Surgery Research Day 2024

22ND ANNUAL WILLIAM C. WOOD RESEARCH SYMPOSIUM

APRIL 18, 2024 | 7 AM - 12 PM | IN PERSON & ZOOM EVENT

Keynote Lecture: **"The Problems are the Opportunities"**

presented by **Yolonda L. Colson, MD, PhD**
Chief, Division of Thoracic Surgery
Hermes C. Grillo Professor of Surgery
Massachusetts General Hospital

EMORY UNIVERSITY SCHOOL OF MEDICINE | **Department of Surgery**

SCHEDULE OF EVENTS

7:00 – 8:00AM	**Introduction of Keynote Speaker by Dr. Onkar Khullar** Title: The Problems are the Opportunities *Yolonda Colson, MD, PhD*
8:15AM	**Welcome remarks by Dr. Craig Coopersmith** **Oral Presentations – Session I** *(in person & virtual)* **Zoom Link (Passcode: sgr)** *Moderators: Paul Ghareeb, Allison Linden*
8:15AM	Chronic Alcohol Exposure Alters the Phenotype of Regulatory T cell Subsets in Septic Mice *Gutierrez MB, Coopersmith CM, Ford ML*
8:25AM	Objective Performance Indicators Facilitate Step-Specific Skill Assessment in Robotic Right Colectomy *Mishal Gillani, Manali Rupji, Glen C Balch, Mallory C Shields, Terrah J Paul Olson, Yuan Liu, Seth A Rosen*
8:35AM	Compliance Monitoring of Intraoperative Lymph Node Assessment in Pulmonary Resections Performed with Curative Intent *Williams, BM, Bonanno, A, Sancheti, M, Fernandez, F, Force, S, Khullar O*
8:45AM	Creation of iPSC-derived lymphatic endothelial cells for use in regenerative therapy for lymphedema *Owsiany K, Carr S, Tu M, Hekman, K*
8:55AM	How does Sleeve Gastrectomy Impact Patient Eating-related Behavior, Distress, and Symptoms? Using the BODY-Q Patient-reported Outcome Measures (PROMs) *Mou D, Smith S, Fer D, Davis Carolyn, Yost C, Srinivasan J, Stetler JK, Patel A, Oyefule O, Lin E, Davis S, Hechenbleikner EM*
9:05AM	How Many Operations Does it Take? Incidence and Risk Factors for Secondary Surgery and Amputation after Lower Extremity Limb Salvage *Ash, Makenna, Brown, Ciara, Menon, Ambika, Knaus, William, Hernandez-Irizarry, Roberto, Ghareeb, Paul*
9:40AM	**Quick Shot Presentations – Basic Sciences** *(in-person only) – Classroom B/C* *Moderators: Luke Brewster, Katherine Hekman, John Calvert*

Quick Shot Presentations – Clinical Sciences *(in-person only) – Classroom A*
Moderators: Mike Lowe, Lauren Postlewait

Oral Presentations – Session II *(in-person & virtual)*
Zoom Link (Passcode: sgr)
Moderators: Onkar Khullar, Heather Faulkner

10:40AM Differential induction of donor-reactive Foxp3+ iTreg via blockade of CD154 vs. CD40
Hongmin Yao, Danya Liu, Mandy L. Ford

10:50AM Effect of Prosthetic Fitting on Mortality after Major Lower Extremity Amputation
Nathaniel Forrester BA, Maja Wichhart Donzo BA, Chengcheng Hu MBBS MPH, Brandi M. Mize MD, Yazan Duwayri MD MBA, Luke Brewster MD PhD, Olamide Alabi MD MS

11:00AM RIPK3 disrupts gut epithelial homeostasis during sepsis
Chloe S Yang

11:10AM Clinical predictors of Spontaneous Intestinal Perforation vs Necrotizing Enterocolitis in extremely and very low birth weight neonates
Goeto Dantes, MD, Olivia A. Keane, MD, Louis Do, BS, Savanah Rumbika BS, Nathaniel H. Ellis, BS Valerie L. Dutreuil, MPH, Zhulin He, PhD, Amina M. Bhatia, MS, MD

11:20AM Chronic Ethanol Consumption Improves Survival in Claudin-4 Knockout Mice in Abdominal Sepsis
Shimazui T, Gutierrez MB, Liang Z, Ford ML, Coopersmith CM

11:30AM A Multicenter Analysis of Pancreatoduodenectomy for Sporadic Duodenal Adenoma: A Novel Risk Score to Guide Shared Decision-Making
Caitlin Sok, Nina Eng, Angelo Marra, Hussein Hariri, Gregory Wilson, Syed Ahmad, Charles Scoggins, Caitlin Hester, Jashodeep Datta, Nipun Merchant, Michael LeCompte, Hong Jin Kim, Gregory Sigler, Nabeel Zafar, Sharon Weber, Christina Kasting, Ryan Fields, Mihir M. Shah, Shishir K. Maithel, David A. Kooby

12:00PM **Closing remarks by Dr. John Sweeney**

12:15PM **Announcement of the symposium winners by Dr. Luke Brewster**

Adjourn

KEYNOTE SPEAKER

Yolonda Colson, MD, PhD

Dr. Colson is the past President of the American Association for Thoracic Surgery, Chief for the Division of Thoracic Surgery at Massachusetts General Hospital and Professor of Surgery in the Field of Thoracic Surgery at Harvard Medical School. She is a member of the prestigious National Academy of Medicine and has served as an Officer and Exam Chair for the American Board of Thoracic Surgery, being integral to the creation and execution of the first virtual ABTS Certifying Exam. In addition to her cardiothoracic surgical training at Brigham and Women's Hospital, her academic training includes a B.S. in Biomedical Engineering from Rensselaer Polytechnic Institute, an M.D. from Mayo Medical School, and a Ph.D. in pathology (transplant immunology) and general surgery residency at University of Pittsburgh. She is the recipient of the George H.A. Clowes, Jr. Research Career Development Award from the American College of Surgeons, the Edward M. Kennedy Award for Health Care Innovation from CIMIT and served as a permanent member of the NIH Developmental Therapeutics Study Section.

She has a specific clinical interest in improving the identification and treatment of lung cancer, extending the chance of cure through novel technologies and broadening our understanding of the unique differences of lung cancer in women. She is co-inventor on three awarded patents, has received over twenty foundation grants and has been PI or co-PI on 11 grants from the National Institutes of Health and National Cancer Institute. She has mentored over 40 undergraduate, post-doctoral & PhD candidates in her laboratory with receipt of dozens of resident research awards & scholarships. Dr. Colson's research focuses on the development of unique mechanisms of polymer and nanoparticle drug delivery aimed at preventing cancer recurrence, and the investigation of novel near-infrared imaging methods to identify hidden tumor that has spread to nearby lymph nodes. She has over 160 peer reviewed publications highlighting her previous work in transplantation, interest in women's lung cancer, and recent investigations in sentinel lymph nodes in lung cancer and polymer-mediated drug delivery.

ORAL PRESENTATIONS: SESSION I

Moderators: Paul Ghareeb, Allison Linden
Location: EUH Auditorium

8:15AM

Category: Basic Science

B7- Chronic Alcohol Exposure Alters the Phenotype of Regulatory T cell Subsets in Septic Mice

Gutierrez MB, Coopersmith CM, Ford ML

Chronic alcohol consumption has been associated with increased mortality in human septic patients. Our lab has shown in murine models that chronic alcohol consumption directly increases sepsis mortality and increases the frequency of $CD4^{+}FoxP3^{+}$ regulatory T cells (T_{reg}). To better understand the phenotype of T_{regs} in alcohol-fed versus water-fed septic mice, C57/BL6 mice received 5% ethanol, increasing 5% every 5d to 20%. Control mice received water. After 3 months, both groups underwent cecal ligation and puncture (CLP). Splenocytes were stained for flow cytometry at 24h. FCS files were pre-gated on the CD4+FoxP3+ T_{reg} population using FlowJo and concatenated for CITRUS analysis using the Cytobank platform. Using LASSO via GLMNET, four T_{reg} populations were significantly different in abundance between alcohol-fed versus water-fed septic mice. Cluster A is $KLRG1^{hi}Helios^{lo}CTLA\text{-}4^{med}CD28^{hi}Ki67^{lo}CD25^{hi}CD103^{hi}CCR4^{hi}Ly6C^{lo}GITR^{med}ICOS^{med}CD69^{hi}CD44^{hi}CD62L^{lo}$ and Cluster B is $KLRG1^{lo}Helios^{lo}CTLA\text{-}4^{lo}CD28^{lo}Ki67^{med}CD25^{lo}CD103^{lo}CCR4^{lo}Ly6C^{hi}GITR^{lo}ICOS^{lo}CD69^{lo}CD44^{lo}CD62L^{hi}$ showed a higher abundance in alcohol-fed mice while Clusters C is $KLRG1^{lo}Helios^{hi}CTLA\text{-}4^{lo}CD28^{lo}Ki67^{hi}CD25^{lo}CD103^{hi}CCR4^{lo}Ly6C^{l}GITR^{hi}ICOS^{hi}CD69^{hi}CD44^{hi}CD62L^{lo}$ and Cluster D is $KLRG1^{lo}Helios^{lo}CTLA\text{-}4^{lo}CD28^{lo}Ki67^{lo}CD25^{lo}CD103^{lo}CCR4^{lo}Ly6C^{lo}GITR^{lo}ICOS^{lo}CD69^{lo}CD44^{lo}CD62L^{hi}$ showed a lower abundance in alcohol-fed mice compared to water-fed. Clusters A and C have effector T_{reg} (eT_{reg}) phenotypes, Cluster B has a central T_{reg} (cT_{reg}) phenotype, and Cluster D has a transitionary cT_{reg} to eT_{reg} phenotype. eT_{regs} are activated suppressive cells primarily located in peripheral tissues while cT_{regs} are more quiescent cells that populate secondary lymphoid organs. Our data show that alcohol exposure alters the expression of activation/effector molecules of eT_{reg} populations in septic mice, and that alcohol-fed mice have fewer transitionary cT_{reg} to eT_{reg}. These findings are potential sources of host response dysregulation during sepsis that stem from chronic alcohol exposure.

8:25AM

Category: Clinical Science

C5 - Objective Performance Indicators Facilitate Step-Specific Skill Assessment in Robotic Right Colectomy

Mishal Gillani, Manali Rupji, Glen C Balch, Mallory C Shields, Terrah J Paul Olson, Yuan Liu, Seth A Rosen

Introduction

Current surgical assessment tools are subjective and non-scalable. Objective performance indicators (OPIs), machine-learning-enabled metrics, provide automated data regarding surgeon movements and robotic arm kinematics. We identified OPIs that significantly differed among expert and novice surgeons during *specific steps* of robotic right colectomy (RRC).

Methods

Endoscopic videos were annotated to delineate individual surgical steps during 25 RRCs. OPIs were compared between 2 experts and 7 novices during mesenteric dissection, ascending colon mobilization (ACM), hepatic flexure mobilization (HFM), and preparation of bowel for transection.

Results

Experts exhibited faster dominant and non-dominant arm acceleration, and dominant arm jerk during all steps except preparation of distal bowel, and faster camera acceleration and jerk during all steps. During mesenteric dissection, experts used faster camera and dominant arm velocity. During medial-to-lateral ACM, experts used less dominant wrist yaw and pitch, shorter dominant arm path length, faster non-dominant arm velocity, and shorter moving times for camera, dominant and non-dominant arms. During lateral-to-medial ACM, experts had faster 3rd arm acceleration, and dominant and non-dominant arm velocity. During HFM, experts exhibited more camera movements, faster 3rd arm acceleration, and greater velocity for camera, dominant and non-dominant arms. During preparation of distal bowel, experts utilized greater dominant wrist articulation, longer non-dominant arm path length and faster camera velocity. During preparation of proximal bowel, experts demonstrated faster non-dominant arm velocity.

Conclusion

OPIs can differentiate experts from novices during distinct steps of RRC. These automated, objective and scalable metrics can be used to provide personalized feedback to trainees.

Table 1: Examples of OPI differences between expert and novice surgeons during specific steps of RRC				
Step	**OPI**	**Expert**	**Novice**	**p value**
Mesenteric dissection	Dominant arm velocity [m/sec]	0.10 [0.08 - 0.13]	0.07 [0.05 - 0.08]	**0.004**
Medial-to-lateral ACM	Task completion time [sec]	110.16 [53.52 - 242.21]	390.27 [190.91 - 676.59]	**0.019**
Medial-to-lateral ACM	Camera moving time [sec]	6.08 [4.16 - 14.61]	21.75 [11.05 - 24.67]	**0.017**
Lateral-to-medial ACM	3rd arm acceleration [m/sec^2]	0.67 [0.62 - 0.85]	0.33 [0.26 - 0.54]	**0.046**
HFM	Camera movements [n]	19.5 [8 - 37]	6 [1 - 9]	**0.039**
Preparation of proximal bowel	Non-dominant arm jerk [m/sec^3]	24.61 [21.03 - 31.79]	17.46 [15.62 - 22.11]	**0.004**
Preparation of distal bowel	Non-dominant arm path length [m]	7.34 [3.62 - 9.53]	1.93 [1.27 - 4.39]	**0.043**
Preparation of distal bowel	Dominant arm EndoWrist roll [rad]	54.15 [44.79 - 100.13]	15.18 [12.46 - 25.55]	**0.011**
All variables are presented as median with interquartile range OPI = objective performance indicator, RRC = robotic right colectomy, ACM = ascending colon mobilization, HFM = hepatic flexure mobilization, m/sec = meters per second, sec = seconds, n = numbers, m = meters, rad = radians				

8:35AM

Category: Clinical Science

C40 - Compliance Monitoring of Intraoperative Lymph Node Assessment in Pulmonary Resections Performed with Curative Intent

Williams, BM, Bonanno, A, Sancheti, M, Fernandez, F, Force, S, Khullar O

Introduction

In January 2021, the American College of Surgeons Committee on Cancer updated its guidelines for intraoperative lymph node sampling during resection of primary lung malignancies with curative intent. Guidelines now require sampling of at least three mediastinal (N2) and one hilar (N1) lymph node station (the 3+1 rule). An 80% compliance rate is required; however, achieving this rate can be challenging and the association between compliance rates and oncologic outcomes is unknown.

Methods

We performed a retrospective analysis of all curative intent pulmonary resections from January 2021 to August 2023. Beginning in November 2021, institutional audits were performed every 6 months monitoring adherence with the 3+1 rule and reasons for noncompliance. Regular

feedback of audit results was provided to each individual surgeon. Compliance rates pre- and post-intervention were evaluated. Univariate linear regression was used to evaluate change in compliance over time.

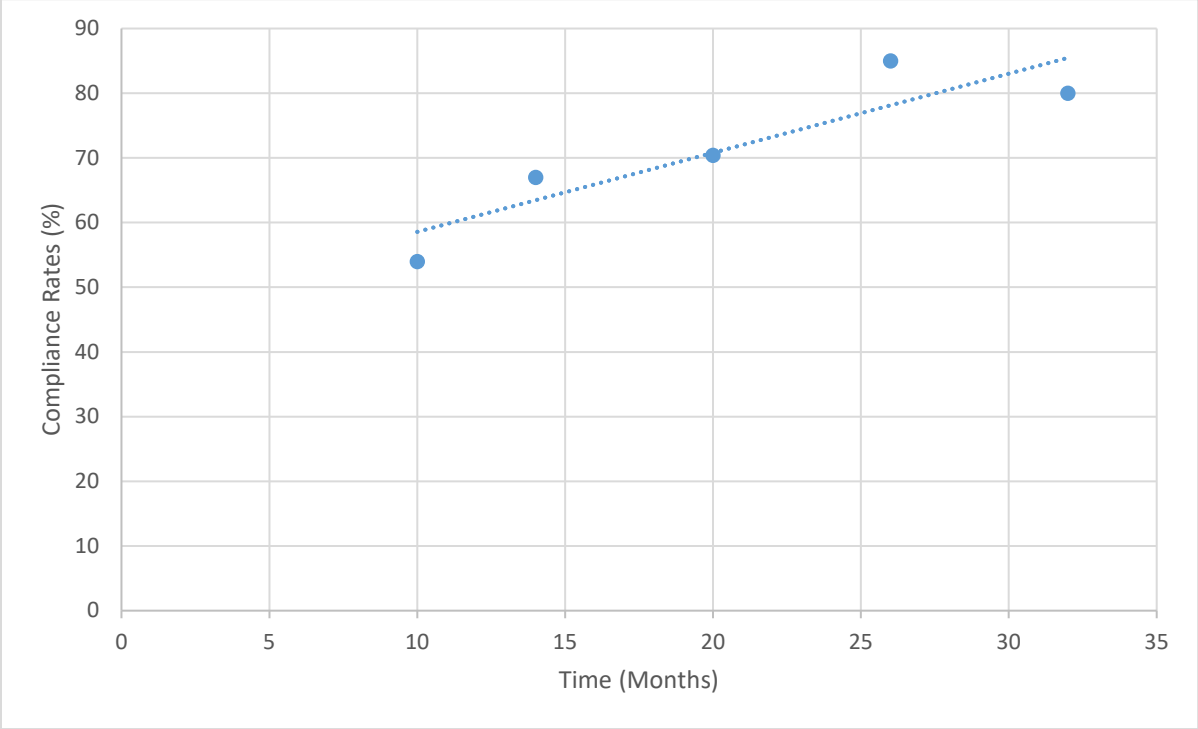
Results

Over the study period, 479 pulmonary resections were performed with curative intent. The rate of adequate nodal staging increased from 54% to 79.8% (R^2=0.81, $p<0.05$, Fig 1). Reasons for noncompliance were most commonly lack of adequate N2 nodal station sampling followed by no nodal dissection performed, occurring in nonanatomic resections.

Conclusion

Through regular auditing and feedback with surgeons, institutional compliance with intraoperative lymph node sampling minimums significantly increased. Further evaluation of the association between compliance rates and upstaging is ongoing. Future research on the barriers to achieving guideline minimums and its effect on oncologic outcomes is necessary to ensure adequate systematic nodal staging in pulmonary resections.

Figure 1. Improvement in Lymph Node Assessment Rates from Jan 2021-Aug 2023



8:45AM

Category: Basic Science

B13 - Creation of iPSC-derived lymphatic endothelial cells for use in regenerative therapy for lymphedema

Owsiany K, Carr S, Tu M, Hekman, K

Background

Lymphedema is caused by impaired flow of interstitial fluid through the lymphatic system, resulting in peripheral edema, lipodystrophy and fibrosis, and chronic obliteration of distal lymphatic collecting vessels. Despite advances in our knowledge of the development of lymphatic vessels, there has been little progress translating this knowledge into clinically relevant regenerative therapies. Although lymphatic endothelial cells (LECs) share a lineage with arterial and venous endothelial cell progenitors, currently described processes to derive LECs from stem cells in vitro take up to a month, require embryoid body formation, and have been minimally characterized.

Methods

We have developed a protocol for the generation of LECs from induced pluripotent stem cells (iPSCs). First, iPSCs are directed to become endothelial cell progenitors and purified with CD144 magnetic beads. Then, ECs are differentiated into LECs using a 5-day treatment with Ang1 alone or in combination with VEGFc.

Results

Treating iPSC-derived endothelial cells for 5 days with Ang1 +/- VEGFc yields iPSC-LECs with morphological similarity to primary lymphatic controls and expression of multiple lymphatic markers including podoplanin, Lyve1, Prox1, and VEGFR3. Their identity has been characterized by multiple modalities, including flow cytometry showing up to 75% co-expression of podoplanin and lyve1, as well as immunofluorescent staining, western blotting, and single cell RNA sequencing.

Conclusions

Treatment with Ang1 with or without VEGFc allows fast and efficient generation of LECs from iPSCs. This allows LEC differentiation in vitro from a wide variety of patient specific cell types and improves the practicality of regenerative therapy for lymphedema.

8:55AM

Category: Clinical Science

C7 - How does Sleeve Gastrectomy Impact Patient Eating-related Behavior, Distress, and Symptoms? Using the BODY-Q Patient-reported Outcome Measures (PROMs)

Mou D, Smith S, Fer D, Davis Carolyn, Yost C, Srinivasan J, Stetler JK, Patel A, Oyefule O, Lin E, Davis S, Hechenbleikner EM

INTRODUCTION

Patients undergoing sleeve gastrectomy (SG) experience transformative change in eating. Assessment of this change with rigorous patient-reported outcome measures (PROMs) is lacking, so we evaluated it with the novel Body-Q Eating Modules, which assess eating-related behavior (ERB), eating-related distress (ERD), and eating-related symptoms (ERS).

METHODS

All patients at an academic institution undergoing evaluation for bariatric surgery were given the Body-Q Eating Modules electronic questionnaire at their preoperative and postoperative visits. Individual questions of each scale were dichotomized between presence and absence of symptoms/distress type/behavior to assess their prevalence before and after SG. Cross-sectional data were obtained preoperatively, and 3 post-operative time points.

RESULTS

Overall, 526 questionnaires were completed; compliance was 82%. Baseline demographics of pre-operative and post-operative groups did not differ in age or gender, but the post-operative group had lower BMI (41 vs. 46, $p < 0.001$). Mean post-operative follow-up was 19 months. Compared to their pre-operative symptoms, patients' eating-related symptoms worsened 1 year after SG (Figure 1A). Eating-related distress significantly improved in the first 6 postoperative months, but this improvement disappeared at the 13+ month post-operative time period (Figure 1B). At 1-year post-op, patients suffer from worse eating-related behavior than their pre-operative baselines. (Figure 1C).

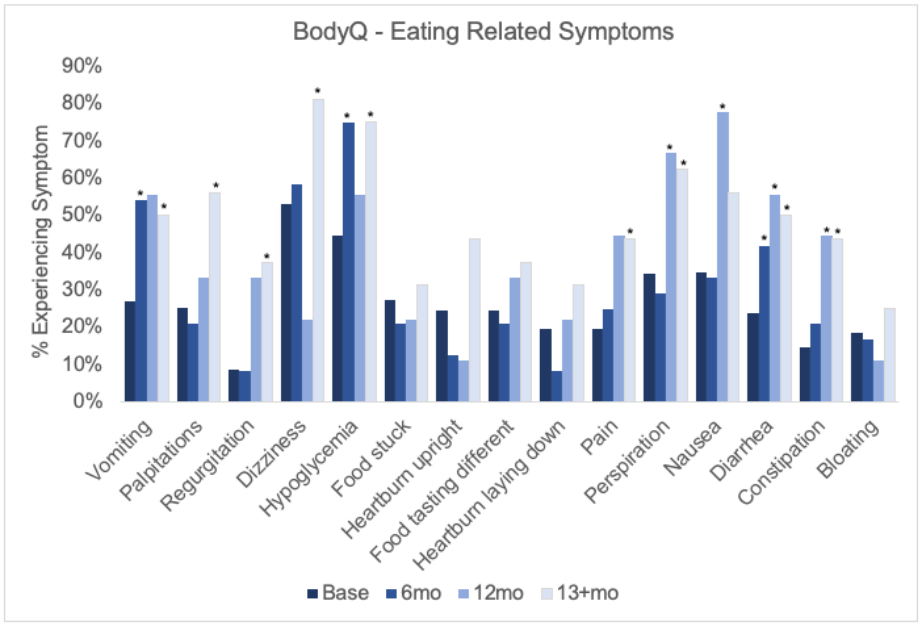
CONCLUSIONS

Eating-related symptoms worsen after SG and persist long-term. While eating-related distress (lack of control, embarrassment, shame) and eating-related behaviors (satiety, feeling in control) improve transiently following SG, these improvements return to preoperative levels by 1 year postoperatively. This highlights a period of patient vulnerability and opportunity for intervention within bariatric programs.

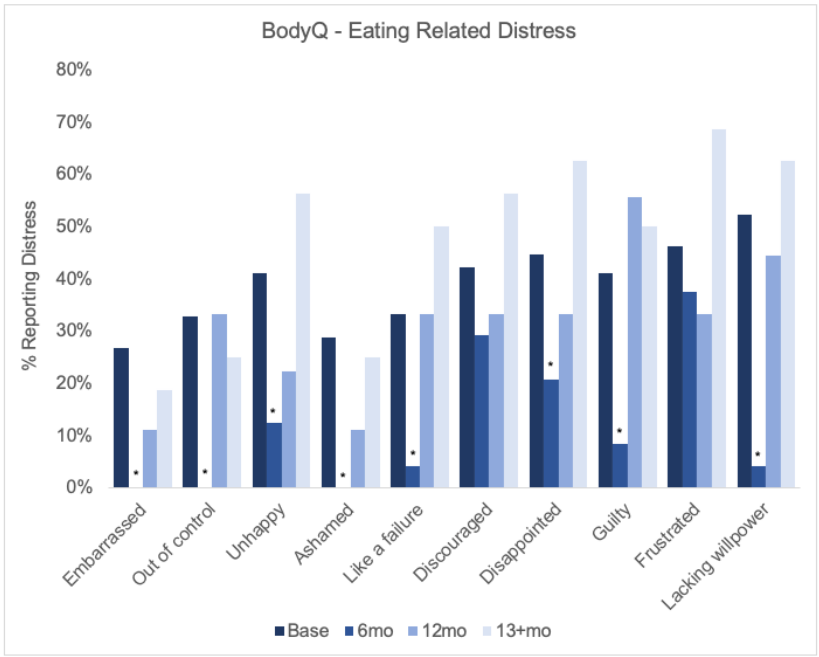
(C7, Smith cont'd)

Figure 1. Trends of BODY-Q PROMs measured before and after sleeve gastrectomy. Specific domains include Eating-related symptoms (A), eating-related distress (B), and eating-related behavior (C)

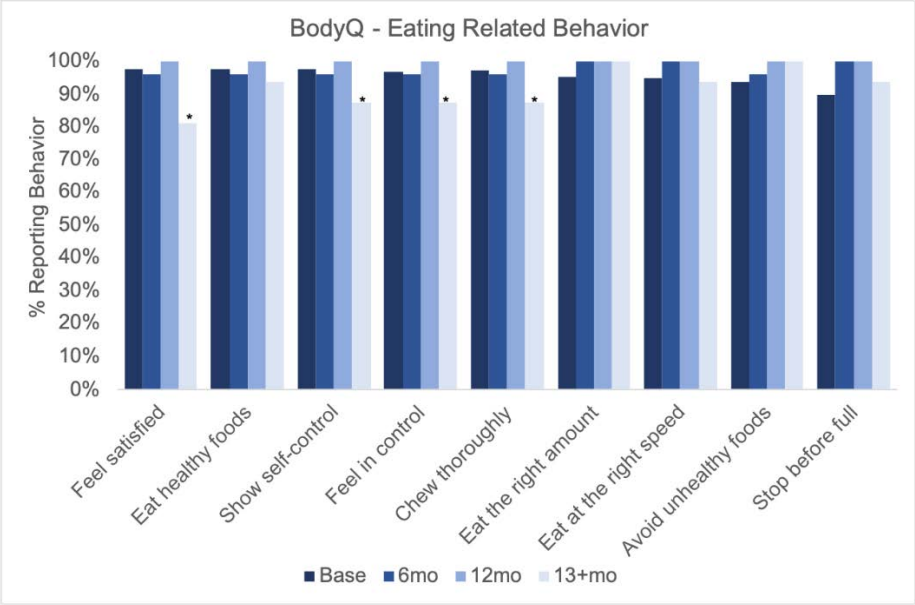
A.



B.



C.



9:05AM

Category: Clinical Science

C13 - How Many Operations Does it Take? Incidence and Risk Factors for Secondary Surgery and Amputation after Lower Extremity Limb Salvage

Ash, Makenna, Brown, Ciara, Menon, Ambika, Knaus, William, Hernandez-Irizarry, Roberto, Ghareeb, Paul

Background

Traumatic defects of the lower extremity require robust soft tissue coverage to cover critical structures and facilitate healing. Free tissue transfer is often necessary when local tissue is inadequate. While much of the literature emphasizes free flap viability in successful limb salvage, there is limited understanding of the need for additional surgeries or eventual amputation. We investigated a single institutions limb salvage efforts to better understand the need for additional procedures following free tissue transfer.

Methods

All patients that underwent LE free tissue transfer were retrospectively reviewed from 2014-2022 at a single level-1 Trauma center. Patient demographics and surgical characteristics were documented. Our primary clinical outcome was the incidence and indication of secondary surgeries following free tissue transfer.

Results

92 free flaps were performed during the study period. The mean age was 45 and the majority were male. 72% of flaps performed were fasciocutaneous while 28% were muscle flaps (Table 1).

72% of patients required a secondary surgery following flap procedure, with a mean of 7 total surgeries per salvage attempt. 10% of patients proceeded to amputation (Table 2). BMI >30, higher frailty scores, flap type, and masquelet technique were significant associated with subsequent amputation (p= 0.17, p=.024, p=0.005, p=.04 respectively).

Conclusion

Free tissue transfer is an important component of limb salvage. Patients undergoing limb salvage should be counseled on the need for secondary reconstructive surgeries, as the salvage process is often not complete following free flap transfer. Furthermore, risk factors identified in this study may increase the likelihood of subsequent amputation. Thorough preoperative counseling is necessary to optimize the post-operative course and expectations in this population.

Table 1: Secondary Surgeries & Comorbidities

	Total	**Average**
Secondary Surgeries Required	168	1.82
Return for Removal of Hardware	28	16.67%
Return for Nonunion/Malunion	19	11.3%
Total Surgeries Required	622	6.76
DM2	6	6.50%
Smoking	27	29.30%
HTN	11	12.00%

Table 2. Amputation Characteristics following Attempted Limb Salvage

Patient #	**Indication**	**Days following free flap**	**Additional Surgeries Prior to Amputation**
1	Preference	14	2
2	Foot ischemia	7	1
3	Osteomyelitis	98	0
4	Painful non-union	598	3
5	Prior free flap failure	52	2
6	Infection	47	1
7	Prior free flap failure	22	3
8	Infection	46	2
9	Infection	125	2

QUICKSHOT PRESENTATIONS: BASIC SCIENCE

Moderators: Luke Brewster, Katherine Hekman, John Calvert
Location: EUH Classroom B/C

9:40AM

B2 - Tfr Deficiency Leads to Inferior, Not Superior, Antigen-Specific B Cell and Donor-Specific Antibody Responses
Menshikov D, Crichton ES, Zeng S, Ford ML, Badell IR

Introduction
Donor-specific antibodies (DSA) are associated with allograft injury, but effective therapies are unavailable. T follicular regulatory (Tfr) cells have been considered suppressors of germinal center (GC) reactivity and DSA, but their role in transplant is unclear.

Methods
We utilized a full MHC mismatch Balb/c to B6 murine skin allograft model in Tfr conditional knockout (cKO, $Foxp3^{Cre}Bcl6^{fl/fl}$) mice and wild-type (WT, $Foxp3^{wt}Bcl6^{fl/fl}$) controls. Flow cytometry was performed for dLN analyses and crossmatches, ELISA for Balb/c MHC-specific IgG, and urea affinity assays for evaluating binding strength of DSA.

Results
Flow crossmatches with serum from Balb/c transplanted mice indicated that Tfr cKO and WT mice produced similar amounts of anti-Balb/c IgG through day 14. The cKO IgG response began to decline by day 21 and was significantly inferior by day 35 (Figure1). The frequency and number of H2-Kd-specific GC B cells were reduced in Tfr cKO recipients. ELISA demonstrated equivalent baseline total mouse IgG levels. There was a reduction in Balb/c monomer-specific DSA in Tfr cKO recipients that persisted as late as 90 days post-transplant. The DSA generated in the absence of Tfr cells exhibited a lower affinity for MHC class I Balb/c monomers compared to WT.

Conclusion
Tfr cell deficiency led to lasting reductions in DSA and donor-specific GC B cells post-transplant. Contrary to current ideas regarding the role of Tfr cells as inhibitors, our findings indicate that Tfr deficiency results in reduced (not greater) quantities of lower affinity DSA. Hence, inhibiting rather than enhancing Tfr may be a more effective strategy to treat DSA.

(B2, Menshikov cont'd)

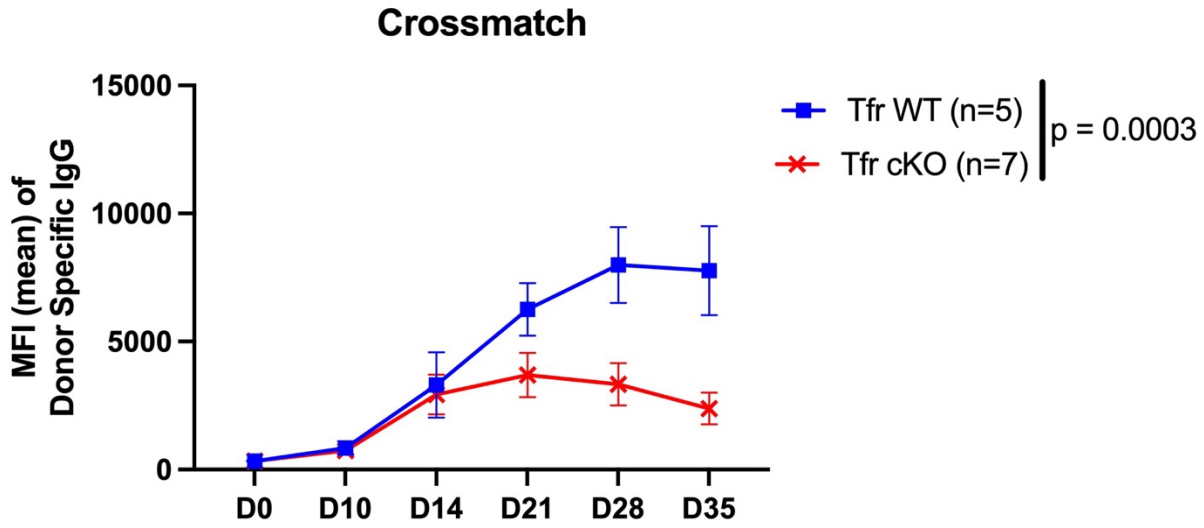


Fig1

9:45AM

B9 – CD26 is a Prognostic Biomarker That Can Be Leveraged to Enhance Response to T Cell Therapy in Advanced Melanoma

Swisher, SK, Wyatt, MM, Wittling, MC, Ruffin, AT, Delman, KA, Lesinski, GB, Lowe, MC, Paulos, CM

Introduction

We identified a novel subset of CD4+ T cells that express high levels of CD26. This CD4+ $CD26^{high}$ T cell subset has enhanced stemness and polyfunctionality *in vivo*. We reported that presence of CD4+ $CD26^{high}$ T cells in patients with metastatic melanoma correlated with response to treatment with the immune checkpoint inhibitor (ICI), Nivolumab. The presence of CD4+ $CD26^{high}$ T cells were also associated with significantly improved clinical outcomes, including progression-free survival (PFS) and overall survival (OS). Based on this data, we posit that presence of CD26 on T cells can be leveraged to improve cellular therapies in advanced melanoma and to inform clinical decisions that impact disease-specific outcomes.

Methods

Mouse models that express a transgenic T cell receptor (TCR) specific for tyrosinase on melanoma were used to evaluate the impact of these novel CD4+ T cells on the immune response *in vivo*. Mouse TRP-1 CD4+ T cells were sorted by flow cytometry based on CD26 expression: yielding two enriched groups of $CD26^{neg}$ or $CD26^{high}$ CD4+ T cells. B16F10 melanoma-bearing mice were lymphodepleted prior to infusion of these cells and monitored for tumor response.

CD26 enzymatic activity was then blocked in TRP-1 CD4+ CD26^{high} T cells *in vitro* using sitagliptin [2mM] to determine if CD26 activity was required to generate the observed anti-tumor response. Cells were administered to mice with melanoma and tumor growth was compared to mice that received infusion of uninhibited TRP-1 CD4+ CD26^{high} T cells.

Peripheral blood of healthy donors was compared to that of patients with metastatic melanoma to quantify, phenotype, and further characterize CD4+ CD26^{high} T cell functionality in these populations with spectral flow cytometry. All data obtained was analyzed on FlowJo. Statistical analyses were performed with GraphPad Prism.

Results

Using a TCR-transgenic system where T cells recognize TRP-1 melanoma antigen (Ag), we found that CD4+ CD26^{high} T cells elicit potent antitumor activity *in vivo* compared to mice infused with CD4+ CD26^{neg} T cells ($P < 0.05$) or no treatment ($P < 0.001$), as depicted in Figure 1A.

CD26 enzyme activity was required for improved tumor regression, as administration of sitagliptin impaired antitumor killing among TRP-1 CD4+ CD26^{high} T cells in B16F10 mice with melanoma. At 125 days, 80% of mice that received CD26 enzymatically active cells were alive compared to 10% in the CD26-inhibited group (Figure 1B).

Patients with metastatic melanoma had fewer CD4+ CD26^{high} T cells than healthy donors ($P = 0.001$) present in the peripheral blood at baseline. Metastatic melanoma patients were then stratified into two groups based on the baseline frequency of CD4+ CD26^{high} T cells to determine their impact on tumor killing and establishment of a durable response to treatment. Patients with fewer CD4+ CD26^{high} T cells had significantly worse outcomes with decreased PFS ($P = 0.014$) and OS ($P = 0.010$), as demonstrated in Figure 1C. Furthermore, the presence of CD4+ CD26^{high} T cells successfully predicted response to anti-PD-1 therapy, suggesting their utility as a biomarker for response to treatment and to guide individualization of treatment regimens. Continued analysis of the mechanism by which these cells enhance the immune response is ongoing and we are investigating how these effects can be harnessed to improve cellular therapies *in vivo*.

Conclusions

We discovered that T cells with high CD26 levels can effectively regress solid tumors *in vivo*. CD26 enzymatic activity is required for enhance tumor regression, and the degree of CD26 expression predicts response to ICI therapy, which improves prognostication in advanced melanoma. This may serve as a biomarker for response to therapy and allow for individualization of treatment regimens and improve cellular therapies for patients with melanoma. Ongoing analyses aim to reveal the mechanism by which these cells augment the immune response.

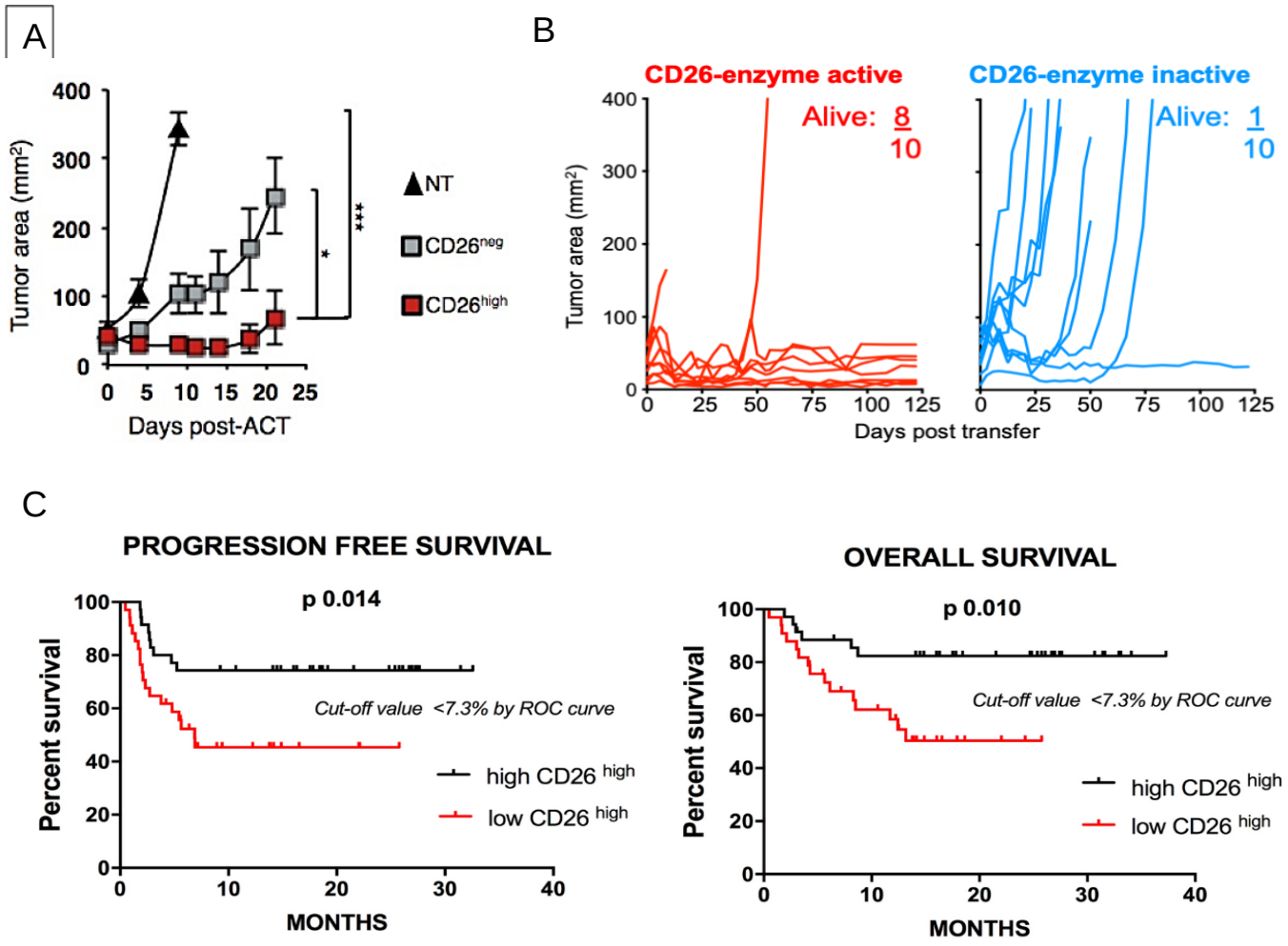


Figure 1.

(A) CD4+ CD26^{high} T cells improve melanoma regression compared to CD4+ CD26^{neg} T cells.
All mice were lymphodepleted one day prior to administration of Adoptive Cellular Therapy (ACT) with either CD4+ CD26^{high} or CD26^{neg} T cells. N = 6 mice per group. One-way ANOVA was used to calculate the P values for the tumor curve. Data with error bars represent the Mean ± the Standard Error of the Mean (SEM).
*, P < 0.05; **, P < 0.01.; ***, P < 0.001; ****, P < 0.0001.

(B) Inhibiting CD26 enzyme activity impairs CD4+ CD26^{high} T cells *in vivo*.
TRP-1 CD4+ CD26^{high} T cells were grown *in vitro* with no treatment (red) or with sitagliptin, a known CD26 enzyme inhibitor [2mM] (blue). These cells were then infused in B16F10 melanoma-bearing mice. Tumor growth was measured for 125 days. N = 10 mice per group.

(C) Low frequencies of circulating CD4+ CD26^{high} T cells are associated with reduced survival in patients with metastatic melanoma. Kaplan Meier curves depict the difference in progression-free survival (PFS) and overall survival (OS) in patients with high or low baseline circulating levels of CD4+ CD26^{high} T cells.

9:50AM

B11 - Sex-Specific Differences in Thrombospondin-1 Modulation in Flow-mediated Atherosclerotic Plaque

Michael Tu, Feifei Li, Gloriani Sánchez-Marrero, Dennis Foster, Luke Brewster, Dong Wan Kang, Sandeep Kumar, Kyung In Baek, Hanjoon Jo

Background

We previously demonstrated that areas of disturbed flow (d-flow) have upregulated TSP-1, that inhibition of TSP-1 activation of TGF-β decreased fibrotic pathways, and that flow-mediated stiffening was favorably moderated in TSP-1 knockout (KO) mice. In apoE/TSP-1 dKO atherosclerotic plaques, there are disparate results, and the impact of blood flow is not well understood. We hypothesized that TSP-1 KO arteries would have less atherosclerotic plaque.

Methods

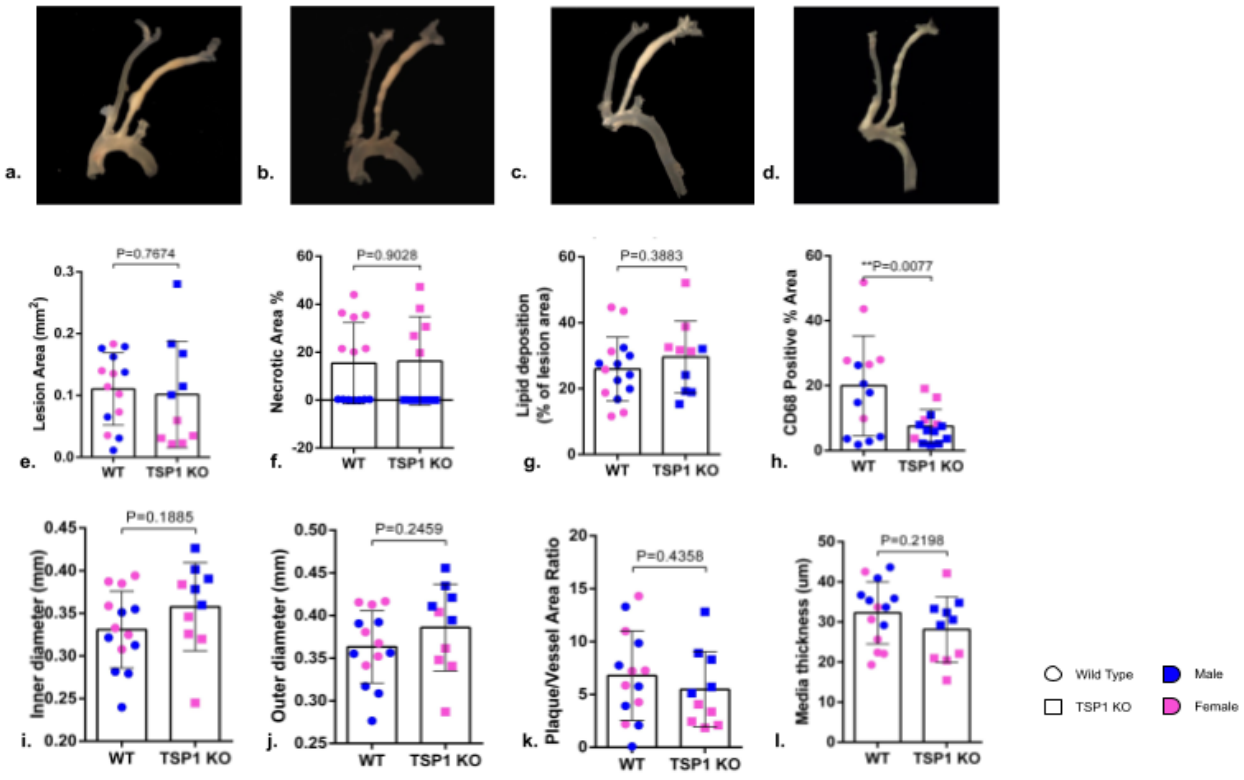
D-flow was induced, and atherogenic conditions were imposed and validated. Histology was performed on harvested arteries. To test for sex-specific differences, human aortic endothelial cells (HAECs) were cultured under oscillatory and laminar wall shear stress (WSS) conditions for 24 and 96 hours while TSP-1 activation of TGF-β was inhibited. RNA was collected and qPCR was performed.

Results

In TSP-1 KO arteries, plaques had less macrophage content and there were interesting sex-based differences. In vitro, male HAECs had decreased fibrotic gene expression at 24 hours while this was delayed to 96 hours in female HAECs. TSP-1 and markers of endothelial-to-mesenchymal transition were significantly upregulated in symptomatic carotid endarterectomy samples. Similarly, TSP-1 was increased in PAD patients.

Conclusion

TSP-1 KO mice have general and sex-based differences. This may be related in part to sex differences in the inhibition of TSP-1 activation of TGF-β in the EC response to d-flow. TSP-1 is active clinically in PAD and carotid artery disease, both of which are marked by d-flow conditions. Future work will help delineate mechanistically the role of these sex differences in flow-mediated focal atherosclerotic plaque.



9:55AM

B12 - Functional Depletion of Natural Killer Cells in Pig-to-Nonhuman Primate Renal Xenotransplantation

Keiler J, Habib J, Wilson B, Guo L, Ford ML, Larsen C, Kim S

Introduction

Xenotransplantation is a promising solution to the shortage of suitable donor organs. While the challenge of hyperacute rejection has largely been overcome, acute rejection remains a risk to intermediate and long-term graft survival. Furthermore, the most successful preclinical studies thus far utilize an immunosuppressive regimen (anti-CD154) that is not currently clinical available. Preliminary studies from our group investigated CD28 targeted therapy in a preclinical xenotransplantation model which revealed increased trafficking of NK cells to the xenograft at time of rejection compared to rejecting allografts in animals that received the same regimen. Subsequent in vitro experiments demonstrated treatment with belatacept and αIL-15 resulted in significantly reduced proliferation of bulk T cells (largely CD8+ T cells) and NK cells. Here, we investigate the impact of NK cell depletion in a preclinical model of pig-to-NHP renal xenotransplantation

Methods

Renal xenograft from GalKO/hDAF pigs were transplanted in Rhesus Macaque following bilateral native nephrectomy. NHPs received NK cell depletion with αIL-15 in addition to a clinically available immunosuppression protocol of CD4/CD8 T cell depletion (αCD4 and αCD8), MMF, steroids, and belatacept.

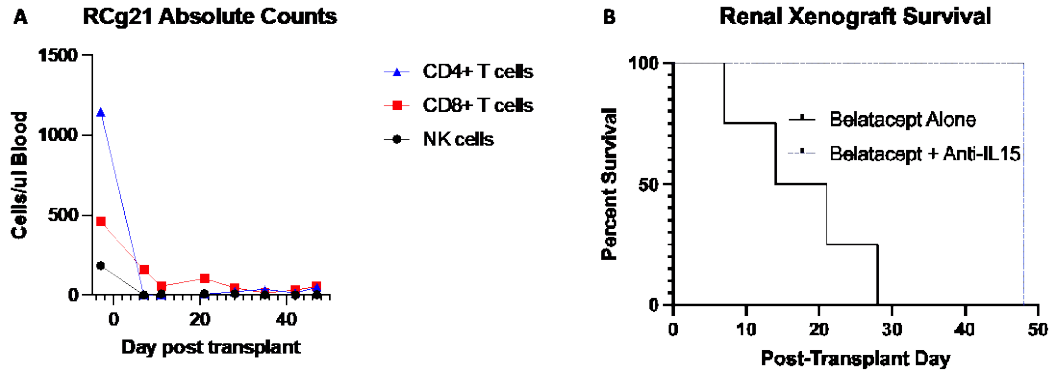


Figure 1.

Results

Counting assays performed via flow cytometry demonstrated durable depletion of NK, CD4+, and CD8+ T cell populations in vivo (A). NK cell depletion promoted survival longer than historical controls receiving a clinically available immunosuppression regimen (A; MST = 19 days).

Conclusion

These data suggest a role for improved survival following NK cell depletion in a preclinical model of pig-to-NHP renal xenotransplantation. Further investigation is warranted in light of these preliminary findings.

10:00AM

B1 - Ganglioside Metabolism Functionally Regulates The Spectrum of CD8+ T Cell Alloreactivity

Bazzano, J.M.R, Baecher, K., Liu, D., Fribourg, F., Cravedi P., Heeger, P., Ford, M. L.

CD8⁺ T cells are critical mediators of allograft rejection, and a fundamental step in alloreactive T cell activation is the recognition of donor antigen. However, the pathways governing strength of T cell allorecognition are incompletely understood. Here, we identified a novel regulator of TCR expression that controls the extent of the allogeneic response. Using data from the CTOT-09 clinical trial in which kidney transplant recipients were weaned from tacrolimus immunosuppression, CD8⁺ T cells from stable patients were found to exhibit increased transcript levels of the glycosphingolipid-catabolizing protein *Gm2a* compared to patients who went on to reject. To investigate the role of Gm2a in alloimmunity, we performed skin graft surgery in

wildtype recipients of wildtype *vs* *Gm2a*$^{-/-}$ CD8^{+} T cells. Results indicate that recipients of *Gm2a*$^{-/-}$ CD8^{+} T cells exhibited accelerated allograft rejection along with increased accumulation of donor-reactive CD8^{+} T cells *vs* recipients of wildtype cells (*p<0.05*), illuminating a CD8^{+} T cell-intrinsic role for Gm2a in regulating alloreactivity. Mechanistically, *Gm2a*$^{-/-}$ CD8^{+} T cells exhibited sustained TCR expression following activation compared to wildtype CD8^{+} T cells, conferring increased responsiveness to low-affinity alloantigen (*p<0.01*). Moreover, an in vivo mixed lymphocyte reaction showed 50% augmentation in the frequency of alloreactive precursors *among Gm2a*$^{-/-}$ *vs wildtype T cells. Finally, a TCR sequencing analysis demonstrates that Gm2a deficiency increases the number and diversity of alloreactive* CD8^{+} T cell *clones. Therefore, we show that* Gm2a regulates the spectrum of CD8^{+} T cell alloreactivity by reducing TCR expression, thus increasing the T cell threshold of activation and limiting the number of alloreactive ligands to which a given T cell can respond.

10:05AM

B4 - Role of TIGIT in regulating alloreactive memory CD8+ T cell responses

Martinez C.D., Hartigan C.R., Wagener M.E., Ford M.L.

Belatacept (CTLA-4Ig variant) is associated with improved kidney function in renal transplant recipients but comes at a cost of increased rates of early acute rejection compared to current standard-of-care calcineurin inhibitors. We interrogated the phenotypes of human memory T cell subsets associated with belatacept-resistant rejection and identified the shared expression of a coinhibitory molecule TIGIT. To determine the role of TIGIT in regulating memory T cell responses in a murine model of transplantation, recipients containing donor-reactive memory CD8+ T cells were challenged with an allogeneic skin graft. The combination of CTLA-4Ig plus TIGIT agonist significantly improved graft survival as compared to CTLA-4Ig alone (p=0.0296). The addition of the TIGIT agonist also resulted in a reduction in the frequency (p=0.0446) and number (p=0.0006) of graft-infiltrating CD8+ memory T cells on day 6 post-transplant. Because TIGIT is highly expressed on both CD8+ memory T cells and Foxp3+ Treg, we sought to determine whether the TIGIT agonist suppressed memory CD8+ T cell responses directly via TIGIT+ memory CD8+ T cells, or indirectly via TIGIT+ Foxp3+ T cells. Using Treg-specific TIGIT conditional knockouts, we show that TIGIT agonism significantly altered the frequencies of both IFN-g (p=0.0012) and IL-2 producers (p=0.0408) among donor-reactive CD8+ memory T cells only when TIGIT was conditionally deleted from Tregs. We conclude that TIGIT signaling regulates memory CD8+ T cell responses indirectly via its effect on Foxp3+ T cells. TIGIT agonism may hold promise as an adjunct immunotherapy to attenuate memory CD8+ T cell mediated costimulation-blockade resistant rejection.

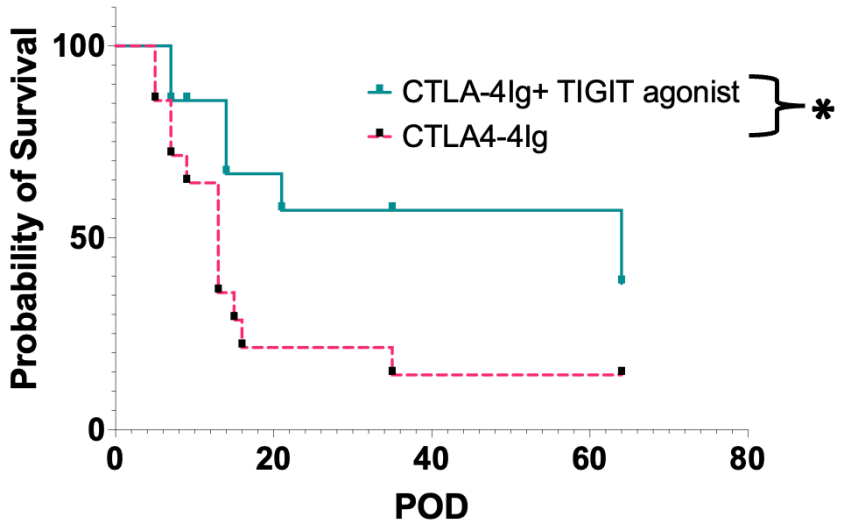


Figure 1. TIGIT agonism reduces costimulation blockade-resistant rejection in a murine skin graft model of memory CD8+ T cell alloimmunity.

10:10AM

B5 – Making Their Own Off Switch: Fgl2 Produced by Tumor-specific CD8+ T cells Tempers the CD8+ T Cell Response

Bennion KB, Liu D, Dawood A, Wyatt MM, Alexander KL, Abdel-Hakeem MS, Paulos CM, Ford ML

CD8+ T-cell tumor infiltration is a critical factor to immunotherapeutic success. Our lab recently discovered that FcγRIIB, the sole inhibitory IgG-Fc receptor, is upregulated on effector CD8+ T cells at the tumor and that signaling through FcγRIIB regulates CD8+ T cells in a cell-intrinsic manner. We discovered that fibrinogen-like protein 2 (Fgl2) binds FcγRIIB and induces FcγRIIB-mediated cell death in vitro, but the source of Fgl2 was unknown. Here, we investigate the possibility that CD8+ T cells produce Fgl2 in an auto-regulatory feedback loop. We show that CD8+ T cells can produce Fgl2 upon activation in mice and humans. To determine the clinical relevance of Fgl2 on CD8+ T cells, we analyzed two datasets of melanoma patient TIL. We found that Fgl2 is expressed on patient CD8+ TIL ($p<0.0001$) and that this expression is correlated with decreased patient survival ($p<0.05$). To establish the isolated impact of Fgl2 from CD8+ T cells, a conditional knockout model was generated wherein only the tumor-specific CD8+ T cells lack Fgl2. B16-challenged mice given Fgl2-deficient tumor-specific CD8+ T cells exhibited enhanced antitumor response ($p<0.05$) compared to mice given WT tumor-specific CD8+ T cells. Increased persistence of Fgl2-/- tumor-specific CD8+ T cells was underpinned by a decrease in apoptosis of FcγRIIB+ CD8+ T cells ($p<0.05$). These data demonstrate a regulatory signaling axis whereby CD8+ T cells produce their own off-switch. The discovery of this pathway opens potential avenues to manipulate the expression and signaling of this axis to increase patient treatment options.

10:15AM

B14 - Metabolic Regulation of Induced Pluripotent Stem Cell Derived Endothelial Cells Regenerative Capacity

Carr, SM., Owsiany, K, Tu, M, Hekman, KE.

Introduction

Induced pluripotent stem cells (iPSCs) derived endothelial cells (ECs) have emerged as a novel treatment strategy to restore limb perfusion in a murine model of peripheral artery disease (PAD). However, our lab has demonstrated that iPSC-ECs in culture experience a loss of cellular identity and metabolic control, limiting therapeutic implementation.

Methods

y6 human iPSCs were differentiated as previously described (Patsch Nat Cell Bio 2015) into ECs. iPSC-ECs were cultured under varying oxygen conditions (standard 21% vs. physoxic 4%). Markers of cellular identity and metabolic profile were analyzed.

Results

iPSC-ECs lost cellular identity marker VE-Cadherin 55% positive in physoxic vs. 29% positive in standard over a period of two weeks ($p<0.01$). Single-cell RNA sequencing demonstrated loss of cellular identity coincided with upregulation of endothelial-to-mesenchymal transition (EndMT). Physoxia significantly altered key metabolic proteins compared with standard conditions. Neuropilin 1 (Nrp1), an angiogenic related protein, was significantly increased in standard conditions (40% increased, $p<0.01$). PFKFB3, pathological upregulation of which correlates with increased EndMT, was downregulated in physoxia (52% lower, $p<0.05$) compared to standard conditions.

Conclusion

iPSC-ECs under standard culture conditions demonstrated loss of EC identity with EndMT by single-cell transcriptomic, and Western blot analysis of key metabolic proteins. Physoxia favorably impacted retention of key iPSC-EC identity markers. While increased Nrp1, under standard conditions, can be associated with angiogenesis, concomitantly overactivation of PFKFB3 suggests an unfavorable metabolic activation, net loss of energy, a shift towards EndMT, and ultimately impaired regenerative capacity. Our results demonstrate iPSC-ECs maintain metabolic control when grown in physoxic conditions. 10:20AM

10:20AM

B3 - CD154:CD11b Blockade: A Novel Costimulatory Target That Maintains Protective Immunity While Attenuating Allograft Rejection

Alexander KL, Liu D, and Ford ML

CD154 pathway antagonism is promising target for inducing long-term graft survival, in some cases showing superior efficacy compared to anti-CD40, likely due in part to its interactions with the alternate receptor CD11b. Recently, we showed that CD154:CD11b blockade improved long-term graft survival, indicating therapeutic potential for transplantation. However, the impact on protective immunity is unknown. The goal of this study was to determine the impact of a CD154:CD11b-specific peptide inhibitor on protective T cell immunity to a murine EBV homolog (MHV68) and to compare this to its effect on alloimmunity using murine skin graft models. During transplantation, CD154:CD11b blockade significantly decreased graft-specific TCR transgenic CD8+ T cells in the spleen and infiltration into the allograft 10 days post-transplantation. In contrast, CD154:CD11b blockade increased tetramer+ virus-specific CD8+ T cells 10 days post-infection. CD154:CD11b blockade during viral infection also significantly increased the frequency of CD127hiKLRG1lo memory precursor effector cell (MPEC) CD8+ T cells, with a commensurate increase in phosphorylation of S6 downstream of mTOR signaling and the transcription factor cJun. In contrast, MPEC differentiation of graft-specific CD8+ T cells was not altered by CD154:CD11b blockade. A direct comparison of antigen-specific CD8+ T cells elicted via either infection or transplantation showed significant differential induction of transcription factors known to determine MPEC differentiation, Eomes and T-bet, as well as CD11b and phosphorylation of S6. These data demonstrate that while CD154:CD11b blockade suppresses alloimmunity, it paradoxically enhances the quantity and quality of virus-specific CD8+ T cells. These disparate outcomes are underpinned by differential activation of mTOR signaling and induction of key transcription factors in graft- vs. virus-elicited antigen-specific CD8+ T cells. Targeting CD154:CD11b interactions therefore holds promise for inhibiting alloreactivity while maintaining protective immunity following transplantation.

QUICKSHOT PRESENTATIONS: CLINICAL SCIENCE

Moderators: Mike Lowe, Lauren Postlewait
Location: EUH Classroom A

9:40AM

C21 - Undocumented Immigrants with ESRD Experience a Significant Disadvantage in Standard Care Surrounding Hemodialysis

Ramazani CA, Rooney E, Metts K, O'Leary H, Wasserman C, Johnson S, Garcia-Toca M, Rajani RR, Benarroch-Gampel J, Ramos CR

INTRODUCTION

Hemodialysis care in the United States for undocumented immigrants remains challenging and limited to emergency-only dialysis. The objective of this study is to evaluate the timeliness of medical care provided for undocumented immigrants with ESRD compared to their documented counterparts.

METHODS

A retrospective chart analysis was performed of patients undergoing first-time arteriovenous access (AVA) creation at a single center from 2012-2018 to compare outcomes between documented and undocumented patients. Patient demographics and operative details were collected. The primary outcome was time to initial evaluation by nephrology, vascular surgery, and AVA creation.

RESULTS

290 patients underwent first-time AV access creation (62 undocumented, 228 documented). Undocumented patients were younger and more commonly Hispanic (Table I). Undocumented patients were more likely to be evaluated by nephrology at the time of HD initiation (59.7% vs 25.4%, P<0.001) and already be on HD when first evaluated for AVA creation by vascular surgery (74.2% vs 38.6, P<0.001). After vascular surgery evaluation, there was no difference in time from evaluation to surgery (25 days vs 20 days, P=0.95) or from surgery to AVA maturation (77 days vs 57 days, P=0.31). As a result, undocumented patients were more likely to start dialysis with a central venous catheter (CVC, 90.3% vs 66.7%, P<0.001) and had longer CVC duration (429 days vs 202 days, P<0.001).

CONCLUSION

Due to limited access to healthcare, undocumented immigrants with ESRD had a significant delay in evaluation by nephrologists and vascular surgeons for AVA creation with a higher use of CVC for dialysis initiation.

Table I: First-time AV access creation in undocumented immigrants and documented patients.

	Undocumented (N=41)	Documented (N=228)	P-value
Age at surgery (Mean, years)	*46.6*	*55.0*	*<.0001*
Male	*47%*	*58%*	*0.2*
African American	*8%*	*90%*	*<.0001*
Hispanic	*92%*	*6%*	*<.0001*
Hypertension	100%	98%	0.6
Diabetes	55%	61%	0.5
Smoking history	*27%*	*51%*	*<.0001*
Myocardial Infarction	6%	20%	0.01
HIV	*0%*	*9%*	*0.01*
CKD Etiology - Hypertension	69%	73%	0.7
CKD Etiology - Diabetes	50%	52%	0.9
CKD Etiology - Other	19%	16%	0.7
Catheter for initial dialysis	*90%*	*67%*	*0.0004*
Catheter Duration (Median, Days)	*429*	*202*	*<.0001*
HD to Nephrology Evaluation (Median, Days)	*0*	*-213**	*<.0001*
HD to Vascular Surgery Evaluation (Median, Days)	*76*	*-6**	*<.0001*
Vascular Evaluation to Surgery (Median, Days)	25	20	0.95
Surgery to AV Maturation (Median, Days)	*77*	*57*	*0.3*
HD to AV Maturation (Median, Days)	*306*	*53*	*<.0001*

(* negative values are number of days prior to HD initiation)

9:45AM

C8 - Primary Intimal Tear Distribution in Patients with Acute DeBakey I Aortic Dissection

Lauren V. Huckaby, MD, MS; Helen O'Leary, BS; Alexander P. Nissen, MD; Bradley G. Leshnower, MD

Objective

A tear-oriented operative strategy has been proposed for patients with acute aortic dissection in order to promote false lumen thrombosis and favorable aortic remodeling. We sought to characterize primary intimal tear (PIT) spatial orientation in relation to baseline characteristics, operative approach, and outcomes in patients undergoing surgical repair of acute DeBakey I aortic dissection.

Methods

Among 529 consecutive patients undergoing acute type A aortic dissection repair from 2004-2019, 283 had detailed descriptions of direct intraoperative visualization of the PIT and were included in the final analysis. PIT location was categorized as being located at the root, ascending aorta, or aortic arch. Kaplan Meier analysis was utilized to compare survival between the groups.

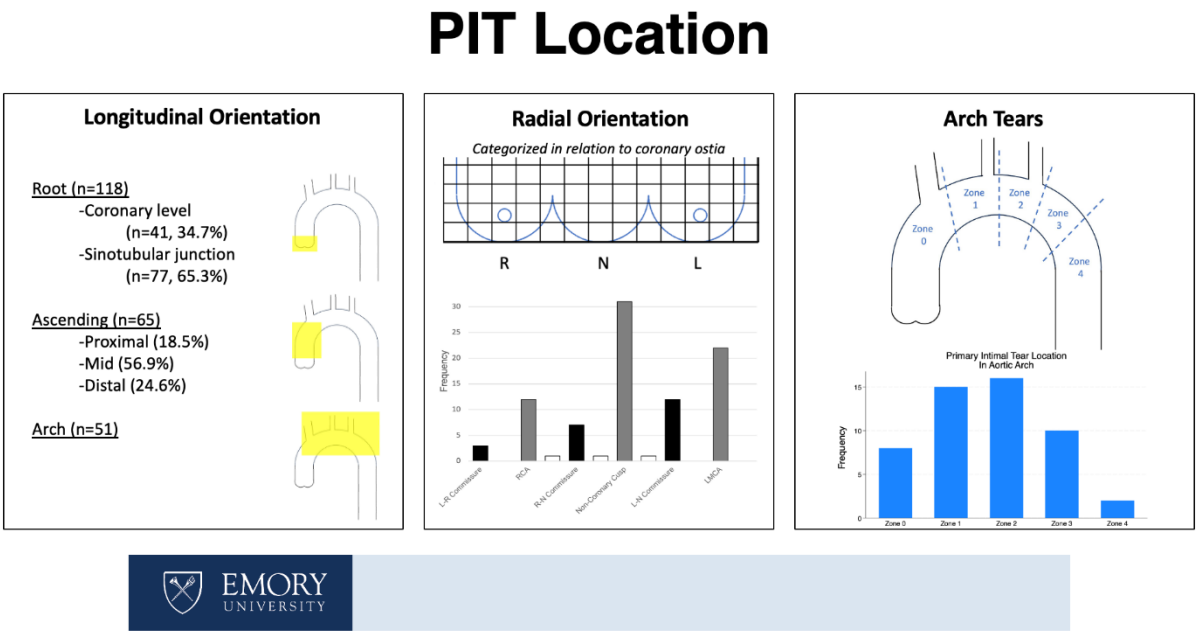
Results

The majority of PITs were located in the aortic root (n=118), followed by the ascending aorta (n=65), and arch (n=51) (Table). Within the aortic root, the majority of PITs were located at the level of the sinotubular junction (n=77/118, 65.3%). Ascending PIT was most common in the mid-ascending aorta (n=37/65, 56.9%). The majority of arch PITs were located in zone 2 (n=16/51, 31.3%) with zone 1 tears being the next most common (n=15/51, 29.4%). Multiple tears were noted in 15.5% (n=44/283) of patients. There were no significant differences in demographics or comorbidities between the three groups. Aortic root diameter was significantly greater in those with root tears (3.86cm) versus ascending (3.77cm) and arch (3.44cm) tears (p=0.001); maximum aortic size did not differ significantly (5.24cm versus 5.33cm versus 5.72cm; p=0.088). There were no differences in malperfusion (including renal, coronary, mesenteric, and limb malperfusion) in relation to the PIT site. Root replacement and valve-sparing root replacement were more common in root PIT (40.2% and 15.4%) compared to ascending PIT (20.0% and 4.6%) and arch PIT (13.7% and 3.9%, p<0.001 and p=0.018). Valve resuspension was performed more frequently in those with arch PIT (88.2% versus 59.0% for root PIT, p<0.001); rates of aortic valve replacement did not differ significantly (16.2% versus 7.7% versus 7.8%, p=0.138). Total arch replacement was performed in 41.2% of patients with arch PIT. Among those with root PIT, the majority underwent hemiarch replacement (n=110, 94.0%). There were no differences in operative approach among patients with one versus multiple PITs. All-cause 30-day (14.4% versus 7.7% versus 17.7%; p=0.254) and 1-year mortality (21.1% versus 9.2% versus 23.5%; p=0.076) were similar for all three groups. By Kaplan-Meier analysis, overall post-operative survival at 10 years was 60.0% for root PIT, 51.9% for ascending PIT, and 45.8% for arch PIT (p=0.316). Post-operative permanent neurologic dysfunction was

significantly greater in those patients with arch PIT (19.6% versus 6.0% for root PIT and 6.1% for ascending PIT; p=0.011). Distal reoperation occurred more frequently in the arch PIT group (17.8%) compared to root (13.7%) and ascending (3.1%) PIT (p=0.031) though false lumen patency was equivalent on follow-up imaging (p=0.443).

Conclusions

Primary intimal tear site correlates with operative approach and outcomes in patients with acute DeBakey I aortic dissection. Further work will be needed to improve understanding of incorporation of arch PIT location to better guide decision-making for extent of surgical resection to mitigate risk of long-term aortic events.



9:50AM

C20 - Examining Trends in Sex Disparities in Access to Kidney Transplantation – Evidence from a Nationwide Cohort Study from 1997 to 2020

Chengcheng Hu, Stephen O Pastan, Rachel E Patzer, Jessica L Harding

Introduction

Women with end-stage kidney disease (ESKD) have reduced access to kidney transplantation (ATT) as compared with men. Whether this sex disparity has improved over time is unknown.

Methods

Using data from the United States Renal Data System, we identified all adult patients (aged 18-79 years; N=2,232,444; 43.33% women) with ESKD between 1997 and 2020 in the U.S.

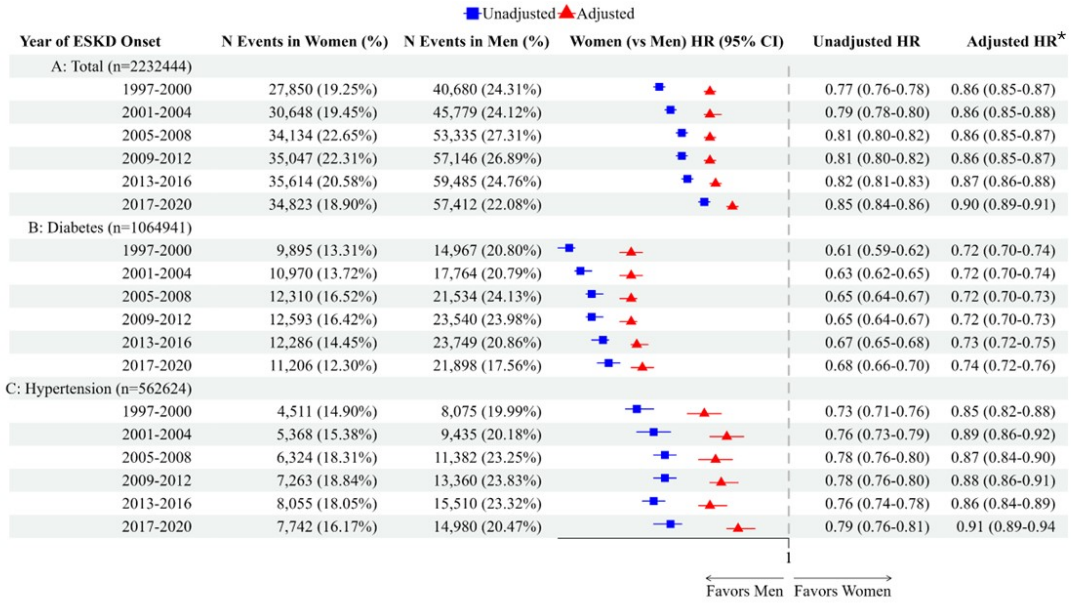
Individuals were grouped into six cohort eras of 1997–2000, 2001–2004, 2005–2008, 2009–2012, 2013–2016, or 2017-2020 based on ESKD diagnosis date, and followed for a maximum of four years, until death, waitlisting, living donor, or end of follow-up (12/31/2021), whichever occurred first. ATT was defined as waitlisting or living donor transplants. Using multivariable Cox models, we analyzed the association between sex and time to ATT, censored for death, by era. We did this overall and separately among people with diabetes or hypertension-attributed ESKD where known sex disparities are greatest.

Results

In adjusted models, sex disparities in ATT (favoring men) decreased from a 14% disparity in 1997-2000 (HR (women vs. men): 0.86; 95%CI: [0.85-0.87]) to 10% in 2017-2020 (0.90 [0.89-0.91], Figure). In people with diabetes-attributed ESKD, sex disparities improved over time, but women remained 26% (0.74 [0.72-0.76]) less likely to have ATT compared to men in 2017-2020. For hypertension-attributed ESKD, patterns were similar to the overall population.

Conclusion

From 1997 to 2020, sex disparities in ATT improved but remained significant, especially for women with diabetes-attributed ESKD where interventions and policies to address sex inequities should be prioritized.



Year of ESKD Onset	N Events in Women (%)	N Events in Men (%)	Women (vs Men) HR (95% CI)	Unadjusted HR	Adjusted HR*
A: Total (n=2232444)					
1997-2000	27,850 (19.25%)	40,680 (24.31%)		0.77 (0.76-0.78)	0.86 (0.85-0.87)
2001-2004	30,648 (19.45%)	45,779 (24.12%)		0.79 (0.78-0.80)	0.86 (0.85-0.88)
2005-2008	34,134 (22.65%)	53,335 (27.31%)		0.81 (0.80-0.82)	0.86 (0.85-0.87)
2009-2012	35,047 (22.31%)	57,146 (26.89%)		0.81 (0.80-0.82)	0.86 (0.85-0.87)
2013-2016	35,614 (20.58%)	59,485 (24.76%)		0.82 (0.81-0.83)	0.87 (0.86-0.88)
2017-2020	34,823 (18.90%)	57,412 (22.08%)		0.85 (0.84-0.86)	0.90 (0.89-0.91)
B: Diabetes (n=1064941)					
1997-2000	9,895 (13.31%)	14,967 (20.80%)		0.61 (0.59-0.62)	0.72 (0.70-0.74)
2001-2004	10,970 (13.72%)	17,764 (20.79%)		0.63 (0.62-0.65)	0.72 (0.70-0.74)
2005-2008	12,310 (16.52%)	21,534 (24.13%)		0.65 (0.64-0.67)	0.72 (0.70-0.73)
2009-2012	12,593 (16.42%)	23,540 (23.98%)		0.65 (0.64-0.67)	0.72 (0.70-0.73)
2013-2016	12,286 (14.45%)	23,749 (20.86%)		0.67 (0.65-0.68)	0.73 (0.72-0.75)
2017-2020	11,206 (12.30%)	21,898 (17.56%)		0.68 (0.66-0.70)	0.74 (0.72-0.76)
C: Hypertension (n=562624)					
1997-2000	4,511 (14.90%)	8,075 (19.99%)		0.73 (0.71-0.76)	0.85 (0.82-0.88)
2001-2004	5,368 (15.38%)	9,435 (20.18%)		0.76 (0.73-0.79)	0.89 (0.86-0.92)
2005-2008	6,324 (18.31%)	11,382 (23.25%)		0.78 (0.76-0.80)	0.87 (0.84-0.90)
2009-2012	7,263 (18.84%)	13,360 (23.83%)		0.78 (0.76-0.80)	0.88 (0.86-0.91)
2013-2016	8,055 (18.05%)	15,510 (23.32%)		0.76 (0.74-0.78)	0.86 (0.84-0.89)
2017-2020	7,742 (16.17%)	14,980 (20.47%)		0.79 (0.76-0.81)	0.91 (0.89-0.94

Figure 1 Unadjusted (blue) and adjusted (red) association between sex and time to ATT in (A) all participants individuals, (B) individuals with diabetes or, and (C) hypertension as the primary cause of kidney failure.
Note: the reference line of 1 (dotted line) indicates equity (i.e., no difference in rates of each outcome between men and women whereas <1 indicates an ATT disparity for women)
* Models were adjusted for age, BMI, chronic heart failure, atherosclerotic heart disease, other cardiac disease, cerebrovascular disease, peripheral vascular disease, hypertension, diabetes, history of cancer, tobacco use, and attributed cause of ESKD (as appropriate),

9:55AM

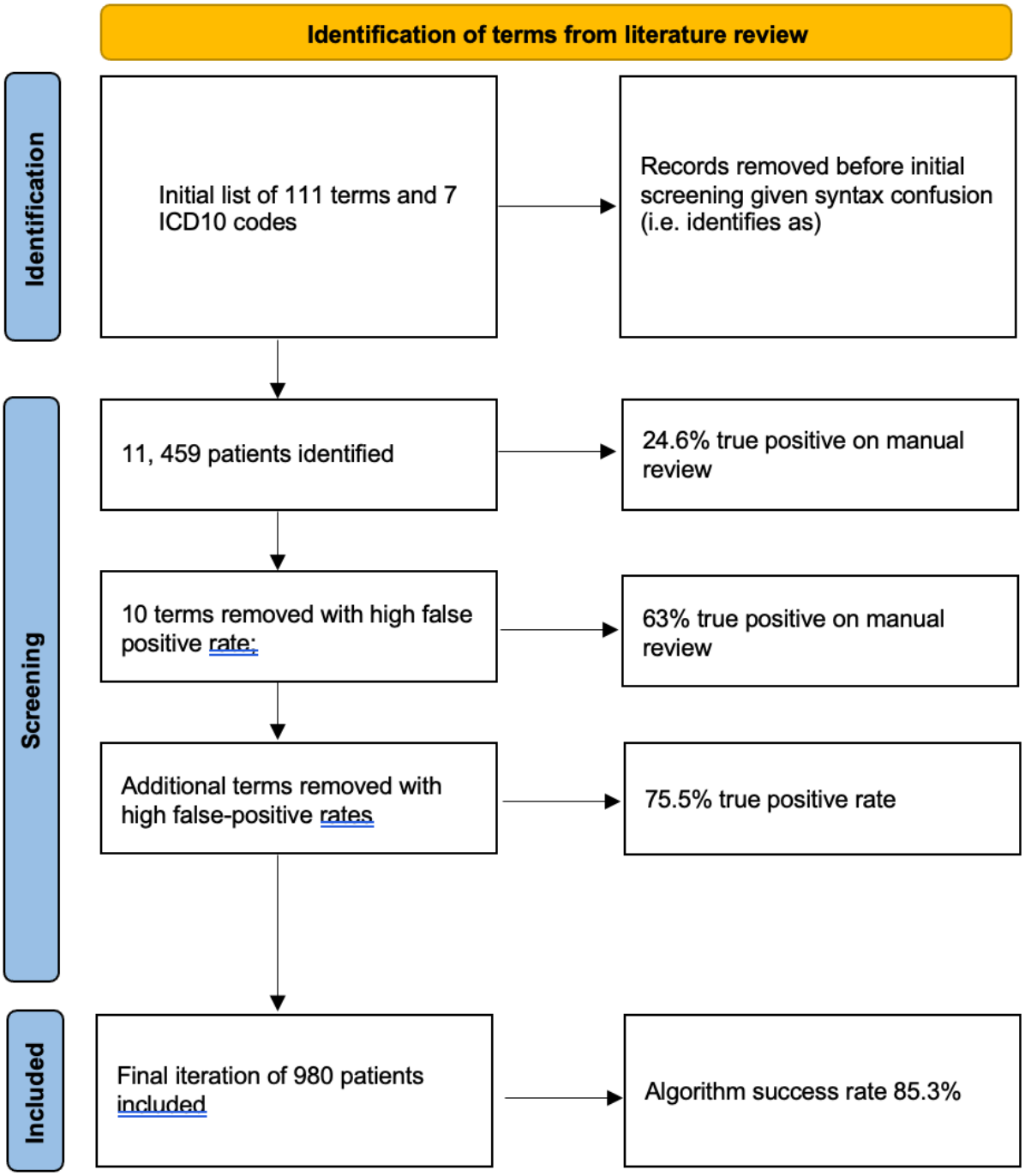
C22 - A Novel Technique to Identify Violent Trauma in the Gender Diverse Community
Madeline Roorbach MD, Dustin Hanos MD, Azade Tabaie PhD, Amy Zeidan MD, Randi Smith MD MPH

In the US, there are 1.4 million transgender adults. Due to limited research on the identification, classification and tracking of injury in this population, understanding of health inequity is lacking. The goal of this study was to develop an algorithm using natural language processing (NLP) to identify gender-diverse patients experiencing violent trauma.

In this observational cohort study, we utilized patient notes from the electronic health records (EHR) at an urban Level 1 Trauma Center in a demographically diverse area from 2012-2020. Using a text-based strategy, natural language processing was used to develop an algorithm for identification of transgender individuals via the following steps: 1) determination of ICD-codes associated with transgender health; 2) derivation of terminology associated with gender-diverse individuals from existing literature; and 3) use of machine learning and computational linguistics.

ICD codes specific to gender-diverse individuals resulted in only two encounters. 101 pre-determined terms were used in the text classification. Five iterations were conducted, manually reviewing terms to determine their true positive or false positive rate each time. After each, terms were removed that generated high false positive rates. In the final iteration, 30 terms were included that generated high true positive rates. This algorithm identified 980 unique patients with a success rate of 85.3% upon manual review.

We successfully developed a novel natural language processing algorithm capable of identifying gender-diverse individuals in the medical record. Identifying the intersection of trauma, gender identity and sexual orientation is critical for providing care and potential targets for violence prevention initiatives.


Identification of terms from literature review
Identification
Initial list of 111 terms and 7 ICD10 codes
Records removed before initial screening given syntax confusion (i.e. identifies as)
Screening
11, 459 patients identified
24.6% true positive on manual review
10 terms removed with high false positive rate;
63% true positive on manual review
Additional terms removed with high false-positive rates
75.5% true positive rate
Included
Final iteration of 980 patients included
Algorithm success rate 85.3%

10:00AM

C30 - Clinical Outcomes Following Treatment for Tricuspid Regurgitation: Repair vs. Replacement

Chodisetty, S., Guyton, R., Kalra, K.

Background

Whether tricuspid repair or replacement is the optimal therapy for tricuspid regurgitation is not fully understood. Therefore, we sought to compare outcomes and survival after the techniques. This would allow us to determine if we should favor one procedure or if certain factors can allow us to predict outcomes.

Methods

Our institutional STS database was queried to identify patients who underwent surgery for TR from 2017-2022. Of the 200 patients identified, 74 were excluded due to major concomitant procedures. After exclusion, 74 patients underwent tricuspid replacement and 52 underwent repair. Pre-, intra- and post-operative characteristics were tabulated and compared using t-tests and Fisher's exact tests. 5-year survival was analyzed using Kaplan-Meier curves.

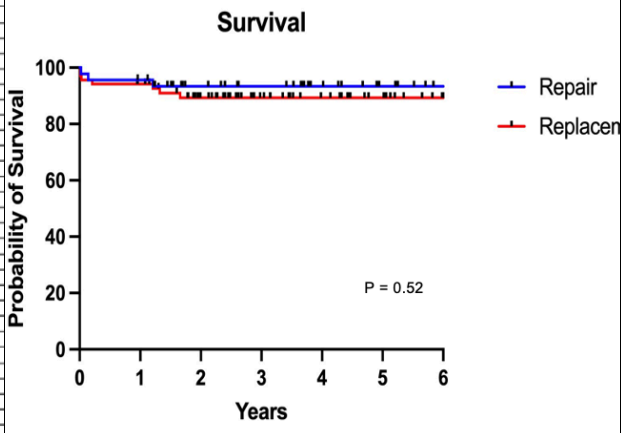
Results

Tricuspid repair was done in a significantly older patient population compared to replacement ($p=0.013$) likely due to presence of more endocarditis in the younger population. Tricuspid repair was associated with a significantly longer cross-clamp time. Post-operative complications including pacemaker implantation rates were not significantly different. Risk factors for 30-day mortality included liver dysfunction, neurological issues, renal failure requiring dialysis, and implantation of a permanent pacemaker. After analysis of ECHO data, lower preoperative and postoperative LVEF was significantly correlated with worse outcomes. Risk factors for 5-year mortality included renal failure requiring dialysis. After analysis of ECHO data, postoperative valve gradient was significantly correlated with worse outcomes.

Conclusions

Younger patients with endocarditis underwent more replacements than repairs. 30-day outcomes and 5-year survival were not significantly different. However, RV function seemed to worsen in patients who underwent TV repair.

Preoperative Characteristics			
	Tricuspid Replacement (n=74)	Tricuspid Repair (n=52)	p-value
Age	49.38 ± 18.10	57.60 ± 17.95	0.013
Female Sex	49 (66.22%)	30 (57.69%)	0.330
Hypertension	52 (70.27%)	38 (73.08%)	0.731
Diabetes	14 (18.92%)	14 (26.92%)	0.287
Chronic Lung Disease	22 (29.73%)	14 (26.92%)	0.810
Coronary Artery Disease	42 (56.76%)	29 (55.77%)	0.912
Cerebrovascular Disease	9 (12.16%)	9 (17.31%)	0.416
Renal Failure with Dialysis	5 (6.76%)	3 (5.77%)	0.822
Endocarditis	36 (48.65%)	7 (13.46%)	4.11E-05
Tobacco Use	42 (56.76%)	23 (44.23%)	0.082
Sleep Apnea	15 (20.27%)	14 (26.92%)	0.382
Liver Dysfunction	24 (32.43%)	10 (19.23%)	0.100
Intraoperative Characteristics			
	Tricuspid Replacement (n=74)	Tricuspid Repair (n=52)	p-value
Sternotomy	48 (64.86%)	24 (46.15%)	0.019
Other Approaches	26 (35.14%)	28 (53.85%)	0.019
Cardiopulmonary Bypass Time	113.39 ± 46.96	132.78 ± 58.16	0.064
Cross Clamp Time	67.06 ± 26.74	86.72 ± 44.24	0.016
Postoperative Characteristics			
	Tricuspid Replacement (n=74)	Tricuspid Repair (n=52)	p-value
30-Day Mortality	6 (8.11%)	2 (3.85%)	0.334
5-Year Mortality	5 (6.76%)	4 (7.69%)	0.840
Length of Stay (Days)	13.38 ± 11.70	10.78 ± 9.83	0.202
Neurological Issues	6 (8.11%)	1 (1.92%)	0.135
Renal Failure Requiring Dialysis	6 (8.11%)	6 (11.54%)	0.518
Permanent Pacemaker	3 (4.05%)	4 (7.69%)	0.380
Re-exploration for Bleeding	0 (0.00%)	2 (3.85%)	0.089



30- Day Mortality Risk Factors		
Risk Factors	Odds Ratio	p-value
Postop Liver Dysfunction	5.115	
Postop Neurological Issues	7.553	0.
Postop Renal failure requiring Dialysis	17.1	0.
Postop Pacemaker Implantation	0.934	0.
Preop LVEF	1.106	0.
Postop LVEF		

5-Year Mortality Risk Factors		
Risk Factors	Odds Ratio	p-value
Postop Renal failure requiring Dialysis	13.819	
Postop Valve Gradient	1.314	

Figure 1. Table demonstrating pre, intra, and post-operative characteristics in addition to risk factors for patients undergoing isolated tricuspid repair vs. replacement with graph depicting 5-year survival

10:05AM

C39 - Multi-institutional analysis of choledocholithiasis in pediatric vs adult patients: Taking Back the Duct

Dantes G, Rauh JL, Smith SR, Aworanti E, Wallace M, Collings A, Sanin, GD, Cambronero GE, Bosley ME, Ignacio R, Knod JL, Slater B, Callier K, Livingston MH, Dukleska K, Scholz S, Zamora IJ, Clifton, M, Knauer EM, Santore M, Neff LP, H Alemayehu

Background

Management of choledocholithiasis can be challenging. In adults, intraoperative cholangiogram (IOC), with laparoscopic common bile duct exploration (LCBDE) is well accepted. Recent evidence has supported LCBDE utility in pediatric cohorts as well however due to perceived difficulties, surgeons remain hesitant. We utilized a multicenter collaborative to compare LCBDE success rates between adult and pediatric patients.

Methods

A multicenter, retrospective review of pediatric (<18 years) and adult patients with choledocholithiasis managed from 2018-2022 was performed. Demographic and clinical data were obtained. Our primary outcome was rate of successful duct clearance with upfront

LCBDE. Outcomes and complications (infections, bleeding, pancreatitis, bile leak) were also compared.

Results

333 (45.9%) pediatric and 391 (54.0%) adult patients were evaluated. Median age of pediatric vs adult patients was 15.2 vs 55.5 years, respectively. IOC was performed in 178 (53.5%) pediatric and 166 (42.5%) adult patients (p=0.003). Eighty-four (25.2%) pediatric vs 140 (35.8%) adults underwent LCBDE (p=0.002). LCBDE success was no different between pediatric and adult patients (85.7% vs 76.4%, p=0.12). ERCP was performed prior to laparoscopic cholecystectomy in 132 (39.6%) pediatric vs 222 (56.8%) adult patients (p=0.984). Four (3.03%) vs 7 (3.15%) pediatric vs adult patients required LCBDE following ERCP, p=1.00. Surgical complications were similar in pediatric vs adult patients (3.0% vs 3.8%, p=0.68).

Conclusion

LCBDE is successful in adults and children with similar complication rate. Limited access to ERCP for children, with a 3% ERCP failure rate, indicate continued training and dissemination of LCBDE techniques in pediatrics is necessary.

Table. Demographic and Surgical Data in Management of Choledocholithiasis in Pediatrics and Adults

Characteristic	Total (n=724)	Pediatrics (n=333)	Adult (n=391)	P-Value
Male (n, %)	231 (31.9%)	87 (26.1%)	144 (36.8%)	0.002
BMI (kg/m^2, Median, IQR)	28.8 (24.2, 34.9)	27.2 (21.4, 32.2)	29.7 (25.9, 36.4)	<0.001
Age (Years, Median, IQR)	22.9 (15.3, 57.8)	15.2 (13.1, 16.6)	55.5 (34.1, 70.5)	
Pre-op Diagnosis (n, %)				<0.001
Cholecystitis	54 (7.5%)	11 (3.3%)	43 (11.0%)	
Primary Choledocholithiasis	130 (18.0%)	51 (15.3%)	79 (20.2)	
Cholelithiasis	95 (13.1%)	62 (18.6%)	33 (8.4%)	
Gallstone Pancreatitis	100 (13.8%)	46 (13.8%)	54 (13.8%)	
Other	25 (3.5%)	8 (2.4%)	17 (4.3%)	
Choledocholithiasis and Cholelithiasis	179 (24.7%)	115 (34.5%)	64 (16.4%)	
Choledocholithiasis and Cholecystitis	138 (19.1%)	38 (11.4%)	100 (25.6%)	
Cholangitis	2 (0.3%)	2 (0.6%)	0 (0%)	
ERCP Performed (n, %)	447 (61.7%)	165 (49.5%)	282 (72.1%)	<0.001
Pre-Lap Chole	354 (48.9%)	132 (39.6%)	222 (56.8%)	0.98
Post-Lap Chole	115 (15.9%)	43 (12.9%)	72 (18.4%)	0.98
Pre-Op RUQ US (n, %)	563 (77.8%)	288 (86.8%)	274 (70.1%)	<0.001
Pre-Op CT (n, %)	262 (36.2%)	45 (13.5%)	217 (55.5%)	<0.001
Pre-Op MRCP (n, %)	248 (34.3%)	138 (41.4%)	110 (28.1%)	<0.001
CBD Size (median, IQR)	9 (7, 11)	8 (7,11)	9 (7,11)	0.03
IOC Performed (n, %)	379 (52.3%)	178 (53.5%)	166 (42.5%)	0.003
LCBDE Attempted (n, %)	224 (30.9%)	84 (25.2%)	140 (35.8%)	0.002
LCBDE Duct Clearance (n, %)	179 (79.9%)	72 (85.7%)	107 (76.4%)	0.12
Operative Time (Minutes, Median, IQR)	109.5 (80, 155)	104 (78, 146)	115 (83.5, 163.3)	0.03
Operative Radiation Exposure (units, Median, IQR)	44.0 (15.6, 92.3)	24.3 (5.8, 71.5)	61.8 (28.7, 109.8)	<0.001
Hospital Length of Stay (Hours, Median IQR)	71.4 (43.6, 108.9)	71.9 (42.1, 110.8)	70.9 (46.4, 108.7)	0.85
Surgery Complications (n, %)	25 (3.45%)	10 (3.0%)	15 (3.8%)	0.68
Endoscopic Complications (n, %)	5 (0.7%)	2 (0.6%)	3 (0.8%)	0.73
ED Visit Within 30 Days (n, %)	52 (7.2%)	18 (5.4%)	34 (8.7%)	0.08
Readmission Within 30 Days (n, %)	36 (5.0%)	17 (5.1%)	19 (4.9%)	0.90

BMI, body mass index; Pre-op, preoperative; ERCP, endoscopic retrograde cholangiopancreatography; RUQ, right upper quadrant; US, ultrasound; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; CBD, common bile duct; IOC, intraoperative cholangiogram; LCBDE, laparoscopic common bile duct exploration; ED, emergency department

10:10AM

C3 – Accuracy of Trauma Surgeons Perspective Estimation of the Injury Severity Score

Eli Mlaver, Courtney Meyer, Gina Solomon, Joe Sharma, Morgan Krause, Matthew Vassy, Chris Dente, S. Rob Todd, Patricia Ayoung-Chee

Objectives

Injury Severity Score (ISS) is used for risk adjustment and directly correlates with trauma patient outcomes. However, its use as a predictive variable is limited, as it is scored post-discharge by trained registrars. Our aim was to determine the accuracy of ISS estimation within 24 hours of admission.

Methods

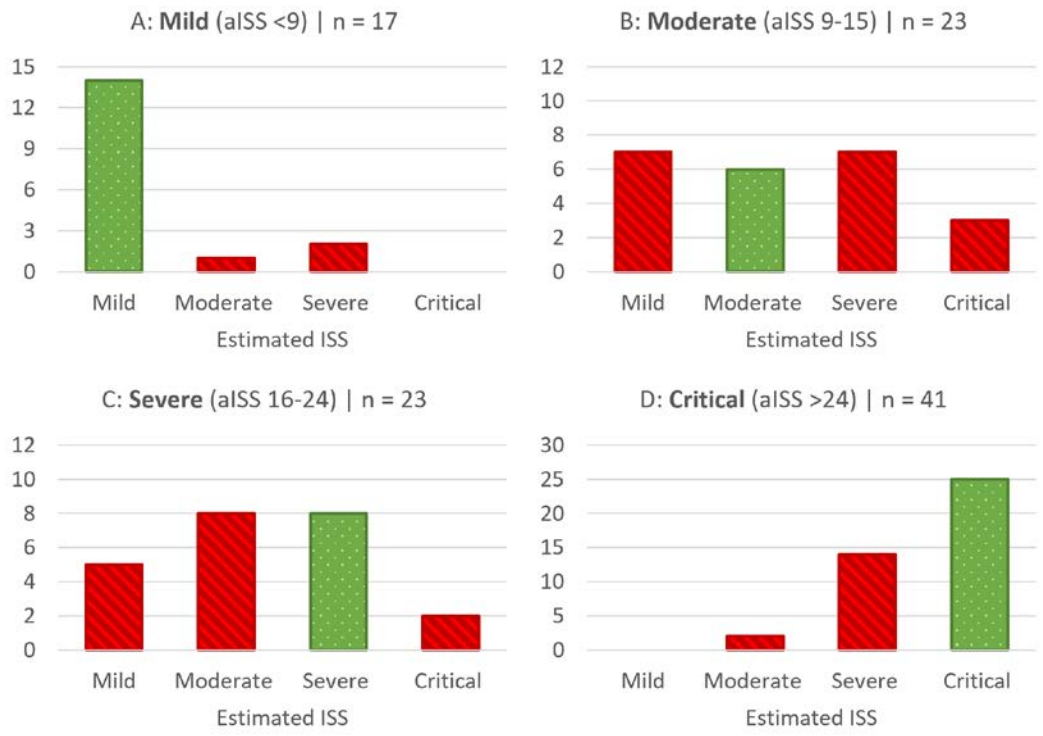
Attending trauma surgeons estimated the Abbreviated Injury Scale (AIS) for each of seven body regions (head, face, neck, chest, abdomen, spine, and extremity) for patients admitted during their call. AIS estimations were used to calculate estimated ISS (eISS), which was later compared to the abstracted ISS (aISS) in the trauma registry. ISS was categorized as mild (< 9), moderate (9-15), severe (16-25), or critical (> 25). Concordance was defined as eISS and aISS being in the same category and was measured with a kappa (k) statistic.

Results

Ten surgeons completed 104 surveys. Overall concordance was 51.0%; 82.4%, 26.1%, 34.8%, and 61.0% for patients with mild, moderate, severe, and critical aISS, respectively; unweighted k = 0.34, weighted k = 0.68. AIS concordance was < 50% for all body regions.

Conclusions

While accuracy of estimated AIS was low, there was fair concordance between eISS and aISS, with estimations most accurate for patients with mild and critical injury severity. This preliminarily supports attending trauma surgeons' ability to prospectively predict injury severity, which has important clinical and research implications. High weighted kappa gives hope that small improvements to precision might greatly improve overall concordance. Future directions thus include addition of an educational reference tool to accompany the survey.



10:15AM

C26 - Peripheral Intravascular Lithotripsy to Facilitate Transfemoral Transcatheter Aortic Valve Replacement – Defining Optimal Lesions

Tom, S.K., Tully, A., Kikuchi, Y., Crawford, K., Binongo, J., Wei, J., Gleason, P., Xie, J., Devireddy, C., Grubb, K.J.

Background

Transfemoral transcatheter aortic valve replacement (TF-TAVR) approach has proven to be superior to alternative access. However, a subset of patients being evaluated for TF-TAVR are deemed unfit secondary to peripheral arterial disease. For patients anatomically unfit for standard transfemoral access, peripheral intravascular lithotripsy (IVL) has emerged to facilitate femoral access for TAVR.

Methods

Single center, retrospective analysis queried from 1/2018 through 7/2023 for all patients undergoing TAVR. All patients undergoing IVL facilitated lithotripsy for transfemoral access were analyzed.

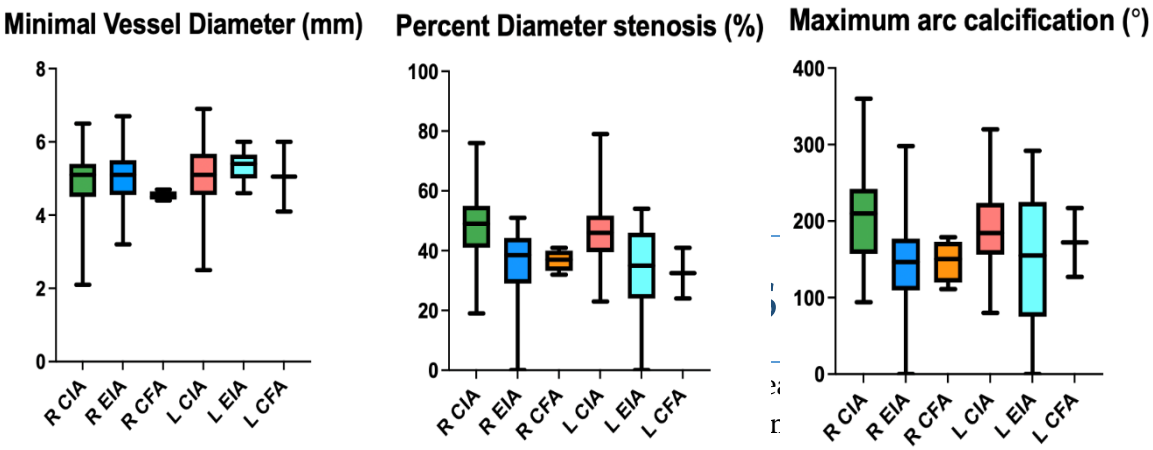
Results

A total 2,862 TAVR cases were identified, with 92 (3.2%) having undergone lithotripsy. The lithotripsy cohort consisted of 45% female with mean age of 78±9.2 years. 59 of the 92 patients underwent multiple treatment segments (64%) with a total of 145 lesions treated. The

right common iliac artery (n=47) was most treated. Most lesions fell below 5.5mm (70.3%). Average percent diameter vessel stenosis was 41.1±15.2%. Average maximum arc calcification 171.9±75.2 degrees. Majority of IVL was performed with 7-mm lithotripsy catheter (72.5%). Valve delivery was successful in all cases. The average length of stay was 2.5±2.9 days. Complications requiring secondary vascular procedure occurred in 4.3% (n=4/92). Mortality at 30-days 1.1% (n=1/92).

Conclusions

In 92 consecutive patients, the addition of IVL treatment allowed passage of the TAVR delivery catheter in all cases despite presence of severe calcific disease of the iliofemoral axis. The IVL facilitated TF-TAVR is feasible, safe, and effective at preserving the transfemoral TAVR route in patients with severe peripheral artery disease.



ORAL PRESENTATIONS: SESSION II

Moderators: Heather Faulkner, Onkar Khullar
Location: EUH Auditorium

10:40AM

Category: Basic Science

B8 – Differential induction of donor-reactive Foxp3+ iTreg via blockade of CD154 vs. CD40
Hongmin Yao, Danya Liu, Mandy L. Ford

Introduction
Anti-CD154 reagents have been shown to exhibit higher efficiency in inducing allograft survival compared to anti-CD40 Abs in both murine and non-human primate transplantation studies. A major mechanism of action of anti-CD154 is the differentiation of donor-reactive Foxp3+ iTreg, however the ability of CD40 blockade to donor-reactive Foxp3+ iTreg is unknown. Here, we compared the induction of donor-reactive Foxp3+ iTreg in anti-CD154 vs. anti-CD40 mAb treated allograft recipients.

Methods
Donor-reactive CD4+ Thy1.1+ T cells were transferred into WT recipients of allogeneic skin grafts that were treated with either anti-CD154 or anti-CD40. The induction of Foxp3+ iTreg among donor-reactive T cells was interrogated.

Results
Results indicated that while anti-CD154 mAb significantly increased the frequency of donor-reactive Foxp3+ iTreg after transplantation as previously reported, neither anti-CD40 mAb treatment nor the use of CD40-/- recipients resulted in the induction of donor-reactive Foxp3+ iTreg. CD11b was identified as an alternate receptor for CD154 during alloimmunity, the role of CD154:CD11b interactions in preventing the generation of donor-reactive Foxp3+ iTreg was interrogated. Blockade of CD11b in CD40-/- recipients resulted in increased donor-reactive Foxp3+ iTreg as compared to CD40 deficiency alone. Mechanistically, CD154 was expressed on CD11b+CD11c+ DC, and specific inhibition of CD154:CD11b resulted in decreased IL-1β secretion from CD11b+CD11c+ DC. To determine if this decreased IL-1β mechanistically underpinned the ability of CD154 blockade to induce donor-reactive Foxp3+ iTreg, WT vs CD40-/- recipients were treated with anti-IL-1β. Results indicated that blockade of IL-1β synergized with CD40 deficiency to promote Foxp3+ iTreg and prolong allograft survival.

Conclusions
Taken together, these data provide a mechanistic basis for the observed inferiority of anti-CD40 as compared to anti-CD154, and illuminate an IL-1β-dependent mechanism by which

CD154:CD11b interactions, which proceed uninhibited in the context of CD40 blockade, prevent the generation of donor-reactive Foxp3+iTreg during transplantation.

10:50AM

Category: Clinical Science

C16 – Effect of Prosthetic Fitting on Mortality after Major Lower Extremity Amputation

Nathaniel Forrester BA, Maja Wichhart Donzo BA, Chengcheng Hu MBBS MPH, Brandi M. Mize MD, Yazan Duwayri MD MBA, Luke Brewster MD PhD, Olamide Alabi MD MS

Introduction

The purpose of this study was to examine a contemporary cohort of patients who underwent lower extremity amputation (LEA) and determine if there is an association between fitting for a prosthetic and mortality.

Methods

We reviewed all patients who underwent LEA between 2015 and 2022 at two academic healthcare systems in a large metropolitan city. The exposure of interest was prosthetic fitting after LEA. The primary outcomes were mortality within 1- and 3-years of follow-up. Patients with prior LEA were excluded. Extended Cox models were used for survival analysis.

Results

Among 702 patients who underwent LEA, 329 (46.6%) were fitted for prosthesis. Of note, 14.3% of all subjects who were non-ambulatory preoperatively were fitted for prosthetic at some point after LEA, and 28.5% of patients not ambulatory preoperatively were eventually ambulatory after LEA. The rate of death among those fitted for a prosthetic was 12.0/100 person-years at 1 year and 15.8/100 person-years at 3 years of follow up and among those not fitted for a prosthetic, the rate of death was 55.7/100 person-years and 50.7/100 person-years at 1- and 3-years of follow up, respectively. After adjusting for several patient and procedural factors, prosthesis fitting is associated with decreased likelihood of mortality within 1 year and 3 year of follow-up as shown in Table 1.

Conclusions

Our data suggests that prosthesis fitting is associated with improved survival, and preoperative functional status does not always predict postoperative functional status. Further evaluation into optimizing receipt of prosthetic after LEA in reasonable candidates is necessary.

Table 1. Association between Prosthesis Fitting and Mortality During 1 year and 3 years of Follow up After Lower Extremity Amputation, 2015-2022

	1-year Mortality		3-year Mortality	
Prosthesis Fitting	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	0.25 (0.15-0.41)	0.24 (0.14-0.40)	0.36 (0.27-0.48)	0.40 (0.29-0.55)
*adjusted for age, sex, ADI, ethnoracial background, obesity, PAD, CKD status, preoperative ambulatory status, mFI5 score, surgical team, procedural site, level of amputation, pre or post-COVID pandemic timeframe				

11:00AM

Category: Basic Science

B10 – RIPK3 disrupts gut epithelial homeostasis during sepsis

Chloe S Yang

The gut epithelium is a barrier between self and other, and loss of epithelial integrity drives immune stimulation and organ failure in sepsis. RIPK3 triggers intestinal epithelial cell (IEC) death through necroptosis by phosphorylating mixed lineage kinase domain-like protein (MLKL). However, RIPK3 also drives inflammation via kinase-independent binding interactions. Loss of RIPK3 improves sepsis survival, though underlying mechanisms remain unclear. We evaluated the impact of RIPK3 on gut epithelial change during sepsis.

Wild-type (WT), Mlkl-/-, Ripk3-/-, and Ripk3K51A/K51A (which lack kinase activity) mice underwent cecal ligation and puncture (CLP). Mice were followed for survival or sacrificed at 24 h for tissue assays. Gut permeability was measured by detecting serum levels of orally administered creatinine. IEC proliferation was analyzed by histologic quantification of BrdU-positive cells. Gut protein levels were assayed via immunoblot and ELISA.

Sepsis increased gut RIPK3 expression. Ripk3-/- mice were protected from septic mortality, but Mlkl-/- mice were not. Loss of RIPK3 prevented septic gut hyperpermeability, while no permeability changes were observed in septic Ripk3K51A/K51A or Mlkl-/- animals. RIPK3 knockout increased IEC proliferation during sepsis, while MLKL knockout or RIPK3 kinase inactivation did not. Septic Ripk3-/- mice displayed lower intestinal levels of proinflammatory IL-1□compared to WT controls, while no differences were seen in septic Ripk3K51A/K51A or Mlkl-/- groups.

RIPK3 drives gut inflammation and dysregulation during sepsis, increasing gut permeability and suppressing IEC proliferation. Findings in Ripk3K51A/K51A and Mlkl-/- animals suggest these changes are not caused by RIPK3 kinase activity or necroptosis, but rather by kinase-independent binding interactions.

11:10AM

Category: Clinical Science

C24 – Clinical predictors of Spontaneous Intestinal Perforation vs Necrotizing Enterocolitis in extremely and very low birth weight neonates

Goeto Dantes, MD, Olivia A. Keane, MD, Louis Do, BS, Savanah Rumbika BS, Nathaniel H. Ellis, BS Valerie L. Dutreuil, MPH, Zhulin He, PhD, Amina M. Bhatia, MS, MD

Purpose

Spontaneous intestinal perforation (SIP) and necrotizing enterocolitis (NEC) are distinct disease processes associated with significant morbidity and mortality. Initial treatment, laparotomy (LP) versus peritoneal drainage (PD), is disease specific however it can be difficult to distinguish these diagnoses preoperatively. We investigated clinical characteristics associated with each diagnosis and constructed a scoring algorithm for accurate preoperative diagnosis.

Methods

A cohort of extreme and very low birth weight (<1500g) neonates surgically treated for SIP or NEC between 07/2004-09/2022 were reviewed. Clinical characteristics included gestational age (GA), birth weight (BW), feeding history, physical exam, and laboratory/radiological findings. Intraoperative diagnosis was used to determine SIP vs NEC. Pre-drain diagnosis was used for patients treated with PD only.

Results

338 neonates were managed for SIP (n=269, 79.6%) vs NEC (n=69, 20.4%). PD was definitive treatment in 146 (43.2%) patients and 75 (22.2%) patients were treated with upfront LP. Characteristics associated with SIP included younger GA, younger age at initial laparotomy or drainage (ALD), and history of trophic or no feeds. Multivariate logistic regression determined pneumatosis, abdominal wall erythema, higher ALD and history of feeds to be highly predictive of NEC. A 0-8-point scale was designed based on these characteristics with the area under the receiver operating characteristic curve of 0.804 (95% CI 0.737-0.871) for the diagnosis of NEC. A threshold score of 1.5 had a 90.3% specificity for NEC.

Conclusion

Utilizing clinical characteristics associated with SIP & NEC we developed scoring system designed to assist surgeons accurately distinguish SIP vs NEC in neonates.

Laboratory and clinical characteristics associated with increased risk of NEC compared to SIP with additional logistic regression analysis

Characteristic	**SIP** N=269 (79.6%)	**NEC** N=69 (20.4%)	**P-value**
Age (days) at initial laparotomy or drainage (mean, SD)	7.9 (6.0)	21.6 (17.6)	**<0.001**

Gestational age in weeks (mean, SD)	25.60 (1.99)	26.38 (2.46)	**0.016**
At goal or Advancing feeding history (n, %)	29 (11.7%)	38 (62.3%)	**<0.001**
CRP (mean, SD)	3.10 (3.91)	10.90 (11.77)	**0.003**
Logistic Regression Results	**Odds Ratio (OR)**	**95% Confidence Interval (CI)**	
Pneumatosis Intestinalis	22.3	(3.22, 452)	**0.007**
Abdominal wall erythema	4.39	(1.23, 14.9)	**0.019**
Feeding history (At goal or Advancing)	3.68	(1.50, 8.77)	**0.004**
Age at first intervention (ALD)*	2.39	(1.41, 4.44)	**0.003**

Results for categorical data are presented as counts (percentages) and p-values are calculated by Fisher's exact test.

Results for continuous data are presented as mean (SD) and p-values are calculated by two sample t-test.

**Infants, who were 14 days older for first intervention, have 2.39 times the odds of having NEC compared to SIP, while adjusting for other three covariates*

11:20AM

Category: Basic Science

B6 – Chronic Ethanol Consumption Improves Survival in Claudin-4 Knockout Mice in Abdominal Sepsis

Shimazui T, Gutierrez MB, Liang Z, Ford ML, Coopersmith CM

Introduction

Chronic ethanol (EtOH) consumption worsens mortality, increases gut permeability, and alters T-cell expression/phenotypes in sepsis. Claudin-4 is a tight junction protein that mediates gut permeability and also plays a role in T-cell differentiation. Claudin-4 levels are decreased in mice with chronic EtOH consumption prior to sepsis.

Methods

Claudin-4 knockout (KO) mice were fed EtOH or water for 12 weeks and then made septic via cecal ligation and puncture. Mice were either followed for survival or sacrificed 24 or 48 hours after sepsis to assess gut permeability, plasma cytokine levels and flow cytometry.

Results: Seven-day survival was improved in mice that drank EtOH (94.7% vs. 62.5%). Despite EtOH's effect on the gut barrier, there were no differences in pore, leak or unrestricted pathways of permeability. Numbers of splenic CD4+ and CD8+ T-cells were significantly increased in EtOH mice prior to the onset of sepsis as were central memory CD4+ T-cells, activated CD25+CD4+ and CD69+CD8+ T-cells. Following sepsis, central memory CD8+ T-cells increased at 48 hours. Further, activated CD25+CD4+ T-cells increased at 24 and 48 hours while CD25+CD8+ were also increased at 24 hours. CD69+CD8+ T-cells were also increased at 24 hours while CD69+CD4+ T-cells were increased at 48 hours. There were no differences in plasma cytokines.

Conclusion
Claudin-4 KO mice had an unexpected survival advantage following chronic EtOH consumption compared to mice that drank water prior to sepsis onset. EtOH may play a protective role in sepsis with claudin-4 deletion by modulating the immune system.

11:30AM

Category: Clinical Science

C33 – A Multicenter Analysis of Pancreatoduodenectomy for Sporadic Duodenal Adenoma: A Novel Risk Score to Guide Shared Decision Making

Caitlin Sok, Nina Eng, Angelo Marra, Hussein Hariri, Gregory Wilson, Syed Ahmad, Charles Scoggins, Caitlin Hester, Jashodeep Datta, Nipun Merchant, Michael LeCompte, Hong Jin Kim, Gregory Sigler, Nabeel Zafar, Sharon Weber, Christina Kasting, Ryan Fields, Mihir M. Shah, Shishir K. Maithel, David A. Kooby

Introduction
Although many duodenal adenomas (DA) are removed endoscopically, pancreatoduodenectomy(PD) is sometimes indicated for complete removal. PD for benign disease is often associated with increased morbidity. The Spigelman Classification guides decision-making based on malignancy risk for patients with familial adenomatous polyposis (FAP). No guidance exists for patients with sporadic DAs. We developed a Malignancy Risk Score for patients with sporadic DAs that are not histologically proven malignant prior to PD.

Methods
Patients who had PD for sporadic DA at six institutions (2010-2022) were reviewed. Patient and tumor factors were correlated with malignancy by univariate association and multivariable logistic regression. Weighted odds ratios for variables associated with malignancy were used to create the Malignancy Risk Score.

Results
Ninety-four patients were included. Median age was 65yrs (34-89), 56% female, 75% white, and 43(46%) had malignancy on final pathology. A risk score ranging from 0-6 (Table) was created using the strongest predictors of malignancy, including male sex(OR:2.5,p=0.06), bile duct diameter>9mm(OR:2.6,p=0.049), preoperative symptoms(OR:5.5,p=0.01), and preoperative high-grade dysplasia(OR:4.3, p=0.004). Malignant pathology was identified in 8% of patients in the low-risk group, 29% in the intermediate-low group, 42% in the intermediate-high group, and 86% in the high-risk group(p<0.001). Compared with a final malignant diagnosis, patients with benign final pathology had a three-fold higher rate of post-PD major complications(45%vs.15%, p=0.005).

Conclusions

We developed a novel Malignancy Risk Score for patients with sporadic DAs. This score can be used to counsel patients regarding risks of harboring malignancy balanced with risks of major postoperative complications. This predictive score can optimize shared patient-surgeon decision-making for this complex clinical scenario.

Criteria	Points		
	0	1	2
Sex	Female	Male	-
Bile Duct Diameter	<9 mm	≥9 mm	-
Preoperative Symptoms	No	-	Yes
Dysplasia on Biopsy	None/Low-Grade	-	High-Grade
Score 0-1 (low-risk) = 8% risk of malignancy Score 2 (intermediate-low risk) = 29% risk of malignancy Score 3-4 (intermediate-high risk) = 42% risk of malignancy Score 5-6 (high-risk) = 86% risk of malignancy			

ACKNOWLEDGEMENTS

Emory Department of Surgery
John Sweeney, MD, Professor and Chair, Department of Surgery
Craig Coopersmith, MD, Professor and Vice Chair of Surgical Research

Special Thanks
William C. Wood, MD, Professor of Surgery Emeritus

Surgery Research Advisory Committee
Olamide Alabi, Luke Brewster, John Calvert, Paul Ghareeb, Heather Faulkner, Kendra Grubb, Alison Linden, Michael Lowe, John Lyons

Moderators & Judges
Luke Brewster, John Calvert, Heather Faulkner, Paul Ghareeb, Katherine Hekman, Onkar Khullar, Allison Linden, Michael Lowe, and Lauren Postlewait

Website & Communications Support
Rashielle Clarke

Symposium Logistics
Ashley McCullough