ISHLT2023 Roving Reporters – Reports from Advanced Heart Failure and Transplantation (AHFTX)

- **Wednesday, 19 April, 2023**
  - FEATURED ABSTRACT 02 at General Session I. Subgroup Safety Analysis in SOT Recipients in a Phase 3 Trial of Maribavir (MBV) versus Investigator-Assigned Therapy (IAT) For CMV Infection (Refractory with or without Resistance)
  - SESSION 03 (SYMPOSIUM). Back to the Future of AMR: A Multidisciplinary Symposium
  - SESSION 17 (SYMPOSIUM). Donor Lung Allocation: Prioritizing Urgency, Access or Outcomes - What Matters Most?
  - SESSION 22 (SYMPOSIUM). Pregnancy and Beyond: Reproductive Health in Heart and Lung Failure
  - SESSION 07 (ORAL). There and Back Again: Science of Lung Ischemia-Reperfusion Injury and Primary Graft Dysfunction
  - MINI ORAL 02. The Force Awakens: Advances in Lung Preservation to Improve Donor Selection and Recipient Outcomes
- **Thursday, 20 April, 2023**
  - SESSION 38 (SYMPOSIUM). The Unusual Suspects: Immune and Tissue Drivers of Lung Allograft Pathologies
  - SESSION 35 (ORAL). An Unexpected Journey: Perfusion Science in Lung Transplantation
  - SESSION 49 (ORAL). Days of Our Lives: Lung Donor-Recipient Allocation and Outcomes
- **Friday, 21 April, 2023**
  - SESSION 52. Immune Checkpoints in Thoracic Transplantation: Lessons Learned from Cancer
  - SESSION 59. Die Hard: Preventing and Managing Hard-to-Treat Fungal and Bacterial Infections in the Perioperative Setting
  - SESSION 80. Rocky Mountain High: Scaling New Heights in CMV
  - MINI ORAL 17. The Clone Wars: OR and Peri-operative Improvements in Lung Transplantation

- **Saturday, 22 April, 2023**
  - SESSION 88 (ORAL). Contagion Meets Outbreak: Lessons Learned from COVID-19 in Lung Transplantation
  - SESSION 102 (ORAL): Love, Actually: Rejection in Lung Transplantation

Thank you to all of our ISHLT2023 Roving Reporters.

ADVANCED HEART FAILURE AND TRANSPLANTATION (AHFTX)

Jason Goldberg, MD, MS, Inova LJ Murphy Children's Hospital, Fairfax, VA USA
Luise Holzhauser, MD, University of Pennsylvania, Philadelphia, PA USA
Pei Jun Zhao, MD, MPH, London Health Sciences Centre / Western University, London, ON Canada

ADVANCED LUNG FAILURE AND TRANSPLANTATION (ALFTX)

Lourdes Chacon Alberty, MD, MCTM, Texas Heart Institute, Houston, TX USA
Rebecca Klingbeil, MSN, DNP, CRNA, Mayo Clinic, Jacksonville, FL USA

MECHANICAL CIRCULATORY SUPPORT (MCS)

Anju Bhardwaj, MD, University of Texas / McGovern Medical School, Houston, TX USA
Anjan Tibrewala, MD, Northwestern University, Chicago, IL USA

PULMONARY VASCULAR DISEASE (PVD)

Nancy Luo, MD, MHS, Sutter Health, Sacramento, CA USA

FEATURED ABSTRACT 02 at General Session I. Subgroup Safety Analysis in SOT Recipients in a Phase 3 Trial of Maribavir (MBV) versus Investigator-Assigned Therapy (IAT) For CMV Infection (Refractory with or without Resistance)

Presenter: ***Ricardo La Hoz, MD****, University of Texas Southwestern Medical Center, Dallas, TX USA*

During this research abstract presentation, we first heard about the limited treatment options for cytomegalovirus (CMV) infection post-solid organ transplant (SOT) due to toxicities associated with conventional anti-CMV therapies (doi: 10.1080/17474086.2016.1174571) (doi: 10.1089/sur.2015.266) and development of resistance (doi: 10.1182/blood-2016-06-688432), followed by a summary of the results from the phase 3 SOLSTICE study (NCT02931539) in transplant recipients with refractory resistance (R/R) to CMV infection (n=352) who received MBV or IAT (val/ganciclovir, foscarnet, or cidofovir).

The study showed CMV viremia clearance at week 8 (55.7% vs 23.9% respectively) with important benefices in SOT recipients (55.6% vs 26.1%). Dr. La Hoz presented the safety data from the SOT subgroup (n= 211) in the SOLSTICE trial. The safety outcomes included graft outcome, tx-emergent adverse event (TEAEs), and TEAEs considered related to transplant. Among the results in this relatively small number of SOPT recipients, no recipient graft loss was observed in either treatment arm. Additionally, the TEAE rates of AKI and neutropenia were found to be lower in the patients receiving MBV compared to IAT. Dysgeusia was higher in the MBV arm, but this did not lead to discontinuation of the study treatment.

Dr. La Hoz concluded that the data presented in this sub-analysis is consistent with the overall population safety results seen in the SOLSTICE study.

VIEW FULL ABSTRACT

– Commentary by Lourdes Chacon Alberty, MD, MCTM

SESSION 03. Back to the Future of AMR: A Multidisciplinary Symposium

After an inspiring opening plenary, "Back to the Future of AMR," co-chaired by **Glen Westall, FRACP, PhD** from Alfred Hospital in Melbourne, and **Meghan Aversa, MD**, from the University of Toronto, engaged attendees seeking an update about the current state of knowledge on the detection, pathogenesis, and treatment of antibody-mediated rejection (AMR).

Jake Natalini, MD, MSCE, from NYU Langdon Health in New York, set the tone for the session by presenting the case of a 62-year-old female, bilateral lung-transplant recipient, noted to have new onset non-productive cough and a 15% decline in FEV1 from baseline at three months post-transplant. The patient's pre-transplant slight sensitization (cPRA 10%; B42 crossed at MFI 2400), newly determined positive donor-specific antibodies (DSAs), positive BAL adenovirus, and lack of ischemic or stenotic changes on fiberoptic exam, further complicated the scenario.

Using the 2016 ISHLT consensus guidelines, five domains were assessed to help determine the definite, probable, or possible likelihood of AMR. Arguably, positive allograft dysfunction, exclusion of other causes, no compatible lung histopathologic findings, and positive class I and class II DSAs pointed to a "probable" diagnosis, though initial C4d biopsy results were pending. Dr. Natalini's team discussed numerous treatment options, but ultimately ordered additional tests, including PFTs. In the interim, the patient's FEV1 continued to decline, DSAs remained stable, C4d stains returned negative, and chest x-ray resulted normal. Dr. Natalini left the audience questioning what would they do in Shakespearian fashion: "To treat or not to treat?"

To help answer the question, **Debbie Levine, MD**, from Stanford University in Palo Alto, took the stage and applauded the case presentation's ability to highlight the conundrum of diagnosing, managing, and monitoring pulmonary AMR. The 2016 consensus statement guidelines are currently being updated. Although the new 2023 iteration provides details about various aspects of AMR, Dr. Levine urges that as clinicians, the two most important questions to answer are: 1. How confident are we about diagnosing a patient with AMR? and 2. How and when should we treat the patient? Before outlining key differences in the consensus, she reminds the audience that the main goal of the 2016 AMR workgroup was to set a foundational standardized AMR nomenclature for the pulmonary transplant community. The original guidelines were intended to be a living document, accounting for variations in resources, testing techniques, and reporting. Since 2016, there has been substantial growth culminating from the areas of evidence, experience, and innovation reported in the literature.

In particular, the 2023 guidelines will expand upon the original five criteria and include new areas of consideration such as biomarkers and assays of acute lung allograft dysfunction (ALAD). Clinicians now recognize that likely it is not one or two distinct pathologic diagnoses that are important; rather, there are patterns of "non-rejection or non-histologic changes" that must be considered.

Dr. Levine then highlighted two projects that she believes are instrumental moving forward and warrant further review: The Lung Allograft Standardized Histological Analysis (LASHA) grid and the Sensitization in Transplantation Assessment of Risk 2022 Working Group Meeting Report (STARR 2022). In closing, by using a modified Delphi framework, the 2023 ISHLT Pulmonary AMR Working Group aims to: 1. update the consensus definition, assessment score and recommendations, 2. decrease practice heterogeneity through a standardized nomenclature, and 3. identify the best endpoints for diagnostic studies and therapeutic trials.

Next, **Adriana Zeevi, PhD**, of the University of Pittsburgh, gave a beautiful lecture on the evaluation and detection of pulmonary AMR, where she tackled the questions: how and why should antibody characteristics be evaluated? In rhetorical fashion, Dr. Zeevi questioned if it is possible to use the widely accepted qualitative and quantitative HLA-Ab characteristics (MFI, titer, and complement binding) and associate the results with clinical outcome. To build her case, she described three well-known problems: 1. saturation of (single-antigen) beads 2. inhibition, resulting from prozone creation by serum complement (C1q) and 3. the dilution effect arising from shared epitope by multiple HLA-Ags, resulting in a diluted MFI value.

Dr. Zeevi concludes that the personalized use of serial dilutions of single-antigen beads have applications pre- and post-transplant, and can further provide information for desensitization, waitlist management, risk stratification, and response to AMR treatment in the sensitized patient. She then applies this information to the aforementioned case report, suggesting a 1:4 or 1:16 dilution technique could be used to define if all DSAs are low-titer or complement-binding, and possibly explain the C4d negative biopsy. Dr. Zeevi closed by reminding the listeners that the utilization of HLA-DSA in AMR diagnosis requires molecular donor and recipient typing. Further, in determining the impact of circulating DSA, multiple tests should be performed to evaluate strength, titer, and function.

To round out this multidisciplinary session, pharmacist **Adam Cochrane, PharmD, MPH, BCTXP** of Inova Fairfax Hospital, wrapped up the symposium by discussing the present and future of AMR treatment through an illustrative “bucket” analogy. Current treatments were said to fall into one of three buckets, intervening against: antibodies, B-cells, or plasma cells. Current treatments were further classified as belonging in “leaky buckets,” as rituximab only affects the CD20 receptor, and proteasome inhibitors only affect class I DSAs. Unsatisfied with the current treatments, Dr. Cochrane kept the audience’s attention by exploring future treatments, most of which come out of kidney transplant literature.

Daratumumab (anti-CD38 agent) and tocilizumab (IL-6 antagonist), both having limited or no studies in lung transplant recipients, were placed in a “potentially leaky” or “maybe-okay bucket.” Clazakizumab (binds IL-6), Fostamatinib (tyrosine kinase inhibitor), and Felzartamab (Anti-CD38), all in phase II trials with limited data, were placed in “tiny buckets.” Eculizumab (a complement inhibitor), with larger multi-center studies having been abandoned due to lack of efficacy and being known as one of the most expensive drugs in the world, was placed into a “bucket full of money.” Cochrane closed by acknowledging that more buckets are needed, and the future of AMR

treatment will certainly not fit in just “one big bucket.”

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 17. Donor Lung Allocation: Prioritizing Urgency, Access or Outcomes - What Matters Most?

The aim of this session was to provide an overview of three donor lung allocation systems, including the new continuous allocation system in the United States using the composite allocation system, France's relatively new lung allocation system utilizing supply and demand, and Scandiatransplant's Urgent Lung Allocation System (ScuLAS). The session was co-chaired by **Luke Benvenuto, MD**, of Columbia University in New York, and **Carli Lehr, MD, PhD**, of the Cleveland Clinic in Cleveland.

Composite Allocation System (CAS): What to Expect

Maryam Valapour, MD, MPP, of the Cleveland Clinic, described the framework of the new US lung allocation system and the projected impact of the system on the transplant population.

Supply-Demand Ratio for Lung Allocation in France

Antoine Roux, MD, PhD, of Foch Hospital in Paris, provided a general overview of the allocation in France, and pros/cons of the system, equitability, and the opportunities for improvement. How does the does the IT compare to other systems?

Multinational Urgent Lung Allocation in Scandiatransplant

Hans Henrik Schultz, MD, PhD, of Rigshospitalet in Copenhagen, provided an overview of the organ exchange organization for Scandinavian countries (a total population of 29.3 million people). The Scandiatransplant Urgent Lung Allocation System (ScuLAS) was introduced in 2009, and since then 155 urgent calls out of 1,841 lung transplants have been performed in Scandinavia (DOI: 10.1016/j.healun.2018.08.002). Additionally, Dr. Schultz described the benefits and limitations of the system.

How the Lessons Learned from the US LAS Can Be Used to Inform International Models

Jens Gottlieb, MD, of Hannover Medical School, discussed the impact of the LAS system on international transplant systems and how the expected changes to the United States system may be useful to other countries.

Dr. Gottlieb focused on the following lessons to be learned from the new US lung allocation policy;

- Composite scores and how they may work
- Development of a new score
- The way out of rescue allocation
- Geographic sharing

Additionally, Dr. Gottlieb described the need of non-US countries to improve data quality and data management to build their own allocation models. He also shared how the EU General Data Protection Regulation (GDPR) has been a major obstacle to develop a Europe specific model.

Dr. Gottlieb concluded that the LAS successfully validated in four non-US countries and is functional there for > 5-11 years. The composite score attempts to compensate for biological barriers of patients in the urgency/survival LAS model (50%) to optimize equity, utility, and efficacy. These additional criteria (50%) were established by a public ethical consensus and impact on allocation was estimated mathematically. Moreover, an "adjusted benefit" score may be useful to allocate donor lungs to recipients corrected for biology and efficacy based on contemporary data, to encourage non-US countries in developing their own composite score models and solve the problem of rescue allocation in Eurotransplant and to allow broader geographic sharing in supranational allocation systems.

Pediatric Organ Allocation: Similarities and Differences Around the World

Christian Benden, MD, MBA, FCCP, of the University of Zurich, discussed how organs are allocated to pediatric recipients in the United States and internationally, and highlighted considerations unique to the pediatric population (DOI: 10.1016/j.healun.2016.10.007). Dr. Benden concluded that overall, there is substantial variation worldwide in the pediatric lung organ allocation, both in terms of prioritization and distribution. However, this is expected given the variability in health care and in medical practices in pediatric LTX internationally. Further, variations exist regarding cutoff between adult and pediatric donor and recipients, and pediatric candidate prioritization. Improving organ allocation in pediatric LTX is crucial in providing high quality and equitable transplant care for children around the world.

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

SESSION 22. Pregnancy and Beyond: Reproductive Health in Heart and Lung Failure

Pregnancy in patients with end-stage heart and/or lung disease is considered high risk, and often poses a clinical and ethical dilemma for the patient and the provider. This session discussed controversial topics related to pregnancy in this high-risk population. The session was co-chaired by **Anique Ducharme, MD, MSC**, of Université de Montréal, and **Jesper Magnusson, MD, PhD**, of Sahlgrenska University Hospital in Göteborg.

Reproductive health in end stage heart and lung failure is a topic that bears serious discussion, especially given the United States' Supreme Court decision in Dobbs v. Jackson Women's Health Organization, in which the Court held that the Constitution of the United States does not confer any right to abortion. This ruling may impact the medical care of transplant recipients and those with durable MCS.

Pregnancy in Pulmonary Arterial Hypertension

Jennifer Haythe, MD, of Columbia University Medical Center in New York, began the session by defining pulmonary hypertension (doi: 10.1093/eurheartj/ehac237) and the normal hemodynamic changes of pregnancy (doi: 10.1016/j.ccm.2020.10.006), its effects on cardiopulmonary circulation in pulmonary hypertension (doi.org/10.1161/JAHA.113.000712) and clinical management (doi: 10.1086/682230).

Pregnancy after Transplantation (Heart/Lung)

Lynn Punnoose, MD, of Vanderbilt University Medical Center in Nashville, discussed counseling for pregnancy timing (when stability has been achieved in graft and recipient) (doi: 10.1016/j.healun.2022.10.009) (doi: 10.1016/j.healun.2015.08.014). She also discussed risk stratification (assessing comorbidities and infection), and the assessment of graft function and rejection risk. The shared details on the outcomes of pregnancy in lung and heart transplantation, including low birthweight and preterm birth as frequent complications, as well as maternal and fetal comorbidity, which are higher than in non-transplant population.

A planned approach to pregnancy allows transition of teratogenic agents (DOI: 10.1055/s-0035-1556743). Dr. Punnoose concluded her presentation with the importance of establishing a stepwise approach to pregnancy:

Counseling for all women of reproductive age, pre-transplant:

- Timing of pregnancy
- Maternal and fetal outcomes (short and long term)
- Contraception

Planning is important for patients who intend pregnancy:

- Changes to immunosuppression and other medications
- Consider genetic counseling
- Assess psychological morbidity

- Risk stratify based on graft function, comorbidities

Multidisciplinary approach to managing pregnancy:
- Create a plan for periodic assessment

Pregnancy in Patients with Left Ventricular Assist Devices

Francesca Macera, MD, of the Erasmus Medical Center in Brussels, discusses how LVADs impact pregnancy. She began with discussing the need for reliable anticoagulation (Registry Of Pregnancy And Cardiac disease (ROPAC) (escardio.org). Uterine encumbrance could hypothetically impinge the LVAD components (elevation of the diaphragm -> displacement of the left ventricle -> possible malposition / rotation of LVAD components -> potential driveline infection).

Dr. Macera finalized her presentation with a glance to the future, highlighting recent literate relevant to the session:
- Sex Differences in Patients Receiving Left Ventricular Assisted Devices for End-Stage Heart Failure (DOI: 10.1016/j.jchf.2020.04.015)
- Sex Differences in Characteristics and Outcomes Following HeartMate3 Left Ventricular Assisted Device Implantation (doi.org/10.1016/j.healun.2020.01.371)
- Sex Differences Outcome Disparities in Patients Receiving Continuous-Flow Left Ventricular Assist Devices: A Systematic Review and Meta-Analysis (DOI: 10.1097/MAT.0000000000000695)
- Gender Differences and Outcomes in Left Ventricular Assist Device Support: The European Registry for Patients with Mechanical Circulatory Support (DOI: 10.1016/j.healun.2017.06.016)

Pregnancy in High-Risk Population in the Era of Abortion Bans

Mary Walsh, MD, of the St. Vincent Heart and Vascular Institute in Indianapolis, discussed medical recommendations for termination of pregnancy in patients with end stage heart and lung failure where the risk of maternal mortality is high.

Dr. Walsh presented some possible indications for pregnancy termination:
- Treatment of spontaneous miscarriage
- Prohibitive maternal risk
- Fetal abnormality
- Maternal choice

Moreover, Dr. Walsh pointed out the barriers to reproductive healthcare, the importance of multidisciplinary models for shared decision-making in contraception, and pregnancy counseling for women with cardiovascular conditions (doi: 10.1016/j.jacc.2021.01.057).

During this presentation, current abortion data in the United States was showed (doi: 10.1056/EVIDra2200300), including abortion access by state, from most restrictive to most protective, with the state of Louisiana being the most restrictive.

Dr. Walsh finalized her talk by highlighting the importance of talking to patients about pregnancy risk, and advocate.

Assisted Reproduction in High-Risk Populations (Heart and Lung Failure)

To conclude the session, **Patricia Ging, MSc**, of Mater Misericordiae University in Dublin, gave an overview of recommendations for assisted reproduction in patients with end stage heart and lung failure.

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

SESSION 07. There and Back Again: Science of Lung Ischemia-Reperfusion Injury and Primary Graft Dysfunction

The aim of this session was to explore the basic mechanisms of ischemia reperfusion injury (IRI) and primary graft dysfunction (PGD) and elucidate potential therapeutic targets. The session was co-chaired by **Mena Botros, MD**, of Houston Methodist Hospital, and **John McDyer, MD**, of the University of Pittsburgh.

A Single Nucleotide Polymorphism in Donor MICB Protects from NKG2D-Mediated Primary Graft Dysfunction and Death

Daniel Calabrese, MD, University of California San Francisco, San Francisco, CA USA

Based on previous studies (DOI: 10.1172/jci137047) (DOI: 10.1136/thoraxjnl-2018-212345) (doi.org/10.1038/nrc1252), the investigators evaluated the hypothesis that single nucleotide polymorphisms (SNPs) in donor MICB led to decrease in Natural Killer (NK) NKG2D receptors and would be protective from primary graft dysfunction (PGD). Dr. Calabrese showed that among recipients from the 10 center lung transplant outcome group cohort (n=619) analyzed in this study, donor MICBG406A SNP rs1051788 was associated with decreased risk of PGD3 on days 2 or 3, as well as graft failure. Additionally, in-vitro the authors demonstrated that natural killer cells cultured with transfected mouse cells with human variant MICB D136N resulted in less NKG2D receptor downregulation, a key surrogate of NK cell activation. The researchers concluded that targeting MICB-NKG2D axis may be a plausible therapeutic option to decrease IRI in lung transplantation.

CCR5 Mediates Natural Killer Cell Airway Trafficking in Lung Ischemia Reperfusion Injury

Jesse Santos, MD, University of California San Francisco, San Francisco, CA USA

Dr. Santos presented data about natural killer cells trafficking to airways via chemokine receptor signaling during IRI. Using two mouse models, the investigator showed that chemokine signaling pathways were increased in lung tissue during IRI. Receptor ligands CCR5 and CCR1 were increased in NK cells during IRI. Additionally, when mice were treated with CCR5 blockade (Maraviroc) preceding IRI surgery, NK cell recruitment to the airways was blunted.

The Role of Heparanase Activation on Ischemia-Reperfusion Injury in Mice

Kentaro Noda, PhD, University of Pittsburgh, Pittsburgh, PA USA

Dr. Noda started his presentation describing the role of glycocalyx shedding as a trigger of endothelial disfunction leading to edema, cellular migration, inflammation, shear stress, and finally PGD. By using knockout mice and lung hilar occlusion models, the authors tested the hypothesis that inhibition of heparanase (heparastatin SF4) may preserve the endothelial glycocalyx, contributing to better organ preservation and overall outcomes in lung transplantation. Dr. Noda showed an improvement in lung function and a decrease in pathological changes and inflammation after IRI injury in the heparastatin treated group after 4-hours

reperfusion group.

Increased Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) Expression in Epithelial Club Cells in Acute Lung Allograft Dysfunction
Olivia Mekhael, PhD, University Health Network, Toronto, ON Canada

Dr. Mekhael presented data testing the hypothesis that chronic lung allograft dysfunction (CLAD)—the major barrier to lung-term survival after lung transplantation—develops as a consequence of epithelial club cell death (doi: 10.3390/biomedicines10061423) by tumor necrosis factor-related apoptosis inducing ligand (TRAIL) (doi: 10.1111/ajt.16360 binding to its receptors (TRIAL-R1 and TRIAL-R2)) during episodes of acute lung allograft dysfunction (ALAD). By analyzing airway brushings (n=6) of patients at 3-12 months post-lung transplant, the authors found that both TRAIL+ club cells and TRAIL+ non-club epithelial cells were significantly higher in ALAD in lung transplant recipients and might be the potential mechanisms of club cells loss in CLAD.

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

MINI ORAL 02. The Force Awakens: Advances in Lung Preservation to Improve Donor Selection and Recipient Outcomes

This lightning oral abstract session, co-chaired by **Varun Puri, MD, MSCI**, of the Washington University School of Medicine in St. Louis, and **Puneet Garcha, MD, MBA**, of Baylor College of Medicine in Houston, highlighted recent advances in donor lung preservation, new aspects of donor and recipient selection and important implications in DCD lung allocation.

From the University Health Network in Toronto, **Bonnie Tso-Yu Chao, BASc**, began the session by presenting her team's work entitled "***A Machine Learning Approach to Processing and Interpreting Ex Vivo Lung Radiographs Predicts Transplant Outcomes***." Based on prior experience that EVLP radiographs can distinguish declined lungs from transplanted lungs through regression analysis, the team sought to develop a novel computer vision algorithm utilizing machine learning methods to identify abnormalities in EVLP lung radiographs and predict transplant outcomes. First, a validated dataset of 800 clinical EVLP case radiographs was curated and organized. Then, convolutional neural networks were pre-trained using n=112,120 radiographs publicly available from the National Institutes of Health Chest X-ray Database. The base model for each neural network was subsequently fine-tuned using n=214 clinical EVLP radiographs to identify the presence of abnormal findings including consolidation, infiltration, atelectasis, nodule, and interstitial lines. The team's results showed that a machine learning approach successfully automated EVLP radiograph image processing and analysis at 1hr and 3hr with an accuracy of >88% (AUROC 93.1%).

Next, **Guillaume Fadel, MD**, of Marie Lannelongue Hospital in France, presented "***Pressure Controlled Hypothermic Lung Perfusion is not Better Than Cold Storage for Lung Preservation***." Hypothermic perfusion is associated with a decrease of ischemia/reperfusion injuries in kidney and liver transplantation. The aim of the study was to compare lung hypothermic perfusion to cold storage using seven paired swine lungs. HP lungs were perfused using cold preservation solution (Perfadex®) with controlled pulmonary pressure under 5mmHg and graft temperature of 10°C. The team found that controlled-pressure hypothermic perfusion using Perfadex allowed for controlled and stable preservation temperature. However, it did not prove better physiological results when compared to cold storage and ended with significant pulmonary edema after 6h of perfusion. The crowd praised Fadel for reporting a negative result.

Filip Rega, MD, PhD, of University Hospital Leuven in Brussels, then presented the provocative topic, "***Ice is Not 4c: Thermodynamic Characterization of Lungs and Hearts Preserved on Ice***." Extensive clinical literature states that the assumed temperature of organs stored on ice is 4°C. However, this assumption is not supported by empirical data. To investigate thermodynamics of organ cooling when packaged for transport on ice, porcine lungs (n=3) and hearts (n=3) were packaged within 3 bags (3M) and placed on ice in a cooler. Temperature probes were inserted into the left ventricle myocardium, left inferior lung lobe, the preservation solution in contact with the organ, and in the saline bag. The team analyzed a total of 19,458 temperature measurements (6,489 for heart, 12,969 for lung). Average lung surface temperature evolved from an initial 6.7°C

to 0.8°C (1 hr) to 0.1°C (4 hrs) and heart surface temperature evolved from an initial 6.1°C to 0.4°C (1 hr), to 0.1°C (4 hrs). Similar results were noted in the average left inferior lung lobe and ventricle myocardium temperatures. They concluded that lungs and hearts packaged and preserved on ice undergo rapid drop in temperature and approach freezing in an uncontrolled manner. Actual temperatures are lower than the historically assumed 4°C and temperature gradients across organs stored on ice are not uniform.

Basic science research engaged the audience in the next presentation, "**24-Hour Negative Pressure Ventilation Ex-Situ Lung Perfusion (NVP-ESLP) with Transplantation in a Porcine Model**," by **Keir Forgie, Hons. BSc, MD** of the University of Alberta. Dr. Forgie described the results of their refined, reliable (>80% success) 24-hour NPV-ESLP protocol with transplantation in a large animal model in which acceptable oxygenation, compliance, and vascular resistance during 24-hours of preservation were maintained. When asked what the next step will be, Dr. Forgie is hopeful to bring the preservation period to 2 full days. Look for more to come from that group.

The Early Career and Trainee group was represented well by Temple University medical student **Meredith Brown, BS**, who presented "***Does Donor Age Impact Survival Outcome of Increased-Risk (IRD) Lung Transplantation?***" This retrospective analysis of the UNOS database (Feb 2014-Mar 2020) identified n=3242 IRD lung transplant recipients, divided them into five age range cohorts, and compared survival. The key findings of the study were: The IRD cohort is young (nearly half were <30 y/o), substance abuse patterns varied by age, and underlying conditions increased with age. Additionally, young IRDs were associated with less underlying disease and improved survival outcomes.

Next, **Yu Xia, MD, MS**, of the University of Wisconsin, presented "***Ex-Vivo Lung Perfusion May Have a Detrimental Impact on Lung Transplants from Donation after Circulatory Death Donors***." This team sought to determine the characteristics and outcomes of DCD lungs managed by standard cold storage versus EVLP. They reported a significantly worse 2-year survival rate in EVLP-managed DCD-lung recipients. This presentation brought to light the limitations of data pulled from the UNOS registry as it lacks granularity regarding indications for EVLP, the specific EVLP-protocols utilized, and the lung acceptance criteria.

The collaborative work of the Mayo Clinic in Rochester and the University Health Network in Toronto was presented by **Sahar A. Saddoughi, MD, PhD**, as she described the "***National Trends of Lung Allograft Utilization During Donation-After-Circulatory-Death (DCD) Heart Procurement in the United States***." Since 2019, the volume of DCD hearts has risen, unlike the state of DCD lungs, which has remained stable at 5-6%. Their analysis revealed that after DCD heart procurement, approximately 19% of DCD donor lungs were procured. Also, DCD lungs had a much higher discard rate (appx 30%) than DCD hearts, yet outcomes were not significantly different.

Back to basic science as **Yujiro Kubo, MD** from Okayama University Hospital reports his team's murine model "***Histidine-Rich Glycoprotein Ameliorates Lung Ischemia-Reperfusion Injury in a Mouse***." Histidine-rich glycoprotein (HRG) is a multifunctional plasma glycoprotein involved in the regulation of coagulation, fibrinolysis, and inflammation. In this mouse model, supplementary

HRG treatment suppressed neutrophil-associated inflammatory responses and improved lung ischemia-reperfusion injury (IRI). HRG may be a potential therapeutic agent for lung IRI and warrants further investigation.

Early Career and Trainee member and second-year medical student **Tahir Malik, MD**, from NYU presented: "***Are We Discarding Too Many DCD Lung Allografts for the Wrong Reasons?***" His team sought to identify donor risk factors predicting DCD lung discard (DSRI) and evaluate their association to recipient survival. They were able to identify nine characteristics independently significant for lung allograft discard and conclude that an increasing likelihood of discard does not correlate with increased post-transplant mortality outcomes, and thus, may represent a significant opportunity for expanding the donor pool.

The final presentation, "***Results of ECLS Support Comparing DCD and DBD Lung Transplantation***," presented by **Mohammed Abdul Kashem, MD, PhD** from Temple University in Philadelphia, reported the results of their analysis of the National ECLS Registry, stratified by donor technique. Analysis of differences in patient/donor demographics, preoperative, intraoperative and post-operative ECLS usage, post-operative complications, and patient survival were used to compare the DCD and DBD donor groups. They found no differences in survival outcome whether DCD or DBD donors were used, however, when analyzed using ECLS as a variable, non-ECLS showed better survival. Dr. Kashem indicated that further long-term follow-ups are needed to validate proper DCD utilization.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 38. The Unusual Suspects: Immune and Tissue Drivers of Lung Allograft Pathologies

This high-level session co-chaired by **Benjamin Renaud-Picard, MD** of Nouvel Hospital Civil in Strasbourg and **Christine Falk, PhD** of Hannover Medical School took a deep dive into immune cell metabolism, lymphocyte and lymphatic regulation, and epithelial and endothelial cell biology as diverse mechanisms of lung allograft primary graft dysfunction and rejection.

Professor **Andrew Gelman, PhD** of Washington University School of Medicine in St. Louis opened the session with a question: "Why target myeloid metabolism as an immunosuppression strategy?" He went on to explain that there are distinct metabolic requirements for developing and activating pro-inflammatory rather than reparative myeloid cells. Differentiation represents possible targets to prevent lung graft injury and/or rejection. Some of the major metabolic signals associated with acute lung injury include succinate, a pseudo-hypoxic factor. Additionally, citrate, which accumulates in the activated macrophage's mitochondria, induces epigenetic-mediated changes in gene expression. Also well studied is the mitochondrial electron transport chain, which generates numerous interesting targets in order to modulate metabolism. Next, he explored targeting glycolysis in CLAD and discussed his team's recent work that noted early onset of BOS was found in lung recipients that carry ATG16L1. He concluded by reminding the audience to follow the mitochondria as they alter inflammatory gene expression in a variety of ways. The co-chairs and audience engaged Dr. Gelman in a lively discussion, which ended with a thought about the microenvironment and its role in metabolic mitochondria activity: Can we metabolically optimize patients?

With piqued interest, the audience pondered how **Daniel R. Calabrese, MD**, of the University of California in San Francisco, would answer the question and the title of his talk: **Innate Lymphoid Cells: Nice Neighbors or Unruly Residents After Lung Transplant?** Dr. Calabrese began with an overview of the immunobiology of natural killer (NK) cells and innate lymphoid cells (ILCs) in the lung and then discussed their role in propagating tissue injury or inducing tolerance. Tissue resident NK cells (and ILC1s) are migrating to the airways during ischemic reperfusion injury and causing damage. He summed it up with, "NK cells are like rock musicians and sometimes come in and break everything they see."

Wayne Hancock, MD, PhD, from the Children's Hospital of Pennsylvania in Philadelphia, stayed in the lymphatics realm with his elegant presentation entitled **Lymphocytes and Lymphatics: Implications for Tolerance**. His talk presented new information on the metabolic requirements for lymphatic development and regulatory CD4+ T cell-mediated immunosuppression with its implications for promoting transplant tolerance.

Endothelium and Barrier Dysfunction in Lung Allograft Injury was presented by **Ciara Shaver, MD, PhD**, of Vanderbilt University Medical Center in Nashville. Dr. Shaver began with a focus on the functional aspects of the endothelial cell and dysfunction in injury. The pulmonary endothelial and epithelial glycocalyx protects the alveolar-capillary (a-c) barrier during homeostasis. It stands

to reason that the disruption of (shedding) the endothelial glycocalyx during EVLP is associated with lung discard and PGD3. In rat models, inhibition of this shedding has been shown to protect the a-c barrier. Likewise, TRPV4 calcium channels play a role in vascular function, and their inhibition reduces ischemia-reperfusion injury in mice. Dr. Shaver contended that this is an exciting area of ongoing research, as pre-clinical data supports the development of endothelial-targeting therapeutics.

To round out the session of the unusual suspects, **John Greenland, MD, PhD** of the University of California at San Francisco, engaged the audience as he brought to light the importance of bronchiolar epithelium in his talk **Epithelial Cell Reprogramming: How Lung Transplant Injury Impacts Epithelial Cells**. In summary, Dr. Greenland aimed to persuade the audience that airway epithelial cell reprogramming is an important driver of chronic lung allograft dysfunction. This manifests through differences in cell composition, particularly club and basal cell dysfunction driven by type-1 immune responses with an epithelial to mesenchymal transition. Lastly, he noted that there is a phenotype of epithelial cell aging that is driven by epigenetic changes and telomere dysfunction. We were certainly convinced that "the epithelial cell has its own life!"

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 35. An Unexpected Journey: Perfusion Science in Lung Transplantation

Dirk Van Raemdonck, MD, PhD of University Hospitals Leuven in Belgium and **Matthew Hartwig, MD**of Duke University Medical Center in Durham, NC, led this session that explored the current data regarding how machine perfusion techniques, preservation strategies, and normothermic regional perfusion affect lung transplantation outcomes.

Kamal S. Ayyat, MD, PhD of the Cleveland Clinic kicked off this session by presenting "***Screening for Donor Lung Pulmonary Emboli During Ex-Vivo Lung Perfusion***." Donor lung pulmonary emboli incidence as high as 38% is reported in the literature, occurring typically at one of three time points: donor preadmission, donor hospitalization, and procurement. Common features associated with donor emboli are higher lactate and changes in thermography findings; however, a method for confirmative diagnosis and treatment tool would be beneficial for managing PE prior to transplantation. This novel off-label technique utilizes a sterile standard adult fiberoptic bronchoscope to assess the donor lung pulmonary arterial tree for emboli. The audience was wowed by an impressive video of the EXPLORE angioscopy technique in action, both identifying and removing a clot from the pulmonary vasculature.

Dr. Ayyat reported his team's findings after applying the EXPLORE method in their EVLP program. All lungs received retrograde flush prior to EVLP. PE were identified and removed in 15 cases out of 52 donor lungs screened by EXPLORE angioscopy before EVLP; 10 cases went on to be transplanted. The cases with identified PE had significantly lower lactate levels and higher glucose levels in perfusate during EVLP when compared to cases with no PE or where EXPLORE was not performed (7.5 ± 0.9 vs 10 ± 0.5 vs 10.7 ± 0.7 mmol/L, p = 0.01 and 133 ± 23 vs 111 ± 26 vs 114 ± 35 mg/dl, p = 0.04, respectively). Additionally, the donor lungs had significantly higher dynamic compliance and perfusate glucose levels during EVLP (82.3 ± 26 vs 72.6 ± 26 ml/cmH2O, p = 0.03 and 128 ± 38 vs 109 ± 40 mg/dl, p < 0.01, respectively). Although diagnosing PE in donor lungs post procurement can be challenging, Dr. Ayyat gave a compelling argument that using EXPLORE angioscopy for screening can aid in the diagnosis and treatment of easily missed PE.

Next up, **John Haney, MD** of Duke University provided an update from last year's registry report in his presentation, "***Not Too Warm, Not Too Cold: Real-World Multi-Center Outcomes with Elevated Hypothermic Preservation of Donor Lungs***," using the only FDA- and CE-cleared preservation technology: LUNGguard (LG) Donor Lung Preservation System. Utilizing the multicenter GUARDIAN Lung Registry, a retrospective review of clinical outcomes, data showed that the LG cohort had a clinically (though not statistically) meaningful 54% reduction in primary graft dysfunction at 72 hours (p=0.058). Dr. Haney noted the trends are encouraging to support that 10-degree C storage, rather than ice, is optimal.

The second half of the session addressed another hot topic: Normothermic Regional Perfusion. First, **Jad Malas, MD** of Cedars-Sinai Medical Center in Los Angeles described his team's work as they compared the impact of DCD heart procurement via thoracoabdominal normothermic regional perfusion (TANRP) versus direct procurement and perfusion (DPP) on concurrently

procured lung allograft utilization and recipient outcomes. Utilizing the UNOS database, they identified 721 DCD donors whose hearts were procured from December 2019 to December 2022. Although UNOS does not specifically identify the heart procurement strategy, data was extrapolated using time of death declaration and time of aortic cross clamp, which yielded n=211 regionally perfused vs. n=416 directly procured (n=94 excluded due to missing essential time stamps). TANRP vs. DPP lung allograft utilization was 14.9% and 13.8%, respectively. No statistically significant differences in discard rate or reason were noted. Although Dr. Malas acknowledged several limitations in this study, the 6-month survival outcomes showed a signal that "***Thoracoabdominal Normothermic Regional Perfusion Does Not Adversely Impact Early Outcomes in Donation after Circulatory Death Lung Transplantation***."

After a lively audience discussion, where participants brought their personal experiences with TANRP to light, **Yu Xia, MD, MS** of the University of Wisconsin in Madison took the stage to close the session with findings reported in his team's abstract, "***Normothermic Regional Perfusion in Donation after Circulatory Death Heart Donors May Not Have a Detrimental Effect on Lung Transplant Outcomes***." Again, utilizing the UNOS database necessitated a uniform method of identifying the utilization of TANRP as time from brain death declaration to aortic cross clamp great than 30 min. Concomitant DCD heart donors and lung donors were identified by linking the donor ID. Both donor and recipient characteristics between the two groups were not statistically significant, apart from an increased LAS score in the DPP group [40 (36-51) vs 38 (34-44) p=0.04]. Likewise, differences in transplant characteristics, in-hospital outcomes, and survival were not statistically significant.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 49: Days of Our Lives: Lung Donor-Recipient Allocation and Outcomes

The aim of this session was to provide an update on diverse topics within donor-recipient allocation science and related outcomes. The session was co-chaired by **John Dark, MB, FRCS**, of Newcastle University in the UK, and **Sofya Tokman, MD**, of Norton Thoracic Institute of Phoenix.

Lung Transplantation from HCV NAT+ Donors: Reassuring Mid-Term Outcomes

The session started with **Samuel Kim, BA**, of the University of California, discussing the Hepatitis C (HCV) NAT+ allograft recipient's outcomes, including postoperative complications, 30-day mortality, and 1–3-year survival, including a sample size of n= 15,414 patients. The investigators found no significant differences in postoperative ECMO, dialysis, reintubation, acute rejection, or 1- and 3-year survival—and concluded that HCV NAT+ donor allografts might help to expand the donor pool and alleviate donor shortages.

Impact of Donor Age on Survival of Lung Transplant Recipients According to Their Primary Diagnosis

In this presentation, **Abdel Moneim Tantawi, MD**, of the Cleveland Clinic first discussed the changes in organ donor age limits to expand the organ donor pool. Investigators evaluated recipients' survival after older donors according to recipient diagnosis (obstructive, pulmonary vascular, cystic fibrosis, and restrictive diseases). In n=25,376 lung transplant recipients, donor age was among the 10 highest risk factors of death in recipients with pulmonary vascular and restrictive groups. However, this association was not observed in patients with cystic fibrosis. Moreover, the restrictive cohort, donor age>55, was significantly worse than the age groups <30 and 30-55 years, these findings were not significant in the other study groups.

International Multicenter Extracorporeal Life Support in Lung Transplantation Registry Impact of Cold Ischemic Time on Primary Graft Dysfunction and One-Year Mortality

Mauricio Villavicencio, MD, MBA, of the Mayo Clinic, began with a discussion of the effects of cold ischemic time (CIT) in lung transplant. In this research project, the investigators assessed the effect of CIT in PGD3 at 48-72hrs and PGD3 at 0-24hrs, tracheostomy, dialysis, ventilation time, length of stay and 1-year mortality using the ECLS registry (9 US and 2 European centers). CIT was associated with higher incidence of PGD3 at 0 or 24hrs, tracheostomy, and length of stay. However, no associations were found with dialysis, ventilator time and 1-year mortality. Dr. Villavicencio concluded that lung transplantation may be performed with long ischemic times with acceptable outcomes.

The UK Lung Risk Index (UKLRI); An Objective Prognostic Score Based on Donor and Recipient Factors to Aid Decision Making in Lung Utilization

Gillian Hardman, MBBS, BSc, MSc, FRCS CTh, of NHS Blood and Transplant, initiated by presenting some reports about lung transplant recipients per 100 deceased donors, with the United Kingdom the lower and Australia the higher. In this research project, the investigators aimed to develop an objective scoring system to aid selection of donor organs and recipients to improve utilization in

UK transplantation.

Including data from 1,720 lung transplants, investigators identified three donor factors (donor past smoking, donor type, donor age) and 3 recipient factors (primary disease, ethnicity, and registration BMI) for the prediction of PGD3 and 5 recipient factors (ethnicity, registration BMI, registration creatinine, registration prednisolone dose, and recipient diabetes) for the prediction of death at one year.

Dr. Hardman summarized that:

- This is the first study of PGD after lung transplantation in the UK
- The incidence of PGD was 45%
- Incidence of grade 3 PGD was 11%
- The UK Lung Risk Index is an additive tool
- Risk stratify combinations of donor and recipient by prediction of PGD 3 and 1-year mortality
- Aid decision making
- Facilitate organ allocation
- Effective utilization
- Guide peri-operative management

Next Steps:

- Validate the UKLRI in an external cohort
- Test the UKLRI in new internal cohort
- Additional of PGD to UKTR
- Pilot prospective applications of the UKLRI

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

SESSION 52. Immune Checkpoints in Thoracic Transplantation: Lessons Learned from Cancer

This session was co-chaired by **Ravi Kumar Ratnagiri, MD, PhD**, of MGM Hospital in Chennai, and **Lorenzo Rosso, MD, PhD**, of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan. This session featured a state-of-the-art analysis of immune checkpoints: from the knowledge accumulated in oncology to their likely role in tolerance, with a focus on possible innovative therapeutic protocols.

Review of the Immune Checkpoint System in Thoracic Transplant and Malignancy

Eric Morrell, MD, of the University of Washington in Seattle, gave a review of immune checkpoint pathways and what has been learned from thoracic oncology to apply it in solid organ transplantation (DOI: 10.1172/jci71359; DOI: 10.1111/ajt.14437). He discussed the development of donor-specific antibodies (DSA) after lung transplantation, and increased mortality after lung transplantation using Belatacept (DOI:10.1111/ajt.17028).

Dr. Morrell concluded his presentation with the following points:

- Immunosuppression for lung transplant patients has been adapted from other organ recipients.
- Current immunosuppression is not tailored for lung transplant recipients.
    - Mouse models are good platform for mechanistic studies, but needs validation in large animal models.
- Some current immunosuppressants may be detrimental for "tolerance" induction.
- Urgent need to develop new immunosuppressants for lung transplantation.

Is Thoracic Allograft Rejection Caused By Checkpoint Receptors? Lessons Learned From Oncology

Letizia Corinna Morlacchi, MD, of the University of Milan, discussed what is known about immune checkpoint inhibitors triggering T-cell immune responses that may contribute to rejection (DOI:10.1016/j.healun.2020.02.015) and the evidence for PD-1 in organ rejection (DOI:10.1111/j.1600-6143.2009.02805.x). Moreover, in a murine model, data about co-stimulation blockade-mediated tolerance after lung transplantation dependent on programmed cell death 1 (PD-1) expression CD8+ cells was shown (DOI:10.1111/ajt.14437) as well as results from human transbronchial biopsies focusing on PD-1 (DOI:10.3389/fimmu.2022.1024021). Dr. Morlacchi ended with data about how the early increase of CD4+CD57+ILT2+ T cells (which are selectively inhibited by the immune checkpoint HLA-G) after lung transplantation may be associated with CLAD onset (DOI:10.1016/j.healun.2022.01.013).

The take home message:

- "Little number >> little evidence"
- In case of ICI use:
    - Identification of patient's characteristics which can predict a favorable or unfavorable response to the use of ICI

- Modulation of immunosuppressive treatment in order to minimize adverse outcomes from ICI use? Strategies for graft surveillance?

Ice and Fire: Treating Malignancy With Checkpoint Inhibition After Thoracic Transplantation

Michael Shullo, PharmD, of West Virginia University Hospitals in Morgantown, reviewed the factors associated with immune checkpoint inhibitor response and rejection in thoracic transplant recipients (DOI:10.6004/jnccn.2022.7009; DOI: 10.1111/ajt.15811). Dr. Shullo showed data about higher survival probability in patients with at least one drug other than corticosteroids compared to no drugs or steroids alone, he concluded "Use is Risk vs Benefit."

Present and Future Applications: Engineering the Immune Checkpoint System to Promote Tolerance

Daniel Kreisel, MD, PhD, of the Washington University School of Medicine in St. Louis, ended the session by discussing how interruption of immune checkpoint pathways may be manipulated as a novel form of immunosuppression by inducing tolerance of organ allografts.

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

SESSION 59. Die Hard: Preventing and Managing Hard-to-Treat Fungal and Bacterial Infections in the Perioperative Setting

This multidisciplinary rapid-fire session was co-chaired by **Paulo M. Pego-Fernandes, MD, PhD**, of Universidade de Sao Paulo, and **Georgina Waldman, PharmD, BCTXP**, of Massachusetts General Hospital in Boston, and focused on novel aspects of perioperative infection management. A range of topics from recipient colonization, emerging fungal agents and anti-infective considerations were discussed.

The session started with **Brace Yourself - Infections are Coming: Bacterial Colonization Management**. **Fernanda Silveira, MD, MS, FIDSA, FAST**, of the University of Pittsburgh Medical Center, delivered an engaging first talk that focused on colonization and infection with multiple drug resistant organisms in the transplant candidate which, she points out, has an unfortunately high mortality rate. She approached the topic by focusing on the colonization that is directly related to the reason for transplantation (i.e., MCS in heart transplantation). Importantly noted was the fact that ISHLT Listing Criteria for Heart Transplantation does not currently have specific guidelines about candidates with MDROs. The American Society of Transplantation infectious disease community practice guidelines state that all infectious VAD components should be removed, and transplantation is often life-saving even in the setting of "reasonably controlled infection" without hemodynamic stability. She argued this point is important because a "cure" from colonization is not required. Perioperative management should include coverage of known pathogens and intraoperative cultures to guide microbial therapy as the concern is continuous spread of the primary pathogens during the surgical procedure. Specifically, Dr. Silveira discussed four culprits: Burkholderia cenocepacia, Carbapenem-resistant Enterobacterales (CRE), Carbapenem-resistant Acinetobacter (CRAB), and Clostridioides difficile. Again, the importance of a healthy gut microbiome was highlighted in the talk and the audience discussion that followed.

Next, **Catherine Orla Morrissey, MD, PhD**, from Alfred Health in Kew, presented her perspective on inhaled anti-infective agents for the treatment of pre-transplant complicated bacterial and fungal infections. First, inhaled tobramycin, which was studied in non-CF patients and shown to "do what it is supposed to do." Prof. Morrissey noted that the inhaled formulation is approved by the FDA for some situations. Other therapeutics discussed were inhaled colistin, amikacin liposome inhalation suspension (see landmark CONVERT study), and the inhaled antifungals. She closed with a few novel therapeutics on the horizon. Take home message: the goal of inhalation formulation is to keep the drug in the lungs, avoiding the bloodstream to subsequently avoid toxicity and drug-drug interactions (especially tacrolimus). Be on the lookout for more to come.

Another excellent talk, **Fungus is Among Us: Emerging Life-Threatening Fungal Infections in Thoracic Transplant**, was presented by **Me-Linh Luong, MD**, of the Centre Hospitalier de l'Université de Montréal, and focused on the management of highly resistant Lomentospora prolificans and Scedosporium apiospermun infection before and after thoracic transplantation. Although both pathogens have very high mortality profiles, Dr. Luong assured the audience that all is not gloomy, as future drugs like Olorofim are in the pipeline.

Drugs are sticky and can stick to tubing. **Haifa Lyster, MSc, FRPharmS, FFRPS**, of the Royal Brompton & Harefield Clinical Group in Harefield, addressed the pharmacokinetic (PK) changes of antimicrobial agents in patients on ECMO in her talk, ***Sequestered: Anti-Microbial Loss in the ECMO Circuit***. Three things must be considered: patient factors, drug factors, and pathogen factors. She highlighted that highly protein-bound and lipophilic drugs are of most concern for ECMO circuits. The sequestration effect may change over time as the binding sites are saturated and create a drug reservoir. Likewise, the sequestered drugs may have a prolonged effect even after the infusion is stopped (Shekar et al, *Critical Care*, (2015), 19:164). In closing, she reviewed several findings from the long-awaited multicenter descriptive PK study: Antibiotic, Sedative, and Analgesic PK during ECMO (ASAP), by Shekar et al (*AJRCCM*, 2022). Recommendations for dose adjustments were discussed for agents most used in the perioperative settings.

Lara Danziger-Isakov, MD, MPH, of the Cincinnati Children's Hospital Medical Center, rounded out the session with a talk that focused on risk factors and outcomes of hard-to-treat fungal infection and MDR bacteria after pediatric thoracic transplantation entitled **Not So Small At All: Perioperative Bacterial and Fungal Infections in Pediatric Thoracic Transplant**. She proposed that this population can be used as a model for how the transplant community approaches the treatment of MDROs like Mycobacterium Absecessus. She encouraged the audience to perform targeted assessments of the transplant candidate and donor, and to consult infectious disease early as new biomarkers and medications (including the inhaled options presented today) are emerging.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 80. Rocky Mountain High: Scaling New Heights in CMV

This session, co-chaired by **Jennifer Chow, MD, MS**, of Tufts Medical Center in Boston, and **Michael Perch, MD**, of Rigshospitalet in Copenhagen, focused on new approaches for CMV prophylaxis and treatment in lung transplantation.

New Strategies for CMV Prophylaxis Including Letermovir

Miranda So, PharmD, MPH, BScPhm, of University Health Network in Toronto, began the session discussing new agents for CMV prophylaxis, including discussion of relative efficacy and side effects of each agent.

New Antivirals for CMV Treatment Including Maribavir

Emily Blumberg, MD, of the University of Pennsylvania in Philadelphia, spoke about new antivirals for treatment of CMV reactivation and when to select these agents over more traditional antivirals.

CMV-Specific T-Cell Response and Control of Primary Infection and Reactivation

Laurie Snyder, MD, MHS, of Duke University in Durham, during her presentation talked about how to use CMV-specific T cell responses to guide prevention and management of CMV infection in thoracic transplant recipients.

Clinical Applications of CMV Immune Monitoring in Lung Transplantation

Glen Westall, FRACP, PhD, of Alfred Hospital in Melbourne, presented data on monitoring CMV-specific cell-mediated immunity, which may guide decision making regarding the type of CMV preventive strategy in kidney transplantation (10.1093/cid/ciz1209). Additionally, in lung transplant recipients, Dr. Westall discussed how dysfunctional CMV immunity is associated with an increased risk of viral reactivation post lung transplantation (n=39) (DIO: 10.1093/infdis/jiaa750), and how CMV-specific cell-mediated immunity may be useful in CMV preventive strategies after lung transplant (DIO: 10.1093/infdis/jiaa727)

Adoptive T-Cell Therapy for Refractory Cases in Adults and Children

Daniel Chambers, MBBS, MRCP, FRACP, MD, of The Prince Charles Hospital in Ashgrove, provided new insights into developing and using T cell therapy for refractory CMV (10.1016/j.healun.2015.12.031; 10.1038/cti.2015.5) Dr. Chambers discussed the outcomes from the phase I prospective clinical trial (ACTRN12613000981729) that evaluated the response to autologous CMV-Specific T-cell therapy in 22 solid organ transplant recipients (13 renal, 8 lung, and 1 heart transplants) with recurrent or ganciclovir resistant CMV infection. The treated patients, no therapy associated serious adverse events were observed, 84% of the treated patients showed clinical improvement following T cell therapy. After 28-weeks of therapy INF-gamma CMV specific T cells increased from 0.03% to 9.3% and they remained polyfunctional; 38% off any

therapy; 30.8% requiring VGCV maintenance. (DO: 10.1093/cid/ciy549)

VIEW SESSION DETAILS

– Commentary by Lourdes Chacon Alberty, MD, MCTM

MINI ORAL 17. The Clone Wars: OR and Peri-operative Improvements in Lung Transplantation

This Mini Oral session included 10 rapid fire abstract presentations and was co-chaired by **Pedro Undurraga, MD**, of Clinica Las Condes in Providencia, and **Barbara Wilkey, BDN, MPAS, MD**, of the University of Colorado in Denver. Diverse peri-operative approaches to improve lung transplantation outcomes and pre-transplant predictors of peri-operative transplant outcomes were examined.

The session began with "***Outcomes of ECMO as Bridge to Lung Transplant in Children with Pulmonary Hypertension***." **Amalia Guzman-Gomez**, of the Cincinnati Children's Hospital, shared her team's work to evaluate the UNOS database for children (<18yo) on ECMO at time of lung transplantation between 1990-2021. In this cohort, they found that children on ECMO at lung transplant have similar outcomes and survival regardless of the presence of pulmonary hypertension (PH). Furthermore, both PH and non-PH groups have similar late hazard of mortality to those without ECMO. Therefore, they concluded that this high-risk patient population should be considered for lung transplant if the need for respiratory support includes ECMO.

"***12-Year Experience with Postoperatively Extended Intraoperative Extracorporeal Membrane Oxygenation in Lung Transplantation for Patients with Severe Pulmonary Arterial Hypertension***:" **Maximilian Franz, MD**, of the Hannover Medical School, presented his institution's 12-year experience with protocol-guided postoperative extension of intraoperatively initiated veno-arterial extracorporeal membrane oxygenation (vaECMO). Outcomes were compared between severe PAH patients (n=90) and patients transplanted for all other indications (n=1329). Postoperatively extended intraoperative vaECMO support allowed for safe transplantation of patients with sPAH. Despite increased morbidity in the early postoperative period, propensity score analysis did not show sPAH to be associated with increased mortality or CLAD.

Although an association between intra operative massive blood transfusion and primary graft dysfunction has been reported, little is known about the effects of pre-lung transplant blood transfusion. **Yuriko Yagi, MD** and his team from Northwestern University in Chicago conducted a retrospective study of 206 patients who underwent lung transplant at a single institution from January 2018 through July 2022. The results were presented in the talk entitled "***Pre-Transplantation Recipient Blood Transfusions Increase the Risk of Primary Graft Dysfunction Following Lung Transplantation***."

Several meaningful contributions to this session came from members of the Early Career and Trainee group. **Samuel Kim**, a medical student at UCLA, presented "***Predictors and Outcomes of Post-Operative Extracorporeal Membrane Oxygenation at 72 Hours Following Lung Transplantation***;" **John A. Treffalls**, a medical student at University of Texas Health in San Antonio, presented "***Comparison of Multimodal Pain Control Following Bilateral Lung Transplantation***;" and **Meredith Brown**, a medical student at the Lewis Katz School of Medicine at Temple University in Philadelphia, presented "***Concomitant Heart and Lung Surgery During Lung Transplantation***."

Additionally, **Sahar Saddoughi, MD, PhD**, of the Mayo Clinic in Rochster, delivered the results of "***Impact of Intraoperative Therapeutic Plasma Exchange on Bleeding in Lung Transplantation***," a retrospective review of 897 lung transplant recipients to determine the Impact of Intraoperative Therapeutic Plasma Exchange (iTPE) on bleeding in lung transplantation. iTPE was associated with an increased odds of high perioperative transfusion requirements (OR 1.6, 95% CI: 0.9-2.8, p=0.08), but was not associated with an increased incidence of hemothorax (5% in both groups, p=0.99). This study demonstrated that the use of iTPE in lung transplantation may increase perioperative bleeding, but not to a clinically meaningful degree.

"***Combined Lung Transplantation and Coronary Artery Bypass Grafting: To Graft or Not to Graft?***:" Because concomitant coronary artery bypass grafting (CABG) and lung transplantation (LT) remains controversial, **Lara Schaheen, MD**, and her team at the Norton Thoracic Institute in Phoenix and conducted a retrospective analysis of all patients who underwent concomitant CABG and LT between May 2014 and September 2022 at one institution. She explained that this study is unique because the operative approach is standardized: a beating heart, off-pump CABG utilizing endoscopically harvested saphenous vein grafts. N= 40. Complication rates were low with 7.5% patients requiring dialysis, 2% suffering from a stroke, and 7.5% requiring return to the operating room for bleeding. The median length of stay was 18 days and survival to discharge was 98%, 30-day survival was 100%, and 1-year survival was 81%. It was further noted that no causes of death were related to cardiac disease.

Stuart Azzopardi, MD, of Alfred Health in Melbourne sought to provide literature to help inform future analgesic guidelines by conducting a retrospective descriptive review of all pediatric patients undergoing lung transplantation from 2005-2021 at a single tertiary hospital. Analysis of the 44 cases identified showed that "***Epidural Analgesia Reduces Total In-Hospital Opioid Use by 57% in the Paediatric Lung Transplant Population***" and an averaged 70% less intubated days (3.84 vs 12.86, unpaired t test, $p < 0.001$).

The final talk in this session, "***Perioperative Desensitization Changes the Plasma Cytokine Milieu in Lung Transplant Patients with Preformed Donor Specific Antibodies***," was given by **Fabio Ius, MD**, of the Hannover Medical School, who reported on an established treatment protocol at a single institution. Since 2013, recipients with pre-formed anti-HLA donor-specific antibodies pf-DSA) have received a treatment protocol based on a combination of repeated IgA/IgM-enriched intravenous immunoglobulin infusions with plasmapheresis. Analysis revealed 9-year graft survival similar to non-DSA-control patients Dr. Ius' team concluded that pf-DSA treatment caused consistent reduction of multiple cytokines and may have contributed to improved graft survival.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 88. Contagion Meets Outbreak: Lessons Learned from COVID-19 in Lung Transplantation

Marie Budev, DO, MPH, of the Cleveland Clinic, **Cameron Wolfe, MD**, of Duke University Medical Center, kicked off the last day of ISHLT2023 as they co-chaired this abstract session.

The session started with **Hiromu Kehara, MD, PhD**, of Temple University in Philadelphia, who was first to the podium to present his research: "***A Single-Center Experience with More Than 200 Lung Transplant Recipients with COVID-19 Infection***." His team identified 210 lung transplant patients from March 2020 - September 2022 who were diagnosed with COVID-19 (C-19) infection. The cohort was divided into three strata according to the time of diagnosis and identified as first wave (n=35), second wave (n=69), and third wave (n=106). At the time of diagnosis, 40% of patients had not received the C-19 vaccine. Of the 60% vaccinated, 31% had additionally received a booster. Vaccination was the only significant predictor for hospital admission. However, their analysis revealed that ICU admission correlated with very high hospital mortality. His team also assessed the effect of C-19 on lung allograft versus native lung. Computed Tomography scan (n=101) obtained from DLT and SLT recipients with C-19 were assessed for ground glass opacity (GGO) and revealed that overall, GGO was observed in 79% of allografts as compared to 30% of native lung with C-19.

This presentation was followed by a lively audience discussion before **Mallory Hunt, MD**, of the Hospital of the University of Pennsylvania in Philadelphia, came to the stage to present "***ECMO as a Bridge to Lung Transplantation for Covid-19 Respiratory Failure: Outcomes and Risk Factors for Early Mortality***." Using the UNOS database, her team identified 442 patients who underwent lung transplantation for COVID-19 respiratory failure (August 2020 – September 2022), 253 of which required ECMO as bridge to lung transplant. After analysis, they concluded that bridge to transplant with ECMO is safe in select patients, prolonged support (appx. 70% >1 mo.; 30% >3mo.) is common, and caution should be taken in patients with potential risk factors for early mortality (higher donor age, higher recipient BMI, low center case volume, bacterial infection at transplant, need for vaECMO, prior cardiac surgery, and SLT).

UNOS data (March 2020 – August 2022) was evaluated by **Panagiotis Tasoudis, MD**, of the University of North Carolina in Chapel Hill, and his team, who sought to describe the safety and efficacy of lung transplantation for COVID-19 related to either acute respiratory distress syndrome (ARDS) or pulmonary fibrosis (PF). He presented results of their study, "***Lung Transplantation for Covid-19 Related Complications: Early Outcomes Across the United States***," which concluded that lung transplantation provides benefit to patients with irreversible respiratory failure due to COVID-19 ARDS or PF, with a similar survival profile to other pre-transplant etiologies. Interestingly, an 11-day list waiting period was noted in this study, mirroring previous reports.

Luke Benvenuto, MD, of Columbia University Medical Center in New York City, closed the session with "***Changing Patterns in Lung Transplant for Respiratory Failure Due to COVID-19 in the U.S.***" He noted that prior to the COVID-19 pandemic, lung transplant for ARDS was rarely done, but quickly

emerged as an accepted treatment for respiratory failure due to COVID. His team did a retrospective analysis from the UNOS database to identify patterns in patient demographics, illness severity, and frequency of listing and transplantation for COVID-19. Although there were no official guidelines delineating the usage of the diagnoses COVID ARDS vs. COVID-pulmonary fibrosis, they concluded that patients listed for COVID ARDS had a significantly higher median Lung Allocation Score, were younger, more likely to be in the ICU, and with ventilator and ECMO support at time of listing and transplant. This brought to light that there may have been potential overlap in the patient groups due to heterogeneity among institutional diagnosis reporting. He concluded by noting that the trends reveal lung transplantation for COVID-19 is changing; the incidence is decreasing, and the indication is shifting from COVID-ARDS to COVID-pulmonary fibrosis.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA

SESSION 102: Love, Actually: Rejection in Lung Transplantation

After an action-packed week, the final session of ISHLT2023 did not disappoint. **Kieran Halloran, MD, MSc**, of the University of Alberta, and **Stephanie Chang, MD**, of NYU Langone Health, co-chaired this session, which highlighted scientific advances in the diagnosis and prevention of acute and chronic rejection after lung transplantation.

Merel Hellemons, MD, PhD, of Erasmus MC University Medical Center in Rotterdam, reported on "***The Ability of an Electronic Nose to Distinguish Between Acute Cellular Rejection and Infection in Lung Transplant Recipients***." This novel technique uses an eNose (SpiroNose) for exhaled breath analysis. The eNose accurately discriminated ACR from infection with an area under the curve of 0.90 (CI 0.81 - 0.99, Figure 1), a sensitivity of 67%, specificity of 96%, and accuracy of 82%. This may be a promising marker to distinguish between CLAD and infection. The audience was intrigued as they discussed with the presenter the utility of using this new modality in combination with other tools like donor derived cfDNA to help to guide clinical decision making.

Basic science again took center stage as "***Downregulation of LKB1-Stradα Pathway in Circulating Exosomes as a Biomarker for Chronic Murine Lung Allograft Rejection***" was presented by **Mohammad Rahman, MBBS, PhD**, of St. Joseph's Hospital & Medical Center in Phoenix. This NIH grant-supported research hypothesized that LKB1-STRADα pathway regulation in circulating exosomes can be a biomarker for chronic rejection following lung transplantation in the mouse. They found increased levels of circulating exosomes on days 14 and 34 post murine lung transplant, and downregulation of LKB1, STRADα, and pAMPK in the transplanted lung. STRADα knockdown decreased LKB1 expression in BEAS-2B cells. They concluded that since the STRADα-LKB1 signaling pathway regulates tissue fibrosis of transplanted lungs, determining the circulating exosomal LKB1 levels could serve as a potential biomarker for BOS in lung transplant recipients. Dr. Rahman was applauded by the audience for this work as developing a murine model for CLAD is arduous.

The final two speakers presented research conducted at Kyoto University, beginning with **Yoshito Yamada, MD, PhD**, in his talk, "***CD26/Dipeptidyl Peptidase-4 Inhibitors as Prophylaxis of Chronic Lung Allograft Dysfunction after Lung Transplantation, a Clinicopathological Evaluation***." His team focused on CD26/DPP-4 activity and clinical application in the context of continued poor long-term lung recipient prognosis despite the improvements in surgical technique and immune suppression. This retrospective single-center analyzed 250 lung transplant recipients from 2019-2021 that were divided into two cohorts delineated by the diagnosis of diabetes mellitus (up to 6 months post-lung transplant) or not. The DM group was further divided by treatment with CD26/DPP4 inhibitors or not. Dr. Yamada's team concluded that CD26/DPP-4 inhibitors positively affect postoperative prognosis, and CD26/DPP4 may be a target to attenuate CLAD development in lung transplant recipients.

The session closed with **Katsutaka Mineura, MD**, also from Kyoto University, presenting his team's research findings: "***The Effect of CTLA-4-Ig on the Progression of Fibrosis from Acute Cellular***

Rejection in a Murine Model of Chronic Lung Allograft Dysfunction." In the restrictive allograft syndrome (RAS) CLAD murine model, CTLA-4-Ig effectively prevented allograft fibrosis when started immediately post-transplant. Conversely, CTLA-4-Ig failed to halt progression to fibrosis when it was initiated after the occurrence of acute cellular rejection (day 15). Through additional analysis, they concluded that this is a consequence of fibroblast activation on day 15. Dr. Mineura encouraged further research in this area to elucidate the mechanism of progression from cellular rejection to fibrosis.

VIEW SESSION DETAILS

– Commentary by Rebecca Klingbeil, MSN, DNP, CRNA