

THE 30TH ANNUAL
**RESEARCH
DAY SYMPOSIUM**

APRIL 23, 2019

7:30 am
Lecture Hall 2222
Medical Education Bldg

**Extracellular Matrix-adipocyte
Crosstalk and Metabolic Disease**



Visiting Speaker | Robert Ward O'Rourke, MD

Chief of the Division of General Surgery
Director of the Bariatric Surgery Program
University of Michigan



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7:30 AM	Breakfast & Registration	
7:45 AM	Welcome & Introduction	
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8:15 AM	Linda Schutzman: Soluble P-Selectin Promotes De Novo Pulmonary Arterial Thrombosis Following Blunt Thoracic Trauma	Page 11
8:30 AM	Dake Hao: Engineering collagen hydrogel with a novel ligand against integrin $\alpha v \beta 3$ to improve endothelial cell survival after transplantation	Page 12
8:45 AM	Carl Beyer: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) Induced Cardiac Injury Is Mitigated by Partial Occlusion	Page 13
9:00 AM	Maggie Spruce: Rapid Intramuscular Administration of TXA Results in Equivalent Total Drug Exposure and Reversal of Hyperfibrinolysis in a Swine Controlled Hemorrhage Model	Page 14
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10:15 AM	Christina Theodorou: Practice, Practice, Practice! REBOA Volume Matters	Page 23

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10:15AM	Mimmie Kwong: Endograft repair with in-situ laser fenestration feasible for total arch repair	Page 28
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- 1:20 PM **Jessica Cox:** Hospital-level Intensive Care Unit Admission for Patients with Isolated Blunt Abdominal Solid Organ Injury Page 34
- 1:30 PM **Carl Beyer:** Multimodal Analgesia Decreases Opioid Use in Critically Ill Trauma Patients Page 35
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- 1:20 PM **James Clark:** A Prospective Trial of Intraoperative Liposomal Bupivacaine (Exparel) versus Bupivacaine/Lidocaine for Thoracoscopic Surgery Page 38
- 1:30 PM **Ping Song:** An alternative option for reconstruction of a complex wound: Combining bilaminar dermal matrix and vacuum assisted closure therapy Page 39
- 1:40 PM **Timothy Guenther:** De Garengot's Hernia: Case Report with Analysis of 177 Published Cases and a Proposed Classification System Page 40
- 1:50 PM **Timothy Guenther:** Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery: Analysis of 192 Published Cases with a Proposed Classification System Page 41

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Moderators: Dr. Kiho Cho and Dr. Payam Saadai

- 1:10 PM **Siqi He:** Functionalized ECM scaffolds loaded with endothelial progenitor cells potentiates neovascularization and promotes diabetic ischemic wound healing Page 42
- 1:20 PM **Lalithasri Ramasubramanian:** Development of Exosome Mimics for Vascularization in Ischemic Wound Sites Page 43
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- 1:40 PM **Maggie Spruce:** IF Then: What to Do with Incidental Findings Page 45

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Moderators: Dr. Kent Lloyd and Dr. Robert Canter

- 2:00 PM **Michelle Wan:** Assessment of the Risk Analysis Index For Evaluating Frailty of Surgical Patients Page 46
- 2:15 PM **Sean Judge:** PD-1 Checkpoint Marker Expression on Natural Killers Cells in Human and Murine Models Page 47
- 2:30 PM **Jonathan Lin:** Reassessing the Role of Fasciotomy After Revascularization of Non-Traumatic Acute Lower Limb Ischemia Page 48
- 2:45 PM **Kaitlin Clark:** Translational Applications of Placental Derived Mesenchymal Stem Cells for the Treatment of Spina Bifida: a Canine Model Page 49
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Nam K. Tran, PhD
Artificial Intelligence in Point-of-Care Testing: Proof of Concept for Acute Kidney Injury Detection
- 4:00 PM **Concluding Remarks**

Welcome

Welcome from the Chairs,

Welcome to the 30th annual Department of Surgery Research Symposium at the University of California, Davis. This program was made possible by collaboration between the Department of Surgery at the University of California, Davis and Shriners Hospital for Children, Northern California.

This year we are hosting Robert O'Rourke MD, Professor of Surgery, Chief of the Division of General Surgery, and Director of the Bariatric Surgery Program at the University of Michigan. Dr. O'Rourke has managed an NIH-funded research program studying the molecular and cellular mechanisms of adipose tissue dysfunction in metabolic disease. In addition, he is active in medical education and serves on the editorial board for the journals Obesity Surgery and SOARD (Surgery for Obesity and Related Diseases).

The 30th Annual Department of Surgery Research Symposium is a forum that unites faculty, residents, fellows, students, and laboratory researchers to share the diverse innovative research being done in the Department of Surgery. The Symposium also provides an opportunity for trainees to hone their research presentation skills as they share their work. Research is a core value of the Department of Surgery and is made possible by the hard work of our faculty, staff, and trainees. Our program includes oral presentations, quick-shot oral poster presentations, and plenary sessions. We will award prizes for the top clinical and basic science oral presentations as well as the best quick-shot oral presentation tonight.

Thank you for joining us today to celebrate research in the Department of Surgery!

Sincerely,
Diana L. Farmer, MD, FACS, FRCS
Professor and Chair, Department of Surgery
UC Davis Health
Surgeon-in-Chief, UC Davis Children's Hospital

Tina L. Palmieri MD, FACS, FCCM
Professor and Director, Firefighters Burn Institute Burn Center at the University of California, Davis
Assistant Chief of Burns, Shriners Hospital for Children, Northern California



Research Committee



Gregory J. Jurkovich, MD



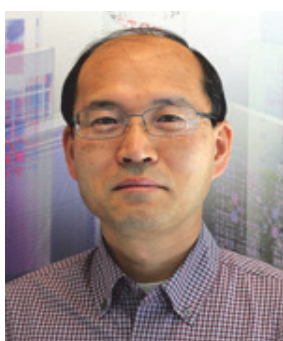
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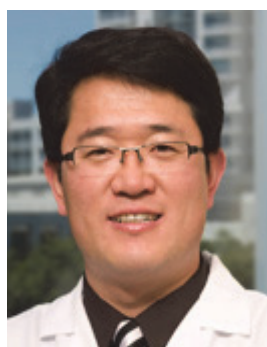
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Kiho Cho, DVM, PhD



Kent Lloyd, DVM, PhD



Aijun Wang, PhD



Mohamed Ali, MD



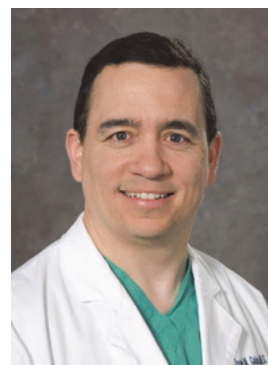
Garth H. Utter, MD



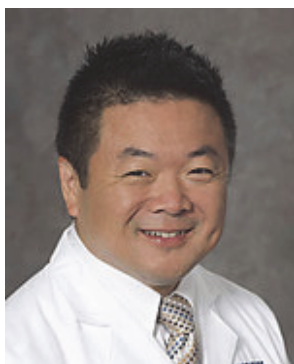
David Sahar, MD



Richard V. Perez, MD



Joseph Galante, MD



Shinjiro Hirose, MD

Keynote Speaker– Robert W. O’Rourke, MD

Dr. O'Rourke is a Professor in the Department of Surgery at the University of Michigan, Michigan Medicine and serves as Chief of the Division of General Surgery and Director of the Bariatric Surgery Program at the Ann Arbor Veterans Affairs Healthcare System. He graduated from the Massachusetts Institute of Technology in Cambridge, MA in 1986 with degrees in Chemical Engineering and Molecular Biology, obtained his M.D. in 1993 from UCLA Medical School in Los Angeles, CA, and completed his general surgery residency training in 2001 at UCSF in San Francisco, CA. He completed an Advanced Minimally Invasive Surgery Fellowship in 2003 at Legacy Health Systems in Portland, OR. Dr. O'Rourke joined the faculty at the University of Michigan Health System in 2013, after ten years as a faculty in the Department of Surgery at Oregon Health & Science University in Portland, OR. He practices clinical general and bariatric surgery, and manages an NIH-funded research program that studies molecular and cellular mechanisms of adipose tissue dysfunction in the context of metabolic disease. He is active in resident and medical student education, and serves as an active member of multiple national surgical societies and on the editorial boards of the journals Obesity Surgery and SOARD.



Faculty Speaker– Nam Tran, PhD

Dr. Tran is Associate Professor and Director of Clinical Chemistry, Special Chemistry/Toxicology, and Point-of-Care Testing at UC Davis. He completed his PhD degree in Comparative Pathology in 2008 and conducted a postdoctoral training fellowship under the National Institute of Bioimaging and Bioengineering (NIBIB) sponsored UC Davis Point-of-Care Technologies Center focused on developing novel molecular technologies for bedside infectious disease testing. These studies translated to a large multicenter trial evaluating the clinical impact of rapid molecular testing in sepsis in severely burned patients. Dr. Tran also completed a National Heart Lung and Blood Institute (NHLBI) K12 Emergency Medicine training program in 2016. Presently, he continues to focus his research on the development of point-of-care technologies for acute care, with recent work involving acute kidney injury recognition, sepsis biomarkers, cardiac injury biomarkers, and solid-state viscoelastic coagulation sensors for use in austere settings.



Shawn Tejiram

Examining 1:1 Versus 4:1 Packed Red Blood Cell to Fresh Frozen Plasma Ratio Transfusion During Pediatric Burn Excision

S. Tejiram, MD¹, S. Sen, MD¹, D.G. Greenhalgh, MD¹, T.L. Palmieri, MD¹

¹Department of Burn Surgery, University of California, Shriners' Hospital for Children Northern California, Davis Sacramento, CA

Introduction: Blood transfusions after burn injury occur due to operative losses, blood sampling, and burn physiology, but literature examining its effect on the critically ill pediatric population is limited. This study prospectively examined outcomes in major pediatric burns receiving a 1:1 vs 4:1 packed red blood cell (RBC) to fresh frozen plasma (FFP) transfusion strategy during massive burn excision.

Methods: Children with >20% total body surface area burns were randomized to a 1:1 or 4:1 PRBC/FFP transfusion ratio during burn excision. Parameters documented included patient demographics, burn size, Pediatric Risk of Mortality (PRISM) scores, Pediatric Logistic Organ Dysfunction (PELOD) scores, laboratory values, total blood products transfused, blood stream infections, urinary tract infections, and pneumonia.

Results: A total of 68 children were randomized into two groups (n=34). Mean age, PRISM scores, estimated blood loss (453 cc v 450 cc, p = 0.42), ventilator days (5 v 9, p = 0.47), and length of stay (57 v 60, p = 0.24) had no difference. Groups had equal numbers of infections (n = 24) and BSI (20 v 18, p = 0.46), although more PNU was documented in the 4:1 group (68 v 116, p = 0.08). On multivariate analysis, only TBSA, inhalation injury, and PRISM scores (p < 0.05) were significantly associated with infections.

Conclusion: No significant differences were identified in outcomes between transfusion strategies as measured by overall ventilator days, length of stay, or rates of infection. These findings suggest noninferiority to either transfusion practice based on outcomes.

Linda Schutzman

Soluble P-Selectin Promotes *De Novo* Pulmonary Arterial Thrombosis Following Blunt Thoracic Trauma

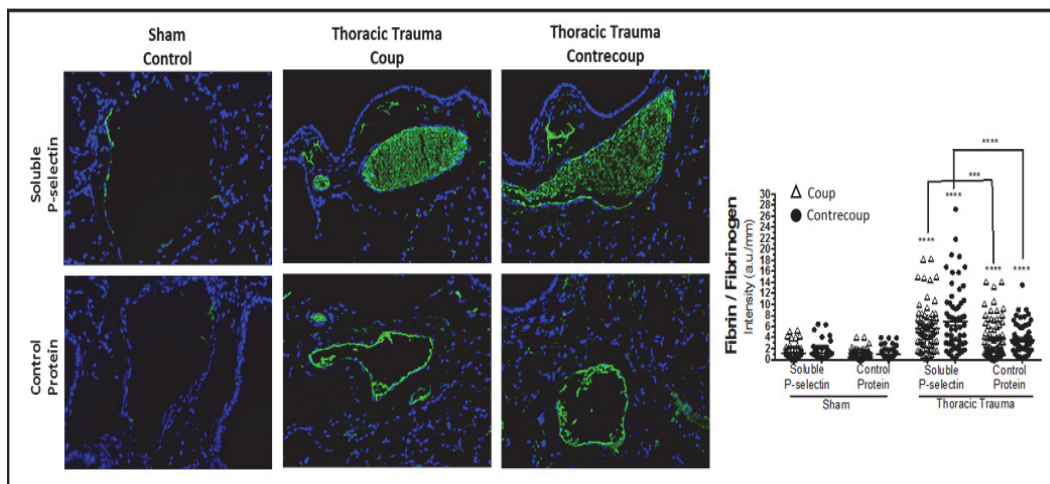
Linda M Schutzman MD, Robert R Rigor PhD, Joseph M Galante MD, Ian E. Brown MD, PhD; Division of Trauma Surgery

Introduction: Blunt thoracic trauma is associated with significant morbidity secondary to thromboembolic events of the pulmonary arterial vasculature. Previously, we provided evidence of *de novo* pulmonary arterial thrombosis associated with increased expression of the cell adhesion molecule, P-selectin (P-sel). Here we investigate the contribution of soluble (s) P-sel to pulmonary thrombosis. We hypothesize that elevated sP-sel will increase pulmonary arterial fibrin accumulation following blunt thoracic trauma.

Methods: A murine blunt thoracic trauma model was used. Adult male C57BL/6 mice were injected with activated sP-sel, or control peptide. Plasma P-sel levels were quantified. Tissue sections were stained with hematoxylin-eosin (H&E) or fibrin and P-selectin immunofluorescence.

Results: H&E stained lung tissue sections were scored to confirm pathologic injury. Plasma P-sel levels were significantly increased in injured mice compared to shams ($p < 0.001$). In injured mice, fibrin accumulation was significantly greater after pretreating with sP-sel compared to control peptide ($p < 0.001$).

Conclusions: Plasma P-sel levels were elevated 24 hours after thoracic trauma. After injury, infusion of sP-sel increased pulmonary arterial fibrin accumulation compared to infusion with control peptide. No difference in fibrin deposition was identified between sham controls that received the sP-sel versus those that received the control peptide. These data imply that increased concentration of soluble P-selectin promotes pulmonary arterial thrombosis in the setting of blunt thoracic injury.



Engineering collagen hydrogel with a novel ligand against integrin $\alpha\beta3$ to improve endothelial cell survival after transplantation

Dake Hao¹, Kewa Gao¹, Ruiwu Liu², Diana Farmer¹, Alyssa Panitch³, Kit Lam², Aijun Wang^{1,3}

¹Surgical Bioengineering Lab, Department of Surgery, ²Department of Biochemistry and Molecular Biology, ³Department of Biomedical Engineering, UC Davis

Introduction: Endothelial cell (EC) transplantation with injectable collagen hydrogel has received much attention as potential treatments for various diseases. However, the therapeutic effect is limited by poor viability of the transplanted ECs. One critical cause of this issue may be due to cellular apoptosis that is triggered by the disruption of cell-cell interactions upon cell harvesting and insufficient cell-extracellular matrix engagement at transplantation. Integrin binding to ECM is crucial for cell anchorage to the surrounding matrix, spreading, migration, and further activation of intracellular signaling pathways. Thus, in this study, we hypothesize that conjugation of synthetic ligands to engage integrin $\alpha\beta3$ to matrix will improve EC survival after transplantation.

Methods: We previously identified LXW7, an integrin $\alpha\beta3$ ligand by one-bead one-compound combinatorial technology. Binding specificity and functions of LXW7 on ECs were examined via cell binding assay, flow cytometry, MTS assay and Western-blot. We then functionalized collagen hydrogel with SILY, a type I collagen binding peptide. By introducing a combo peptide LXW7-SILY, collagen hydrogel is functionalized with LXW7 via the 'SILY-collagen' binding approach. The effects of LXW7-modified collagen gel on EC functions and survival were examined *in vitro* via caspase activity assay, MTS assay and Western-blot, and *in vivo* in a mouse subcutaneous implantation model.

Results: LXW7 showed strong binding affinity to ECs, promoted EC proliferation and enhanced the phosphorylation of VEGF receptor 2 (VEGF-R2) and the activation of mitogen-activated protein kinase (MAPK) ERK1/2 in ECs. *In vitro*, LXW7- functionalized collagen significantly improved EC attachment, proliferation and survival in the hypoxic environment under both two-dimensional and three-dimensional culture conditions compared to unmodified collagen. *In vivo*, LXW7- functionalized collagen significantly improved EC survival at week 4 after transplantation compared with unmodified collagen.

Conclusion: We demonstrated that integrin $\alpha\beta3$ binding ligand LXW7 significantly enhanced EC functions. LXW7-functionalized collagen significantly improved EC survival and functions compared with unmodified collagen both *in vitro* and *in vivo*. Our results showed LXW7-functionalized collagen possesses the promising potential to improve vascularization and tissue regeneration.

Carl Beyer

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) Induced Cardiac Injury Is Mitigated by Partial Occlusion

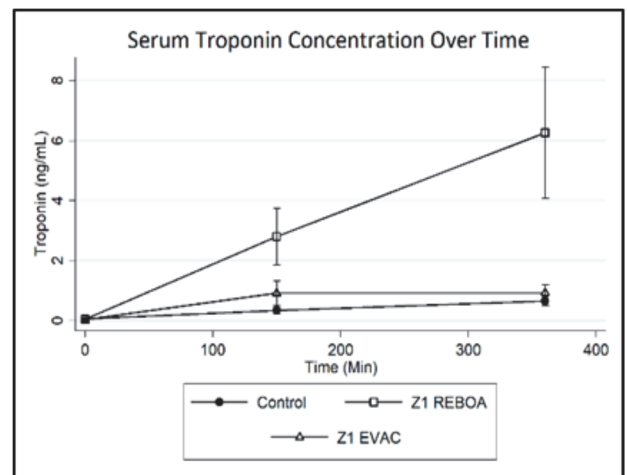
Carl Beyer, Emily Tibbits, Guillaume Hoareau, J Kevin Grayson, Luke Neff, Timothy Williams, and M Austin Johnson
Clinical Investigation Facility, Travis, AFB

Introduction: The cardiac effects of REBOA are largely unknown. We hypothesized that increased afterload from REBOA would lead to cardiac injury and that partial flow using endovascular variable aortic control (EVAC) would mitigate this injury.

Methods: Eighteen anaesthetized swine underwent controlled hemorrhage of 25% blood volume. Animals were randomized to either Zone 1 REBOA, Zone 1 EVAC, or no intervention (control) for 45 minutes. Animals were then resuscitated with shed blood, observed during critical care, and euthanized after a six-hour total experimental time. Left ventricular function was measured with a pressure-volume catheter and blood samples were drawn at routine intervals.

Results: There were no differences in cardiac output or ejection fraction between groups at any time. At the end of the intervention, the preload recruitable stroke work (PRSW) was significantly higher in both the REBOA and EVAC groups compared to controls [111.2 (102.5-148.6) and 116.7 (116.6-141.4) versus 67.1 (62.7-87.9), $P=0.02$ and $P<0.01$]. The higher PRSW was maintained throughout the experiment in the EVAC group, but not in the REBOA group. Serum troponin concentrations after six hours were higher in the REBOA group compared to both the EVAC and control groups (6.26 ± 5.35 ng/mL versus 0.92 ± 0.61 ng/mL and 0.65 ± 0.38 ng/mL, $P=0.05$ and $P=0.03$). Cardiac intramural hemorrhage was higher in the REBOA group compared to the control group (1.67 ± 0.46 vs 0.17 ± 0.18 , $P=0.03$), but not between EVAC and control.

Conclusions: In a swine model of hemorrhagic shock, complete aortic occlusion resulted in cardiac injury, although there was no direct decrease in cardiac function. EVAC mitigated this cardiac injury and improved cardiac performance during resuscitation and critical care.



Maggie Spruce

Title: Rapid Intramuscular Administration of TXA Results in Equivalent Total Drug Exposure and Reversal of Hyperfibrinolysis in a Swine Controlled Hemorrhage Model

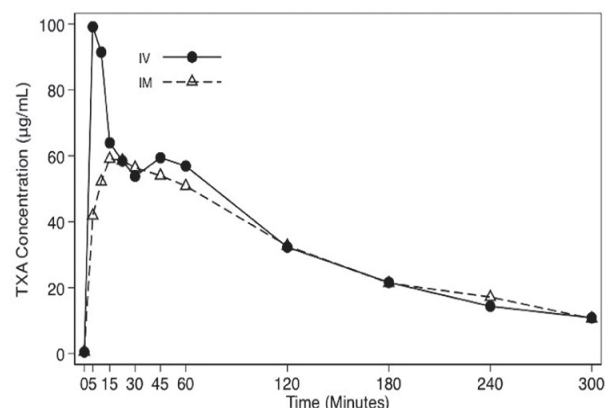
Authors: M Spruce, C Beyer, C Caples, E DeSoucy, H Kashtan, G Hoareau, JK Grayson, MA Johnson; UC Davis Department of Surgery, Division of Trauma

Introduction: Tranexamic acid (TXA) improves survival in traumatic hemorrhage, but its use can be limited in austere environments where obtaining intravenous access is difficult. We hypothesize that the intramuscular route could be used as an alternative.

Methods: Ten Yorkshire cross swine were anesthetized and subjected to a 35% controlled hemorrhage during which time they were randomized to receive either a 1g intravenous (IV) TXA infusion over 10 minutes or 1g intramuscular (IM) TXA in a single injection. Serial serum TXA concentrations were determined using mass spectrometry, and serial plasma samples supplemented with tissue plasminogen activator (tPA) were analyzed by rotational thromboelastometry (ROTEM).

Results: All animals achieved moderate shock as evidenced by blood loss, heart rate elevation, and mean arterial pressure decline. There was no difference between the concentration-time areas under the curve (AUC) of TXA given by the IV and IM routes (IV 10168.3 mg.min/mL \pm 1076.2 and IM 9445.6 mg.min/mL \pm 687.8, $p = 0.59$). The absolute bioavailability of IM TXA was 93%. IV TXA administration only resulted in a significantly higher peak serum concentration during the 10 minute infusion (IV 105.1 mg/mL \pm 10.7 and IM 65.3 mg/mL \pm 5.7, $p = 0.01$). Once infusion ceased, there were no significant differences in concentration between the two groups for the remainder of the experiment. Both IV and IM TXA administration caused complete reversal of in vitro tPA-induced hyperfibrinolysis on ROTEM. LI30 22 minutes after the start of TXA administration was corrected to 99% in both groups.

Conclusion: IM administration of TXA resulted in equivalent total body exposure and correction of in vitro hyperfibrinolysis as IV TXA during hemorrhagic shock in this swine model. IM TXA may prove effective in scenarios where difficulty in establishing dedicated IV access could otherwise limit or delay its use.



Jamie Anderson

Fetal repair of surgically-created gastroschisis in a lamb model may improve postnatal feeding tolerance and intestinal motility: A pilot study

Jamie E. Anderson, MD MPH; Laura A. Galganski, MD; Christopher D. Pivetti, MS; Melissa A. Vanover, MD; Jacob T. Stephenson, MD FACS; Rachel Brownlee, LATG DVM; Betty Ma, DVM DACLAM; Diana L. Farmer, MD FACS FRCS; Shinjiro Hirose, MD FACS; Division of Pediatric Surgery

Introduction: Gastroschisis is a morbid congenital defect due to sequelae of intestinal dysmotility and malabsorption. Although fetal surgical repair has been demonstrated in a lamb model, it is unclear whether this improves intestinal motility and feeding tolerance.

Methods: Fetuses from five time-mated ewes (*Ovis aries*) underwent defect creation at gestational age (GA) 76-80 days. The experimental group underwent *in utero* repair of gastroschisis at GA 99-100. The positive control group underwent post-natal repair of at time of cesarean section at GA 139-141. On day of birth, lambs were fed barium sulfate, followed by *ad lib* colostrum/milk. Lambs were monitored for up to 72 hours to determine feeding tolerance and duration of time for complete passage of barium through the gastrointestinal tract.

Results: Eight fetuses underwent gastroschisis defect creation and five survived to birth. Of the three lambs repaired at birth, one required resection of necrotic bowel and two had significant intestinal stricture at the abdominal wall defect and did not tolerate feeding. Of the two lambs repaired *in utero*, one tolerated feeding normally without complications and one had a small intestine atresia preventing normal feeding.

Conclusions: Fetal repair of gastroschisis may improve postnatal intestinal motility resulting in feeding tolerance at birth.

Laura Galganski

Identification of Intestinal Ganglion Cells in the Murine Model of Hirschsprung's Disease Using Multimodal Label-free Optical Techniques

LA Galganski, MA Soares de Oliveira, C Chang, CD Pivetti,
KE Matsukuma,, JW Chan, P Saadai

Division of Pediatric Surgery, Department of Pathology and Laboratory Medicine

Introduction: Hirschsprung's disease (HD) is a congenital disorder resulting in life-threatening bowel obstruction. The gold standard for diagnosis of HD is histologic evaluation for the absence of ganglion cells in the colon, however this is time-consuming and error-prone. We hypothesized that a combination of label-free optical modalities, second harmonic generation (SHG), two-photon autofluorescence (2PF), and Raman spectroscopy could acquire a molecular fingerprint of ganglion cells to aid in diagnosis.

Methods: The distal colon and rectum from a wild-type female mouse was resected, placed in 10% formalin, and paraffinized. Serial 5 micron sections were placed on quartz cover slips with adjacent sections on TOMO slides. Following deparaffinization, hematoxylin and eosin (H&E) staining was performed on TOMO slide specimens. Specimens on quartz slides were imaged using SHG, 2PF, and Raman microscopy. Results are validated by correlation with H&E images of adjacent tissues.

Results: Locations of ganglion cells were identified on both H&E stained and unstained tissue sections by a negative fluorescence contrast in the 2PF and SHG images. The bright-field image showed the location of a ganglion cell cluster in the H&E section. The same tissue section appeared to show little or no 2PF and SHG signals at the location of the ganglion cell clusters. Images of the adjacent unstained section also showed a negative contrast in the 2PF and SHG images, indicating the presence of the same ganglion cell cluster identified in the H&E stained section. Raman spectra acquired from the ganglion cell cluster also showed unique spectral features compared to surrounding tissue. Raman vibrational peaks associated with collagen, proteins, and lipids were identified.

Conclusions: Both 2PF and SHG microscopy were used to identify locations of ganglion cells, and an optical signature of ganglion cells was identified using Raman spectroscopy.

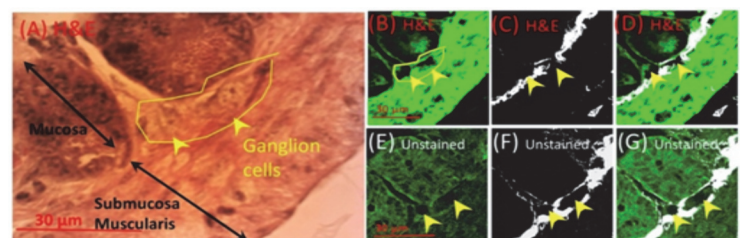


Figure 1. Bright-field image (A), 2PF fluorescence (B, E), second harmonic generation (C, F) images, and overlays of 2PF and SHG images for H&E stained and unstained tissue section (D, G). Yellow arrows indicate ganglion cells.

Kaeli Yamashiro

Long Term Survival of Lambs with Myelomeningocele

Kaeli Yamashiro, Laura Galganski, Jamie Peyton, Christopher Pivetti, Priyadarsini Kumar, James Becker, Benjamin Keller, Zachary Paxton, Kalie Haynes, Victoria Vicuna, Aijun Wang, Diana Farmer

Introduction: Long term outcomes of lambs who underwent *in utero* repair of myelomeningocele has not been studied. As a function of the myelomeningocele model creation, the lambs have absent paraspinal muscles, lumbar spinous processes and lumbar lamina creating an area of weakness. We hypothesized that bracing and physical therapy would counteract the effects of absent paraspinal muscles allowing long term survival of lambs with myelomeningocele.

Methods: Three lambs underwent *in utero* myelomeningocele (MMC) repair with placental mesenchymal stem cells after measuring the defect length. At birth, motor function was assessed using the sheep locomotor rating (SLR), and those with a score of 15, on a scale of 0-15, were survived for up to 6 months. Control animals who did not receive any additional treatment were compared to animals who received bracing and physical therapy (B/PT). Bracing consisted of a thoracic-lumbar-sacral brace worn 12 hours per day, 5 days per week. Physical therapy targeted strengthening of the pelvic and gluteal muscles for 1 hour sessions, twice a day, 5 days per week. Lambs were euthanized after a sustained SLR score less than 15.

Results: The MMC defect lengths in control lambs (n=2) were 3.2cm and 3.4cm with no cord injury or hematoma. The B/PT lamb (n=1) had a defect length of 3.1cm with no cord injury or hematoma. One control lamb was euthanized at 29 days for a SLR score of 7. The second control lamb was euthanized at 65 days for a SLR score of 13. Both of these lambs developed lumbar kyphosis with spinal cord compression (Figure 1). The B/PT lamb is currently at 65 days with no signs of lumbar kyphosis and a SLR score of 15.

Conclusion: Long term outcomes of lambs with myelomeningocele is limited by lumbar kyphosis and spinal cord compression, but may be counteracted with bracing and physical therapy.

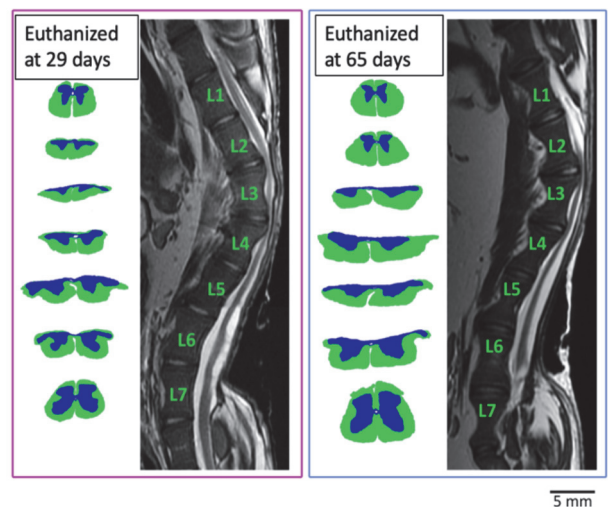


Figure 1. Lumbar kyphosis and cord compression in the control lambs.

Kaeli Yamashiro

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in a

Pediatric Swine Liver Injury Model: A Pilot Study

Kaeli Yamashiro*, Andrew Wishy*, Carl Beyer, Harris Kashtan, J. Kevin Grayson, M. Austin Johnson, Laura Galganski, Jacob Stephenson, A. Francois Trappey. Division of Pediatric Surgery and Clinical Investigation Facility.

Introduction: Resuscitative Endovascular Balloon Occlusion of the Aorta has not been studied in children and current devices are too large for pediatric patients. We hypothesized that complete aortic occlusion following a liver injury was feasible with smaller existing balloons and sheaths and would improve hemorrhage control and survival time compared to no intervention in a pediatric swine model.

Methods: Pediatric swine weighing 20-30kg underwent splenectomy and liver amputation. Following 5 minutes of free hemorrhage, they were randomized to 30 minutes of complete Zone 1 REBOA with a 5Fr Fogarty balloon through a 6Fr sheath or no intervention. Swine then underwent a damage control laparotomy and critical care for 180 minutes or until death. Data was analyzed with t-tests, mixed models and Kaplan-Meier curve for survival.

Results: Compared to control swine (n=5), REBOA swine (n=6) had less blood loss (34.0 ± 1.6 vs 61.3 ± 2.5 mL/kg, $p < 0.01$), higher end hematocrit (28.1 ± 2.1 vs 17.1 ± 4.1 %, $p = 0.03$), higher end creatinine (1.42 ± 0.06 vs 1.21 ± 0.07 mg/dL, $p = 0.05$) and required more norepinephrine during critical care (1.4 ± 0.3 vs 0.3 ± 0.3 mg/kg, $p = 0.04$). Proximal mean arterial pressure was higher during aortic occlusion (90.6 ± 9.8 vs 36.2 ± 5.6 mmHg, $p < 0.01$) but not during critical care (66.2 ± 3.1 vs 60.1 ± 2.2 mmHg, $p = 0.39$). All REBOA swine survived, whereas 2 control swine died, one at 22 minutes and the other at 33 minutes ($p = 0.10$) (Figure 1).

Conclusion: Complete Zone 1 aortic occlusion is feasible and decreases blood loss during non-compressible torso hemorrhage in pediatric swine. Survival was universal with REBOA, although increased critical care needs.

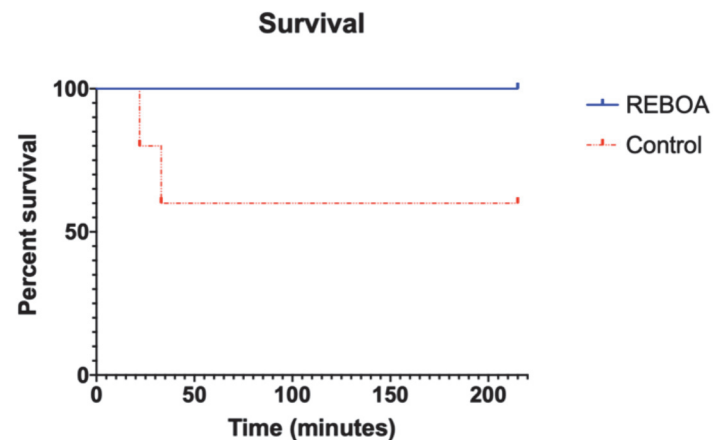


Figure 1. Kaplan-Meier curve

Erik DeSoucy

An Adaptation of the Broselow Tape - Approximation of Pediatric Morphometry for Resuscitative Endovascular Balloon Occlusion of the Aorta

ES DeSoucy, AF Trappey, AM Wishy, MA Simon, AJ Davidson, JJ DuBose,

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Background: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) may be beneficial in the management of traumatic and iatrogenic vascular and solid organ injuries in children, but requires an understanding of vessel diameter at the access site and landing zones. We sought to adapt the Broselow Tape method to estimation of aortic and femoral artery diameters for this purpose.

Methods: Computed tomography scans from trauma and non-trauma pediatric patients at a level 1 trauma center were reviewed for vascular dimensions at aorta Zone I, Zone III and the common femoral artery (CFA). Height was used to create linear regression equations for each location and calculate ranges for each Broselow Tape category.

Results: We reviewed scans from 110 patients ages 2-14 years with less than 8% interobserver variability. 64% were male and 46% were trauma patients. Height based regression equations were closely correlated with vessel diameter and used to calculate vessel diameters for use on a Broselow Tape (**Table 1**):

Zone I (mm) = $[0.093 \pm 0.006 \cdot \text{height (cm)}] + 0.589 \pm 0.768$; $R^2 = 0.714$, $p < 0.001$

Zone III (mm) = $[0.083 \pm 0.005 \cdot \text{height (cm)}] - 0.703 \pm 0.660$; $R^2 = 0.728$, $p < 0.001$

CFA (mm) = $[0.043 \pm 0.003 \cdot \text{height (cm)}] + 0.644 \pm 0.419$; $R^2 = 0.642$, $p < 0.001$

Conclusion: Knowledge of the access vessel and occlusion zone diameters in pediatric patients is crucial for future research and application of REBOA in this population. Furthermore, an adapted Broselow Tape including these measurements would assist in appropriate sheath and balloon catheter selection in emergent settings.

Table 1: Broselow category vessel diameters calculated for Zone I, Zone III and common femoral artery (CFA) including recommended access sheath sizes

Broselow Color	Zone I Diameter (mm)		Zone III Diameter (mm)		CFA Diameter (mm)		Introducer Sheath (Fr) *
	Min	Max	Min	Max	Min	Max	
Pink	3.9	6.8	2.3	4.7	2.1	3.6	1-3
Red	4.6	7.5	2.9	5.4	2.4	3.9	2-4
Purple	5.2	8.4	3.5	6.2	2.7	4.4	2-5
Yellow	6.1	9.6	4.2	7.2	3.1	4.9	3-5
White	7.1	10.8	5.1	8.4	3.5	5.5	3-6
Blue	8.2	12.1	6.1	9.5	4.1	6.1	4-7
Orange	9.3	13.0	7.1	10.3	4.6	6.5	5-8
Green	10.2	14.3	7.8	11.4	4.9	7.1	5-9

Guy Jensen

Calculation of the Burden of Injury in Baghdad During the Iraq War.

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UC Davis Department of Surgery, 2. Al Munstansiriya University, College of Medicine, 3. Johns Hopkins School of Public Health, 4. Institute for Health Metrics and Evaluation, 5. University of Washington School of Public Health.

Introduction: The Disability Adjusted Life Year (DALY) has become the primary metric for the measure of disability and premature mortality. This work proposes a novel method for calculating the burden of disease in conflict and details the differences between this approach and the traditional Global Burden of Disease (GBD) framework.

Methods: Lafta et al. completed a randomized cluster household survey to capture information regarding injuries, disabilities, and outcomes from 2003-May 2014. GBD metrics for life expectancy and disability weights were applied to this data to generate a burden of injury calculation stemming from intentional injuries. A bootstrapping technique was utilized to sample the study population and disability weight draws were repeatedly sampled and applied to injured subjects to account for variability within the population.

Results: We estimate that there were 5.6 million DALYs incurred due to intentional injuries between 2003 and 2014 in the city of Baghdad. 4.99 million DALYs were lost due to mortality and 606,000 lost due to non-fatal injury. Small arms fire was the most common cause of injury and death accounting for 55.8% of all DALYs lost. Injuries from shelling made up the next largest contributor, accounting for 27% of all DALYs lost.

Conclusion: The GBD methodology has not previously been applied to conflict populations. This study both utilizes the well accepted framework of the GBD and proposes alterations to its method of calculation to better capture the effects of conflict on affected populations.

Jessica Cox

Older Adults with Isolated Rib Fractures Do Not Require Routine ICU Admission

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(^a Division of Trauma, Acute Care Surgery, and Surgical Critical Care; ^b Department of Emergency
Medicine)

Introduction: Western Trauma Association guidelines recommend Intensive Care Unit (ICU) admission for patients ≥ 65 years old with ≥ 2 fractured ribs but supporting evidence is scant. We sought to identify characteristics of patients with isolated rib fractures that predict the need for ICU care.

Methods: We analyzed patients ≥ 50 years old with isolated rib fractures at UC Davis Health from 2013-2017. The primary outcome was the need for ICU care, defined as the occurrence of a critical care intervention or event (CCE). CCEs included interventions (e.g., intubation, vasopressor use) and adverse events (e.g., hypoxemia, pneumonia) and were based on American College of Critical Care Medicine Guidelines. We used stepwise logistic regression to identify characteristics that predict CCE occurrence.

Results: Among 401 patients, 251 (63%) were admitted to an ICU. 83 (33%) patients admitted to the ICU and 7 (5%) patients admitted to the ward had any CCE. The most common CCEs were desaturation (10%), respiratory therapy more frequent than every 4 hours (9%), and hypotension (8%). 64 (85%) CCEs occurred within 2 days of admission. Emergency department incentive spirometry < 1 L, dementia, Injury Severity Score (ISS), and age predicted CCE occurrence. Of patients admitted to an ICU, 34% were transferred out within 12 hours and 48% within 24 hours.

Conclusions: Routine ICU admission is unnecessary for most older adults with isolated rib fractures. Patients with dementia, incentive spirometry < 1 L, and greater injury burden more likely need ICU care. These characteristics warrant prospective evaluation for clinical decision rule development.

Amanda Phares

Away rotations in General Surgery: To do or not to do? A Pilot Study

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Introduction: Prior research has shown that 65% of medical students applying into General Surgery complete away rotations during their fourth-year of medical school. Also, only 25% of students who complete away rotations match at one of the programs where they rotated, which is the lowest percentage out of all of the specialties. This discrepancy led us to question, “Does participation in away rotations help students match into residency?” Our study investigated the reasons why students chose to complete away rotations and if participation in away rotations led to improved matched outcomes.

Methods: An anonymous, online survey was sent to all civilian, categorical general surgery residents at the University of California, Davis. The residents were asked whether or not they completed away rotations, what factors influenced their decision to do away rotations, whether they found them to be beneficial or harmful, and where they matched on their rank list.

Results: 31 of 42 (74%) residents responded to the survey. 21 of 31 (68%) respondents completed away rotations. The most common approaches to choosing rotations were based on geographic location (95%), program reputation (86%), and ties to the area (57%). 90% of residents found away rotations to be a valuable experience and 14% of residents thought that they had a negative impact. Benefits associated with away rotations included confirming interest in the program (62%) and gaining experience for residency (71%). For the residents who did not do away rotations, the most common reasons cited were advisor recommendation (80%), cost (60%), and belief that it lacked benefit (50%). Of residents who did away rotations, 57% matched at their first-choice program compared to 70% of residents who did not do away rotations, but this was not statistically significant ($p=0.5$).

Conclusions: Most residents who completed away rotations found them to be valuable experiences with multiple benefits. However, statistically, participation in away rotations did not lead to improved match outcomes.

Christina Theodorou

Practice, Practice, Practice! REBOA Volume Matters

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Introduction: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a minimally invasive intervention in the hemorrhaging patient. Success relies on multiple institutional factors and a learning curve must be expected. We hypothesize that high-volume centers will be more successful than low-volume centers.

Methods: Retrospective study from the American Association for the Surgery of Trauma (AAST) Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) Registry, a multi-institutional registry of patients undergoing aortic occlusion. Patients ≥ 18 years who underwent REBOA from 11/2013 to 1/2018 were included. Centers were stratified into high (≥ 80 cases), middle (10-20 cases), and low volume (< 10 cases); success rates, defined as hemodynamic improvement with balloon inflation, were compared.

Results: Of 271 patients, 212 (77.5%) had successful REBOA deployment. Odds of success were increased at high-volume vs. low-volume centers (OR 4.19, 95% CI 1.34-13.10, $p=0.014$). 34.5% of patients had CPR ongoing at time of REBOA; odds of success were decreased among these patients (OR 0.11, 95% CI 0.04-0.33, $p<0.001$)

Conclusion: Successful REBOA use depends not only on surgeon training, but multiple systems factors, which are not intuitive to groups who rarely, if ever, see endovascular techniques. High-volume centers are more likely to be successful. Ongoing CPR is associated with a decreased odds of success.

Jennifer Olson

Agree to Disagree: Discordance at the Heart of Surgical Guidelines

Jennifer Olson, MD, Karen Matsukuma, MD, Julie Sutcliffe, PhD, Richard Bold, MD

Surgical Oncology

Introduction: Incidental pancreatic intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) are being identified more often harboring unknown malignant potential. Surgical and gastroenterologist societies have established consensus management guidelines predicated on radiologic and histologic factors which heavily rely on subjective assessment and may not provide a reliable indicator on which to base management decisions.

Method: Tissue specimens from resected IPMNs and MCNs at UC Davis between 2008 and 2017 were independently assessed by three pathologists from different institutions for cyst type, epithelial lining, dysplasia grade, and immunohistochemical (IHC) integrin staining. Statistical analysis was performed using Fleiss kappa scores to measure concordance.

Results: 37 mucinous tumors were identified with pathology tissue slides available. There was disagreement in every category of assessment even including the type of cyst. The concordance score was only fair for epithelial lining (0.31/1), dysplasia grade (0.34/1), and IHC staining (0.29/1). This limited the elucidation of significant associations with those factors and invasiveness or radiologic risk factors.

Conclusion: Current consensus guidelines for the management of mucinous pancreatic tumors rely on subjective pathologic assessment that varies greatly by the individual pathologist. Estimation of malignant potential directs the decision to undergo a pancreatic resection but the current markers are unreliable.

Cole Nishikawa

Delayed Sheath removal after catheter directed thrombolysis does not decrease complications

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Vascular Surgery

Purpose: Treatment of acute limb ischemia by catheter directed thrombolysis has associated bleeding risks, which have led some physicians to delay sheath removal after tissue plasminogen activator (tPa) is discontinued. We aimed to determine rates of complications for early (<6 hours) versus late (>6 hours) sheath removal after lytic treatment.

Methods: Retrospective study of patients with acute limb ischemia from Aug 2010 – Apr 2018 treated with catheter directed thrombolysis. The primary end point was any access site complication (hematoma, pseudoaneurysm, dissection, arteriovenous fistula, or hemorrhage). Continuous variables were compared using t-test, and Chi-square analysis was used to determine differences between categorical variables.

Results: 52 patients were treated (36 men/16 women) with a mean age of 60 (sd \pm 11) years. Early sheath removal was performed in 30 patients, and 22 patients had late sheath removal. There was no difference in mean duration of lysis (early = 16.7 hours, late = 19.4 p = 0.32), mean tPa dose (early = 13.1 mg, late = 15.9, p = 0.3), or post procedure fibrinogen (early = 271, late = 298, p = 0.48). Patients that had early sheath removal were more likely to have a closure device used (early = 7, late = 0, p = 0.43). The overall access site complication rate was 5.8%. One patient in the early sheath removal group developed a hematoma and two patients in the late sheath removal group developed pseudoaneurysm (p = 0.34).

Conclusions: While some practitioners believe in delayed sheath removal after catheter directed thrombolysis, this may be associated with a higher rate of pseudoaneurysm, and no decreased rate of bleeding risk. Until further data is available, we recommend removal of femoral sheaths as soon as post-operative bleeding risk is minimized. Closure devices may be of benefit in this population, however more data are needed.

James Clark

Do the 2018 Leapfrog Group Minimal Hospital and Surgeon Volume Thresholds for Esophagectomy Favor Specific Patient Demographics?

James M. Clark, MD, David T. Cooke, MD, Habiba Hashimi, MD, David Chin, PhD, Garth H. Utter, MD, MSc, Lisa M. Brown, MD, MAS, Miriam Nuño, PhD

Section of General Thoracic Surgery, Department of Surgery

Introduction: Esophagectomy outcomes are associated with surgeon and hospital operative volumes, leading the Leapfrog Group to recommend minimum volume thresholds of 7 and 20 respectively. We examine how esophagectomy volume thresholds impact outcomes relative to patient characteristics.

Method Patients undergoing esophagectomy for cancer were identified from the 2007-2013 New York and Florida Healthcare Cost and Utilization Project's State Inpatient Databases. Logit models adjusted for patient characteristics evaluated in-hospital mortality, complications, and prolonged length of stay (PLOS). Median surgeon and hospital volumes were compared between young-healthy (age 18-57, Elixhauser Comorbidity Index [ECI] <2) and older-sick patients (age ≥71, ECI >4).

Results: Of 4330 patients who underwent esophagectomy by 539 surgeons at 156 hospitals, 3515 (81%) were male, median age was 64 (interquartile range 58-71), and mortality was 4.0%. Patients treated by both low-volume surgeons and hospitals had the greatest risk of mortality (5.0%), except in the case of older-sick patients where mortality was highest at high-volume hospitals with high-volume surgeons (12%) (Figure 1). For mortality <1%, annual hospital and surgeon volumes needed were 23 and 8, respectively; mortality rose to 4.2% when volumes dropped to the Leapfrog thresholds of 20 and 7, respectively. Complication rates rose from 53% to 63% when hospital and surgeon volumes decreased from 28 and 10 to 19 and 7, respectively. PLOS rates rose from 19% to 27% when annual hospital and surgeon volumes decreased from 27 and 8 to 20 and 7, respectively.

Conclusion: Current Leapfrog Group esophagectomy volume guidelines may not predict optimal outcomes for all patients, especially at the extremes of age and comorbidities.

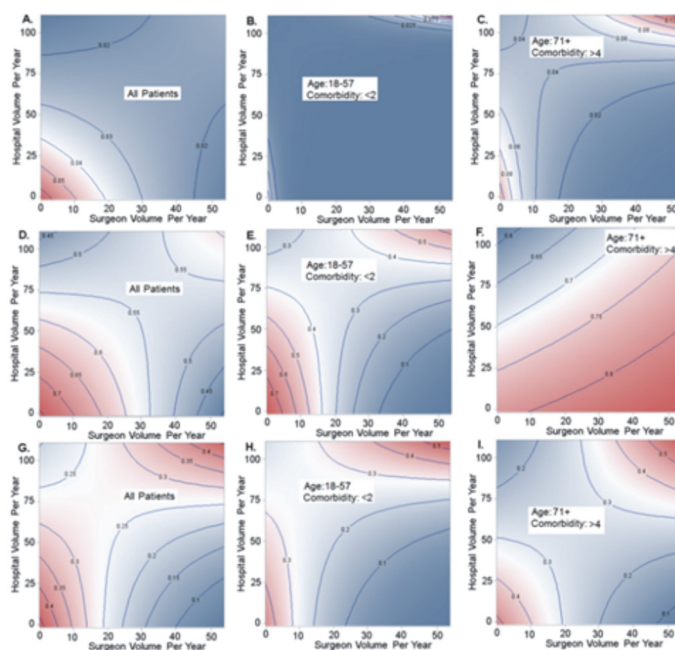


Figure 1. Contour plots of predicted mortality (A,B,C), complication (D, E,F) and prolonged length of stay (G, H, I) for all patients (left), young-healthy (middle), and older-sicker cohorts (right).

Matthew Zeiderman

Factors Affecting End-to-Side Peripheral Nerve Injuries: A Meta-analysis

Matthew R. Zeiderman MD; Dattesh R. Dave MD, MSc; Derek B. Asserson BS; Chetan S. Irwin MD; Clifford R. Pereira MD, FACS, FRCS Division of Plastic Surgery

Introduction: Efficacy of end-to-side (ETS) nerve coaptation for peripheral nerve repair remain controversial given the breadth of applications, injury mechanism and location. We hypothesize differences in age, sex, and time to surgery all influence outcomes.

Methods: The PubMed database was searched for ETS peripheral nerve coaptation in the upper extremity from 1988-2018. Age, sex, time to surgery, and change in strength and/or sensation as measured by Medical Research Council (MRC) scale was recorded. Meaningful recovery was classified as MRC Grade 3 or greater function. Independent sample t-test was performed to compare functional outcomes for groups. Linear regression analysis was used to correlate time to surgery and age with functional outcome. Logistic regression was performed to correlate time to surgery with meaningful recovery.

Results: 96 adult and 10 pediatric patients were included. Independent sample t-test yielded no statistically significant relationship between change in sensation ($p=0.366$) or strength ($p=0.933$) for adults vs. pediatric, nor for change in sensation ($p=0.572$) or strength ($p=0.891$) between adult males vs. females. Motor improvement in adults aged 18-25 vs. 26+ ($p=0.056$) approached statistical significance. Time to surgery weakly correlated with motor improvement ($\Gamma = -0.254, p=0.078$). On logistic regression analysis, time to surgery and meaningful recovery had a coefficient Γ of -0.214 ($p=0.214$).

Conclusions: Adults aged 18-25 may have better motor outcomes from ETS nerve coaptation than older adults. Expected negative correlation between time to surgery and motor outcomes approached statistical significance. No statistically significant functional improvement was identified among any group. Efficacy of ETS nerve coaptation is difficult to evaluate, neither age nor gender seem to affect outcomes.

Mimmie Kwong

“Endograft repair with in-situ laser fenestration feasible for total arch repair”

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Open total arch surgery remains a morbid procedure with mortality rates of 5-15% and stroke rates of 2-8%¹⁻⁴. Hybrid approaches with aortic arch debranching and use of thoracic endograft placement have been proposed as a safer alternative. However, comparative studies suggest no significant difference in mortality⁵⁻⁷. Total endovascular approaches avoid the need for median sternotomy and aortic arch manipulation, however, their use has been limited by availability of pre-fabricated endografts and production delays with custom devices. In-situ retrograde fenestration has been proposed as an accessible method for in-line revascularization after endograft placement, with several case series published using a needle fenestration technique⁸. However, this has not been widely adopted due to lack of experience with in-situ fenestration and with cerebral perfusion during coverage of the supra-aortic trunk orifices. Laser fenestration is a faster and technically simpler method that may be easier to learn and more readily available in the vascular surgery armamentarium. In-vitro and clinical series demonstrate feasibility^{9,10}. However, endovascular total arch repair with zone 0 deployment and in-situ laser fenestration of the arch branch vessels has only been described once in the literature.

Here we present one case of a 67-year-old woman with bovine arch anatomy presenting with an aortic arch pseudoaneurysm eroding into her sternum one year after a Bentall procedure and Frozen Elephant Trunk for management of Type A dissection. She underwent a successful endovascular total arch replacement using an in-situ laser fenestration to revascularize her innominate and left subclavian arteries with left subclavian-carotid bypass and intraoperative bilateral carotid bypass for neuroprotection.

In-situ laser fenestration of an aortic endograft combined with temporary bypass for perfusion of the brain is a feasible alternative for complex total arch reconstruction in patients in whom the mortality and morbidity of a median sternotomy for open or hybrid repair would be prohibitive.

James Clark

Does One Size Fit All? An Evaluation of the 2018 Leapfrog Group Minimal Hospital and Surgeon Volume Thresholds for Lung Surgery

James M. Clark, MD, David T. Cooke, MD, David Chin, PhD, Garth H. Utter, MD, MSc, Lisa M. Brown, MD, MAS, Miriam Nuño, PhD

Section of General Thoracic Surgery, Department of Surgery

Introduction: In 2018, the Leapfrog Group (LFG) set minimum annual lung cancer surgery case hospital and surgeon volume (HV, SV) thresholds of 40 and 15. We examined if the LFG volume thresholds are associated with optimal outcomes equally for patients of age and comorbidity extremes.

Method: Lobectomy and pneumonectomy lung cancer patients were evaluated from the 2007-2013 New York and Florida Healthcare Cost and Utilization Project's State Inpatient Databases, studying perioperative complications, prolonged length of stay (PLOS; ≥ 14 days) and mortality. Median HV and SV were compared between young-healthy (age 18-60, Elixhauser Comorbidity Index [ECI] < 1) and older-sicker patients (age > 77 , ECI > 3).

Results: We identified 27,841 patients; 13,277 (48%) male, median age was 69 years (interquartile range 61-77), and mortality was 2.1%. In Figure 1, patients treated by both low-volume surgeons (< 15 annual cases) and hospitals (< 40) had the greatest risk of mortality (2.5%), except when operating on young-healthy patients (mortality $< 2\%$). Mortality for older-sicker patients was highest for high-volume surgeons (12%), though higher HV was protective. Increasing HV and SV was associated with a reduction in mortality, complications, and PLOS ($p < 0.05$). To achieve a mortality $< 1\%$, HVs and SVs needed were 38 and 21, respectively. Mortality odds increased as HV decreased, with the highest mortality decile (9.5%) having an SV and HV of 19 and 34.

Conclusion: Hospital volume affects outcomes more than surgeon volume especially for older-sicker patients, suggesting LFG volume guidelines should emphasize hospital volume over surgeon volume, and may be less relevant for young-healthy patients.

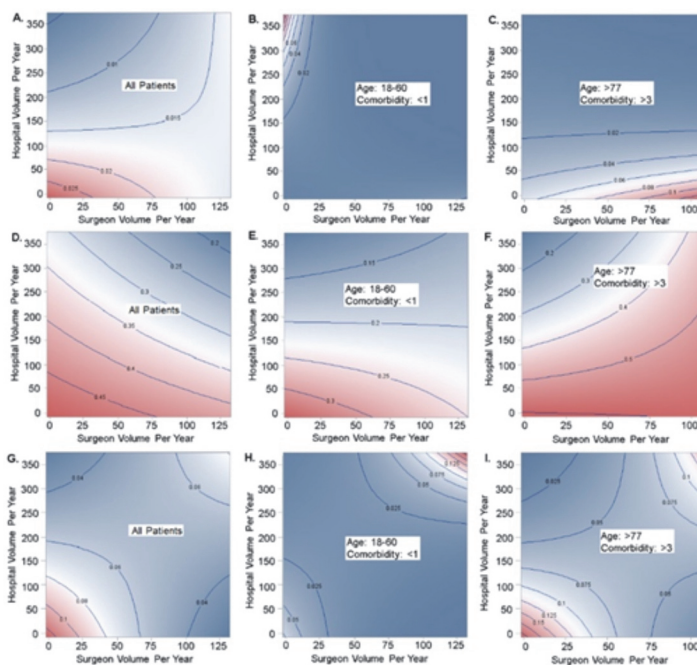


Figure 1. Contour plots of predicted mortality (A,B,C), complication (D, E,F) and prolonged length of stay (G, H, I) for all patients (left), young-healthy (middle), and older-sicker cohorts

Temporal Presence of two novel hyperactive human glucocorticoid receptors in a patient with severe burns

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Burn Division, Department of Surgery, UC Davis, and Shriners Hospitals for Children

Introduction: Patient response to glucocorticoid (GC) treatment can vary widely and complicate care management. Changes in the human glucocorticoid receptor (hGR) expression, which binds to GCs to produce factors involved in stress response, may be an underlying factor influencing an individual patient's reaction to stress. We examined the variability of naturally occurring variant hGR isoforms, expressed either transiently or constitutively based on the type and severity of the stressor, in burn patients.

Methods: Under IRB approval, patients with >20% total body surface area (TBSA) burns were recruited. Blood samples were collected at admission and then biweekly throughout the burn unit stay, with additional samples taken during septic episodes. RNA was extracted and RT-PCR was used to identify novel hGR variants at the various timepoints. Expression constructs of these variants were evaluated for their transactivation potential after hydrocortisone (0.01 - 10 μ M) stimulation in a luciferase assay.

Results: A male subject with >90%TBSA full thickness burns remained in the burn unit for 262 days. An additional sample was obtained 123 days post-discharge. A wide variety of hGR isoforms were identified and selected variants, which were detected at multiple timepoints, were then analyzed. Two novel isoforms that displayed unusual transactivation potentials were identified. One was a splice variant with 103 bp deleted at position 1547 of the reference hGR (hGR α). It displayed higher constitutive activity than reference hGR α and was not further induced by the addition of hydrocortisone. When the variant was co-transfected with hGR α , the response seemed to be a simple combination of the two hGR isoforms' activity. Another variant, with a single nucleotide polymorphism (SNP) at position 1376 from G to T, also displayed hyperactivity, but only in a concentration-dependent manner after stimulation with hydrocortisone. The un-induced activity of the SNP variant was noticeably less compared to reference hGR α , but was significantly greater at some tested doses of hydrocortisone. In combination with hGR α , however, this hyperactive response to hydrocortisone disappeared.

Conclusions: We have found a number of naturally occurring hGR variants in volunteer and patient populations. Identifying specific variants that transiently occur throughout a disease treatment course, and especially determining their functional activity, may provide valuable insight into understanding differential patient stress response and developing individualized treatment regimens.

Alicia Gingrich

Differential Gene Expression Analysis of Canine and Human Natural Killer Cells as Immunotherapy Target.

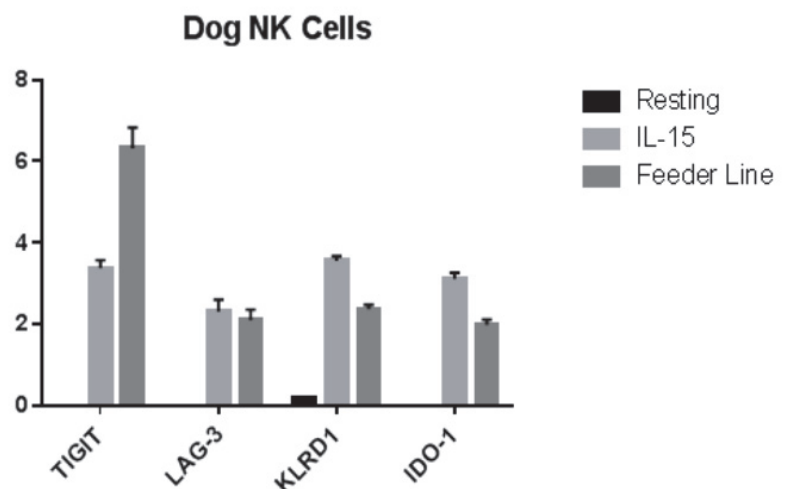
Gingrich A, Yanagisawa M, Sturgill I, Stoffel K, Murphy W, Canter RJ.

Introduction: Since the discovery of natural killer (NK) cells in the 1970s as innate lymphoid cells with the ability to spontaneously kill virally-infected and transformed cells without prior antigen sensitization, the goal of translating NK immunotherapy to the treatment of cancer patients has held tremendous appeal. However, success in this translation has been slow. Recently, dogs have emerged as an important link between murine models and human clinical studies in cancer immunotherapy research.

Methods: In this study, we compared the expression of key NK activation and inhibitory genes in dog and human NK cells following standard ex vivo activation and expansion techniques. We used qPCR to assess for negative regulators of NK activation as well as the overlap between dog and human NK cells after 3 days of IL-15 versus 14 days of co-culture with feeder cells.

Results: We observed statistically significant inductions of inhibitory proteins TIGIT (3.7-fold versus 6.2-fold), LAG-3 (2.1-fold versus 2.0-fold), KLRD1 (3.8-fold versus 2.1-fold, and IDO-1 (2.6-fold versus 1.9-fold) in dog NK cells ($P < 0.05$ for all). In human NK under similar conditions, there was comparable upregulation of negative checkpoint proteins, including TIGIT, LAG-3, and TIM-3 ($P < 0.05$). At day 14, Ki-67 expression remained elevated in both dog (2.3-fold increased) and human (1.8-fold increased) NK cells ($P < 0.05$) despite induction of negative checkpoint molecules. More formal transcriptional profiling and bioinformatic differential expression analysis of activated dog and human NK cells using next generation Illumina RNA-seq and single cell RNA-seq is underway.

Conclusion: Induction of immunoregulatory molecules appears to be a barrier to successful translation of NK immunotherapy. Targeting of key negative checkpoints may advance the clinical application of NK immunotherapy.



In Utero Treatment with Placental Mesenchymal Stromal Cells Produces Ambulation in the Ovine Model of Myelomeningocele – Selection of the Optimal Cell Donor

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Division of Pediatric Surgery

Introduction: In preparation for clinical trials, we sought to determine how *in vitro* identity assays inform which placental mesenchymal stromal cell (PMSC) donors produce high rates of ambulation following *in utero* treatment in the ovine model of myelomeningocele.

Methods: PMSC banks were created following explant culture of three discarded early gestation placental donors. At passage 5, *in vitro* neuroprotection for each donor was assessed by indirect co-culture of PMSCs in a neuronal injury model. Donor ability to rescue neurons was compared to treatment without PMSCs. Secretion levels of brain-derived neurotrophic factor (BDNF) and hepatocyte growth factor (HGF) were measured by ELISA. For *in vivo* testing, myelomeningocele defects were surgically created in 28 fetuses and repaired with PMSCs at 3×10^5 cells/cm² of extracellular matrix (ECM) from Donor 1 (n=7), Donor 2 (n=6) and Donor 3 (n=5) and compared to ECM alone (no PMSCs, n=10). Ambulation was defined as scores of ≥ 13 on the Sheep Locomotor Rating Scale (SLR).

Results: Neuroprotective capability was 1.7 (Donor 1), 1.6 (Donor 2) and 1.3 (Donor 3). Donor 1 and 2 had significantly higher neuroprotection than no PMSCs ($p=0.01$, ANOVA, Tukey's). All donors secreted both BDNF and HGF with mean levels 304.8 ± 194.2 pg/ml and 57.9 ± 14.2 ng/ml (Donor 1), 290 ± 69.2 and 86.8 ± 29.2 (Donor 2) and 294.3 ± 186.8 and 75.9 ± 11.2 (Donor 3) respectively, without differences among donors ($p=0.99$, $p=0.27$, ANOVA). *In vivo*, median SLR score was 14 (Donor 1), 15 (Donor 2) and 14 (Donor 3) compared to 7.5 without PMSCs ($p=0.11$ ANOVA). The rate of ambulation in lambs was highest in the two donors with significantly improved neuroprotection (71% in Donor 1 and 83% in Donor 2) and lowest in Donor 3 (60%) compared to without PMSCs (20%).

Conclusion: The *in vitro* neuroprotection assay may allow selection of optimal PMSC donors that produce high rates of ambulation in the ovine model of myelomeningocele.

Shawn Tejiram

The Effect of Methamphetamine Abuse on Discharge Opioid Requirements in Burn Injured Patients

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Introduction: Methamphetamine abuse in burn injured patients is linked to larger burns, inhalation injuries, and higher complication rates, but literature examining its role in pain management is limited. The aim of this work was to examine the impact of methamphetamine abuse on discharge pain scores and opioid requirements.

Methods: A retrospective review was performed on burn injured patients admitted to a burn center in 2016. Data on demographics, burn size (TBSA), social history, admission toxicity screening, discharge pain scores, length of stay (LOS), and opioid equivalents (OE) in their last 24 hours of admission were collected. OEs were determined by converting all narcotics to oral morphine equivalents.

Results: Of 281 patients meeting inclusion criteria, 201 (71%) received an admission toxicology screen and 81 (40.3%) patients were positive for MA use. There were no differences in LOS (13.3 v 18.9 days, $p=0.059$), OEs (77.8 v 90.5, $p=0.22$), or OE/TBSA (16.6 v 18.2, $p=0.65$) between screened groups. Meth positive patients had higher discharge pain scores (4.37 v 3.48, $p=0.03$). Patients with a social history of illicit drug had no difference in LOS (16.1 v 15.8, $p=0.98$) or OE/TBSA (18.5 v 19.6, $p=0.79$) compared to those without. However, they did use more OEs in the last 24 hours of hospitalization (92.2 vs. 72.9, $p=0.057$) and had higher pain scores at discharge (4.10 vs. 3.21, $p=0.01$).

Conclusion: Patients positive for methamphetamine use and those with a history of drug use had higher pain scores at discharge.

Hospital-level Intensive Care Unit Admission for Patients with Isolated Blunt Abdominal Solid

Organ Injury

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Introduction: The optimal level of care for hemodynamically stable patients with isolated blunt hepatic, renal, or splenic injuries (solid organ injuries, or SOIs) is unknown. We sought to characterize the inter-hospital variability in intensive care unit (ICU) admission of hemodynamically stable patients with isolated SOIs and to determine whether greater hospital-level use of ICU admission would be associated with improved outcomes.

Methods: We used the 2015 National Trauma Data Bank to identify adult blunt trauma patients with isolated, intermediate-grade (Abbreviated Injury Scale score 2-4) SOIs. We excluded patients with hypotension or another indication for ICU admission. We categorized hospitals into quartiles based on the proportion of patients admitted to an ICU. The primary outcome was a composite of organ failure, infection, or death.

Results: Among 5,629 patients at 279 facilities, 1,887 (34%), 1,425 (25%), and 2,909 (52%) had hepatic, renal, and splenic injuries, respectively. ICU use ranged from 0-94% (median 42%, IQR 25-60%). The composite outcome occurred in 76 patients (1.4%), with death in 30 (0.5%), organ failure in 35 (0.6%), and infection in 39 (0.7%). Relative to hospitals with the lowest ICU use, greater hospital-level ICU use was not associated with decreased likelihood of the composite outcome or its components. Unplanned ICU transfer was not less likely with greater hospital-level ICU use.

Conclusions: Admission location of stable patients with isolated intermediate-grade abdominal SOIs is variable across hospitals, but hospitalization at a facility with greater ICU use is not associated with substantially improved outcomes. It may be safe to manage these patients in non-ICU settings.

Multimodal Analgesia Decreases Opioid Use in Critically Ill Trauma Patients

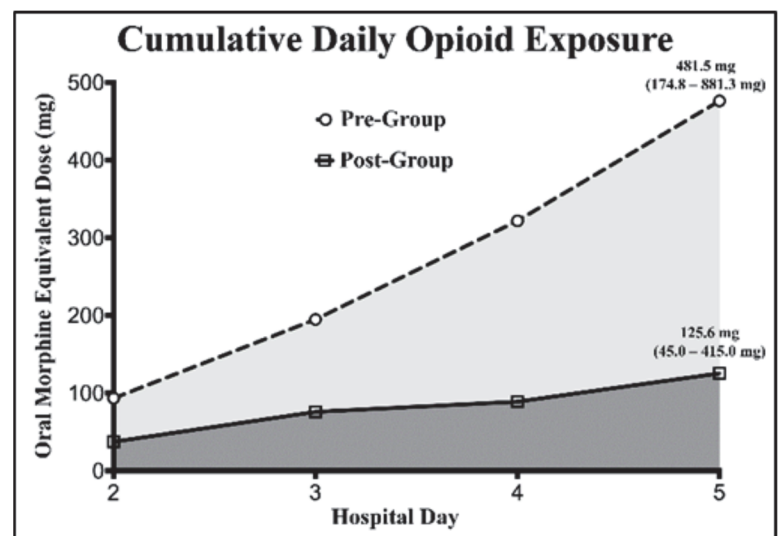
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Introduction: Opioids are the mainstay of pain management in critically ill trauma patients, but their risks mandate a different approach. Multimodal analgesia employs a combination of agents with different mechanisms to treat pain. We hypothesized that implementation of a multimodal analgesia order set would reduce opioid use in critically ill trauma patients.

Methods: This was a pre-post cohort study of adult trauma ICU patients before and after the implementation of a multimodal pain management order set. Patients were excluded if their hospital stay was less than five days, head abbreviated injury scale score was greater than 1, or pre-injury medications included methadone or buprenorphine. The total oral morphine equivalent (OME) dose was calculated for each 24-hour period on days 2 through 5 of admission and the last 24 hours prior to discharge using standardized ratios. The primary endpoint was cumulative OME doses over the 2nd through 5th days of admission.

Results: There were 65 patients in the pre-group and 62 in the post-group. Median cumulative OME dose was significantly lower in the post-group (125.6 mg, Interquartile Range (IQR) 45.0-415.0 mg) compared to the pre-group (481.5 mg, IQR 174.8-881.3 mg), $P < 0.001$. Patients who received 3 or more multimodal agents had a lower cumulative OME dose (116.3 mg, IQR 52.5-496.5 mg) compared to those who were on 1 to 2 multimodal agents (363 mg, IQR 115.5-743 mg) or zero multimodal agents (479 mg, IQR 185-736.5 mg), $P = 0.024$. There were no differences between pre-group and post-group mean pain scores on hospital day five (4.48 ± 0.34 vs 3.50 ± 0.38 , $P = 0.058$) or at hospital discharge (3.43 ± 0.34 vs 3.56 ± 0.32 , $P = 0.789$).

Conclusions: The implementation of a multimodal pain management strategy significantly reduced opioid use in critically ill trauma patients without compromising patient comfort.



Matthew Zeiderman

Time to soft-tissue coverage of open tibia fractures is not associated with chronic osteomyelitis or return to ambulation: A UC Davis review.

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Introduction: The appropriate timing of soft-tissue coverage in open lower extremity fractures has been debated since the advent of free tissue transfer. We reviewed UC Davis data to determine whether time to soft-tissue coverage of open tibial fractures is associated with better clinical outcome.

Methods: Charts of all patients with open tibia fractures requiring soft-tissue coverage from 2007-2017 were reviewed. Demographics, comorbidities, timing and method of soft-tissue coverage, complications, and functional status were recorded. Descriptive statistics, univariate, and multivariate analyses were performed with a focus on chronic osteomyelitis and return to ambulation with and without assistive devices.

Results: 89 patients were included. 54 Gustilo IIIB and 18 Gustilo IIIC fractures required soft-tissue coverage. 47% received a skin graft only, 43% a pedicled flap, and 10% free tissue transfer. 26% developed chronic osteomyelitis. 32 IIIB/IIIC fracture patients returned to ambulation. Median time to soft-tissue coverage was 8 days. 2 acute and 3 delayed amputations were performed. Multivariate analysis identified only coronary artery disease as a risk factor for chronic osteomyelitis (OR 4.21, CI 1.02-17.85, $p=0.047$). Type of soft-tissue coverage, time to soft-tissue coverage and length of negative pressure wound therapy were not associated with return to ambulation or chronic osteomyelitis.

Conclusions: Consistent with previous reports, outcomes in lower extremity trauma are tied more to patient co-morbidities and injury severity than to the length of time to definitive soft-tissue coverage. Our data suggests that coronary artery disease increases the risk of developing chronic osteomyelitis.

James Clark

Time Since Smoking Cessation and Lung Function Predict Pulmonary Complications after Lobectomy

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Introduction: Smoking status and lung function are associated with pulmonary complications after lung resection. However, it is unknown whether dose (pack-years) and time since smoking cessation (TSC) beyond one month also have an impact. We sought to determine which lung specific predictors are associated with pulmonary complications after lobectomy.

Method: We performed a single institution cohort study of all current and former smokers (quit ³¹ month prior to surgery) undergoing lobectomy from 2008-14. Logistic regression analysis including age, sex, TSC, pack-years, FEV₁ % predicted, DLCO % predicted and interstitial fibrosis was done to determine independent predictors of a pulmonary complication. The primary outcome was a composite of 11 pulmonary complications.

Results: Our cohort included 448 patients: 342 (76.3%) former and 106 (23.7%) current smokers (Table 1). Former smokers were older, had fewer pack-years, higher DLCO, and lower incidence of chronic obstructive pulmonary disease, but no difference in pulmonary complications (31.1% vs 23.1%; $p=0.09$). FEV₁ was the only independent predictor of a pulmonary complication. For each 5% increase in FEV₁, the odds of a pulmonary complication decreased by 11.1% ($p=0.003$). To assess the effect of recent smoking cessation, we performed a subset analysis of current smokers and former smokers with TSC ≤ 12 months. For each additional month of TSC, the odds of a pulmonary complication decreased by 19.5% ($p=0.02$), and for each 5% increase in FEV₁, the odds of a pulmonary complication decreased by 15.1% ($p=0.015$).

Conclusion: FEV₁ and TSC for former smokers who recently quit are strong independent predictors of a pulmonary complication after lobectomy. Although TSC beyond one month may be considered non-modifiable as most lobectomies are for lung cancer and are done expediently, it should be included in the preoperative risk/benefit discussion.

	Former Smokers n=342 (76.3%)	Current Smokers n=106 (23.7%)	p-value
Age (years)	69 (63-75)	63 (56-70)	<0.001
Male sex	157 (46.0%)	53 (50.0%)	0.48
Pack-years	31 (13-49)	48 (33-63)	<0.001
FEV ₁ (% predicted)	82 (70-94)	79 (67-91)	0.91
DLCO (% predicted)	71 (59-83)	63 (50-76)	<0.001
Chronic obstructive pulmonary disease	79 (23.1%)	44 (41.5%)	<0.001
Interstitial fibrosis	4 (1.2%)	3 (2.8%)	0.36
Any pulmonary complication	79 (23.1%)	33 (31.1%)	0.09
30-day mortality	6 (1.8%)	3 (2.9%)	0.45

Table 1. Demographics, pulmonary status, and outcomes by patient smoking status.

James Clark

A Prospective Trial of Intraoperative Liposomal Bupivacaine (Exparel) versus Bupivacaine/Lidocaine for Thoracoscopic Surgery

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Section of General Thoracic Surgery, Department of Surgery

Introduction: Given the worsening opioid crisis, enhanced recovery protocols often utilizing intraoperative liposomal bupivacaine (LipoB) have been implemented in a variety of surgical specialties to improve patient recovery and reduce reliance on narcotics. Adequate pain control after thoracic surgery has traditionally been elusive, but usage of LipoB in various thoracic surgery practices have shown decreased postoperative narcotic usage and hospital length of stay. No study to date has examined the effect of LipoB on patient reported outcomes (PROMs), and there is a paucity of data on the effect of long-term narcotic usage up to 2 months postoperatively.

Method: Through a prospective cohort trial we enrolled 20 patients to receive 1:1 0.25% bupivacaine:1.0% lidocaine (control) followed by 20 patients to receive LipoB via intraoperative posterior intercostal nerve block. Eligible patients were those undergoing planned video-assisted or robot-assisted thoracoscopic lung resection, lung biopsy, or pleural biopsy. Patient post-operative narcotic usage in morphine equivalent doses (MEDs) was calculated, and PROMs were recorded via a validated survey in the preoperative area, on day of discharge, at postoperative month 1, and at postoperative month 2.

Results: We have enrolled over 75% of our patients at the time of abstract preparation, and will have 1 month follow up PROM outcomes for all patients at the time of abstract presentation.

Conclusion: We hypothesize that liposomal bupivacaine will improve both PROMs and reduce postoperative reliance on narcotics in lung surgery patients. Further data on PROMs and narcotic usage at postoperative month 2 will be forthcoming.

Ping Song

An alternative option for reconstruction of a complex wound: Combining bilaminar dermal matrix and vacuum assisted closure therapy

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Introduction: Soft-tissue reconstruction of complex wounds have become algorithmic; often with free tissue transfer at the apex. Yet the advent of bilaminar dermal matrices and vacuum assisted closure therapy now allow reconstructive surgeons another option to obtain soft-tissue coverage at a cost much lower than traditional free tissue transfer.

Method: We performed a case series review (N=3) of complex soft tissue defects which were treated by a two-stage approach with the use of Integra bilaminar wound matrix combined with vacuum assisted closure therapy.

Results: Two pediatric patients and one adult patient underwent the above treatment plan. All three patients achieved successful soft tissue coverage with eventual skin grafting within three weeks of the placement of bilaminar dermal matrix and vacuum assisted closure therapy. No infections were encountered throughout the treatment course. The adult patient did require one additional procedure before final reconstruction was complete.

Conclusion: This case series demonstrates the efficacy of bilaminar dermal matrix in achieving reliable soft tissue coverage in appropriately selected patients. Each patient had indications for free flap coverage, but were spared the concomitant morbidity of a microsurgical procedure. This is especially important in the pediatric population, for both donor and recipient site concerns. Ultimately, with appropriate patient selection, two-stage dermal matrix and vacuum assisted closure therapy with skin grafting can be a viable alternative approach for soft tissue coverage of complex wounds from head to toe.

Timothy Guenther

De Garengeot's Hernia: Case Report with Analysis of 177 Published Cases and a Proposed Classification System

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Introduction: A De Garengeot's hernia is a femoral hernia that contains the appendix. We present one case of a De Garengeot's hernia and provide a comprehensive literature review of other published cases since 1925. A classification system based on the gross appearance of the appendix and related structures is also proposed.

Methods: A literature review was undertaken using PubMed, Google-Scholar, and our institutional library database for case reports of a femoral hernia containing the appendix. In addition, basic demographic information of the patient (age/gender), presenting symptoms and/or physical exam findings, and a gross description of the appearance of the appendix and related structures within the femoral hernia was required for inclusion. Additional information from each case reports that met eligibility was gathered and all data were tabulated in Microsoft Excel. A classification system was created based on the gross appearance of the appendix and any other involved structures within the femoral hernia, and each case report was categorized using this classification system.

Results: A total of 177 cases were identified in 155 articles. Cases were most commonly performed in Europe, but case reports were published globally. Most cases occurred in females (79.7%) and the most common presenting symptom was pain and a bulge located in the groin (81.4% and 85.9% respectively). In 94.3% of cases, a groin bulge was observed on physical exam and erythema over the hernia was present 33.3% of the time. A pre-operative diagnosis was established in 23.7% of cases and the most common approach for repair was through a groin incision. Based on our classification system, the most common stage was stage 2A, corresponding to an isolated congested/inflamed appendix, which was found in 42.4% of cases.

Conclusions: De Garengeot's hernias are a rare and clinically heterogeneous type of hernia as highlighted by our proposed classification system. Acute care surgeons should be aware of this type of hernia for the interesting set of diagnostic/management challenges this condition presents.

Timothy Guenther

Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery: Analysis of 192 Published Cases with a Proposed Classification System

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Division of Cardiothoracic Surgery, UCD

Introduction: Anomalous origin of the right coronary artery from the pulmonary artery (ARCAPA) is a rare congenital cardiac defect with an estimated prevalence of 0.002%. It has been diagnosed in both children and adults with symptoms ranging from an asymptomatic murmur to sudden cardiac death. Numerous case reports of ARCAPA have been published, though little is known about this rare condition. The aim of our study was to characterize all available published cases of ARCAPA to better understand and classify this rare congenital cardiac defect.

Methods: A thorough literature search was performed using Pubmed, Google Scholar, and the UCD library database (powered by Primo). Keywords searched were: “anomalous origin of the right coronary artery from the pulmonary artery” and “coronary artery anomalies.” To be included for analysis, we required the ARCAPA case report to describe relevant details of presenting symptoms, pre-operative work-up, other associated cardiac anomalies, or management.

Results: A total of 197 cases of ARCAPA were identified in 167 case reports. There was a slight male predominance (55% n=102) and the average age of presentation was 24. Thirty seven percent (n=74) of patients were asymptomatic at the time of diagnosis and most commonly identified during work-up of a murmur. A murmur was present in 47% (n=92) of all cases. In symptomatic patients, angina and dyspnea were the most common presenting symptoms (21% n=42 and 17% n=33, respectively) An average Qp:Qs shunt of 1.76:1 was observed (n=28). A concomitant cardiac lesion was observed in 26% of cases (n=52), aorto-pulmonary window being the most common (n=23). Most cases were repaired surgically (83% n=140) and re-implantation of the right coronary artery onto the aorta was the most common method of repair (60% n=118). A classification system based on the patient’s age and presence of symptoms was created to further characterize this cardiac defect.

Conclusions: ARCAPA represents a rare and clinically heterogeneous congenital cardiac lesion that is diagnosed in patients of all ages. Given its rarity, evaluation of published case reports serves as the best avenue to understand the pathophysiology and treatment strategies of this uncommon condition.

Functionalized ECM scaffolds loaded with endothelial progenitor cells potentiates

neovascularization and promotes diabetic ischemic wound healing

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Diabetic ischemic wound treatment remains a critical clinical challenge. We previously identified a cyclic peptide LXW7 that specifically binds to integrin $\alpha\beta 3$ on endothelial progenitor cells (EPCs) and endothelial cells (ECs), activates VEGF receptors, and promotes EC proliferation and maturation. In this study, we propose to modify LXW7 with a collagen-binding proteoglycan mimic DS-SILY to make a pro-angiogenic molecule LXW7-DS-SILY to functionalize ECM scaffolds, promote neovascularization and accelerate ischemic wound healing. *In vitro*, the effects of LXW7-DS-SILY on EPC biological functions were assessed by cell attachment, MTS assay and Western blotting. *In vivo*, we established a Zucker Diabetic Fatty (ZDF) rat ischemic skin flap model and evaluated the function of LXW7-DS-SILY functionalized SIS scaffolds seeded with EPCs in promoting neovascularization and wound healing. The percentage of reepithelialization, granulation tissue area, cellular organization, and amount of visible scar tissue was determined by the histology of excisional wounds. The new capillary formation was determined by immunohistochemistry. LXW7-DS-SILY modified SIS significantly promoted EPC attachment, spreading and survival in ischemic environment. The function of LXW7-DS-SILY functionalized SIS seeded with EPCs is being evaluated and data will be collected in the coming weeks. LXW7-DS-SILY combined with SIS scaffold and EPCs will lead to a novel treatment to accelerate healing of ischemic diabetic foot ulcers, thereby reducing limb amputation and mortality rates of diabetic patients.

Lalithasri Ramasubramanian

Development of Exosome Mimics for Vascularization in Ischemic Wound Sites

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Introduction: Exosomes derived from endothelial progenitor cells (EPC) have been shown to facilitate vascularization but their therapeutic translation has been greatly hindered by the inherent disadvantages in exosome isolation, purification, and standardization. Here, we sought to overcome these shortcomings by engineering a biomimetic synthetic exosome that can recapitulate the pro-angiogenic, targeting, and cell recruiting properties of native EPC-derived exosomes.

Methods: Exosome mimics (EM) will be synthesized by coating a miRNA-126-loaded poly(lactic-co-glycolic acid) (PLGA) core with a endothelial cell-targeting ligand LXW7-functionalized EPC-membrane shell in order to mimic the miRNA cargo, targeting potential, and physical characteristics of native EPC exosomes. The miRNA-loaded PLGA cores will be made using a nanoprecipitation method and coated with isolated EPC plasma membrane via mechanical extrusion. The LXW7 ligand will be conjugated to the plasma membrane shell using Click chemistry. The EMs will be characterized for physical properties (e.g size, release kinetics, stability) as well as for their angiogenic potential using *in vitro* assays (e.g tube formation, migration, scratch) and an *in vivo* murine hindlimb ischemia model.

Progress: PLGA nanoparticle cores were successfully synthesized and demonstrated high stability in water, remaining a homogenous and consistent size of ~90 nm over 15 days at 4°C. Molecules were also able to be loaded within the PLGA core using Dil as a proof-of-concept cargo. SDS-PAGE and western blotting confirmed plasma isolation from cells and fluorescence microscopy showed successful coating onto the PLGA cores. The PM: PLGA ratio was seen to affect the size and stability of the EMs, with higher plasma membrane: PLGA ratios resulting in smaller sizes of ~250 nm and increased stability.

Conclusion: The proposed system shows potential as an exosome mimic. Future work will focus completing and optimizing the EM structure and subsequently assessing angiogenic properties *in vitro* and *in vivo*.

Laura Galganski

Congenital Diaphragmatic Hernia Mortality in California 1995-2012

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Division of Pediatric Surgery

Introduction: Mortality rates associated with congenital diaphragmatic hernia (CDH) have improved in single institution studies, however the overall mortality at a population-level remains high. The impact of health care services on mortality remains unclear.

Methods: Patients with CDH were identified by the ICD-9 diagnosis code in the Linked Birth and Inpatient Databases from the California Office of Statewide Health Planning and Development from 1995-2012. Counties with regional (level IV) neonatal intensive care units (NICU) were identified by state records. Logistic regression identified risk factors for mortality.

Results: The incidence of CDH in California between 1995 and 2012 was 2,295 with an average of 127 births per year. The overall mortality rate was 28.1% with a median age at death of 1.5 days (IQR 0-20). Thirty-four percent (220) of patients died on the first day of life. Six percent (139) were treated with ECMO. Nearly half (44%) of patients were transferred after birth. Following adjustment for birthweight, APGAR score at 5 minutes of life and presence of congenital heart disease, transfer following birth was associated with decreased mortality (OR 0.33, 95% CI 0.21-0.52, $p < 0.001$). Sixty-five percent of patients were from a county with a regional NICU. Though patients from a county with a regional NICU had a decreased rate of mortality on univariate analysis, it was no longer significant on multivariate analysis (OR 1.08, 95% CI 0.70-1.66, $p = 0.72$). No maternal factors including age, race, level of education, parity, method of delivery, use of cigarettes were associated with mortality ($p > 0.05$).

Conclusions: Congenital diaphragmatic hernia continues to have a high, early mortality rate in California. Though low birthweight and APGAR scores are associated with increased mortality, transfer following birth is associated with decreased mortality.

Maggie Spruce

IF Then: What to Do with Incidental Findings

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Introduction: Incidental radiographic findings (IFs) are common among trauma patients, creating difficulty in appropriate documentation and patient notification.

Methods: We performed a retrospective review of adult trauma patients admitted to a Level 1 trauma center from January-May 2017, excluding patients without complete radiographic imaging. IFs from abdominal, chest, and neck imaging were categorized based on previously published guidelines focused on clinically significant IFs. Outcome measures included documentation and patient notification of IFs. Documentation included discharge summaries and instructions, which inform and guide other providers and patients, respectively. We used logistic regression to identify variables associated with appropriate documentation.

Results: Of 1673 patients, 675 met criteria. 415 (61.5%) of these had any IF. Radiologists included specific follow up recommendations for 33.8% of patients with any IF and for 54.2% of patients with any Category 1 IF (solid organ mass). Among patients with IFs, 77.0% of discharge summaries and 40.5% of discharge instructions reported IFs. Documentation of inpatient notification occurred 54.9% of the time. Odds of documenting IFs in the discharge summary were significantly greater when radiologists included follow up recommendations (OR 3.1, 95% CI 1.7-5.9) and were significantly lower when patients were transferred to another hospital service prior to discharge (OR 0.2, 95% CI 0.1-0.4).

Conclusion: Follow up recommendations in radiology reports improved physician documentation of IFs upon discharge. Therefore, expanding IF-specific guidelines, collaborating with radiologists to facilitate their inclusion in reports, and ensuring that IFs are part of patient hand-offs would provide systematic methods of improving this important documentation.

Michelle Wan

Assessment of the Risk Analysis Index For Evaluating Frailty of Surgical Patients

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Section of General Thoracic Surgery, Department of Surgery

Introduction: The ideal method of screening for frailty in patients undergoing surgery is unknown. Our objective was to compare the administrative Risk Analysis Index (RAI-A) and five-variable modified frailty index (mFI-5) for predicting postoperative morbidity and mortality in these patients.

Method: We performed a retrospective analysis of the National Surgical Quality Improvement Program (NSQIP) of patients undergoing surgery from 2006-2017. RAI-A (male sex, age, cancer diagnosis, weight loss, renal failure, heart failure, appetite, dyspnea, non-independent living, cognitive deterioration, and functional status) and mFI-5 (diabetes, dyspnea, heart failure, hypertension, and functional status) were calculated. Multivariable logistic regression and receiver operating characteristic Area Under the Curve (AUC) were used to compare each score's predictive ability.

Results: The cohort included 6,638,405 patients. The RAI-A and mFI-5 were strongly predictive of mortality in the total cohort (Table 1) but were less robust in predicting mortality for those undergoing coronary artery bypass grafting, lung resection, pancreaticoduodenectomy, and esophagectomy. Both indices performed similarly for predicting complications.

Conclusion: The RAI-A and mFI-5 frailty indices are effective predictors of mortality for surgical patients. They must be improved to better predict mortality in patients undergoing pancreaticoduodenectomy and cardiothoracic surgery.

Surgery Type		Area Under the Curve	95% CI	p-value
All surgeries	RAI-A	0.83	(0.82-0.83)	<0.001
	mFI-5	0.74	(0.73-0.74)	<0.001
Total hip arthroplasty	RAI-A	0.77	(0.75-0.80)	<0.001
	mFI-5	0.70	(0.67-0.72)	<0.001
Colectomy/proctectomy	RAI-A	0.74	(0.74-0.75)	<0.001
	mFI-5	0.70	(0.70-0.71)	<0.001
Coronary artery bypass graft	RAI-A	0.63	(0.61-0.66)	<0.001
	mFI-5	0.63	(0.61-0.66)	<0.001
Lung resection	RAI-A	0.62	(0.60-0.64)	<0.001
	mFI-5	0.64	(0.62-0.66)	<0.001
Pancreaticoduodenectomy	RAI-A	0.61	(0.60-0.63)	<0.001
	mFI-5	0.61	(0.59-0.62)	<0.001
Esophagectomy	RAI-A	0.54	(0.51-0.57)	0.02
	mFI-5	0.59	(0.56-0.62)	<0.001

Table 1. ROC AUC c-statistics for mortality by surgery type.

Sean Judge

PD-1 Checkpoint Marker Expression on Natural Killers Cells in Human and Murine Models

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Introduction: PD-1 expression is a hallmark of T cell activation and exhaustion, and targeting of the PD-1 pathway has revolutionized cancer immunotherapy. Natural killer (NK) cells are another key cytotoxic immune cell, and expression of exhaustion markers in these effector cells is controversial. Our objective was to determine the expression of PD-1 on resting and activated NK cells in clinically relevant human and murine models.

Methods: Human NK cells were isolated and expanded ex vivo using a feeder line and cytokine culture. Murine NK cells were assessed in vivo in tumor-bearing mice and post-MCMV infection in both immunocompetent and immunodeficient mice. NK cell phenotype, activation markers, and intracellular cytokine expression were analyzed by flow cytometry and qRT-PCR.

Results: Despite maximal activation and proliferation of human NK cells by cytokines and feeder line co-culture, PD-1+ frequency was consistently less than 0 - 2% by flow cytometry and negligible by PCR ($P < 0.05$). *In vivo* studies with 4T1 (mammary carcinoma)-bearing mice showed negligible PD-1 from intra-tumoral and splenic NK cells, while CT26 (colon) tumor studies showed $< 5\%$ PD-1+ NK cells in both tumor and spleen in immunocompetent BALB/C and immunodeficient SCID mice. NK cells isolated from livers in C57BL/6 mice after acute MCMV infection showed high activation by CD69 ($> 90\%$ positive) but $< 2\%$ PD-1 expressing NK cells, while T cells exhibited high activation and a 5-fold increase in PD-1 expression. In T-cell deficient Rag2^{-/-} mice exposed to MCMV, hyper-activated NK cells isolated from the spleen and liver on post-infection day 3 showed minimal PD-1 expression by flow cytometry and PCR, but $> 90\%$ CD69 expression ($P < 0.05$). TIGIT expression was consistently upregulated post activation in all models ($P < 0.05$).

Conclusion: Unlike T cells, our results show that highly activated human and murine NK cells do not significantly upregulate PD-1. Our data suggest that PD-1 is not a consistent marker for NK exhaustion, with significant implications for NK immunoregulation and strategies to therapeutically exploit these cytotoxic cells.

Jonathan Lin

Reassessing the Role of Fasciotomy After Revascularization of Non-Traumatic Acute Lower Limb Ischemia
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Division of Vascular Surgery

Objectives: The use of fasciotomies to prevent complications of compartment syndrome after the treatment of acute limb ischemia (ALI) is widespread, however minimal objective data supports this practice. We present a single institution experience in which fasciotomies are not regularly performed after revascularization.

Methods: Using ICD-9 and 10 codes, we identified patients presenting to UCDMC between January 2003 and July 2018 with ALI, excluding those with traumatic injuries. Primary outcomes were amputation and new motor deficit. We summarized our findings in those patients with and without fasciotomies excluding those with grade 3 ischemia.

Results: We identified 275 limbs treated for acute limb ischemia; 22 had grade 3 ischemia and 253 had Rutherford grade 1 (52), 2A (92), or 2B (109) ischemia. Of these, 230 (91%) were successfully revascularized while 23 had non-reconstructable disease (Table 1). The overall amputation rate was 8% (2.6% of revascularized limbs and 65% of non-reconstructable limbs). A total of 11 fasciotomies were performed in the successfully revascularized limbs. Of the 230 limbs with reconstructable disease, 135 limbs had grade 1/2A ischemia; and 95 limbs had 2B ischemia. 134/135 of the Rutherford 1/2A ischemic limbs did not undergo fasciotomy after revascularization. One hundred-two limbs, (76%) in this group presented with ischemic symptoms >6 hours. Retained motor function after revascularization was seen in 95% of these limbs. New onset foot drop occurred in 2/102 limbs (2%) with >6 hours of ischemic symptoms and none with <6 hours. In the 95 limbs with grade 2B ischemia (Figure 1), 65 had >6 hours of symptoms. Of these, 58 did not get a fasciotomy and 69% of these limbs had improved motor function, 14% had persistent motor deficit, and 7% were amputated. Of the 7 receiving fasciotomy, 43% experienced improved motor function while 14% had persistent foot drop, and no amputations. In the 30 limbs with <6 hours of ischemic symptoms, 27 did not have a fasciotomy and 74% of these had improved motor function, 11% had persistent foot drop, and 4% were amputated. Of the 3 receiving fasciotomy, 67% had improved motor function and there were no persistent motor deficits or amputations.

Conclusions: Our experience demonstrates an acceptable amputation rate and low rate of new onset motor dysfunction in salvageable limbs; thereby suggesting that fasciotomies may not be always necessary in patients presenting with acute limb ischemia due to isolated arterial occlusion.

Table 1. Outcomes by Rutherford Grade

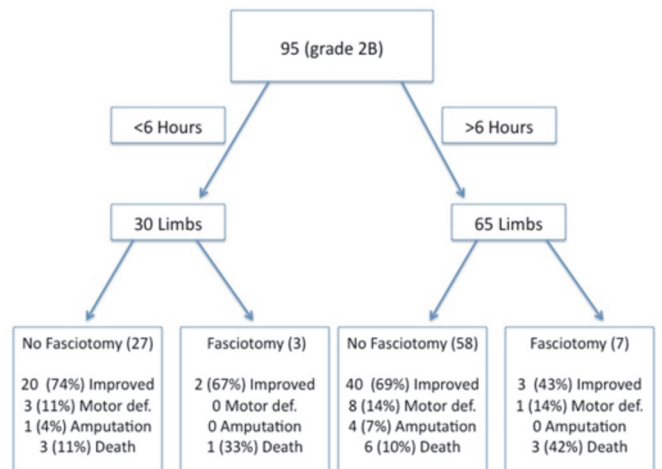
Rutherford 1		
	No Fasciotomy n=48 (%)	Fasciotomy n=0 (%)
Prolonged ischemia (>6 hours)	37 (77.1)	0
Preserved Motor Function	46 (95.8)	0
Motor Dysfunction	1 (2.1)	0
Amputation	0	0
Death	1 (2.1)	0

Rutherford 2A		
	No Fasciotomy n=86 (%)	Fasciotomy n=1 (%)
Prolonged ischemia (>6 hours)	65 (75.6)	0
Preserved Motor Function	81 (94.2)	0
Motor Dysfunction	1 (1.2)	0
Amputation	0	1
Death	4 (4.7)	1

Rutherford 2B		
	No Fasciotomy n=85 (%)	Fasciotomy n=10 (%)
Prolonged ischemia (>6 hours)	58 (68.2)	7 (70.0)
Improved Motor Function	60 (70.6)	5 (50.0)
Motor Dysfunction	11 (13.9)	1 (10.0)
Amputation	5 (5.9)	0
Death	9 (10.6)	4 (40.0)

Excludes limbs with non-reconstructable disease.

Figure 1. Rutherford 2B Outcomes



TRANSLATIONAL APPLICATIONS OF PLACENTAL DERIVED MESENCHYMAL STEM CELLS FOR THE TREATMENT OF SPINA BIFIDA: A CANINE MODEL

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Introduction: The canine is increasingly recognized as a valuable pre-clinical large animal model for many human diseases including inflammatory and neurodegenerative diseases. English bulldogs frequently suffer from the congenital disease spina bifida (SB), which clinically presents very similarly to human SB. The placenta is a unique source of mesenchymal stem cells (MSCs) as compared to adult tissues. Placental-derived MSCs (PMSCs) are being investigated as an adjunct to prenatal repair of SB, and the mechanism by which these cells are immunoregulatory and neuroprotective is largely unknown. The goal of this study was to evaluate the immunomodulatory attributes of canine adipose-derived MSCs (ASCs) and PMSCs to provide potency information to determine the optimal MSC source to treat naturally occurring canine SB.

Methods: Indoleamine 2,3 dioxygenase (IDO) activity and prostaglandin E₂ (PGE₂) concentration were measured after direct stimulation with interferon gamma and tumor necrosis factor alpha. Mixed-leukocyte reactions (MLRs) were performed to compare the ability of ASCs and PMSCs to inhibit mitogen induced peripheral blood mononuclear cell (PBMC) proliferation. A clinical trial for canine SB has been initiated and is currently enrolling patients for postnatal repair using PMSCs.

Results: Activated canine ASCs and PMSCs secrete high concentrations of IDO and PGE₂ after both direct and indirect stimulation. ASCs and PMSCs inhibit PBMC proliferation when co-cultured in contact with stimulated PBMCs. However, PMSCs inhibited PBMC proliferation significantly more than ASCs. Blocking PGE₂ and IDO in co-cultures revealed PGE₂ is critical for ASC inhibition of PBMC proliferation. ASCs inhibit lymphocyte proliferation via cell cycle arrest in G₀/G₁, while PMSCs induce lymphocyte apoptosis. Clinical trial data is currently being collected and results are pending.

Conclusion: Our results have demonstrated that ASCs and PMSCs are both potential targets for cell-based therapies of SB; however, PMSCs more potently inhibited lymphocyte proliferation by inducing apoptosis. These data suggest that the mechanism by which ASCs and PMSCs down-regulate PBMC proliferation differs. The findings from this study will provide critical pre-clinical data assessing PMSCs as a postnatal treatment for SB.



On behalf of the Department of Surgery we would like to thank our staff for organizing this event.

Sonia Kumar

Thoan Tran

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