 Cs" of "clean" (i.e., separate raw food from cooked food when preparing and storing), "cook" (i.e., avoid raw meat, eggs, seafood, and unpasteurized dairy), and "chill" (i.e., refrigerate food before/after cooking).

When it comes to plants and animals, other presenters echoed this emphasis on basic "common sense" (yet easy to overlook) measures over a laundry list of restrictions. Some useful pearls:

- ***In Cat's in the Cradle: Prevention, Diagnosis, and Treatment of Toxoplasma and Bartonella***, **Tara Veasey, PharmD, BCPS**, of Allegheny General Hospital in Pittsburgh, PA USA advised that cat owners avoid bites and scratches, have someone else change the litter box, and avoid adopting stray cats.
- ***In Old McDonald Had a Farm: Overview of Farm Animal-Related Infectious Risks***, **Elena Seminari, MD**, of Fondazione IRCCS Policlinico San Matteo in Pavia, Italy, reminded us that transplant patients should avoiding handling their dogs shortly after they receive the modified live Bordetella ("kennel cough") vaccine.

- Noting their high prevalence of Salmonella infection (83%), **Orla Morrissey, MD**, of The Alfred Hospital in Melbourne, Australia, advised strongly against reptile ownership among transplant recipients in her talk ***Slither: Creepy Crawly Concerns Carried by Reptiles***. However, she ended on a positive note, highlighting the association of pet ownership with better quality of life measures in transplant recipients.
- Gardeners need not abandon their hobby—simple hand washing and wearing gloves will substantially reduce their risk. But transplant clinicians should be aware of their region's endemic fungal pathogens, as noted by **Maricar Malinis, MD**, of Yale University School of Medicine in New Haven, CT USA, in her talk ***Every Rose Has Its Thorn: Uncommon Fungal Pathogens Associated with Plants and Soil***.

The above "pearls" are hardly exhaustive, and recommendations must be tailored to regional and cultural sensibilities. For example, Dr. Mueller supplements his "3 C's" with specific advice to avoid eating raw wild boar liver (a favored delicacy in Switzerland). **Tomoko Kato, MD, PhD**, of International University of Health and Welfare in Tokyo, Japan, who co-chaired the symposium, acknowledged that "our patients cannot live without sushi…so we just recommend going to a 5-star restaurant." Dr. Spak noted that "in my home country of Texas, patients do what patients do"; accordingly, he finds that keeping restrictions focused and few in number offers the best chance of adherence. While joking in tone, these concluding remarks highlight the importance of seeing patients as "people first" when advising lifestyle restrictions.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 34: Real Options in Pediatric Heart Transplant: Small Infants, HLA Sensitization, and Non-invasive Rejection Screening

The Right Match, at the Right Time

There is no substitute for clinical instincts and experience in the care of advanced heart failure patients. However, even the most seasoned of us would acknowledge that clinical decision-making for such patients has become increasingly complex over time, thanks to a growing array of diagnostic and therapeutic options. When should we list a given patient for transplant? And after listing, should we pursue transplant as soon as possible—or wait for the best possible match? Such questions are particularly tough in the pediatric setting—with its highly heterogenous population following an unpredictable clinical course - and the number of variables involved can overwhelm the mind.

Enter mathematics, decision-analytic modeling, and an expert financial economist. For a math nerd like me, all were unexpected but welcome highlights of Thursday's Symposium 34, **Real Options in Pediatric Heart Transplant: Small Infants, HLA Sensitization, and Non-invasive Rejection Screening**.

Said expert was **Laura Delaney, PhD**, of Kings College London, who presented ***A Tough Calculation: Determining the Optimal Transplant Listing Window for Patients with Fontan Physiology***. She presented a mathematical model adapted from the financial discipline of real options analysis, which weighs the value of waiting to list for transplant against the value of listing now. While mathematically complex, the model features parameters that are familiar to any transplant clinician, namely, the patient's risk factors and their severity (θ), which factor into their rate of clinical decline (μ) and life expectancy without transplant (Lnt). In collaboration with a team from Freeman Hospital (Newcastle upon Tyne, UK), her ongoing work will refine the model using retrospective data before deploying it as a decision-support tool for pediatric cardiologists.

Brian Feingold, MD, MS, of Children's Hospital of Pittsburgh, who presented ***Heart Acceptance Strategies for the Highly Sensitized Candidate: Wait for the Ideal Match or Accept a Positive Crossmatch and Deal with the Consequences***. His analysis applied a decision-analytic Markov model to compare the two strategies (i.e., "wait" or "accept"); the answer to this complex question, as one might expect, is "it depends." Rather than advocate for a specific strategy, he presented his model as a framework to discuss the evolving considerations involved. For example, emerging treatment options for desensitization may tip the balance towards "accept" in many cases, and newer solid phase-based cross-matching assays could allow us to better characterize the risk of "accept."

A growing array of diagnostic options has also "complicated" rejection surveillance post-transplant—with the potential to significantly reduce procedural morbidity and costs. These options were detailed by **Justin Godown, MD**, of Vanderbilt University Medical Center in Nashville, TN USA in his talk ***Don't Go Breaking My Heart: Cell-Free DNA, MRI, and Non-Invasive Imaging as Alternatives to Endomyocardial Biopsy after Pediatric Heart Transplant***.

Other presenters during the session tackled the unique challenges posed by dilated cardiomyopathy (DCM) in small infants. These included **Aamir Jeewa, MD**, of Hospital for Sick Children in Toronto, ON Canada who discussed ***DCM in Small Infants: Medical Heart Failure Management***, and **Emma Simpson, BMBS, MMedSci, MRCPCH**, of Freeman Hospital in Newcastle upon Tyne, UK, who discussed ***DCM in Small Infants: PA Band or LVAD Therapy***.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 28: The Heart Will Go On: Cold, Warm, or Assisted?

Impact of 2018 UNOS Heart Allocation policy change on post-transplant Outcomes: Intermediate Term Analysis

Eugene C. DePasquale, MD, University of Southern California, Los Angeles, CA USA

The UNOS heart allocation policy underwent a change in 2018 with the goal of prioritizing recipients of highest acuity in addition to broader geographic sharing. Therefore, 3 tiers were expanded to 6 tiers to account for this heterogenous population. DePasqale et al sought to assess the intermediate-term impact of this change on post-transplant outcomes in the highest urgency statuses. Around 7,710 heart transplant recipients were identified from UNOS/OPTN registry. These recipients were more than 18 years of age who were listed status 1A (per prior allocation criteria) or status 1-3 (per current policy) and who were transplanted during a 2-year period immediately prior & following the allocation policy change were included.

This cohort was stratified per policy change into Pre-policy (n=3764) and post policy change(n=3946). The survival was censored at 12 months. Multivariate Cox proportional hazard regression analysis was adjusted for age, sex, diabetes, race, ischemic time, dialysis, life support, wait time and HLA mismatch. It was observed that there was more use of devices (especially intra-aortic balloon pumps (IABPs). Fewer patients with durable left ventricular assist devices (LVAD)s were transplanted with the new policy. Status 2 patients per new policy had maximum transplants.

With this analysis, it was concluded that the current heart allocation policy didn't adversely affect post-transplant outcomes in the intermediate analysis with a reduction in waiting list time for the higher acuity statuses. Nevertheless, the demographic is changing with increased use of temporary MCS (notably IABPs) with a reduction in LVAD patients moving forward with transplant. Further analyses are warranted to better understand these shifting demographics.

Influence of the 2018 Heart Allocation System Change on Patients With a Durable Left Ventricular Assist Device (LVAD) as a Bridge to Transplantation: A UNOS Registry Analysis

Nicholas R. Hess, MD, University of Pittsburgh Medical Center, Pittsburgh, PA USA

The United States 2018 heart allocation change has brought differential priority for those on various mechanical circulatory support devices—higher priority for temporary, non-dischargeable devices, and decreased priority for durable, dischargeable devices. On preliminary analysis of durable LVAD bridged patients, waitlist mortality has decreased but possibly lesser chances of transplant, and possibly worse post-transplant survival. Hess et al compared outcomes of waitlisted patients with durable LVAD from the time of waitlisting, before and after the 2018 heart allocation policy change.

This was a retrospective review of the UNOS registry. Adult heart transplant recipients who were bridged with isolated, durable LVAD device at listing were included. The study cohorts were stratified into patients listed from two equal-length time periods before and after 10/18/2018—old policy era and new policy era. The primary outcome included: survival from time of initial

waitlisting, composite outcome waitlist mortality, post-transplant mortality if transplanted, or if removed from waitlist due to being "clinically ill for transplantation." It was observed there was higher incidence of death or delisting under the new policy for patients with durable LVAD. The secondary outcomes were: waitlist mortality and/or de-listing due to clinical decline, cumulative incidence of transplantation, and post-transplant survival of those transplanted.

With this analysis, it was concluded that from the initial timepoint of waitlisting, patients bridged with durable LVAD are more likely to die (with or without transplant) or become too ill for transplantation under the new system. These differences in outcomes were primarily driven by increased post-transplant mortality rather than waitlist mortality.

Impact of Donation After Circulatory Death Heart Transplantation on Waitlist Outcomes and Transplantation Activity

Marian Urban, MD, PhD, University of Nebraska Medical Center, Omaha, NE USA

Urban et al aimed to evaluate the impact of DCD heart transplantation on the waitlist activity and transplantation volumes. Of 48 transplants from January to December 2021, 36 were donations after brain death and 12 were DCD. Of the 12 DCDs, 8 used thoraco-abdominal normothermic regional perfusion (TA-NRP) and 4 were Organ Care System (OCS). When compared to year 2020, median time in days to transplant was decreased.

So, more patients were added/removed from the heart transplantation waiting list. Decrease in median time from the registration on waiting list to transplant. Increase in transplantation rates of low acuity (status 6) candidates was noted. There was no change in pre-transplant/after listing mortality.

Heart Transplant Outcomes with Donation After Cardiac Death: UNOS Registry Analysis

Eugene C. DePasquale, MD, University of Southern California, Los Angeles, CA USA

Limitations in organ donation have led to approaches to expand the existing donor pool. DCD has continued to increase after efforts led by the UK and Australia. Results of the DCD trial utilizing OCS are forthcoming. DePasquale et al sought to describe the United States experience thus far. Adult heart transplant recipients from January 2019 to June 2021 were identified from the UNOS/OPTN registry. The cohort was stratified by donation status: donation after brain death and after cardiac death. The survival was censored at 12 months. Multivariate Cox proportional hazard regression analysis was adjusted for age, sex, diabetes, race, ischemic time, dialysis, life support, wait time, and HLA mismatch. Of 5,153 heart transplant patients, 229 (4.4%) were DCD donors and 4,924 (95.6%) were DBD donors.

It was concluded that short term survival of heart transplant recipients was similar regardless of donor type. (DCD vs DBD) Transplant rates increased in VAD recipients and patients in the lower priority statuses. Use of DCD hearts has the potential to increase the donor pool, however, additional study is warranted as the recipient population expands for this donor type.

Results of Heart Transplants from Donation After Circulatory Death (DCD) Donors Using Thoraco-

Abdominal Normothermic Regional Perfusion (TA-NRP) Compared to Donation After Brain Death (DBD)

Claudia G. Gidea, MD, NYU Langone Medical Center, New York, NY USA

Heart transplantation is the definitive therapy for eligible patients with advanced heart failure. Increasing the donor pool can be achieved by accepting longer ischemic times using Organ Care System technology, CAD, improved LV dysfunction, high risk donors (Hep B/HepC), moderate to severe LVH, and to use DCD. TA-NRP DCD is being increasingly used to expand donor pool and decrease waitlist mortality.

Gidea et al presented their experience of DCD transplant using TA-NRP protocol and compared the results to a cohort concomitantly transplanted from standard DBD donation. Of 95 transplants over 2 years, 15 received TA-NRP DCD heart transplant and 80 recipients received DBD heart transplant. Same standardized protocols for post-transplant management and immunosuppression were followed. Survival was the primary outcome and secondary outcomes included rejection, graft function, coronary allograft vasculopathy and primary graft dysfunction.

Over a 2 year period, 19% more recipients received heart transplantation through TA-NRP DCD donation. Majority of DCD recipients were listed at a lower UNOS status. Short term results suggest that transplant outcomes from DCD TA-NRP are comparable to recipients from DBD. Expanding donor pool by using DCD is a viable option and wide adoption should be considered.

Outcomes of Mechanical Circulatory Support for Severe Primary Graft Dysfunction After DBD vs DCD Heart Transplantation

Vasudev B. Pai, MCh, FRCS, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK

Severe primary graft dysfunction is defined by need for mechanical circulatory support (MCS) after heart transplantation. It is associated with increased short-term mortality but reported outcomes vary widely. Mechanism of PGD may differ for DBD and DCD hearts. Pai et al sought to determine whether there were differences in PGD outcomes between DBD and DCD heart transplants.

This was an observational study of all heart transplants from Feb 2015 to June 2021. Baseline donor and recipient characteristics were recorded. Outcome measures included- duration of MCS, length of ICU stay, length of hospital stay, 90-day mortality. Of 280 transplants, 88 were DCD and 192 were DBD. Of total 33 patients with severe PGD, 12 were DCD and 21 were DBD. It was noted that there was no significant difference in PGD incidence or outcomes between DBD and DCD heart transplant recipients. Though not statistically significant, the potential lower-90 day mortality in the DCD group may suggest that the natural history of PGD after DCD heart transplantation is more favorable compared with PGD seen after DBD heart transplantation. So further studies are warranted.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SESSION 37: New Insights in Patients with Advanced Heart Failure and Cardiogenic Shock

Outcomes of Patients Bridged to Heart Transplantation with ECMO Following the UNOS Allocation Policy Change

Sagar Patel, MD, University of Southern California, Los Angeles, CA USA

Short-term outcomes of patients bridged with ECMO to transplant have improved post 2018 heart allocation policy change. The purpose of this study was to assess long-term outcomes in patients bridged with ECMO to heart transplant. Adult heart transplant recipients with ECMO use preceding heart transplant from 2016 to 2020 were identified from the UNOS registry. This cohort was stratified per policy change into pre-policy (n=36) and post-policy change (n=266). Survival was censored at 12 months. Cox-proportional hazard regression analysis was adjusted for age, sex, diabetes, race, ischemic timer, dialysis, life support, waiting time, and HLA mismatch.

Patel et al concluded that following heart allocation policy changes, heart transplant survival has improved in recipients bridged with ECMO with associated reduction in waitlist time. ECMO utilization has significantly increased since policy implementation. Further studies are warranted to better understand the contributing factors.

UNOS Listing Status-Related Changes in Mechanical Circulatory Support Utilization and Outcomes in Congenital Heart Disease Patients

Alice L. Zhou, BA, MS, Johns Hopkins University School of Medicine, Baltimore, MD USA

Adult congenital heart disease (ACHD) population now outnumbers pediatric congenital heart disease population. Rapidly growing population of ACHD patients requiring heart failure therapies, including MCS. The role of MCS as a bridge to transplant and effects of the 2018 allocation policy revision is unclear. Zhou et al investigated the impact of the new UNOS listing criteria on MCS utilization in ACHD patients and investigated the outcomes in ACHD patients bridged with MCS.

Using SRTR database, they identified 12,723 adult heart transplant recipients, of which 535 had ACHD and 12,188 were non-ACHD. Stratified per allocation policy change, 242 patients received transplant in historical era (7 March 2017 to 17 October 2018), and 293 patients in recent era (18 October 2018 to 30 May 2020).

It was observed that ACHD candidates were younger at listing, had similar times on waitlist, were less likely to have MCS support, and were a higher proportion of females. When stratified per policy change, it was noted that temporary MCS use in ACHD patients increased after policy change. Recent ACHD patients spent less time on waitlist compared to historical ACHD patients with no adverse impact on post-transplant outcomes. Nonetheless, there was no change in durable LVAD utilization in ACHD population after policy change.

Cystatin C vs Creatinine-Based Assessment of Kidney Function in Advanced Heart Failure: Insights from REVIVAL

Alberto Pinsino, MD, Columbia University Medical Center, New York, NY USA

Renal dysfunction is one of the manifestations of advanced heart failure. Patient selection for

advanced therapies relies heavily on appropriate renal function. We are aware that durable VAD are associated with worse outcomes in patients with severe renal dysfunction or hemodialysis. Advanced heart failure (HF) patients with severe renal dysfunction are listed for combined heart-kidney transplants. Serum creatinine, the traditional marker of renal function is affected by muscle mass. Advanced HF is associated with sarcopenia and therefore using serum creatinine as a marker of renal function may lead to overestimation of kidney function in patients with advanced disease.

Cystatin C is a marker of glomerular filtration which is not affected by age, sex, race, or muscle mass, thereby is more accurate and has a higher prognostic value compared to creatinine. Among 400 patients enrolled in Registry Evaluation of Vital Information for VAD in Ambulatory Life (REVIVAL), 270 patients had concomitant CysC & sCr measured. It was observed that eGFRcysC reclassified 57% of patients. Cystatin C improved risk stratification for CV outcomes, mortality, and hyperkalemia. It also strengthens the association between kidney function and a composite of death, urgent heart transplant, or durable LVAD. Lower handgrip strength, reduced functional capacity, and frailty are associated with a widened difference between eGFRCysC and eGFRsCr. Further studies are warranted to determine accuracy and prognostic implications of different estimates of kidney function in advanced HF patients.

Circulating Proteomic Analysis Identifies Reduced Inflammation After Initiation of Hemodynamic Support with Either Veno-Arterial Extracorporeal Membrane Oxygenation or Impella in Patients with Cardiogenic Shock

Nikolaos Diakos, MD, PhD, Tufts Medical Center, Boston, MA USA

The use of MCS for CS is growing, but the mortality remains high. There are various hemodynamic and metabolic variables, but we lack the molecular data. Along with the clinical, hemodynamic, and echocardiographic data, Diakos et al collected serum of 11 patients presenting with CS before and 72 hours after MCS (Impella & ECMO). Aptamer based proteomics were used, that is single stranded DNA aptamers that can measure >1,300 proteins using 75microLitre of human sample with high reproducibility. It can also capture low abundance proteins with high sensitivity and specificity.

It was observed that different proteins were upregulated and downregulated with different MCS. Impella support reduced adhesion and migration of monocytes, while ECMO inhibited monocyte activation. Both ECMO & Impella support in patients with refractory CS are associated with reduction in inflammation. Both appear to affect similar biologic functions while acting through different cellular signaling pathways. Circulating proteins may serve as a novel targets of therapy or novel biomarkers to tailor MCS device use and improve patient outcomes.

Five-Year Outcome of Hybrid Transcatheter and Minimally Invasive Left Ventricular (LV) Reconstruction for Ischemic Heart Failure

Romy RMJJ Hegeman, MD, St. Antonius Hospital, Nieuwegein, Netherlands

Left ventricular remodeling after MI can cause LV dilation, shape alteration and heart failure with reduced ejection fraction (HFrEF). Surgical ventricular reconstruction has been proven to be effective in restoring LV shape and size. Hybrid LV reconstruction involves no sternotomy, no cardioplegic arrest, no ventriculotomy.

Hegeman et al presented a single center retrospective analysis of 30 patients from 2016-2021. They included symptomatic HF patients with NYHA class > 2, LVEF < 40% after acute myocardial infarction, with dilated left ventricle with akinetic or dyskinetic scar, and > 50% trans-murality of scar tissue. Operative technique based on micro-anchoring technology. The scar-based reconstruction technique includes Hybrid RV-LV for anteroseptal scar or external LV-LV double purse string for apical aneurysm).

They observed improvement in left ventricular end diastolic and end systolic volume index, LVEF, & NYHA class. 5 year survival was 86.7%. They concluded that in selected patients, hybrid left ventricular reconstruction for ischemic HFrEF is a safe off-pump alternative, associated with significant improvement in left ventricular performance and achieves a significant long term symptomatic improvement with excellent 5-year survival.

Clonal Hematopoiesis Common Within the Advanced Heart Failure (HF) Population and is Associated With Improved Heart Transplant Outcomes

Lakshmi Ravali Gokanapudy Hahn, MD, Washington University in St Louis, St Louis, MO USA

Clonal hematopoiesis (CH) is a phenomenon found in healthy older individuals as well as in children and younger adults with chronic diseases. It occurs when hematopoietic progenitor cells acquire mutations that confer a fitness advantage relative to background population. Mutant progenitor cells subsequently expand giving rise to substantial portion of peripheral blood cells. Certain CH mutations are associated with cardiovascular mortality. Mutations in TET2 and DNMT3A have been shown to have the strongest association with cardiovascular mortality and are prevalent in HF populations.

Hahn et al sought to measure the prevalence of CH across age in advanced HF population and delineate the impact of CH on heart transplant outcomes. They established pediatric and adult advanced HF registries with comprehensive clinical phenotyping. Blood samples of 40 pediatric and 120 adult advanced HF patients were processed for DNA sequencing, single cell RNA sequencing, flow cytometry and functional studies. CH was measured using a custom next generation sequencing pipeline with 500x-4000x coverage of 76 genes. They detected CH in 20% of patients (25% adults and 5.5% pediatric).

As expected, CH was more prevalent in older age groups with some patients having multiple mutations. Among patients who underwent heart transplant, the composite outcome of CV mortality, grade 2R cellular rejection, antibody mediated rejection, and primary graft dysfunction was significantly reduced in individuals with CH. Therefore, it was noted that CH is present across a spectrum of age in the advanced heart failure population and is associated with improved clinical outcomes post heart transplantation. Future studies are required to externally replicate these findings and uncover underlying mechanisms.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SESSION 42: Donor Utilization and Heart Allocation System in the Current Era: For Better or For Worse

This **oral abstract session** included studies focused on waitlist survival and transplant outcomes in association with expanded donor pool and revised heart allocation system.

Donor Utilization in the Recent Era: Effect of Sex, Drugs and Increased Risk **David A. Baran, MD**, Sentara Heart Hospital, Norfolk, VA USA

The investigators sought to examine whether the increase in organ donors and heart transplants has resulted in an increase in the percentage of offered donors utilized as well as the effects of increased risk status and drug use on donor acceptance. They queried the UNOS registry for all transplants between 1 January, 2007 and 31 December, 2017 and compared donor hearts utilized for transplant with those that were rejected. The groups were compared for demographics, hepatitis C serology (HCV), Public Health Service Increased Risk (PHSIR) designation, as well as history of drug use and positive toxicology. They calculated a UNOS Tox Score (UTS), which was the sum of positive historical drug use variables in the UNOS registry, and a Measured Tox Score (MTS), which was the sum of positive donor toxicology categories. Strongest predictors of donor non-use were older donor age, female gender, blood type, HCV, and left ventricular hypertrophy. HCV heart utilization increased minimally from 1% to 3.5% over the study duration.

Heart Transplant Outcomes by Donor HCV NAT Status: Intermediate Analysis

Meghana Yanamandra, MD, MSc, University of Southern California, Los Angeles, CA USA

The investigators sought to compare post-heart transplant outcomes of patients who received hearts from either HCV NAT positive or negative donors. They stratified recipients from the UNOS registry by donor HCV NAT status and compared the groups using standard statistical methods. They also performed adjusted and non-adjusted survival analyses. Of 18,828 recipients, 849 and 17,979 received HCV NAT positive (HCV+) and HCV NAT negative (HCV-) donors, respectively. HCV+ recipients were older, male, Caucasian, with a high incidence of pre-transplant cardiac surgery, life support use, had older donors, longer ischemic times, and worse renal function. There were no differences in waitlist times, all-cause, cardiovascular, or non-cardiovascular mortality between the groups. The authors concluded that utilization of HCV NAT + donors was a safe and effective way to expand the donor pool.

The Regional Impact of the 2018 United States Heart Allocation System Change

Amit Iyengar, MD, MS, University of Pennsylvania, Philadelphia, PA USA

The investigators sought to examine changes in waitlist/transplant outcomes across the United States from the policy change, stratified by geographic region. They performed a retrospective analysis of all patients listed for heart transplant between January 2016 and July 2021 and grouped them by pre- and post-new UNOS allocation system era as well as by OPTN region. They performed competing risk regression for waitlist death, transplant, or delisting with their model censored at 3 years. Key findings were: 1) IABP and ECMO usage amongst waitlist patients increased in Era 2 across all regions; 2) Waitlist mortality improved in all regions except the South (Region 3 and 4) and Northwest (Regions 6-8, $p>0.10$); 3) Odds of transplantation increased in all

regions to varying degrees; 4) In those transplanted, organ procurement distance increased by >80 mi in all regions except Region 1 (Northeast), with increases in ischemic time in all regions except Region 1 (p=0.358).

Adaptive Changes and Estimated Long-Term Survival After Updated Donor Heart Allocation Policy: A UNOS Database Analysis

Takuma Miyamoto, MD, PhD, Thomas Jefferson University Hospital, Philadelphia, PA USA

The investigators sought to characterize adaptive changes to the revised UNOS heart allocation policy, and estimate long-term survival changes on the waitlist and after heart transplantation (HTx). This was also an analysis of the UNOS database. Patients transplanted after implementation of new allocation policy as well as from the preceding 5 years were analyzed. Sub-analyses were performed for extracorporeal membranous oxygenator (ECMO), durable left ventricular assist device (LVAD), intra-aortic balloon pump (IABP), microaxial support (Impella), and no mechanical support (non-MCS). For survival analysis, they used a parametric distribution model and extrapolated based on this. The authors found that since the implementation of the new allocation policy more patients were listed on ECMO and Impella while fewer patients underwent LVAD implant or were transplanted with non-MCS. Most transplants were also performed off ECMO ,IABP, Impella, and less off LVAD and non-MCS. Overall, waitlist survival improved in contrast to worsened post-HTx survival.

Improved Survival Benefit After Implementation of the New Heart Allocation System Amongst Highest Priority Candidates Undergoing Heart Transplant

Stratton Tolmie, BA, University of Chicago, Chicago, IL USA

The authors sought to examine if the highest priority candidates under the new UNOS allocation system had higher survival benefit from transplantation compared with the highest priority candidates in the prior policy. They collected Scientific Registry of Transplant Recipients data on all adult heart transplant candidates listed in seasonally matched pre (2016-2017) and post-new policy (2018-2019) cohorts. Using a cox-proportional hazards model they estimated 1-year survival curves with and without transplantation using these hazard ratios and a non-parametric Nelson-Aalen estimate of the baseline hazard. They found that status 1 recipients under the new policy experience greater survival benefit from transplantation than Status 1A recipients in the previous policy. Their conclusion was that the policy change has resulted in more medically urgent patients being listed as highest priority status, without significantly compromising post-transplant survival.

Waitlist Outcomes in Candidates with Hypertrophic or Restrictive Cardiomyopathy and Congenital Heart Disease After Implementation of the New French Heart Allocation System

Guillaume Coutance, MD, Hôpitaux Universitaires Pitié Salpêtrière, Paris, France

The French heart allocation system launched on January 2018 is based on a national score ranking all candidates. The authors sought to examine the waitlist outcomes in candidates with hypertrophic (HCM) or restrictive (RCM) cardiomyopathy and congenital heart disease (CHD) after implementation of the current French heart allocation system. Twelve-month cumulative incidence of transplantation and waitlist mortality or delisting for worsening medical condition was compared among patients with HCM (n=92), RCM (n=55) or CHD (n=67) and those with other

transplant indication (n=1531). They found that the new French heart allocation system offers equitable access to transplantation throughout all transplant indications.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

MINI ORAL 07: What's the Score? Modeling Outcomes in Heart Transplantation

This **mini oral abstract session** included research focused on exploring factors associated with heart transplant outcomes as well as their predictive value.

Outcomes of Heart Re-Transplantation with Combined Kidney Transplant

Qiudong Chen, MD, Smidt Heart Institute at Cedars-Sinai, Los Angeles, CA USA
This study evaluated outcomes of those patients undergoing redo heart transplantation (HTx) who also required a simultaneous kidney transplant. Twenty-two patients undergoing redo HTx with kidney transplantation were compared to 55 patients undergoing redo HTx alone. The authors found that patients undergoing redo HTx with combined kidney transplant had higher incidence of post-operative dialysis and longer hospital length of stay. However, one year survival, non-fatal MACE, and freedom from CAV and any rejection, were similar between the groups.

Induction Therapy in Heart Transplantation: A Systematic Review and Network Meta-Analysis

Lakshmi Kugathasan, PhD, Toronto General Hospital, Toronto, ON Canada
The investigators performed a systematic review and network meta-analysis (NMA) to examine the safety and efficacy of post-heart transplant (HTx) immunosuppressive induction therapy (IT) and evaluated outcomes at 1-year post HTx. Seven randomized controlled trials (RCTs) and three observational studies with adjusted analyses were included. Results of the NMA suggested that the use of IT did not confer mortality benefit at one year after heart transplantation. Risk of rejection, however, appeared to be reduced by ATG compared to no IT or basiliximab, although this was not statistically significant when only evaluating data from RCTs, likely due to the small number of events and insufficient power.

Cross-Organ Survival in Patients Undergoing Multi-Organ Cardiac Transplantation

Umar A. Siddiqi, University of Chicago Medicine, Chicago, IL USA,br /> Using the UNOS database, the investigators compared survival outcomes between three of the most prevalent multi-organ procedures: heart-lung, heart-kidney, and heart-liver transplantation. A total of 80,058 patients were included in this study. Heart-lung transplant recipients experienced significantly worse survival compared to those receiving heart-kidney, heart-liver, or heart-only transplants (p <0.0001). On the other hand, heart-liver and heart-kidney transplants displayed improved rates of survival relative to heart-only transplants.

Predicting One Year Mortality Using Machine Learning After Pediatric Heart Transplantation: Analysis of the United Network of Organ Sharing (UNOS) Database

Awais Ashfaq, MD, Johns Hopkins All Children's Hospital, St. Petersburg, FL USA
The investigators used machine learning algorithms to help select clinically relevant identifiers that could predict one-year mortality after pediatric heart transplant (HTx). UNOS Database for years 2010-2020 was used. Pediatric patients receiving their first transplant were included (N=4,150). Their key findings included: 1) risk factors for mortality one year post HTx varied based on the pre HTx diagnosis; 2) machine learning modelling effectively predicted the risk of mortality in patients listed for pediatric HTx.

Sex Differences in Clinical Characteristics and Outcomes in Patients Undergoing Heart Transplantation

Christoph Kondziella, MD, University Heart and Vascular Center, Hamburg, Germany

The investigators examined sex differences in heart transplant (HTx) listing and post HTX outcomes. OPTN data was used and 49,200 HTx recipients, including 24.6% females, were assessed. Multivariable Cox regression was used to identify predictors for sex-specific differences in all-cause mortality, graft failure, cardiac allograft vasculopathy (CAV), and malignancy. Pre-HTx, ischemic cardiomyopathy was common in males while dilated cardiomyopathy was common in females. At HTx, males were older than females. Sex differences in CAV and malignancy (more common in males than females) were seen in both univariate and multivariate analyses.

The New UNOS Heart Transplant Statuses: Upgrades, Transplant Rate and Survival

Jaimin R. Trivedi, MBBS, MPH, FACC, University of Louisville, Louisville, KY USA

The investigators sought to evaluate the distribution of patients listed and transplanted based on new UNOS priority status and their waitlist and post-transplant outcome. Their key findings included:

1. Over 60% of patients under new UNOS policy were listed as Status 4, 5 or 6 whereas more than 50% of patients transplanted are Status 1 and 2;
2. Over 33% patients from status 4 and 6 were upgraded to higher statuses before transplant;
3. Status 1 and 2 patients had higher rate of transplant within 30 days of listing;
4. Status 1 patients had worst post-transplant survival.

When asked, the authors added that a significant proportion of patients were transplanted with an exception status, although this data was not included in their presentation.

Instrumental Variable Estimation of the Effect of Increased Donor Heart Ischemic Time on Post-Transplant Survival

Gege Ran, BA, University of Chicago Pritzker School of Medicine, Chicago, IL USA

Under the new UNOS allocation policy, transplant programs are more likely to accept organs with longer ischemic time for more urgent candidates with higher risks of mortality post-transplant. The investigators assessed the isolated impact of ischemic time on post-transplant survival. An instrumental variable (IV) model was constructed to address bias from unobserved confounders in the relationship between the receipt of ischemic organ and mortality post-transplant, while controlling for observed candidate and donor characteristics.

In heart transplant recipients who were "randomized" a graft with > 4 hours of ischemic time by changes in heart allocation policy, no effect on survival within the first-year of transplantation was noted.

Mitigation of Post-Transplant Mortality Risk by Appropriate Donor-to-Recipient Size Matching Using Predicted Heart Mass

Ran Tao, MD, University of Wisconsin Hospital and Clinics, Madison, WI USA

Pretransplant obesity continues to be a risk factor for death post-transplant. The authors investigated whether size matching of donor-to-recipient using predicted heart mass (PHM) can

mitigate some of the risk associated with pretransplant obesity. Using UNOS database, the authors created 6 categories of recipients based on their BMI (underweight, normal, overweight, obese, morbidly obese, severely obese). The found that appropriate size matching for donor hearts by PHM could lower the risk of death compared to under-matching specifically among normal and overweight recipients.

Models with Weight and Height Better Predict Mortality versus BMI After Adult Heart Transplantation

William L Baker, PharmD, University of Connecticut School of Pharmacy, Storrs Mansfield, CT USA

The investigators used SRTR database, applied a flexible weight*height interaction effect, and examined whether this improved prediction of mortality after heart transplant compared with BMI. They found that using weight and height as independent variables improved performance of models predicting mortality after HT compared with BMI.

Donor and Recipient Cytokine Profiles Predict Acute Rejection and Graft-Related Survival After Heart Transplantation

Emil Holmström, MD, University of Helsinki, Helsinki, Finland

The investigators examined donor and recipient plasma and intragraft cytokine profiles and searched for predictive markers for unfavorable outcomes. Their key findings included: 1) severe PGD was associated with a proinflammatory cytokine profile in the recipients; 2) a high immunological risk score based on donor plasma cytokines predicted acute rejection, while recipient cytokine-based risk scores predicted graft-related 1-year mortality.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

MINI ORAL 11: Moving in the Right Direction: A Quick Jaunt Through Pediatric Heart Failure and Transplant

Pediatric Heart-Lung Transplantation Through the Decades: A Single-Center Analysis

Horacio G. Carvajal, MD, Washington University in St. Louis, St. Louis, MO USA

Pediatric heart-lung transplant is getting uncommon, and its indications have changed over time. Cavajal et al evaluated 22 patients who underwent heart-lung transplants from 1993 to 2021 and stratified them by decade. They evaluated indications, post-operative outcomes and survival and observed that 10-year survival was similar in all decades. The complexity of cases referred for HLT has increased while chronic rejection rates have decreased.

Iron Deficiency in Pediatric Dilated Cardiomyopathy is Associated with Clinical, Biochemical and Hematological Markers of Severe Disease and Adverse Outcomes

Jack C. Luxford, BA, MD, The Children's Hospital at Westmead, Sydney, Australia

Iron deficiency (ID) is an established prognostic marker in adult heart failure, and treatment improves morbidity and mortality in acute and chronic HF. Luxford et al sought to establish prevalence of ID in a hospital cohort of dilated cardiomyopathy (DCM) and identify associations between ID and markers of DCM severity.

This was a single center retrospective chart review of all children (0-18 yrs) with DCM and full set of iron studies between 2010-2021. They observed that ID is highly prevalent in pediatric DCM (62%), but iron studies are undermeasured in this population with only 1/3 of patients with DCM in this time period had iron studies drawn. ID in DCM is associated with an increased risk of the composite adverse outcomes. Those who are iron deficient tend to be anemic, with higher NT-proBNP, lower albumin and increased incidence of inotrope/respiratory support requirement. Lower iron and transferrin saturation levels are correlated with LV dysfunction.

A Novel Approach to Pediatric Heart Failure Quality Improvement Within the ACTION Network

Justin Godown, MD, Vanderbilt University Medical Center, Nashville, TN USA

Children with HF are at high risk for mortality, prolonged length of hospitalizations, and readmissions with high resource utilization. There is wide practice variation with little standardization and there is opportunity to impact clinical care through quality improvement efforts. There are many multicenter collaborations routinely used to advance care in pediatric heart disease. Furthermore, pediatric HF is a very heterogenous population, comprising complex congenital heart disease, cardiomyopathies, metabolic heart disease, myocarditis, and acquired cardiac disease.

Godown et al identified children hospitalized with acute decompensated HF across 6 centers that participate in both ACTION network and Pediatric Health Information system (PHIS) between June 2019 to July 2020. A total of 227 patients with 309 hospitalizations were included in this pilot study. This strategy through central data abstraction supplemented with administrative data which includes outcome measures (mortality, LoS, ECMO use), process measures (medication use at discharge and discharge checklist) and resource utilization (overall cost, echo and cardiac MRI

utilization) is a reliable and efficient data collection and provides a valuable platform for QI efforts.

Contemporary Care and Outcomes of Critically Ill Children with Myocarditis

David M. Peng, MD, University of Michigan, Ann Arbor, MI USA

Peng et al utilized the pediatric cardiac critical care consortium (PC4) registry to describe the contemporary characteristics, management, and outcomes of critically ill children diagnosed with myocarditis in the cardiac ICU. They included 847 patients admitted to ICU and diagnosed with myocarditis by the treating clinician from August 2014 to June 2020. They noted that myocarditis often required intensive supportive care such as vasoactive infusions, mechanical ventilation, and MCS and carries added risk of cardiac arrest, renal failure, and death. Small patient size, severe renal dysfunction at presentation, need for mechanical ventilation, and MCS were independently associated with mortality. ECMP remains the most used form of MCS in myocarditis. In critically ill patients with myocarditis in PC4 registry, higher ECMO, eCPR, and overall transplant-free survival to discharge compared with earlier reports suggesting that supportive care has improved over time.

Cardiogenic Shock in Children: Clinical Presentation and Outcomes

Kriti Puri, MBBS, Texas Children's Hospital, Baylor College of Medicine, Houston, TX USA

Puri et al did a retrospective single center analysis of patients hospitalized with acutely decompensated HF at a referral children's hospital from January 2004 to December 2018. They sought to evaluate hospital mortality in patients with CS at presentation as a primary outcome using multivariable analysis by binary logistic regression using generalized estimating equations. They noted that 26% of children hospitalized with acutely decompensated HF presented in CS. It was independently associated with hospital mortality in children with mortality rate around 25%. These patients suffered greater morbidity, including mechanical ventilation, MCS and renal replacement therapy. Risk stratification of pediatric CS should be considered to optimize early use of rescue therapies and improve survival to recovery or heart transplantation.

TPN-Dependence and Paralytics Predict Post-Heart Transplant Mortality in Infants

Jason W. Greenberg, MD, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH USA

Infants represent a unique subgroup within the field of pediatric heart transplantation with greater organ dysfunction, ventilatory and ECMO requirements, a greater burden of congenital heart disease (CHD), and inferior one-year survival. Known predictors of post-transplant mortality in infants are presence of CHD, renal & hepatic dysfunction, ECMO requirement, and mechanical ventilation, while several other important risk factors remain understudied.

Greenberg et al aimed to characterize the effects of pre-transplant TPN-dependence and paralytics—with and without mechanical ventilation—on post-transplant outcomes. This was a retrospective, multi-institutional observational study from UNOS and Pediatric Health Information System (PHIS) infants who received heart transplant in the United States between 2003 and 2020. They noted that infants who require pre-transplant mechanical ventilation, paralytics, or TPN dependence experienced inferior early outcomes and resource utilization. They are at

independent higher risk for one-year mortality. Knowledge of these modifiable risk factors can assist with risk stratification and inform expectations with pre-transplant optimization seeking to correct these modifiable risk factors prior to transplantation. Future studies are warranted to examine impact of other support modalities.

Repeat Pediatric Heart Transplantation in the United States: United Network for Organ Sharing Database Analysis

Georgina Rowe, MD, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA USA

Pediatric heart transplant mortality exceeds 25% and an additional 7% are retransplanted at 10 years. CHD is associated with worse survival following pediatric heart transplant. Rowe et al identified UNOS database to identify all children undergoing isolated heart transplant from 2000 to 2021. There were 7,678 primary transplants and 441 repeat transplants. The repeat transplants were divided into early or late sub-groups according to whether retransplant occurred within 1 year of primary procedure. Primary outcome was all cause mortality with a median follow up of 5 years. It was noted that repeat pediatric transplantation is associated with worse long-term survival compared to primary transplantation, this survival difference is particularly evident among patients with cardiomyopathy and those undergoing early repeat transplantation.

Predicted Heart Mass is Not the Optimal Metric for Size Matching in Pediatric Heart Transplantation

Zhaozhi Li, University of Chicago, Chicago, IL USA

Donor recipient size match is traditionally assessed by body weight. However, some studies suggest that hearts mismatched by weight have similar outcomes with properly matched hearts. Predicted heart mass (PHM) may be a more effective metric for donor-recipient size matching. Recent studies demonstrated that PHM was predictive of survival and primary graft dysfunction in an adult cohort. However, the predictive value of PHM in a pediatric population remains unknown. Li et al sought to assess the ability of PHM donor to recipient ratio to predict 1 year patient and graft survival after heart transplant (HT) in pediatric patients. They retrospectively reviewed 5431 pediatric patients undergoing initial isolated HT from 1/2000 to 12/2020 from the UNOS database. They noted that donor to recipient PHM ratio mismatch is not associated with reduced 1-year patient or graft survival in pediatric HT recipients. The question of the importance of donor-recipient size mismatch persists, particularly in a pediatric population as it is conventionally believed that pediatric hearts have greater adaptability.

Sudden Cardiac Arrest After Pediatric Heart Transplantation

Lynsey M. Barkoff, CPNP, Lucile Packard Children's Hospital, Palo Alto, CA USA

Despite many advancements in the field of pediatric heart transplantation (HT) over last 30 years, long-term survival is still not adequate. Sudden cardiac arrest (SCA) continues to be an important cause of mortality but is understudied. Barkoff et al analyzed the frequency, outcomes and rsk factors of SCA at their center using retrospective data from 1/1/2009 to 9/1/2021. They noted that SCA occurred in 6% of their patients. It is fatal and occurred relatively early after pediatric HT (within 3 years). It often occurs outside the intensive care units. Transplant recipients with younger donors, rejection history, or of black race were at increased risk for SCA. Intracardiac cardioverters defibrillators and pacemakers offer limited protection in this population.

Long Term Survivors Following Pediatric Heart Transplantation: A PHTS Database Analysis

Emily Anne Hayes, MD, Nationwide Children's Hospital, Columbus, OH USA

In a retrospective cohort study, Hayes et al evaluated patients transplanted between 1993 to 2010. Overall survival at 15 years was 53.3%. They noted increased number of long-term survivors. Aggressive coronary allograft vasculopathy and rejection were risk factors for mortality. Of modifiable risk factors, cessation of steroids may provide long-term survival benefit. Further studies on social determinants of health in this population are warranted.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SUNRISE 07: DCD Heart Transplantation and Ex Vivo Repair: Gift Box or Pandora's Box?

Technical Aspects of DCD Heart Transplantation

Stephen Large, MB, MA, MS, FRCS, FRCS (CTH), Papworth Hospital, Cambridge, UK

The speaker discussed the technical aspects of DCD heart transplantation. Ethically, the transplant team will not be a part of the recognition of futile life support therapy nor of confirmation of death following withdrawal of life support. 75% of cases progress to cardio-pulmonary arrest after withdrawal of futile life support. The insult to donor heart by this process is ischemic. We probably have 30 minutes of normothermic anoxia before myocyte loss. The timeline of events involves withdrawal of life support, onset of functional warm ischemic time (FWIT), onset of death and confirmation of death 5 minutes after, 15 minutes of ischemic asystolic period, reperfusion with limited circuit, reanimation, to normothermic regional perfusion (NRP) DCD heart working.

Reperfusion of the ischemic DCD heart in ex situ reperfusion involves direct procurement and preservation using (i) Transmedics Organ care system (OCS) primed with donor blood after white cell filtration and free radical scavengers; donor heart cooled with cardioplegia @ 4C; reperfusion in non-working mode for 60 minutes. The *in situ* reperfusion used TA-NRP or thoracoabdominal that excluded aortic arch vessel and illiacs so isolated thoracoabdominal perfusion; perfuses heart & lungs and all abdominal viscera; did functional assessment after required DCD ischemia, and progress to removal and transportation on ice.

Problems of process include the assessment of donor heart function and selective perfusion. Problem of the device involves the perfusate, weight of the device and limited mobility, and the assessment of function/transplantability of the donor heart. Results of reperfusion of DCD heart revealed an increase in transplant activity by up to 50% (2021) probably settling at 40%. The outcomes in terms of hospital stay, 90-day, 1-, 5-, and 8-year survival was similar compared to DBD. The ischemic times as FWIT (ends with cardioplegia) and then functional cold ischemic time to a total of functional total ischemic time of order 15-30 mins. The average ischemic time in TA-NRP 16.2 minutes: no donor heart related deaths (international cohort) noted in 8 years, and 15% requirement for MCS early after surgery and 15% requirement for treated acute rejection of direct procurement protocol (DPP) and DBD. The DCD donor heart selection for transplantation rests on the pre-withdrawal of futile supportive therapy echocardiogram demonstrating acceptable cardiac function.

Comparison of Outcomes after DCD and DBD Heart Transplantation

Sarah Scheuer, MD, PhD, St. Vincent's Hospital, Sydney NSW Australia

Prior to the recognition and legislation of brain stem death, all heart transplants were performed from DCD donors. The speaker reviewed historical and modern outcomes of DCD.

Historical outcomes:

Pediatric: Denver series—Boucek et al in 2008 reported three successful infant DCD heart

transplants, all co-located and with brief standoff periods. Rajab et al in 2020 reported 10-year outcomes with 66% survival with normal graft function. In an ISHLT retrospective analysis, Kleinmahon et al 2017 reported 21 heart transplants between 2005 and 2014, with 61% survival at one year vs 91% for matched DBD with 24% of DCD recipients dying from primary graft failure. 55% of recipients were on VA ECMO pre-operatively compared with 9% DBD recipients.

Modern Outcomes:
Sydney series: Chew et al reported two-year outcomes in 2018, where 23 DCD transplants had 95% one-year survival vs 88% in DBD. No significant difference in rejection rates was noted. There were relatively high rates of severe PGD, with 35% early VA ECMO support. The Sydney series reported their current outcomes in this meeting. In 74 DCD heart transplants: 94% one-year survival and 88% five-year survival, compared to 87% and 81% one- and five-year survival with DBD. Significant reduction in severe PGD, 16% VA ECMO requirement overall was 8% compared to 35% published from the original cohort. Most significant predictor of sPGD was aWIT greater than 15 minutes.

Papworth series since 2015 (with mix of DPP and TA-NRP): Messer et al reported five-year outcome data on a retrospective, matched, observational cohort study comparing outcomes of DCD to DBD, and noted one-year survival 91% vs 89% for DCD and DBD respectively. They also noted that requirement for post-transplant MCS was 34% for DCD, vs 23% for DBD. VA ECMO or temporary MCS was used in 19% DCD, vs 9% for DBD. Amongst these, 57 were DPP, 22 TA-NRP, survival was 100% for TA-NRP group with no difference in requirement for post-op MCS.

USA experience, Vanderbilt series: Hoffman et al presented 15 TA-NRP/CS DCD transplants, donor age was < 35 yrs, anticipated transport time < 240 mins. Average ischemic was 183 +/- 31 min; no sPGD-LV with 100% 30-day survival. NYU series: Smith et al presented 8 DCD TA-NRP/CS heart transplants, with relocation of donor to recipient hospital. Cold preservation following TA-NRP assessment. 30-day survival was 100% with only one case (13%) requiring VA ECMO.

Provisional results of OCS DCD Heart Trial were announced in November 2021. It was a multicenter RCT with 3:1 randomization of recipients to DBD with CS or DCD with DPP. Six-month survival was 95% for DCD vs 89% for DBD.

There is a growing body of evidence that DCD heart transplantation is as effective as DBD with comparable short-term survival. Higher rates of sPGD were reported in some programs, but appears to be reducing with increasing experience. Rapid uptake of DCD heart transplant throughout USA over last two years leading to significant increases in transplant volume. Future directions include optimizing ex situ management, ex situ regeneration of organs, novel biomarkers for assessment of organs during ex situ perfusion, and more studies comparing outcomes of DPP vs TA-NRP.

Heart in a Box as a Platform for Molecular and Cellular Research
Niels van der Kaaij, MD, PhD, UMC Utrecht, Utrecht, Netherlands
Kaaj et al discussed ex situ treatment of the heart in a bioreactor and described this as a gift box.

We are aware that there is a major shortage of organs. In Dutch experience, only a minority of patients with advanced heart failure get accepted for the transplant waiting list. On top of it, 19% of these are removed from the list due to mortality or clinical worsening. DCD transplants are increasing in number. In comparison to UK or Austria where DBD: DCD is 50:50 or 92:8 respectively, this ratio is 40:60 in the Netherlands.

From 21 March to present, 35 donors were attended of which 29 DCD hearts were transplanted (the rest failed to arrest or were declined). Survival after one year was 96.6% with 3.4% mortality. Ex situ heart perfusion to prevent or minimize additional injury by ischemia and reperfusion injury. Advanced HF treatment options include transplantation, LVAD, or a total artificial heart. Both LVAD and artificial heart have high risk of complications like driveline infection, stroke, technical failure, pump thrombosis, and lack of right ventricular support in LVAD. The ultimate goal is to treat a patient with HF by preserving, regenerating, and possibly testing the heart in a bioreactor without any side effects.

The advantages of this heart would be no immunosuppression requirements, no organ donation requirement, no VAD related complications, and less therapeutic side effects. On our way, we might be able to discover newer technologies that will be applicable for in situ treatment. Over requirements for this cardiovascular moonshot would be bioreactors with perfusion approach for heart survival; extra-corporeal circulatory life support system for patient survival; regeneration would include improvement in cardiac contractility, valvular disease and atherosclerosis, conduction system; and testing would include functional assessment before re-implantation.

Many cardiovascular functions are regulated by the circadian clock. The amount of acute adverse cardiovascular events shows circadian rhythmicity. To study a circadian rhythm, one needs multiple biopsies during 24-48 hrs. Heart box gives the opportunity to study the peripheral heart clock in an isolated organ. Thus, this heart box can be used for DCD heart preservation, modulation & testing. It also gives optimal access for research and sequential analysis and can be used to apply treatment strategies for ex-situ regeneration and repair.

Tips and tricks to set up a DCD Heart Transplantation Program
Kumud Dhital, BM.BCh, FRCS-CTh, FRACS, PhD, Sparsh Hospital, Bangalore, India
There is a big unmet need when it comes to heart transplantation. Using DCD can increase the donor pool. The strategy for this DCD program included laboratory validation, unutilized human hearts, marginal DBD hearts, and DCD hearts.

Recipient protective donor would be Maastricht Category III donors, with Age < 40 years, no history of any cardiac disease, no prior cardiac surgery or trauma, requiring low dose inotropy/vasopressor with stable hemodynamics (MAP > 60, CVP< 10 mm Hg), maximum warm ischemic time ~ 30 minutes, pre-donation echo, and antemortem heparin. If donor age < 40 years, then the process is 30 minutes withdrawal to cardioplegia. But if donor age < 55 years, we opt for 30 minutes SBP < 90 mm Hg to cardioplegia.

The Law and in situ reanimation: In Australia, death definition is irreversible cessation of all

functions of the brain of the person or irreversible cessation of the circulation of blood in the body of the person. An analysis of heart donation after circulatory determination of death showed that only death criteria based on permanency are compatible with the DDR under two conditions:

1. a minimum standoff period of 5 minutes to ensure that autoresuscitation is impossible & all brain functions are lost
2. no medical intervention is undertaken that might resume bodily or brain circulation

The Australia heart DCD program respects the DDR when the criteria of death is permanency. A proposed method of organ retrieval that uses what has been called normothermic regional perfusion (NRP) with controlled donation after circulatory determination of death (cDCD)- referred to as “NRP-cDCD”.

There is an urgent need to relax rules and define marginality. There is an overwhelming need for multidisciplinary teamwork in this regard. To evolve this practice of DCD, we need the following measures:

- To improve DCD legislation, standardizing DCD certification. Antemortem interventions, location of WLST.
- Increasing tolerance to WIT, bank blood vs donor blood collection, better markers of cerebral & myocardial injury, more metrics of physiological assessment, portable or static (+/- cold perfusion) + functional evaluation
- Surgical repair, gene therapy, immunomodulation

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SUNRISE 08: What's New? Updates to the ISHLT Guidelines for the Care of Heart Transplant Recipients

This **sunrise session** presented the proposed updates to the 2010 ISHLT heart transplant guidelines.

Overview of the Guideline Process
Angela W. Velleca, RN, BSN, MHDS, CCTC, Cedars-Sinai Heart Institute, Los Angeles, CA USA
This presentation introduced the members of the writing group and chairs and co-chairs of task forces 1 through 4. Members of the writing group were 54% North American; 56% were female, and 18% were junior faculty. A 75% agreement was needed to achieve recommendation consensus. Class of recommendation and level of evidence was applied using the ACC/AHA recommendation system from 2015. The COVID-19 pandemic prolonged the guideline update writing process, and resulted in inclusion of topics addressing emerging pathogens and pandemic considerations for heart transplant recipients. The documented has completed an expert review and review by the Advanced Heart Failure and Transplantation Interdisciplinary Network and, as of the time of the meeting, was expected to be reviewed by the ISHLT Board soon.

Task Force 1 - Peri-Operative Care of the Heart Transplant Recipient: What's New?
Estela Azeka, MD, University of Sao Paolo, Sao Paolo, Brazil
Task force 1 has put forth new recommendations pertaining to pre-transplant optimization and considerations in patients bridged with mechanical circulatory support. Updates to pre-transplant optimization will focus on frailty/pre-habilitation, vaccinations, and hemodynamic optimization. Task force 1 expansions will include: incorporation of recommendations from the donor consensus statement; primary graft dysfunction; peri-post-operative management of multiorgan transplant; vasoplegia; and care of recipients with congenital heart disease.

Task Force 2 - Immunosuppression and Rejection: What's New?
Michael Shullo, PharmD, University of West Virginia, Morgantown, WV USA
Task force 2 compiled expansions to topics including rejection surveillance; emerging areas in non-invasive surveillance (molecular microscope, micro-RNA, cell free DNA, MRI); immunosuppressive regimens; antibody-mediated rejection (AMR) therapies; and late AMR.

Task Force 3 - Heart Transplant Long-Term Care Complication Management: What's New?
Kyung-Hee Kim, MD, PhD, Sejong General Hospital, Seoul, Korea
Task force 3 addressed new topics including arrythmias, anticoagulation after heart transplant, and monitoring recipients of organs from donors at high risk of infectious diseases. They also proposed expansions to topics including imaging modalities and immunosuppression minimization.

Task Force 4 - Heart Transplant Long-Term Care Prevention and Prophylaxis: What's New?
Howard Eisen, MD, Penn State Hershey Medical Center, Hershey, PA USA
Task force 4 addressed four new topics including substance use and abuse, family screening, travelling after heart transplant, and emerging pathogens, epidemics, and pandemic

considerations for heart transplant recipients. They also composed expansions to topics including nutrition and weight management, intercurrent surgery updates, and psychosocial and psychologic issues.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

SESSION 44: Cancer, Advanced Heart Failure, and Heart Transplant: Do Any of My Cells Work Properly?

Cancer and heart transplantation: once estranged, now commonly kin

The improving safety profile of VAD and heart transplant has allowed us to extend consideration for these therapies to an older, more complex patient population. As palpable evidence of this, consider the opening "one-liner" for the last patient presented at your heart transplant or VAD selection committee meeting. Chances are, it was sufficiently long that only a few salient words stick in your mind. But if "cancer" was mentioned—as is increasingly common—I suspect it was memorable and colored your overall impression of the patient.

Should mention of "cancer" carry such salience in the pre-transplant period? Sometimes yes, but often maybe not; this was my overall impression from today's symposium **Cancer, Advanced Heart Failure, and Heart Transplant: Do Any of My Cells Work Properly?** Indeed, the observational data links pre-transplant history of malignancy with higher risk of post-transplant malignancy and (in some studies) reduced survival. But the list of potential confounders is long, and the same could be said for age and many other pre-transplant comorbidities. Nuanced consideration—weighing the type of malignancy and recurrence risk—is clearly warranted, as concluded by **Neha Bansal, MD**, of Children's Hospital at Montefiore in Bronx, NY USA during her talk ***Heart Transplantation and Cancer: What is the Risk?***. "Blanket" policies (e.g., requiring at least five years of remission before heart transplant (HT) in candidates with any cancer history) should be reconsidered.

That said, the risk of malignancy—both recurrent and *de novo*—is perhaps unduly overlooked in the several years *after* transplant. To this point, Dr. Bansal presented data showing that risk of malignancy and associated mortality increases sharply at five years post-HT and beyond—a period when most other causes of mortality are in decline. By 10 years post-HT, the cumulative incidence of cancer reaches 20%, with non-melanoma skin cancers comprising the majority of cases. To some extent, this is an inevitable consequence of the mutagenic effects of aging and chronic immunosuppression. But Dr. Bansal suggests there's a lot we could do to potentially reduce this risk. For instance, we might exploit the antiproliferative effects of mTOR inhibitors; their substitution (in place of calcineurin inhibitors) is associated with markedly reduced risk of post-HT malignancy. Avoiding induction therapy in those at risk of malignancy is another plausible strategy, though data bearing out the benefits of this approach are limited. When cancer prompts treatment with immune checkpoint inhibitors (ICIs), it should be at the forefront of the transplant clinician's mind. This was emphasized by **Jayant Raikhelkar, MD**, of Columbia University Medical Center in New York, NY USA during his presentation ***Immunotherapy: What Do Transplant Providers Need to Know?*** While uncommon—occurring in 1% those treated with ICI therapy—fulminant myocarditis has a 50% mortality rate in this population. Its early clinical features (e.g., elevated troponin) overlap with those often occurring in HT rejection—and thus a high index of clinical suspicion must be maintained. "Timing matters" is perhaps the most important takeaway—if ICIs are stopped and high-dose IV corticosteroid therapy is started early in the course of ICI-related myocarditis, then mortality risk drops dramatically. Distinguishing it from rejection remains challenging, but

MRI and specific biopsy features can help in its diagnosis.

If active malignancy is felt to preclude consideration for heart transplant, a natural follow-up question is "What about LVAD?". **Farooq H. Sheikh, MD**, of MedStar Heart and Vascular Institute in Washington, DC USA addressed this question in his presentation ***A Balancing Act: Unique Challenges of Cancer in MCS Patients***. Reassuringly, Dr. Sheikh presented data showing that both 1) patients with anthracycline-induced cardiomyopathy and 2) patients with active malignancy have no worse adjusted survival after LVAD implant, when compared with LVAD recipients with no malignancy history. Yet he emphasized the importance of goals of care discussions for cancer patients considering LVAD: "We've moved well-beyond one-year survival as a marker of success after LVAD implant… it's critical to define upfront the goals of therapy beyond prolonging survival."

Does cancer matter in the context of donor selection? The answer remains unclear, but emerging technology may help, as discussed by **Jan von der Thüsen, MD, PhD**, of Erasmus Medical Center in Rotterdam, Netherlands during ***Leveraging Pathology and Molecular Tools to Aid in Heart Donor and Recipient Cancer Risk Assessment***. Even outside the context of MCS and heart transplant, there is an increasingly broad range of considerations affecting patients with concurrent cancer and medically-treated heart failure. These were discussed in depth by **Anju Nohria, MD, MSc**, of Brigham and Women's Hospital in Boston, MA USA during ***Curing Cancer, Causing Heart Disease: Acute Cardiac Dysfunction From Cancer Treatment*** and by **Kirsten Rose-Felker, MD**, of UPMC Children's Hospital of Pittsburgh during ***Developing Cardiomyopathy After Cancer Treatment: A New Journey Begins***.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 49: It's Complicated! Psychosocial and Ethical Issues in Pediatric MCS and Transplantation

What to do When the Parents of the VAD/Transplant Candidate are High Risk? Ethics of Supporting Families Facing Structural Vulnerabilities

Samantha Anthony PhD, MSW, Hospital for Sick Children, Toronto, ON Canada

Bioethics is a critical reflection on moral/ethical problems in healthcare settings. An ethical dilemma is defined as when healthcare providers encounter (i) conflicting values, beliefs, and goals; (ii) have conflicting obligations or responsibilities, (iii) are concerned about rights violations or persons not being respected, fairness & justice, something conflicting with professional code of ethics; and/or (iv) are unsure what, why and how to do it. Fairness is paramount in deciding who is eligible for a lifesaving organ.

Social determinants of health include: education access and quality, healthcare access and quality, economic stability, social and community context, and the neighborhood and built environment. A structural vulnerability is an individual or a population group's condition of being at risk for negative health outcomes through their interface with socio-economic, political, and cultural hierarchies. Patients are structurally vulnerable when their location in their society's multiple overlapping and mutually reinforcing power hierarchies and institutional and policy-level statuses constrain their ability to access health care and pursue healthy lifestyles.

There is immense pressure of best use of available organs, we must optimize graft survival and function, and it should benefit both quantity and quality of life. A patient's psychological health and social support system are key to optimizing quality of life and maintaining medical adherence, thus psychosocial evaluation is very important to identify psychosocial risk factors and appropriately intervene to optimize psychological health. An evaluation of child and their parent and family is necessary. Psychosocial factors are not commonly used in pediatrics to determine eligibility for transplant. Transplant teams are motivated to identify psychosocial concerns early in the transplant process and address deficient resources and facilitate healthy change. However, there may be circumstances when the sum of the psychosocial risk factors is so great that a child should not be transplanted or should have transplant delayed.

Pre-transplant strategies to support families include screening for and addressing a child and family's social needs by a social determinants of health/structural vulnerability assessment tool that includes the following domains:

- Financial security
- Residence
- Risk environments
- Food access
- Social network
- Legal status
- Education
- Discrimination

There should be open conversations about increased psychological support and help from other family members. Adequate information should be provided and understanding ensured regarding pros and cons of VAD and transplantation and the procedures and post-treatment management. Mentorship programs can be started.

Post-transplant strategies to support families include assessments of family's readiness for discharge as a part of routine post-operative care; immediate post-transplant and follow up neuropsychological assessment; and interventions to promote early transplant mobility. Coordinated discharge teaching should be done tailored to the family's needs. The ongoing communication between the transplant team, family and school should be monitored. Parent/family functioning should also be monitored as part of routine follow up. Use of telehealth technology can also be used as a monitoring tool.

Don't Throw Away Your Shot: Vaccine Refusal in Pediatric Transplantation

Lara Danziger-Isakov, MD, MPH, Children's Hospital Medical Center, Cincinnati, OH USA

Firstly, we demonstrate the need for vaccination. Feldman et al evaluated 6,980 pediatric patients with solid organ transplant. There were 1,092 patients with 1,471 cases of RSV or vaccine preventable illness; of these, 187 cases were during transplant hospitalization, and car=se fatality rate was 1.7%/ Of the 1,257 events outside transplant hospitalization, 213 were admitted to the ICU. It was noted that through September 2020 that there was a 26% drop in DTap vaccine administration and MMR administration, and a 16% drop in polio vaccination when compared to 2019. There were around 9 million missed vaccinations in 2020, with 40% of parents confirming that their child missed vaccination due to COVID-19. There is reduced community protection for our children and communities against measles, whooping cough, and polio.

Secondly, the issues need to be framed. Medical contraindications like age or transplant urgency, fefusal, and social/logistical reasons. A 2013 survey of 195 pediatric programs with a 71% response rate revealed inconsistencies across pediatric transplantation programs regarding how parental refusal of vaccination affects listing decisions. Logistical concerns include timing, decentralized care, and clinic-related factors like vaccine availability, clinic time/room turnover, transition to telehealth/remote care, and distraction by ongoing medical issues.

Various opportunities to tackle this include:

- Adequate education: assess underlying reasons for refusal, address risks and benefits, and provide an individualized assessment. Practice with patience, empathy, and persistence.
- Prioritization and routinization of providing the vaccine
- Ensuring Availability
- Coordination with various apps that document vaccination schedules and statuses and innovation. These apps may not be applicable to patients with accelerated schedules, presence of any contraindications, and individuals with specific risks
- Innovation: The Updated 2019 AST ID guidelines- MMR and Varicella vaccination are generally contraindicated post-transplant but may be administered in a carefully controlled setting with appropriate education and close follow up. Outstanding questions remain regarding durability and patient selection.

You Are What You Eat: BMI Considerations in Pediatric Transplant and VAD Patients
Carmel Bogle, MD, University of Maryland Medical Center, Baltimore, MD USA
The definition of obesity in pediatrics is stratified on basis of percentile, unlike adults. Class I obesity is 100-120% of 95th percentile, Class II is 121-140% of 95th percentile, and Class III is > 140% of 95th percentile. There is an increasing trend in obesity among children, and adolescents aged 2-19 years by age had worsened over the course of years (from 1960s through 2018). When adjusted with age and sex, it was noted that BMIs have increased significantly post-pandemic.

A PHTS analysis evaluated obesity and dyslipidemia to predict cardiac allograft vasculopathy and graft loss in children and adolescents post-heart transplant. They noted 10% were overweight, 11% were obese, and there was higher propensity of obesity in recipients over 10 years of age. In a survey of adult and pediatric heart, kidney, liver, and lung programs, it was noted that 59.4% pediatric heart transplant centers encountered patients with BMI> 45. 53.5% pediatric heart transplant centers noted BMI > 45 as an absolute contraindication to adult heart transplant listing.

In another analysis, Ryan et al noted that obesity class does not further stratify outcome in overweight and obese pediatric patients after heart transplantation. Patients with BMI > 85th percentile were more likely to be older, males, Black, or Hispanic with dilated cardiomyopathy, diabetic, and required MCS at both listing and transplant. Overweight and combined obese patients had lower cumulative post-transplant survival compared to normal weight patients. Pediatric patients who are obese at the time of HT and dyslipidemic at one year post-HT are at an increased risk for CAV and graft loss.

Is obesity a contraindication for VAD placement? Puri et al evaluated trends in BMI and association with outcomes in pediatric patients on continuous flow ventricular assist device support. They noted that 18% were overweight, 17% obese, BMI was increased in all categories and overweight patients carried more frequent non-VAD infections. Obese patients required longer duration on VAD support, and were less likely to be transplanted.

In another analysis by Joong et al, it was noted that 74% providers would agree to offer VAD support to an adolescent with a BMI > 35. Fitness programs are recommended to improve outcomes pre- and post-transplant. Chen et al demonstrated excellent adherence with significant improvements in cardiovascular and functional health in pediatric heart transplant recipients with a live video-supervised exercise and diet intervention is feasible.

Delays Shouldn't Leave Me Behind: Transplantation in Patients With Neuro-Cognitive Impairment **Matthew Fenton, MD, MBBS, BSc**, Great Ormond Street Hospital Children's, London, UK
We are now in an era where early mortality post-transplant is rarer. As outcomes have improved, the utility for a broader range of conditions has increased. As survival increases, the value of treatment increases as well. However, organ availability has not kept pace with increasing demand for an effective treatment. Ethical principles in rationing donor organs include:

- Utility: Allocation should maximize the net amount of good. We should balance doing good and not doing harm; determinants will be predicted years of life and wellbeing, with social worth excluded.
- Justice: Fairness in the allocation of organ for individuals and centers; all members of the public are morally entitled to fair access of its benefits; access related to social characteristics conflicts with just principles.
- Respect for person's autonomy: A respect for right to decide, equality of access, and when considering listing those with infectious disease this is quite important
- Rule of rescue: The human desire to help when life is in danger. Utilitarian principles can appear inhumane: rescue first, evaluate effectiveness later.

Prior to the 1990s, intellectual disability was generally regarded as a contraindication for transplant. 1995 American Society of Transplant Physicians state that intellectual disability should only be a contraindication if compliance is impaired and caregivers ae not able to compensate for this. In 1996, the first patient with Down Syndrome received an organ transplant. It is unacceptable to exclude an individual from transplant listing based on disability. Evaluation was to focus on benefit, predicted survival, compliance, and availability of support. It was noted in 2004 that only 3 patients with Down Syndrome were referred for thoracic transplant over 14 years in the UK. Per Broda et al in 2018, only 2.1% of US pediatric hearts were done on patients with chromosomal abnormalities with no difference in outcomes. Patients receiving heart transplants for inherited myopathies and DiGeorge Syndrome have similar outcomes to unaffected heart transplant recipients.

In another survey of heat, kidney, liver, and lung transplantation, Wall et al noted that there are still some programs that consider genetic disease and intellectual disability as an absolute contraindication for transplant, with pediatric centers less likely to do so compared with adult centers. Categorization in general should be avoided and focus should be on individual assessment. General practice guidelines should be formulated to aid assessment.

Blanket discrimination against people with neurocognitive impairment or genetic conditions is unethical and illegal. Patients with comorbidities should be assessed for transplant listing based on their individual circumstances. Guidelines for rare conditions help provide consistency and should be created across centers. Public engagement in driving decision making reveals that perhaps the threshold for a meaningful life is lower than the medics may think. Using a limited resource does not always have to about efficiency but can also be about equality of access to transplantation.

"The Green Revolution": What to do When Your Teenage Patient Smokes Pot?

Robert Page, PharmD, MS, University of Colorado School of Pharmacy, Aurora, CO USA

During the past year, marijuana and substance use has increased among people aged 12 years and older. Marijuana is legalized in many states now, but there are certain age restrictions varying per each state. Younger people are using marijuana mostly due to mental health issues, friends and peer pressure, and media and pop culture. Cannabis has certain neurological effects on teens, like abnormal stress responsivity, glial cell activation, desynchronization of PFC neuronal

networks, excessive synaptic pruning, and dysregulation of monoaminergic pathway. Acute neurological effects include inaccurate perception of time and sounds; slower reaction time affecting driving and increasing injury risk; problems with memory and learning; as well as poor judgement, panic attacks, distrustful thoughts, and symptoms of psychosis. Chronic neurological effects include impaired learning, memory, and attention; increased risk of schizophrenia or other psychotic disorders, especially in vulnerable individuals; and addiction.

Various cardiovascular effects on teens include hypotension/bradycardia with higher doses, arrhythmia due to hyperadrenergic state, stroke due to decreased cerebral blood velocity, ischemia due to arterial vasospasm and tachycardia, thrombosis due to procoagulant state, and platelet activation and atherosclerosis due to oxidative stress/endothelial injury. Matta et al noted that recreational substances including cannabis were independently associated with a higher likelihood of premature and extremely premature ASCVD, and its use confers a greater magnitude of risk for premature ASCVD among women.

Therefore, a discussion of risks and potential of not being listed per center's policy should be discussed, and a psychologist and social worker evaluation is a must. Teens are not invincible and cannabis use can have long term consequences.

When the Team is at Odds: Decision-Making Distress and Conflict Among the Advanced Heart and Lung Failure Teams **Melissa Cousino, PhD**, C.S. Mott Children's Hospital, Ann Arbor, MI USA
Interprofessional teamwork is an interpersonal process characterized by healthcare professionals from multiple disciplines with shared objectives, decision making, responsibility, and power working together to solve patient care problems. The joint commission in 2011 noted that 65% of sentinel events in cardiac operating room are due to communication failures. Transplant medicine is high-stakes and involves end-stage decision making with a lack of predictability and multiple ethical considerations, including large teams with diverse backgrounds. Communication amongst the team is extremely important. Clinician stress and burn out is highly prevalent amongst physicians and nurses.

Group dynamics that can fuel conflicts include hierarchies, trust/rapport, and preference/style. Clinician bias includes race, socioeconomic status, and education. Our goal is to intentionally cultivate and maintain strong personal relationships, reliable and open communication methods, conflict resolution strategies, and shared professional goals to succeed in our challenging work.

Various strategies to improve rapport include clinician wellness, team building, conflict resolution, co-location, communication, and education. We must evaluate the strengths and weaknesses of our teams, realize the team goal, and identify opportunities to work on these goals, along with identifying threats that are outside of our team's control.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SESSION 58: Relative Contraindications to Heart Transplantation: Where is the Line?

A Blurry, Moving, and Faintly-Drawn Line

Today's symposium **Relative Contraindications to Heart Transplantation: Where is the Line?** poses a simple and clear question. The answer is anything but simple; advances in our field (e.g., multi-organ transplantation, mechanical circulatory support) have allowed an increasingly broad range of patients to benefit from heart transplantation (HT); accordingly, the "line" is blurry, moving, and faintly-drawn. This is no doubt a sign of progress—but it also poses a challenge, as we must continually revise our lists of relative and absolute contraindications to HT.

A case in point: diabetes mellitus (DM) or chronic kidney disease (CKD) appeared at the top of these "lists" in the 1980s-1990s, but are exceedingly common among today's HT recipients. In contrast, HIV infection remains an absolute contraindication to HT at some centers—even as it resembles DM and CKD in terms of its effect on life expectancy (reducing it by ~9 years). This apparent paradox was addressed by **Julie Doberne, MD, PhD**, of Duke University Medical Center in Durham, NC USA in her presentation ***HIV: Is It Time To HOPE?***. Her recent study compared outcomes in HIV+ recipients with propensity-matched HIV- recipients in a nationwide cohort; HIV+ recipients had higher rates of acute rejection but equivalent overall survival. On the next frontier—made possible by the HOPE Act—are prospective studies on the use of HIV+ donors for transplant into HIV+ recipients (D+/R+). Dr. Doberne presented data from the first such studies in kidney (Durand et al 2021) and liver (Durand et al 2022) transplants, which found equivalent survival in D+/R+ and D-/R+ transplants.

Age is another HT contraindication where the "line" is blurred. While age ⩾ 70 would preclude transplant in many settings, it is increasingly common in France, according to data presented by **Richard Dorent, MD**, of Agence de la Biomédecine in Saint-Denis, France in ***Happy 70th Birthday! Off You Go***. In a comprehensive sample of septuagenarian transplants in France, his team found that their 10-year survival was lower (34%) than that of younger HT recipients. This may have been expected—but perhaps more noteworthy was that most deaths in these older recipients were due to either infection or cancer. Whether an "age-tailored," lower-intensity immunosuppression strategy could have averted some of these deaths warrants further study.

The "lines" are a bit clearer when it comes to candidates with active tobacco use and alcohol abuse; per 2016 ISHLT Guidelines these are relative and absolute contraindications to HT, respectively. No explicit recommendations were given regarding recreational cannabis use, leaving transplant centers much room for discretion. Chief among the many pertinent considerations, as presented by **Eileen Hsich, MD**, of Cleveland Clinic in Cleveland, OH USA in ***VAPING, NICOTINE and CANNABIS: Going Up in Smoke?*** is the fact that cannabinoids (e.g., THC, CBD) inhibit the metabolism of calcineurin inhibitors (thus potentially increasing their levels) via interactions with cytochrome P450 enzymes. Accordingly, most programs mandate abstaining from cannabis use prior to HT—how long this period of abstinence should be remains open to debate. Per audience comments at this Friday session, such debates are a common occurrence in HT selection

committee meetings.

Additional presentations discussed the challenges posed by HT candidates who are "difficult to match", in terms of size and histocompatibility. These included: ***WEIGHT: Balancing the Scales*** by **Johan Nilsson, MD, PhD**, of Skanes University Hospital in Lund, Sweden and ***SENSITIZATION: Is There a Sensible Solution?*** by **Monica Colvin, MD**, of the University of Michigan in Ann Arbor, MI USA.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 43: ABC, 123, DCD, NRP: Expanding Donor Availability in Heart Transplantation

This **oral abstract session** highlights research focusing on expanding donor availability, including donation after circulatory death (DCD) as well donor selection and procurement during the COVID pandemic.

Heart Transplantation from Donation After Circulatory Death Donors: An Update on the Australian Experience

Yashutosh Joshi, MBBS, St. Vincent's Hospital, Sydney, NSW Australia

The investigators presented the overall impact of DCD over the last eight years on their heart transplant program as well as their early and more contemporary outcomes with utilization of DCD donors. Inclusion criteria for DCD donors included: normal transthoracic echocardiogram, age less than 55 years, and absence of previous cardiac history. Explanted hearts were cannulated onto an ex vivo normothermic machine perfusion device where 1.2-1.5L of donor blood is circulated in a Langendorff fashion. Visual inspection and monitoring of lactate trends were used to assess for viability. Since 2014, 69 DCD heart transplants were performed.

Key findings include:

1. Overall one- and five-year survival for DCD vs BD donor heart transplant recipients was not significantly different (p=0.27).
2. The use of ECMO/mechanical support in the immediate post-op period decreased from 35% to 8.6% over the study period.
3. Donor hearts subject to an aWIT >15mins were more likely to require post-operative ECMO/mechanical support.

Expanding Heart Transplants from Donors After Circulatory Death (DCD) - Results of the First Randomized Controlled Trial Using the Organ Care System (OCS™) Heart - (OCS DCD Heart Trial)

Jacob Niall Schroder, MD, Duke University, Durham, NC USA

The purpose of this study was to evaluate the effectiveness of the OCS Heart technology to resuscitate, preserve and assess DCD hearts for transplantation. Standard donor inclusion/exclusion criteria were applied. Recipient exclusion criteria included: multi-organ transplant candidates, history of prior solid organ or bone marrow transplants, history of chronic renal failure, or unrandomized recipients. Recipients were randomized 3:1 into the DCD or the donation after brain death (DBD) groups. A total of 180 patients were randomized and transplanted in the trial (DCD n=90 and Control n=90) at 13 heart transplant centers in the United States between 2019 and 2020.

Outcomes included: patient survival at 6- and 12-months post-transplant, OCS DCD heart utilization rate, incidence of severe left or right ventricular primary graft dysfunction (PGD). A total of 101 hearts were instrumented on OCS heart technology and 90 of these were transplanted, i.e. utilization rate of 89%. DCD donors were significantly younger than DBD donors. Superior patient and graft survival was seen at 12- and 24-months post-transplant with use of DCD OCS hearts

compared to DBD cold storage hearts (12 months: 93% vs 86%; 24 months: 93% vs 83%). Lower complication rate was seen with DCD OCS hearts.

Early Outcomes of Donation After Circulatory Death Heart Transplantation with Thoracoabdominal Normothermic Regional Perfusion

Marian Urban, MD, University of Nebraska Medical Center, Omaha, NE USA

The purpose of this study was to evaluate the early outcomes of DCD heart transplantation using thoracoabdominal normothermic regional perfusion (TA-NRP). This was a single-center prospective study with single arm. In addition to standard inclusion criteria, recipients listed for dual organ transplantation and patients with previous cardiac operation including durable LVAD implantation were also included. All hearts were recovered with TA-NRP after no more than 30 minutes of warm ischemia (defined as the time period commencing from SBP < 50 mmHg to in situ reperfusion) and details of their TA-NRP protocol were presented. Grafts were recovered using 2,000mL of Celsior® for cardio protection, and transported with colds storage. Eight donor hearts were procured and from each donor at least one other organ was procured.

Key findings:

1. Modality of NRP was cardiopulmonary bypass in 5 cases and VA-ECMO in the remaining three
2. Only 2 recipients required post-transplant MCS in the form of VA-ECMO, all recipients were alive at 30 days post-transplant
3. Inotrope score at 72 hours ranged from 0 to 15, ICU length of stay ranged from 4 to 74 days
4. AKI was the most common adverse event (in 4 out of 8 recipients)

Increasing Utilization of Extended Criteria Donor After Brain Death (DBD) Hearts Seldomly Used for Transplantation in the U.S. Due to Limitation of Ischemic Cold Storage - 2-Year Results of the OCS Heart EXPAND Prospective Multi-Center Trial (OCS Heart EXPAND)

Jacob Niall Schroder, MD, Duke University School of Medicine, Durham, NC USA

The purpose of this study was to evaluate the effectiveness of the OCS heart perfusion technology to preserve and assess extended criteria DBD hearts that are seldom transplanted due to limitations of ischemic cold storage. This prospective, multi-center trial targeted DBD hearts with one or more of the following risk factors: expected cross clamp time of ⩾4 hours; OR expected cross-clamp time of ⩾ 2 hours with one or more of the following risk factors: Older donors age 45-55 years with no coronary cath OR ⩾ 55 years old; history of cardiac downtime ⩾20 min with stable hemodynamics at time of offer; history of LVH with septal or posterior wall thickness between 13-16 mm; LVEF 40-50%; or history of diabetes, or carbon monoxide poisoning or non-specific angiogram irregularities with no significant CAD. Use of these criteria made randomization impractical. A total of 138 extended criteria donor hearts were perfused and assessed on the OCS Heart System between 2015 and 2020. Over the same period, 1,813 standard criteria DBD heart transplants at the same EXPAND centers served as controls.

Key findings:

1. Of the 138 hearts procured, 116 were successfully transplanted resulting in an 84% utilization rate
2. Using KM analysis, survival of EXPAND trial patients was similar to controls (85% vs 88%)

Early Single Center Experience of Heart Transplantation from Donation After Circulatory Death Donors in the United States

Mark J. Kearns, MD, UC San Diego, San Diego, CA USA

The authors presented a single-center experience with DCD heart transplant (HT) using two procurement strategies: 1) direct procurement and perfusion (DPP) protocol, and 2) thoracoabdominal normothermic regional perfusion (TA-NRP) protocol. Data was collected prospectively.

From September 2020 to October 2021, they performed 33 DCD HTs with 13 DPP and 20 TA-NRP procurements. 30-day survival was 100% among all DCD heart recipients. The incidence of primary graft dysfunction and other secondary endpoints was comparable with standard DBD HT.

Transplanting Thoracic COVID-19 Positive Donors: Overcoming the Pandemic

Emily M. Eichenberger, MD, Duke University Medical Center, Durham, NC USA

The authors presented their institutional protocol and early results for thoracic organ transplantation using COVID-19-positive donors. Ten thoracic organ transplants in nine recipients using organs from COVID-19 positive donors (9 hearts; 1 pair of lungs) were performed with patient and graft survival to date of 100% and 91%.

Per protocol:

1. Hearts were procured from donors testing positive for COVID-19 on upper and/or lower respiratory tract specimens, provided severe COVID pneumonia or myocarditis was not the cause of death, and hypercoagulable complications were absent
2. Lungs were procured only if donors were first positive >20 days prior and were PCR-negative on bronchoalveolar lavage. Cycle threshold, duration of infectivity and urgency of recipient need were considered in addition to routine evaluations.

Key findings:

1. Eight heart recipients did not acquire COVID-19
2. One heart-liver recipient required re-do HT due to massive hemorrhage followed by hypercoagulability and coronary thrombus, with an RV biopsy suspicious for SARS-CoV-2 myocyte infiltration
3. Lung recipient did not develop COVID-19

VIEW SESSION DETAILS

– Summary Rachna Kataria, MD

SESSION 51: Will You Be Mine? Choosing Donors and Recipients for Heart Transplantation

Should Age-Based Eligibility Thresholds Differ for Heart Re-Transplantation? Analysis of the United Network for Organ Sharing Database

Qiudong (Kevin) Chen, MD, Cedars-Sinai Medical Center, Los Angeles, CA USA

Heart re-transplantation is associated with worse unadjusted survival compared to primary transplantation. In propensity-matched patients, survival after re-transplant is comparable to that of primary heart transplantation after excluding early/acute re-transplantation.

Chen et al evaluated outcomes of heart re-transplantation in older recipients using the national UNOS database. Of 1,295 heart re-transplants, 1,083 were retransplanted at < 60 years of age and 212 after 60 years of age. Of the 212 patients, 38 were excluded due to early/acute re-transplantation. The remaining 173 patients were compared with 12,833 patients who got primary heart transplantation after 60 years of age from 2003 to 2020.

The primary outcome included post-transplant survival up to 10 years. Secondary outcomes included in-hospital complications like treated acute rejections, stroke, new dialysis requirement, or permanent pacemaker placement, and 30- and 90- day mortality. It was observed that older recipients more than 60 years undergoing re-transplantation had worse unadjusted survival compared to younger recipients, while there was no difference in survival between different age groups when recipient ages < 60 years. It was concluded that retransplanting patients greater than 60 years old is independently associated with increased risk of long-term mortality. Careful consideration of recipient candidacy is warranted in elderly patients undergoing evaluation for heart re-transplantation.

The Effect of Race on Heart Transplantation Survival by Age

Alejandro Plana, MD, University of Chicago, Chicago, IL USA

The 2021 annual ISHLT adult heart transplantation (HT) report demonstrated worse survival for 18-39 year-olds in North America following HT compared to the 40-59 and 60+ age groups. The racial demographics of North America and Europe differs greatly, with a significantly higher proportion of Black patients in North America. African American patients are more likely to be diagnosed with HF at a younger age, with a higher prevalence of non-ischemic dilated cardiomyopathy as an indication for transplant. They are more likely to receive left ventricular assist device (LVAD) later in the disease course, and are subsequently less likely to undergo HT. Furthermore, African Americans undergoing HT have higher mortality and higher rates of graft failure. There is a higher prevalence of hypertension, recipient-donor HLA mismatch, and significantly different demographic characteristics. A higher proportion of young African American recipients die due to cardiovascular causes and graft failure compared to older African American patients and social determinants of health more heavily affect African American patients.

Plana et al aimed to assess each age cohort within the UNOS database for differences in survival after HT stratified by race/ethnicity. It was concluded that African Americans had increased post-

HT mortality compared to their white, age-matched counterparts. This difference was prominent in the youngest age cohort, but was mitigated with increased age. These disparities were likely driven by social determinants of health, which affected younger patients more adversely. Low socioeconomic status (SES) correlates with more frequent HF hospitalizations and increased mortality. Low SES patients have been shown to have poorer adherence to immunosuppressive medications, higher rates of rejection, and higher frequency of infections. Immunologic factors may also play a role given higher PRA and immune activation after transplant, higher rate of DSA formation, and that younger African American females tend to be highly sensitized with an increased risk of rejection. More analysis is needed to determine key drivers of these differences. Key areas of further research would be optimizing immunosuppression management and regimens especially in the first- year post-transplant for young black patients.

Survival After Heart Transplant is Poor With High Venous Pressures and Low Arterial Elastance

Komarakshi Balakrishnan, MD, MGM Hospital, Chennai, India

Increased venous pressure is associated with renal dysfunction and mortality in patients with decompensated heart failure. Impaired right ventricular function is associated with poor survival in heart failure. Heart transplant (HT) is the only option for patients with severe biventricular dysfunction who have failed medical therapy. Lowering arterial elastance with vasodilators is very effective in improving the cardiac output, and vasodilators are an important component of medical management.

Balakrishnan et al sought to evaluate the effect of high venous pressures and a low Ea after HT. They retrospectively studied 250 patients who underwent a HT between October 2012 to March 2020. Venous pressure more than 15 mm Hg was considered high and as evidence of RV dysfunction. Hospital mortality was defined as death within 90 days of the transplant.

It was observed that higher right atrial pressure was a significant risk factor for 90-day mortality. This risk was decreased with increasing arterial elastance. Lower organ perfusion pressure index (that was measured as [mean arterial pressure – right atrial pressure]/BSA) had a significant impact on 90-day mortality. The impact of high RAP and low arterial elastance persisted at medium-term follow up. Higher MELD score significantly increased hospital mortality. A value < 40 is associated with worse outcomes.

They also concluded that compared to isolated LV dysfunction, onset of biventricular dysfunction leads to higher RAP, lower cardiac output, higher arterial elastance, lower mean arterial pressure, and lower OPPI. Aggressive vasodilator therapy to improve cardiac output in the presence of high RAP can lead to increased venous return to the right heart and higher RAP and lower OPPI. This study revealed insight into why onset of RV dysfunction in HF carries an ominous prognosis. Patients with high venous pressures awaiting HT need to be carefully monitored for drop in organ perfusion pressure while on vasodilators, and addition of intra-aortic balloon pump may confer additional benefit.

Comparative Analyses of Donor-Recipient Age Differences in Adult Cardiothoracic Transplantation: An Analysis of the UNOS/OPTN Database

Hari Rajagopal, Carnegie Vanguard High School, Houston, TX USA

Broad trends towards increased thoracic organ transplantation in older recipients are well described and usage of older donor organs is well accepted by many programs. However, little is known about comparative recipient and donor age demographics, and how these may vary with time.

Rajagopal et al evaluated the UNOS/OPTN STAR file for both adult isolated heart and lung transplantation between 1988-2017. Donor organ pool, recipient waitlist pool, and transplanted patient pool were stratified with respect to age, and 30-day and 1 -year survival outcomes were reported, also stratified per age range. They observed that there was an increased percentage of heart recipients aged 60-69 and > 70 years over time. There was a decreased percentage of heart recipients aged 40-49 and 50-59 over time. No clear temporal trends were observed with respect to donor heart age demographics. Short-term survival was inversely related to recipient age.

With respect to lung transplants, they noted similar trends in recipients, but more dramatically, as the age group 60-69 years is close to majority of the recipients. No clear trends in donor age demographics were noted akin to heart transplantation. Short-term survival was inversely related to age except in the 18-29 years age group. Cardiothoracic transplantation involves a transference of organs from younger donors to older recipients but the extent of this has increased recently. Older recipients have decreased short term survival which likely translates to diminished long-term survival. These findings may have implications for organ allocation policies.

Using Hemodynamics to Define Graft Function: Do We Need It?

Marco Masetti, MD, PhD, Heart Failure and Heart Transplant Unit, Bologna, Italy

Evaluation of graft function after heart transplantation (HT) is made by echocardiography to evaluate left ventricular ejection fraction (LVEF), endomyocardial biopsy (EMB) for monitoring for rejection, and coronary angiography to assess allograft vasculopathy. The role of assessment of graft function through hemodynamics as assessed by right heart catheterization (RHC) is unknown.

Masetti et al sought to explore the correlation of RHC with histological findings and the standard methods used to evaluate graft function and its ability to stratify prognosis. Bologna's usual protocol is EMB routinely until five years after HT, and after five years in case of concerns for rejection; echo at every EMB and clinical visit; angiography at first and every five years after HT. They included patients undergoing EMB after the first month from HT for standard monitoring or for symptoms > 5 years from HT.

The follow up was started after first abnormal RHC or, if no abnormal values were found, after the last RHC performed in the observation period. The endpoints were the interplay between RHC, LVEF and EMB; and two years MACE occurrence events. Data was collected at each EMB. The RHC groups were divided as normal (normal filling pressures and normal cardiac index); diastolic

dysfunction (high filling pressures and normal cardiac index) and low cardiac index. 586 EMBs were performed in 113 patients.

They noted poor correlation between LVEF and hemodynamics, particularly cardiac output. Hemodynamics are better correlated than LVEF to histology and helps in stratifying prognosis in patients with rejection. The assessment of graft function by LVEF underestimates the risk of MACE. Assessment of diastolic dysfunction by RHC may help in suspecting AMR.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SESSION 54: A Heart Partnership: When is Two Better Than One?

Considering the benefits—and costs—of two instead of one

Increasing familiarity and improving outcomes with dual-organ transplant has effectively broadened the heart transplant (HT) candidate pool to include those with accompanying end-stage kidney or liver failure. Simultaneous heart-kidney and heart-liver transplant volumes have increased accordingly. These trends are no doubt encouraging, but should be considered alongside a more sobering fact: each of these dual-organ transplants means one fewer organ available to the > 100k patients waiting (months or often years) for kidney-only or liver-only transplant.

This tension demands that we in the HT community consider ourselves in partnership with the broader solid organ transplant community, and ask the question posed by today's aptly-titled session **A Heart Partnership: When is Two Better Than One?**

Maria Currie, MD, PhD, of Stanford University in Palo Alto, CA USA attempted to answer this question in the heart-liver context in her presentation ***Predicting Survival in Combined Heart-Liver Transplantation Compared to Heart Transplantation Alone***. Specifically, her group hypothesized that candidates with higher MELD-Na score would derive greater benefit from heart-liver transplant (vs. heart transplant-only). While certainly plausible, her analysis—which compared survival in 326 simultaneous heart-liver (HLT) recipients in the nationwide UNOS database with 278 heart-only recipients in the Stanford database—showed no interaction between type of transplant (i.e., heart-liver vs. heart-only) and MELD-Na score. She concludes that MELD-Na score is not a useful metric for discerning which patients warrant simultaneous heart-liver (vs. heart-only) transplant.

An analysis by **Pierre-Emmanuel Noly, MD, PhD**, of the University of Michigan in Ann Arbor, MI USA posed a related question: "Might HLT outcomes differ according to the underlying heart failure etiology?" In his presentation ***Outcomes Following Simultaneous Heart-Liver Transplantation: An Analysis of Donor and Recipient Characteristics***, he compared short- and long- term outcomes after SHLT among ischemic cardiomyopathy (ICM), non-ischemic cardiomyopathy (NICM), and adult congenital heart disease (ACHD) patients in a comprehensive US sample spanning 10 years. His findings included similar short-term survival, but better long-term survival among ACHD recipients—perhaps owing to their younger age. Of note, he presented a separate abstract (***Outcomes Following Heart Transplantation in Adults with Congenital Heart Disease***) comparing outcomes after HT-only by heart failure etiology. This analysis actually showed slightly worse short-term survival—but again, better long-term survival—among ACHD (vs. non-ACHD) recipients. Further work identifying which ACHD patients fare better with SHLT (vs. HT-only) could yield guidance for patient selection.

Further complicating patient selection for dual-organ transplant is the potential impact of changing allocation policy, and associated changes in the use of temporary mechanical circulatory support (tMCS), as was addressed by **Arianne Clare Agdamag, MD**, of the University of Minnesota in Minneapolis, MN USA during her analysis ***Simultaneous Heart-Kidney (SHK) Transplant Outcomes Pre- and Post-Heart Allocation System Change: Impact of Temporary Mechanical Circulatory Support***. In

an analysis including all US SHK recipients from 2016-2019, she found that one-year survival was actually worse after the October 2018 allocation change, but that this change could not be ascribed to the dramatic rise in tMCS use (as the tMCS and non-tMCS groups had equivalent one-year survival). This potentially alarming trend warrants our attention, along with further studies extending beyond 2019.

Last but certainly not least was **Umar Siddiqi** of the University of Chicago, who presented ***Graft Rejection and Survival in Patients Undergoing Multi-Organ Heart Transplantation***. In a comprehensive cohort of US heart-only (HT-only), HLT, SHK, and heart-lung recipients dating back to 1988 (total n = 80,058), he found that heart-lung recipients had the worst (multivariate adjusted) graft survival among these groups. But intriguingly, each of the dual-organ groups had significantly lower risk of rejection than HT-only recipients.

So "two is better than one" when it comes to post-transplant rejection; but beyond this, the answer to this session's titular question remains unclear. Kudos to these presenters for their ongoing efforts to answer it, and thus ensure that the limited supply of donor kidneys and livers goes to recipients who will benefit from them most.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 56: Don't Go Breaking My Heart: The Influence of Antibodies, Drugs, and Diagnostics on Pediatric Heart Transplant Outcomes

The aim of **this session** was to explore the impact on anti-HLA sensitization, the donor specific crossmatch, and eplet matching on pediatric heart transplant outcomes. This session also explored how immunosuppression medications and diagnostic imaging are being used in pediatric heart transplant care.

No Association Between Early Donor Specific Antibody and Subsequent Allograft Function at 3 Years Post-Pediatric Heart Transplantation. First Results of a Prospective Multi-Institutional Study

Steven A. Webber, MBChB, Vanderbilt University School of Medicine, Nashville, TN USA

As part of a follow-up of the CTOT-04 study, the authors presented CTOT-09 study wherein they assessed the impact of 'preformed' (at transplant) and first-year newly detected donor specific antibody (ndDSA) on allograft function at three years. Consecutive children listed for transplant at nine centers were prospectively enrolled and the management of sensitization, immunosuppression, and rejection surveillance was standardized across centers. Donor specific antibody or DSA was defined by single antigen Luminex testing with ⩾1 antibody specific towards donor HLA antigens with MFI>1000.

Key findings were:

1. The primary outcome of PCWP at 3 years was similar in transplant recipients with and without early DSA
2. Other invasive hemodynamics, ejection fraction, and BNP were also similar regardless of early DSA
3. Graft and patient survival did not differ between groups, though freedom from all acute rejection types was inferior in subjects with preformed DSA.

A Positive CDC T-cell Crossmatch is Strongly Associated with Allograft Loss and Early Rejection in Pediatric Heart Transplant Recipients

Ryan J. Williams, MD, UCLA Mattel Children's Hospital, Los Angeles, CA USA

The investigators queried the OPTN database for all pediatric heart transplants performed between 1999 and 2019 and assessed the association of donor specific T-cell CDC and Flow XM HT with the risk of rejection and allograft loss in United States pediatric recipients.

Of 4,695 pediatric HT, there were 165 CDC+, 288 Flow+/CDC Unknown, 94 Flow+/CDC-, and 4,148 Flow- recipients. Children receiving a CDC+ XM HT were found to be at higher risk of graft loss and rejection during the first post-transplant year, suggesting higher anti-HLA antibody burden in such recipients. They concluded that the shift away from performing a CDC XM results in a loss of important prognostic information.

Eplet Matching in Pediatric Heart Transplantation

Barbara Cardoso, MD, Freeman Hospital, Newcastle-upon-Tyne, UK

The purpose of this retrospective, single-center study was to compare antigen- to molecular-level

HLA matching in regard to post-heart transplant outcomes in a pediatric population. HLA typing, antigen mismatch, and eplet mismatch analysis were performed on all donor/recipient pairs. 77 patients were included.

Key findings included:

1. Number of HLA Class II DPB donor-recipient eplet mismatches was independently associated with graft loss (HR 8.14 [95% CI: 1.26 - 49], p = 0.02)
2. Neither HLA class I nor class II eplet mismatching nor HLA class I and II antigen mismatching was associated with rejection or graft loss
3. The most accurate prediction was obtained with prior heart surgery, prior ECMO, sensitization against HLA class II antigens, and number of HLA Class II DPB eplet mismatches as independent variables.

Immunosuppressant Drug Level Monitoring in Pediatric Heart Transplant Recipients: A Report from the TEAMMATE Trial

Matthew J. Bock, MD, Rady Children's Hospital, UC San Diego, San Diego, CA USA

The investigators presented results of an analysis from the TEAMMATE trial of everolimus (EVL) with low-dose tacrolimus (LDTAC) vs. standard tacrolimus (TAC) with mycophenolate (MMF) focused on their immunosuppressant drug level monitoring experience in the trial. A total of 211 children were randomized to either EVL/LDTAC (n=107) or usual care TAC/MMF (n=104). After randomization, a therapeutic level was achieved in 94% (EVL) & 91% (MMF) with the median time to a therapeutic level for EVL being 10 (tablet) & 11 (liquid) days. The coefficient of variation was lower for TAC, EVL, and LDTAC (36%, 47%, and 52% respectively) compared to MMF (103%). EVL levels were in target range 80% of times and the standard deviation of levels divided by therapeutic window was lowest for EVL. The authors concluded that EVL achieved stable target levels more frequently than MMF, LDTAC or TAC, likely due to decreased trough level variability and its wider therapeutic window.

Utility of Intravascular Ultrasound Early After Pediatric Heart Transplantation

Michael A. Kuhn, MD, Loma Linda University, Loma Linda, CA USA

The investigators examined the use of IVUS early (< 5 years) after pediatric HTX. They found 71 patients who had IVUS performed within 5 years of HTX. Patients were classified based on Stanford IVUS class (SIC) into SIC 1-2 and 3-4. Freedom from CAV and graft loss from CAV were lower in the SIC 3-4 group [CAV HR 2.7 (1.4-5.4), p=0.01 and graft loss from CAV HR 3.4 (1.3-8.9), p=0.005, respectively]. However, graft loss from all causes and patient survival were not different between the groups (p=NS) suggesting that early changes in IVUS were associated with the development of CAV and graft loss from CAV over time.

Clinical Practice Variation of Statin Use in Pediatric Heart Transplantation

Justin H. Berger, MD, PhD, Children's Hospital of Philadelphia, Philadelphia, PA USA

Data regarding the benefit of statins in pediatric transplant patients is equivocal. The investigators sought to establish statin prescribing practices in a sample of U.S. pediatric HT recipients in the current era, hypothesizing that use of statins in pediatrics increases with age and has increased over time. They used the Marketscan database and identified 876 children who underwent HT

between the ages of 2 and 19 and had ⩾3 years of continuous coverage from 1 January 2013 through 30 June 2018.

A higher proportion of HT recipients received Medicaid than commercial insurance coverage (56% vs. 44%, p<0.001). Thirty-five percent (95% CI 32-38%) of HT recipients were on a statin, at an average age of 11.47 ± 4.6 years at the time of the first statin prescription with the earliest age of statin initiation being 2 years. Likelihood of statin prescription increased with age from 18% for those between 2-5 years of age to 47% in those over 13 years of age.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

Featured Abstract 5 at Closing Plenary Session: The Impact of Evolocumab in Cardiac Transplant Patients with Coronary Allograft Vasculopathy

Presenter: ***Douglas Stoller, MD, PhD****, University of Nebraska, Omaha, NE USA*

Coronary Allograft Vasculopathy (CAV) impacts ~50% of patients at 10 years and is the leading reason for re-transplant. Prevention of its onset and progression with the use of aspirin and statin remain the mainstay of CAV therapy. The investigators of this study hypothesized that PCSK9i will significantly lower LDL and be well-tolerated in transplant patients with CAV.

In a phase II, open label, single center clinical trial, they investigated the impact of the PCSK9i evolocumab in heart transplant patients with CAV. Twenty-six heart transplant recipients, aged 19 to 80 years and with CAV diagnosed on coronary angiography, were enrolled. Patients with recent rejection or infection requiring IV therapy (within the past 3 months), acute liver dysfunction, renal dysfunction with GFR less than 20 ml/min, current or recent use of a PCSK9 inhibitor (within the past 3 months), and/or known allergy to evolocumab, were excluded.

The key findings of this study were:

1. Evolocumab markedly reduced LDL in heart transplant patients with CAV
2. No angiographic progression of CAV was observed during the study period, and a trend towards CAV regression was noted in the LAD
3. Evolocumab exhibited an acceptable safety profile in this specialized patient cohort

VIEW FULL ABSTRACT

– Summary by Rachna Kataria, MD

SUNRISE 16: The Human Microbiome: Hopes, Threats and Promises

This session included talks focused on advances in microbiome research, highlighting the reciprocal relationships between the microbiome and other organs including the heart and lung.

Send In Your Samples: What Can Be Learned From Analyzing Your Microbiome?
Tereza Martinu, MD, University of Toronto, Toronto, ON Canada
The microbiome is a collection of microbes that colonize the body at barrier surfaces and therefore: 1) is highly influenced by environmental and transplant-related factors; 2) significantly influences organ function and transplant-related outcomes (*e.g.*, rejection); 3) has important immunomodulatory effects (*e.g.*, Th17 & Treg).

Important areas of future focus in the study of the microbiome include: 1) Effects of specific microbial perturbations; 2) Timing; 3) Mechanisms; and 4) Virome and fungome (in addition to bacterial microbiome).

The possible clinical applications of the microbiome include: 1) its use as a potential diagnostic tool for personalized assessment and risk stratification; 2) its use for manipulation of the existing microbiome; and 3) its use in prevention and treatment.

Gut Microbiota and Metabolism of Immunosuppressive Drugs: One Size Does Not Fit All
Douglas L. Jennings, PharmD, New York Presbyterian Hospital, New York, NY USA
Alterations in gut microbiome, as seen in patients with heart failure, persist even after LVAD and heart transplant. The obvious question, then, is whether these alterations impact the metabolism of standard immunosuppressive medications used by heart transplant patients. The short answer is, yes: very much so. Greater diversity of gut flora, higher abundance of individual taxa, and lower levels of inflammation and oxidative stress have all been associated with higher tacrolimus dosing requirements.

As for mycophenolate metabolism, beta-D-glucuronidase-producing bacteria were found to be associated with MMF-induced toxicities such as cytopenia. Preliminary data certainly raises concern for important interplay between gut microbiome and transplant immunosuppression. However, additional studies are warranted to determine the clinical applicability of these preliminary findings.

Can Transplantation or LVAD Change My Microbiome?
Melana Yuzefpolskaya, MD, Columbia University, New York, NY USA
Circulating levels of pro-inflammatory cytokines increase with the severity of heart failure symptoms and reduction in functional capacity. However, targeting individual cytokines in heart failure has not yielded promising results. Hence, we should shift our focus to more upstream mediators of inflammation.

In heart failure, both decreased cardiac output and increased venous congestion can result in

increased intestinal permeability, decreased gut microbiome, and decreased nutrient absorption. Worsening heart failure is associated with increasing severity of inflammation and depletion of essential gut microbiota. This reduction in gut microbiome diversity, endotoxemia, and increased TMAO levels persist even after LVAD and heart transplantation, and in fact is associated with increased risk and severity of post-LVAD infections and difficulty attaining target tacrolimus levels. As a result, there is increasing enthusiasm around investigating fecal microbial transplant (FMT) as a potential solution to this conundrum.

The Gut Microbiome and Heart Failure: Are We Ready for Therapeutic Trials Targeting Microbiome?
David Kaye, MD, PhD, The Alfred Hospital, Melbourne, Australia
The role of gut dysbiosis (gut integrity + microflora) has been clearly implicated in many disorders, including cardiovascular diseases. Both the gut microflora and integrity of the gut wall, in particular its ability to prevent leakage of inflammatory cytokines, change in health and disease. In heart failure, both hypoperfusion and gut wall edema affect gut wall integrity.

Animal models have shown that gut microbiome can play a role as a mediator of cardiovascular (CV) physiology. Interestingly, human studies involving patients with HFpEF and those with hypertension have shown a striking decrease in bacteria that produce the short chain fatty acid butyrate, which is normally associated with reduced systemic blood pressure.

Key metabolic targets for the gut microbiome and that influence the CV phenotype include: dietary fiber, amino acids, bile acids, dietary choline, phosphatidylC, lysine, and carnitine. Simple "untargeted" interventions such as diet, fecal microbial transplant (FMT), and targeted interventions such as short chain fatty acid supplements and enzyme inhibition, may have some role in CV disease.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

SUNRISE 18: Who's Keeping Score? Risk Scoring Systems and Contemporary Risk Factors for Primary Graft Dysfunction in Heart Transplantation

Risky Business: Primary Graft Dysfunction and Risk Modeling

Javier Segovia, MD, PhD, Hospital Puerta de Hierro, Madrid, Spain

Primary graft dysfunction is related with frequent, unexpected high lethality, resource consumption with poor results, and frustration amongst transplant physicians. There remains an unmet need for tools to predict, diagnose and treat PGD. Various risk scores used in heart transplantation are RADIAL score which includes recipient age > 60 years, DM, inotrope therapy, RAP > 10 mm hg, donor age > 30 years, ischemic time > 240 mins.

2013 ISHLT Consensus on PGD (Montreal) includes:

1. PGD- left ventricle- includes left and biventricular dysfunction
    i. Mild PGD-LV- One of the following criteria- LVEF < 40%, or hemodynamics with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m2 lasting more than 1 hr requiring low-dose inotropes
    ii. Moderate PGD-LV- One criterion from I, and 1 from II- (I) LVEF < 40%, or hemodynamics with RAP > 15 m Hg, PCWP > 20 mm Hg, CI < 2.0 l/min/m2, MAP < 70 mm Hg lasting more than 1 hr and One criteria from following- high dose inotropes or newly placed IABP
    iii. Severe PGD- LV- Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD or percutaneous LVAD
2. PGD- right ventricle- includes right ventricular dysfunction alone. PGD-RV- Diagnosis requires either both I, ii, or iii alone:
    i. hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m2
    ii. TPG < 15 mm Hg and/or PASP < 50 mm Hg, or
    iii. Need for RVAD

Secondary graft dysfunction occurs when there is discernible cause for graft dysfunction (e.g., hyperacute rejection, pulmonary hypertension, known surgical complication). Donor risk factors include age, cause of death, trauma, cardiac dysfunction, inotropic support, and comorbidities: DM, HTN, downtime of cardiac arrest , drug abuse, LVH, valvular disease, Hormone treatment, CAD/wall motion abnormalities, sepsis, marginal donors, and hypernatremia.

Recipient risk factors include age, weight, mechanical support, congenital heart disease, multiple reoperations, LVAD explant, comorbidities like renal and liver dysfunction, ventilator dependence, multiorgan transplant, elevated PVR, allosensitization, infection and retransplant.

Procedural risk factors include ischemia time, donor recipient size mismatch, non-cardiac organ donation, experience of organ procurement and center volume, cardioplegic solution, increased blood transfusion requirement, elective vs emergency transplant.

Other scores used are PREDICTA score: Preoperative MCS, Recipient DM, Cardiopulmonary bypass

time > 180 min, Implant time, donor Age. ABCE score-treatment with ACE/ARB/ARNI/MRA, treatment with amiodarone and BB, previous cardiac surgery and ischemic time.

PGD has more than 30% hospital mortality and 40% one-year mortality, but good long term outcomes. Predictive models to date have relative value. However, we must be aware of characteristics associated with PGD. The new models using AI may overcome some of the limitations of classical ones- PGD consortium and studies based on pathophysiology of PGD may find these potential risks.

Rise of Machines: PGD Risk Scoring Systems in the MCS Bridge to Transplant Population
Lauren Truby, MD, Duke University Medical Center, Durham, NC USA
Despite ongoing improvements in waitlist outcomes, heart transplant recipients remain at high risk for early post-operative mortality. PGD is a devastating clinical event that is responsible for 60% of deaths in the first 30 days following heart transplantation. It is broadly defined as transient, acute failure of the new allograft to support recipient circulation. Despite recovery of biventricular function in 24-72 hours, it leads to multi-organ failure, prolonged intubation, and significant morbidity. There is increased recognition that patients bridged to transplant with LVAD are at increased risk of PGD.

Truby et al sought to review current evidence for the association between BTT LVADs and PGD, and to discuss the early evidence for PGD risk associated with tMCS in the context of the new allocation system. The RADIAL score predicts incident PGD, and was developed and validated in Europe. Their definition was similar to ISHLT's: hemodynamic compromise necessitating high dose inotropes of MCS. There was very low utilization of pre-transplant IABP or LVAD with poor generalizability to the United States' heart transplant landscape. BTT LVAD is associated with early post-transplant mortality and in a propensity matched cohort, the major cause of one-year cardiovascular mortality in propensity matched cohort was post graft failure.

Various predictors of ISHLT severe primary graft dysfunction in BTT patients is Creatinine, CVP/PCWP ratio, use of amiodarone, and more than one year of continuous flow LVAD support. Clinical features of high risk BTT recipients include recipient age, country, pre-transplant hemodialysis, non-ischemic CMP, and pre HT-CVP/PCWP ratio. Pre-HT VA-ECMO support increases the risk of PGD.

There are many questions that remain unanswered, but in conclusion, PGD remains a substantial clinical challenge following HT, and clinical risk factors alone fail to capture the spectrum of PGD risk in the rapidly changing landscape of transplant. Its underlying mechanism remains poorly understood. Precision medicine approaches hold great potential for the identification of novel biomarkers of PGD risk in the donor and recipient, and have lent insight into potential mechanisms that warrant additional investigation.

Danger Zone: How to Risk Stratify DCD Donors for Primary Graft Dysfunction
Simon Messer, MD, Royal Papworth Hospital, Cambridge, UK
Risk stratifying DCD donor hearts – normothermic regional perfusion, functional warm ischemic

time, perfusate lactate predicting ECMO, Coronary vascular resistance

The Papworth series NRP showed 100% one-year survival, with direct procurement and perfusion. DPP0 showed 86% survival with 18% ECMO with DPP, Sydney had 31% ECMO use. Normothermic regional perfusion: NYU did 7 DCD, no ECMO with 100% survival. Vanderbilt did 15 DCD hearts with no ECMO with 100% survival.

Serum lactate is a highly sensitive and specific predictor of post cardiac transplant outcomes using the organ care system. But lactate during ex situ heart perfusion does not predict the requirement for MCS following DCD heart transplants.

Mohite et al noted that the diastolic pressure and the coronary vascular resistance fell after 30 minutes of organ care system perfusion in the donor hearts that did not suffer PGD, whereas it remained high in the donor hearts that suffered PGD. In conclusion, NRP may reduce the risk of severe PGD in DCD heart transplant recipients. Prolonging the functional warm ischemic time beyond 30 mins may be associated with higher one-year mortality. Prolonged asystole to cardioplegia may be associated with severe PGD. Lactate did not seem to predict the requirement for ECMO post DCD heart transplant. Coronary vascular resistance may be a useful tool in predicting severe PGD in future.

Demystifying Vasoplegia After Heart Transplant: Predictor or Consequence of Primary Graft Dysfunction?

Fabiana Marcondes-Braga MD, PhD, Heart Institute Hospital, Sao Paolo, Brazil

Vasoplegia may be defined as severe hypotension (MAP 50 mm Hg), low systemic vascular resistance, or normal or high cardiac index (CI > 2.5 L/min/m2) in the first 48 hours after HT. It is refractory to vasopressor therapies (IV norepinephrine > 0.5 g/kg/min), and happens immediately after cardiac surgery or within 6-48 hours of weaning cardiopulmonary bypass. Mechanisms include increased systemic inflammation and endothelial dysfunction that leads to persistent hypotension, reduced systemic vascular resistance with normal or increased cardiac output.

Risk factors of vasoplegia after heart transplant include mechanical circulatory support pre-HT, prolonged cross clamp time, prolonged cardiopulmonary bypass time, and large transfusion requirements. Its treatment includes vasopressors to improve vascular tone and restore an adequate perfusion pressure with catecholamines, vasopressin, and methylene blue.

Hostile environment of the recipient results in multiple proinflammatory cytokines and overproduction of NO and other vasodilators. PGD pathogenesis involves:

1. Brain death release of NE-> Calcium overload-> impaired myocardial contractility
2. Low levels of T3/cortisol/insulin leading to depression of myocardial contractility
3. Reperfusion causing calcium overload -> impaired contractility
4. Older donor heart-> susceptible to ischemic injury
5. High PVR in recipient
6. Inflammatory response refractory to conventional vasopressors

Treatment includes low dose of inotropes; high dose of inotropes; or IABP, ECMO, LVAD and BiVAD. Vasoplegia is a risk factor for mortality after HT. However, in patients with no PGD, vasoplegia did not have much impact on outcomes.

Thus, we see that vasoplegia and PGD have common physiological pathways. Many risk factors of both are similar and include pre-transplant MCS, prolonged cross clamp and cardiopulmonary bypass times, and large transfusion requirements. Both are associated with poor prognosis. Vasoplegia may not have much impact on outcomes in absence of PGD. The nature of interplay between vasoplegia and PGD is not completely known.

The Age of Artificial Intelligence (AI): Novel Primary Graft Dysfunction Risk Scores Using Machine Learning

Yasbanoo Moayedi, MD, FRCPC, University Health Network, Toronto, ON Canada

Artificial intelligence is simply defined as a computer system that is able to perform tasks that normally require human intelligence. It involves machine learning, both supervised and unsupervised, and can be classified further. AI increases discriminatory power.

Calibration is defined as the ability of the model to assign an average risk of outcome accurately to a population. When observed outcome is more than estimated, it's underestimating risk, and when it is less than estimated risk, it is overestimating risk. Overfitting is the failure to learn rules that are generalizable; ML algorithms learn rules that perform well on training data but fail on test data. Explainability is a debate over using 'black-box' algorithms with 99% accuracy vs 80% decision tree with recognizable features.

PGD is a heterogeneous entity, has high dimensional data, with unknown distributions as current risk scores may not capture complexity, and the data is time-varying. "There is huge potential for machine learning to transform healthcare, but going from 'code to clinic' is the hard part." Clinicians need to learn AI but don't need to be experts. PGD is a high value problem for machine learning. The PGD consortium that includes 12 international centers provides a first opportunity to identify and predict PGD using more granular data. To achieve standard of care, ML algorithms need to be generalizable and vigorously tested.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

Session 74: Heart, Liver, MCS, Oh My! Walking Down the Yellow Brick Road With Adult Congenital Heart Disease Patients

Changing Landscape of Adult Congenital Heart Disease: Need for Advanced Therapies
Ari Cedars, MD, Johns Hopkins University, Baltimore, MD USA
As the number of individuals with adult congenital heart disease (CHD) increases, their early surgical correction and hearts with defects could fail, needing replacement strategies. Adults with CHD die young, and the number of their hospitalizations is increasing. Heart failure (HF) remains the leading cause of mortality in these patients, and there is no pharmacological therapy available for them.

The most common underlying causes of death differed by lesion severity. Those with severe lesions most commonly died from underlying CHD, whereas those with non-severe disease more commonly died from non-CHD causes. Because of the unique features of HF in CHD as outlined, these patients should be evaluated and managed by or in consultation with cardiologists and cardiac surgeons with expertise in CHD, ideally at a center with expertise in both CHD and HF. Providers should have a thorough knowledge of an individual patient's anatomy and physiology, which requires a thorough review of all surgical and procedural records.

How to Identify Advanced Heart Failure in Adult Congenital Heart Patients: Challenges in Identifying HF in ACHD
Rose Tompkins, MD, Cedars-Sinai Medical Center, Los Angeles, CA USA
The number of adult patients with congenital heart disease is increasing. Heart failure is the leading cause of late mortality in adult congenital heart disease. There is no universally accepted definition for ACHD HF, as their hearts are never structurally normal, they exhibit nonspecific signs and symptoms, and most ACHD patients have high NT-proBNP levels.

The course of HF in ACHD is different than acquired HF with a different age of onset, gradual onset of symptoms, and they never return to baseline—unlike ACHD HF, where the baseline is never normal, but they return to baseline amidst events. The staging of HF in ACHD is also not straightforward due to the vast heterogeneity of ACHD patients. Their NYHA class is unreliable and baseline VO2 abnormal; also, there are challenges in assessment of progressive ventricular dysfunction per echocardiogram. Furthermore, ACHD patients often under-report symptoms until they are quite advanced. Approaching HF management in ACHD is also different, as there is no guideline directed medical therapy in ACHD HF.

If despite optimization there is progressive decline, early referral for OHT/advanced therapies is recommended, ideally at a center with ACHD expertise. It is noteworthy that there are many challenges with regards to listing, waitlist time, transplant surgery and most patients do not get transplanted. We may need frank and honest goals of care discussions sand palliative care team involvement. Timely intervention impacts long term outcomes.

When to Consider Heart/Liver Transplant in Fontan Patients

Sharon Chen, MD, MPH, Stanford University, Stanford, CA USA

All Fontan patients are seen regularly by a transplant hepatologist irrespective of their health status in a multidisciplinary clinic setting with serial assessments over time. One should have regular joint selection and monthly review meetings with the liver transplant team. Final intraoperative assessment of the liver at the time of transplant includes the decision to proceed made after gross inspection +/- biopsy.

Of 18 patients with Fontan listed for HLT, five received heart-only based on intra-operative assessment. All patients did well, though one is being closely monitored for progressive liver disease. All 13 patients who received HLT had pathology confirmed cirrhosis. As per a report from FOSTER study, HLT is better than HT for certain patients. It was a multicenter registry of adult Fontan patients referred for transplant. Over 130 patients, around 40 had HLT.

The survival benefit of HLT over HT, especially in those with more severe fatty liver disease. Liver surveillance is needed for all Fontans, not just at the time of transplant consideration, but should continue for those who receive heart-only transplants. Earlier transplant consideration is needed for many Fontan patients with > 10% Fontans seen for 1st heart failure consultation die or are declined for transplant within 30 days. FALD can progress during long wait times. There may be a potential role for VAD to bridge from heart-liver to heart only.

Durable Mechanical Circulatory Support for Adult Congenital Heart Disease

Fabrizio De Rita, FRCS, Freeman Hospital, Newcastle-upon-Tyne, UK

In adults with CHD, HF remains the leading cause of morbidity and mortality, accounting for > 20% hospital admissions. Details of patient and device selection are critical to understand this very complex group. However, there is a very low level of evidence based on case series and case reports with regards to patient selection, who should perform implantation, and when, and on what type of device.

MCS in failing systemic RV- chronic dysfunction and dilatation leads to elevated end diastolic pressure, valvular dysfunction, and poor compliance of baffles. Three quarters of those catharized for HF have post capillary pulmonary hypertension. Adults with biventricular circulation with a systemic right ventricle develop premature HF. These young, high-risk patients have disproportionately poor access to advanced therapies. A subaortic VAD offers a high chance of bridge to heart transplant. There are certain intra-operative surgical considerations for these patients. The role of tricuspid valve replacement during implantation of a VAD for failing systemic RV to improve hemodynamics is the key question. It is associated with significant reduction in pulmonary wedge- and mean pulmonary artery pressure and subsequent improvement in subpulmonic left ventricular function with no obvious reverse remodeling of systemic RV. Therefore, it may not only expedite reduction in transpulmonary gradient but also prevent progressive subpulmonic LV failure.

MCS in failing Fontan physiology- Proportion of Fontan patients will develop Fontan failure, that is largely non-ventricular function related failure. Ultimate therapy is heart transplantation, but

most of the patients are poor candidates for heart transplantation. Question remains if MCS can reverse end organ dysfunction or reduce morbidity/mortality on the waiting list for/after the transplant. Berlin Heart Fontan Cannula project focuses on RVAD as relief from venous congestion, to create effective access to the venous circulation, and reduce intra-operative risk. REGIVE study is actively enrolling patients.

VIEW SESSION DETAILS

– Summary by Anju Bhardwaj, MD

SESSION 82: Revisiting the Status Quo: Changing Paradigms in Routine Heart Transplant Rejection Surveillance

To Bx or not to Bx? That used to be the question.

But now a growing array of non-invasive options, which can be employed on various schedules and in various combinations, have spawned countless possible strategies for rejection surveillance after heart transplant (HT). Lest we become paralyzed by choice à la Hamlet, we might recall Falstaff's credo that "the better part of valor is discretion."

But what constitutes "discretion" in the context of 21st century post-HT surveillance? This was a prevailing question at the Saturday symposium **Revisiting the Status Quo: Changing Paradigms in Routine Heart Transplant Rejection Surveillance**. **Angeline Leet, MD**, of Alfred Hospital in Melbourne, Australia offered an astute answer: "The question we should be asking ourselves on a regular basis is 'why are we performing this surveillance test?'… as each has associated costs, complications, and limitations in availability and expertise." She argued that any test detecting early, subclinical rejection is "worth it" only if it prompts a significant change in prognosis or a modification in therapy. Speakers at today's symposium shared this pragmatic view, focusing not just on how reliably a given test might predict the results of endomyocardial biopsy, but how it would change management. Such a focus demands a patient-specific approach, in lieu of "one size fits all" protocols.

Shelley Hall, MD, of Baylor University Medical Center in Dallas, TX USA, opened the symposium with an expert overview of the molecular modalities available, in her talk ***Beyond the Surface: Non-Invasive Diagnostics for Rejection Surveillance***. **Katharina Wassilew, MD, DScmed, MHBA**, of Rigshospitalet in Copenhagen, Denmark offered further scrutiny in her talk, ***Do Non-Invasive Diagnostic Results Correlate with Histopathological Diagnoses Based on Endomyocardial Biopsy Interpretation?***, while reminding us that even the "gold standard" (i.e., biopsy) has its limitations. **Emanuele Cozzi, MD, PhD**, of Padua University in Padova, Italy, echoed the importance of the "patient-specific" approach to diagnosing rejection—particularly in the interpretation of DSA measurements among highly-sensitized patients—in her talk ***Diagnosis and Clinical Implication of HLA and Non-HLA DSA in Daily Practice***.

Dr. Leet offered other "candid" insights in her talk, ***Say Cheese: Use of Imaging in Rejection Surveillance***. Surveying the relevant literature, she noted that global longitudinal strain as assessed by two-dimensional speckle tracking exhibits excellent sensitivity for diagnosis of early rejection; however, other echocardiographic markers (e.g., ejection fraction, circumferential strain, ventricular thickness) perform poorly. Cardiac MRI offers the theoretical advantage that it can characterize areas of myocardium not accessible via endomyocardial biopsy. This has been borne out by data showing that T1 relaxation time is predictive of biopsy-negative rejection and that T2 relaxation time predicts not only rejection but adverse outcomes (Miller et al 2019).

Finally, **Eugene DePasquale, MD**, of USC in Los Angeles, CA USA, offered a practical synthesis of

these findings in ***Putting It All Together: Integrating Approaches for Rejection Assessment***. One exciting area of integration is in the combined use of gene expression profiling and donor-derived cell free DNA—analyses by his group and others indicate that their combination performs better than either test alone. The molecular approach has replaced endomyocardial biopsy as the routine mode of rejection surveillance at USC. "To Bx or not to Bx" remains a question, but one asked less frequently—and only "for cause"—at many HT centers.

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD

SESSION 76: Everything You Wanted to Know About ddCF-DNA in Heart Transplant Recipients and Never Dared to Ask

Cell-free donor-derived DNA (cfdNA) has become a powerful marker of myocardial damage with a high negative predictive value for the detection of rejection. **This oral abstract session** provided new insights into the use and implications of donor derived cell-free DNA (dd-cfdDNA) in heart transplant recipients.

Rationale and Design of a Randomized Controlled Trial of Donor-Derived Cell-Free DNA to Detect Rejection in Cardiac Transplantation (DETECT)

Josef Stehlik, MD, MPH, University of Utah School of Medicine, Salt Lake City, UT USA
The investigators presented the rationale and study design of a multi-center, prospective, randomized controlled DETECT trial (NCT05081739). The primary objective of this RCT will be to examine if rejection surveillance of heart transplant recipients with dd-cfDNA using the Prospera test is non-inferior to rejection surveillance with endomyocardial biopsy (EMB) and histology in the first post-transplant year.

Six hundred patients will be randomized 1:1 to the study group (dd-cfDNA) or the control group (EMB). The study duration is estimated to be approximately four years, with up to three years spent enrolling the participants followed by one year follow up for each participant. All patients aged 18 years or greater, who are listed for transplant and willing to provide written informed consent, will be enrolled. Key exclusion criteria will include multiple solid organ or tissue transplant; prior history of organ or cellular transplant; pregnancy; hemodynamic instability; and planned use of commercial or investigational cfDNA or GEP assays.

The primary endpoint will be a composite of treated rejection, graft dysfunction, re-transplantation, or death at 12 months after transplant. Secondary endpoints will include individual components of the primary endpoint; rejection with hemodynamic compromise; de novo donor specific antibodies; cardiac allograft vasculopathy; HR-QOL; and number of EMB. Core labs will be utilized: pathology, echocardiography, DSA, and protein biomarkers, transcriptomics.

Study results are anticipated to directly impact clinical practice in rejection surveillance, and get us closer to using dd-cfDNA in clinical decision making beyond rejection surveillance.

Should We Be Comforted by a "Negative" Endomyocardial Biopsy? Risk of Future Events with Donor Derived Cell Free DNA in the Setting of Histologic Quiescence

Jeffrey Teuteberg, MD, Stanford University, Stanford, CA USA
The investigators sought to examine the significance of elevated levels of donor-derived cell free DNA (dd-cfDNA) in the setting of a "negative" endomyocardial biopsy (EMB). The study reviewed patients from the multi-center Surveillance Using HeartCare Outcomes Registry (SHORE) database who had dd-cfDNA measured within 30 days of a negative EMB (Grades 2R/AMR1 or higher rejection) within the first 100 days of heart transplant (HT). These patients were followed for the subsequent development of significant rejection and de novo donor-specific antibodies (dnDSA)

over the next 365 days.

The study included a total of 648 HT recipients with a mean age of 57, 74% male, 64% white, 60% of which had PRA < 1% and had a total of 982 paired biopsies with a median dd-cfDNA of 0.05% for those with a Grade 0R and 0.06% for Grade 1R biopsy. The dd-cfDNA was measured a median of 112 days post-transplant for Grade 0R and 109 days post-transplant for Grade 1R.

Despite negative histology on EMB, those with a cfDNA >= 0.20% were at significantly higher risk for the development of significant rejection (14.3% v 5.2%, p<0.01) and dnDSA (11.3% v. 6.8%, p<0.01) over the subsequent year. The authors concluded that the use of dd-cfDNA may be a better method to determine true quiescence and called into question the utility of the EMB as the gold standard for cardiac allograft monitoring.

Prognostic Implications and Characteristics of Low dd-cfDNA Results in Heart Transplant Patients with Biopsy Proven Rejection

Roopa Rao, MD, Indiana University, Indianapolis, IN USA

In contrast to the previous abstract, the investigators of this study examined the characteristics and prognostic implications of low level dd-cfDNA in patients with histological evidence of acute rejection. atients enrolled in the Surveillance HeartCare Outcomes Registry (SHORE) with biopsy proven acute cellular rejection (ACR) and antibody mediated rejection (AMR) who had low levels of dd-cfDNA (<0.15%) were evaluated. Patients with ACR 1R were excluded. Only those patients who had a dd-cfDNA level within 30 days of biopsy were included. Sixty-one patients (male 78%, median age 48 years) had low dd-cfDNA and endomyocardial biopsy evidence of ACR ⩾2R and/or AMR ⩾1R. Mean duration of the biopsy from the time of transplant was 196.31 days. ACR was seen in 36 patients (35=2R, 1=3R) and AMR was seen in 27 patients (21=pAMR 1(H+), 6=pAMR2). 2 patients had both ACR and AMR. Mean ejection fraction (EF) at the time of the rejection was mostly preserved. 2 patients died 330±31days after the initial diagnosis of rejection. None of the patients developed graft dysfunction at one year follow up. The authors concluded that patients with low dd-cfDNA and biopsy-confirmed rejection typically had lower grades of rejection and maintained preserved left ventricular function on echocardiography. As such, consideration of dd-cfDNA in treatment and immunosuppression management requires ongoing evaluation.

Absolute Quantification of Donor Derived Cell Free DNA in Heart Transplant Patients

Paul J. Kim, MD, UC San Diego Health, San Diego, CA USA

The authors investigated the performance of absolute quantification to detect acute rejection (AR) in heart transplant recipients. They measured both dd-cfDNA fraction (%) and absolute quantity (copies/mL) using a clinically available SNP-based massively multiplexed PCR dd-cfDNA assay.

Out of 447 samples collected from 150 heart-transplant only patients, 29 had AR and 418 did not. Both dd-cfDNA fraction and absolute quantity were significantly higher in samples with acute rejection (AR) compared to samples with no AR. Median dd-cfDNA fraction for AR was 0.62% (IQR: 0.09-1.43) and significantly higher than no AR at 0.04% (0.01-0.11, p < 0.01). Median absolute dd-cfDNA for AR was 78.8 copies/mL (5.3-125.6) and significantly higher than no AR at 2.7 copies/mL (1.37-6.90, p=1.67e-09).

The results suggest that the absolute quantification of dd-cfDNA may increase the accuracy to discriminate rejection when compared with dd-cfDNA expressed as a percentage of total cfDNA.

Impact on Donor Derived Cell Free DNA (dd-cfDNA) of Procurement Using Paragonix SherpaPak™ (SP) Cardiac Transport System versus ICE Transportation

Johanna van Zyl, PhD, Baylor Scott & White Research Institute, Dallas, TX USA

The authors aimed to determine if differences exist in dd-cfDNA values when using SherpaPak (SP) compared to historical ice transportation methods. They performed a retrospective review of 50 single organ heart transplant (HT) recipients who had heart care measurements within 90 days post-transplant. Twenty-nine recipient hearts were transported on ice and 21 with SP. Recipient and donor characteristics were similar with expected shorter mean and maximum total ischemic times on ice compared to SP. Median dd-cfDNA level was the highest within the first 27 days in both groups and were comparable up to 90 days. In SP patients, long ischemic times had higher dd-cfDNA compared to short ischemic times ($p=0.01$). This relationship was not observed in ice patients ($p=0.41$). The overall cohort with long ischemic times, regardless of transport method, had higher levels of dd-cfDNA within the first 90 days ($p=0.012$). The authors concluded that patients with long ischemic times are more likely to have higher dd-cfDNA vs short ischemic times. Further studies are needed to confirm these preliminary findings.

Relationship of Noninvasive Detection of Allograft Rejection and Injury (Donor-Derived Cell Free DNA and Gene Expression Profiling) and Tissue-Based Molecular Microscopic Diagnosis After Heart Transplantation

Dae Hyun Lee, MD, University of South Florida, Tampa, FL USA

The authors sought to examine the relationship between dd-cfDNA and gene expression profiling (GEP) and molecular microscopic transcript (MMDx) in heart transplant (HTx). A total of 108 patients were included in this retrospective analysis. Using MMDx, there were 9 patients with ACR, 39 with AMR, 2 with mixed rejection (AMR/ACR), and 58 with no rejection. Elevations in dd-cfDNA occurred in the ACR, AMR, mixed rejection groups, when compared to no rejection (Median: 0.24%, 1.20%, 2.90%, 0.12%, respectively, $P<0.001$). However, GEP was not different between different groups of MMDx. The AUC for dd-cfDNA and rejection by MMDx was 0.89 [95% C.I.: 0.83-0.96]. These findings suggest that non-invasive quantitative detection of dd-cfDNA correlates well with the tissue molecular microscopic transcript in both AMR and ACR in heart transplant patients. Future studies should examine how the addition of dd-cfDNA/GEP and MMDx would complement the diagnosis and prognosis of allograft injury in HTx.

VIEW SESSION DETAILS

– Summary by Rachna Kataria, MD

SESSION 80: More Than Meets the Gut: Nutrition and the Microbiome in Heart Transplantation

Time to trust our gut? (as a marker of post-transplant outcomes)

Saturday's oral abstract session, **More Than Meets the Gut: Nutrition and the Microbiome in Heart Transplantation**, featured cutting-edge research exploring the potential role of the gut microbiome in predicting (and perhaps influencing) post-heart transplant (HT) management and outcomes.

It opened with two abstracts presented by **Mark Dela Cruz, MD**, of the University of Chicago, titled ***The Gut Microbiome as a Marker of Early Cardiac Allograft Injury*** and ***The Gut Microbiome and Tacrolimus Dosing in the Peri-Heart Transplant Period***. Both analyses utilized a single-center, prospective cohort (n = 38 and 32, respectively) in which stool samples were collected within the first two weeks post-HT. Overall within-sample (i.e., "alpha") microbial diversity was not associated with markers of injury (i.e., Allosure and Allomap scores) or tacrolimus metabolism; however, a look at specific bacterial taxa was more revealing. Specifically, greater abundances of the phyla Bacteroides and Firmicutes were predictive of lower Allosure and Allomap scores, respectively; both were associated with slower Tacrolimus metabolism. These signals were far from subtle; slow Tacrolimus metabolizers had double the abundance of Bacteroides (39% vs. 19%), and similar ~20% absolute differences were seen for the other observed associations.

The humble, ubiquitous Bacteroides retained the spotlight in the presentation that followed: ***Association of Gut Bacterial Beta Glucuronidase Activity with Mycophenolate Mofetil (MMF) Induced Cytopenia***, by **Lorenzo Braghieri, MD**, of Columbia University Medical Center in New York, NY USA. Stool abundance of β-D-glucuronidases-producing (GUS) bacteria—and of the specific GUS species Bacteroides dorei and Bacteroides cellulosilyticus—were each associated with higher rates of leukopenia after HT in their cohort (n=45). That GUS bacteria are known to influence the metabolism of MMF—a leading cause of post-HT cytopenia—suggests that this association is causal.

For those of us still hesitant to "trust our gut," further compelling evidence was offered by **Joseph Spinner, MD**, of Baylor College of Medicine in Houston, TX USA in his presentation ***Alterations to the Intestinal Microbiome Are Associated with Post-Heart Transplant Outcomes in Children***. In their sample of 105 children undergoing HT, there were significant compositional differences in the gut microbiome both 1) pre- vs. post-HT, and 2) in those with vs. without adverse post-HT events.

All three presenters acknowledged the "chicken vs. egg" dilemma posed by their findings, as articulated by Dr. Spinner: "Whether these compositional alterations are a cause or effect, or if they can be reversed, remains to be elucidated." Indeed, we can now only speculate as to the mechanism of these (fairly convincing) links between gut microbiota and clinical events after HT. Nonetheless, the authors' painstaking efforts to construct these novel cohorts and conduct sophisticated analyses are commendable. And while a mechanistic understanding may be elusive,

perhaps the use of gut microbial markers in prognostication and clinical management (e.g. in guiding MMF dosing) is not as far off?

Additional abstracts presented in today's session explored the importance of metabolism in the HT context on a more macroscopic scale. In ***Metabolic Syndrome in Heart Transplantation: An Underestimated Risk Factor?***, **Veronica Ferrara, MS**, of University of Udine in Udine, Italy presented a rigorous analysis that answered the titular question with a resounding "yes." However, low BMI seems much less influential, as shown by **Jignesh Patel, MD, PhD**, of Cedars-Sinai Medical Center in Los Angeles, CA USA in his analysis ***Severely Underweight: Is It a Risk Factor for Poor Outcomes in Post-Heart Transplant Patients?***

VIEW SESSION DETAILS

– Summary by Brian Wayda, MD