24th Annual Johns Hopkins Anesthesiology and Critical Care Medicine

Research Day

Poster Session

Electronic Posters,
Presentations, and Awards

Wednesday, December 7, 2022
3:00 PM to 6:30 PM

Chevy Chase Conference Room
Zayed 2117

Visiting Scholar

Dr. Beverley Orser, MD, PhD, FRSC, FCAHS, FRCPC

Professor of Anesthesiology and Pain Medicine,
University of Toronto

Thursday, December 8, 2022
7:00 AM to 8:00 AM
Hurd Hall

24th Annual ACCM Research Day

December 7, 2022

On behalf of the Department of Anesthesiology and Critical Care Medicine, we are thrilled to welcome you to the 24th Annual ACCM Research Day, returning to an in-person format! ACCM Research Day is a wonderful forum to share our discoveries and innovative research over the past year. Great minds from the Johns Hopkins ACCM family (OneACCM) coming together in one place will boost creative thinking, energy, collaboration, and innovation, enabling us to accomplish our ACCM mission to be the world leader in discovery, innovation, education, and professional development. We encourage learners of all stages to share in the rich resources of the ACCM community, engage in multidisciplinary projects, initiate research collaborations, and seek out mentorship in the department. The scientific program will be organized in different sessions, providing the latest updates and showcasing the most promising research in the field of anesthesia and critical care medicine. Our research will be showcased in the following categories: Basic Cardiovascular and Pulmonary Science, Basic Neuroscience, Clinical Research, Education, Informatics and Artificial Intelligence, Pain, Quality Improvement, and a cross-categorical feature on Health Equity.

We are honored and delighted to welcome our distinguished Visiting Professor, Dr. Beverley A. Orser, MD, PhD. Dr. Orser is the Professor and Chair of the Department of Anesthesiology & Pain Medicine, Temerty Faculty of Medicine, University of Toronto. She is also a practicing anesthesiologist at Sunnybrook Health Sciences Centre in Toronto, Canada. Her clinical studies and patient advocacy work focus on safety and anesthesia workforce planning in Canada. She has co-founded several organizations that aim to improve patient safety including ISMP Canada, the Canadian Anesthesiologists' Society Quality & Patient Safety Committee, and the Perioperative Brain Health Centre. As a clinician-basic scientist, her preclinical research has offered fundamental insights into the molecular basis of anesthesia and the longer-term effects of exposure to anesthetic drugs on brain function. Her laboratory first demonstrated the unique pharmacological properties of extrasynaptic $GABA_A$ receptors and identified novel roles for these receptors in health and disease. Her discoveries have led to patents and potential new treatments.

Dr. Orser's contributions have been recognized by numerous awards including the Award for Excellence in Research from the American Society of Anesthesiologists Research (2018), one of the highest honors in anesthesia. She received the Gold Medal from the Canadian Anesthesiologists' Society (2017), the Peter Dresel Award in Pharmacology from Dalhousie University (2017), the first Canada Research Chair awarded to an anesthesiologist (2003), the first Frontiers in Anesthesia Research Award from the International Anesthesia Research Society (1995) and awards from the Australian and New Zealand College of Anaesthetists (2014) and the Association of Anaesthetists of Great Britain and Ireland (2009). She is a Fellow of the Canadian Academy of Health Sciences (2013), a Fellow of The Royal Society of Canada (2018), and a Senior Fellow of Massy College (2020). She is one of a few Canadians to be elected as an International Member of the United States National Academy of Medicine (2018). Dr. Orser has published over 200 peer-reviewed publications and has been continuously funded by the Canadian Institutes of Health Research for over 20 years, the NIH equivalent. She will present her research at Grand Rounds on December 8th at 7:00 AM at Hurd Hall.

We thank all the researchers, especially trainees, who made this day possible by sharing their work and the principal investigators for their encouragement and unconditional support. We

greatly appreciate Dr. Sujatha Kannan, Dr. Melania Bembea, and Dr. Charlie Brown for their thoughtful advice, and are particularly grateful for the assistance of Dr. Katie O'Conor and Sarah Danihel in organizing this wonderful event. Finally, we would like to thank Dr. Adam Sapirstein and the ACCM Director's Office for their enthusiastic support and their investment in the variety of departmental resources that enable us to consistently lead the world in discovery and innovation.

Best Regards,

Maria Bauer, MD

ACCM Research Day Faculty Co-Lead
Assistant Professor
Division of Adult Multidisciplinary Anesthesia
Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine

Sung Min Cho, DO, MHS

ACCM Research Day Faculty Co-Lead
Assistant Professor
Divisions of Neurosciences, Critical Care, and Cardiac Surgery
Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine

Katie J. O’Conor, MD

ACCM Research Day Faculty Facilitator
ACCM Research Program Manager
ACCM Chief Diversity Officer
Anesthesiology and Critical Care Medicine
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Schedule at a Glance

3:00 – 3:45

All monitors are available for general poster viewing.*

3:45 – 5:00 **Monitor**

5:00 – 6:15

***All posters can be viewed on monitors 11 and 12 throughout the entire event.**

Presentation Schedule

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Adegboye, Janet	Overtransfusion is common in patients receiving massive transfusion	39	Clinical Research / Critical Care 1	4:34 PM	5
Adegboye, Janet	A novel algorithm to calculate target preoperative hemoglobin for patients declining allogeneic transfusion	59	Informatics & AI	5:07 PM	10
Agarwal, Prachi	Early monitoring of neurological recovery using Poincaré analysis index of heart rate variability - a potential biomarker for asphyxial cardiac arrest related brain injury	61	Informatics & AI	5:21 PM	10
Allende Labastida, Javier	The effect of secreted frizzled related protein 3 (sFRP3) and Wnt signaling on cognitive behavior after traumatic brain injury	21	Basic Neuroscience 1	4:13 PM	1
Almodiel, Diego	Macrophage-targeted Dendrimer-Tesaglitazar therapy for atherosclerosis	06	Basic Science 1	4:20 PM	1
Almodiel, Diego	Effect of maternal inflammation on arterial stiffness in early age	14	Basic Science 2	5:35 PM	2
Aranda-Valderrama, Paola	Effectiveness of single-shot erector spinae blocks on perioperative opioid requirements and length of stay after Nuss procedure	71	Pain	4:20 PM	7
Azamfirei, Razvan	The effects of intraoperative methadone on postoperative pain control in pediatric patients: a systematic review	70	Pain	4:13 PM	7

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Azamfirei, Razvan	Development of a stata command for pediatric risk of mortality (PRISM) calculation	63	Informatics & AI	5:35 PM	10
Bakare, Ahmed Olalekan	Spinal cord stimulation attenuates paclitaxel-induced peripheral neuropathic pain and gait impairment by modulating macrophage-mediated neuroinflammation in peripheral nerves	66	Pain	3:45 PM	7
Bauer, Maria	The role of the unfolded protein response and LOXL-2 in heart failure with preserved ejection fraction	15	Basic Science 2	5:42 PM	5
Beal, James	Improving efficacy of provider communication during pediatric rapid response team calls	81	Quality Improvement	4:27 PM	9
Beiene, Zodina	An educational quality improvement project for the first pediatric anesthesiology resident rotation: a microlearning-based curriculum intervention	54	Education	5:35 PM	8
Bhatia, Pooja	Implementation of consistent medical direction consults during pediatric critical care interhospital transport	41	Clinical Research / Critical Care 2	5:07 PM	6
Booth, Lauren	Standardizing front-line provider handoff in the pediatric intensive care unit	76	Quality Improvement	3:52 PM	9
Brady, Travis	Effect of ECM and mechanical strain on vascular cell plasticity	05	Basic Science 1	4:13 PM	1
Chen, Mengkun	The association of oxygen delivery on cardiopulmonary bypass and postoperative delirium	47	Clinical Research / Critical Care 2	5:49 PM	6

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Chowdhury, Nabila	More than words: language patterns indicative of unrecognized shock in children undergoing interhospital transfer	60	Informatics & AI	5:14 PM	10
Costabile, Philomena	Increasing pediatric interhospital transport efficiency: a quality improvement intervention	77	Quality Improvement	3:59 PM	9
Crasta, Melanie	Clinical methods & results of mass spectrometric examination of exhaled aerosol samples in intubated ICU patients for early Identification of pulmonary infection via proteomics	34	Clinical Research / Critical Care 1	3:59 PM	5
Cui, Xiang	Activation of spinal adenosine 3 receptors contributes to spinal cord stimulation-induced pain inhibition in rats after nerve injury	69	Pain	4:06 PM	7
Damiba, Nelly	White matter injury in a pediatric rabbit model of CNS TB	25	Basic Neuroscience 2	5:07 PM	4
Ford, Neil	Peripheral nerve stimulation-induced adenosine A3 receptor (A3R) signaling contributes to the inhibition of lamina I NK1R-GFP neuron synapses in neuropathic mice	68	Pain	3:59 PM	7
Fujimori, Tomonari	The adenosine A2A receptor regulates miR-181b expression in aorta: therapeutic implications for large artery stiffness	01	Basic Science 1	3:45 PM	1
Gadkari, Mahin	Increased amino acid utilization by the lung vasculature in pulmonary hypertension	03	Basic Science 1	3:59 PM	1
Garg, Anjali	Variation in clinical outcomes for hospitalized children related to childhood opportunity index	37	Clinical Research / Critical Care 1	4:20 PM	5

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Ghobrial, Mina	A novel case-based echocardiography teaching platform for critical care medicine trainees	49	Education	5:00 PM	8
Grindy, Anna	PCCM fellow-led procedure curriculum for pediatric residents	50	Education	5:07 PM	8
Grindy, Anna	Teaching fellows to teach: impact of novel fellows as educators curriculum on fellow procedural teaching	51	Education	5:14 PM	8
He, Shao-Qiu	RNA-sequencing analysis of mice dorsal root ganglion neurons reveals pain-related gene regulations by HC-HA/PTX3	65	Informatics & AI	5:49 PM	10
Heller, Nikki	ACCM Cellular, Molecular & Biomarker Discovery Initiative	31	Basic Neuroscience 2	5:49 PM	4
Huang, Justin	Organ dysfunction recovery in pediatric ECMO patients	38	Clinical Research / Critical Care 1	4:27 PM	5
Humayun, Mariyam	Neuropathological findings in COVID-19 vs non-COVID-19 acute respiratory distress syndrome - a matched case control study	46	Clinical Research / Critical Care 2	5:42 PM	6
Javdan, Cameron	Clinical and telemetric electroencephalographic seizure monitoring in a neonatal piglet model of hypoxic-ischemic encephalopathy and therapeutic hypothermia	18	Basic Neuroscience 1	3:52 PM	3
Joseph, Kristen	COVID-19 pediatric respiratory care educational training program for healthcare workers in Lesotho: an observational study	53	Education	5:28 PM	8

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Kalra, Andrew	Peripheral and arterial blood gas oxygen saturation levels are discordant in various ECMO Cannulation configurations	36	Clinical Research / Critical Care 1	4:13 PM	5
Kalra, Andrew	Discrepancies in hypoxemia detection by race and ethnicity in ECMO-supported patients	40	Clinical Research / Critical Care 2	5:00 PM	6
Kang, Jeeun	Transcranial photoacoustic imaging of middle cerebral artery occlusion stroke model in neonatal piglets in vivo	23	Basic Neuroscience 1	4:27 PM	3
Kapoor, Shrey	Plasma biomarkers as prognostication in patients receiving extracorporeal membrane oxygenation	33	Clinical Research / Critical Care 1	3:52 PM	5
Kariyawasam, Udeshika	Resistin is a critical regulator of inflammasome activation in macrophages	04	Basic Science 1	4:06 PM	1
Kariyawasam, Udeshika	hResistin regulates pulmonary smooth muscle cell activation and proliferation through macrophages	10	Basic Science 2	5:07 PM	2
Kariyawasam, Udeshika	B cells are regulated by RELMα in pulmonary hypertension	11	Basic Science 2	5:14 PM	2
Kobayashi, Yuta	Prediction of lactate concentrations after cardiac surgery using machine learning and deep learning approaches	58	Informatics & AI	5:00 PM	10
LaRosa, Jessica	Evaluation of a simulation curriculum to improve nursing-Led early physical rehabilitation of critically ill children	52	Education	5:21 PM	8

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Laytin, Adam	Utilizing an Ethiopian ICU registry to identify opportunities for quality improvement	78	Quality Improvement	4:06 PM	9
Leon, David	Perioperative opioid tapering in patients on methadone medication-Assisted treatment (MAT) for opioid use disorder (OUD)	74	Pain	4:41 PM	7
Li, Qun	The effect of J147 as a novel therapeutic on apoptosis in hippocampus with neonatal hypoxic-Ischemic encephalopathy	24	Basic Neuroscience 2	5:00 PM	4
Limerick, Gerard (& Ankit Uniyal)	Synergistic effects of peripherally restricted dual cannabinoid and mu-opioid receptor agonists in mouse model of neuropathic pain	67	Pain	3:52 PM	7
Liu, Jing	EZH2 in primary sensory neurons contributes to the development of neuropathic pain	72	Pain	4:27 PM	7
Macmillan, Katherine	Population-based study of inpatient and outpatient encounters following pediatric drowning in Maryland	32	Clinical Research / Critical Care 1	3:45 PM	5
Maheshwari, Raj	An educational quality improvement project for NICU nursing staff: using cognitive aids to improve understanding and management of neonatal epidurals	57	Education	5:56 PM	8
Martinez Yus, Marta	Targeting LOXL2 in angiotensin II-induced hypertension	02	Basic Science 1	3:52 PM	1
Martinez Yus, Marta	Sex differences in vascular stiffening with age	09	Basic Science 2	5:00 PM	2

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Mathur, Rohan	Time burden of high intracranial pressure (ICP) in patients with acute brain injury and the need for an early ICP crisis detection system	44	Clinical Research / Critical Care 2	5:28 PM	6
Morgenstern, Stephanie	High risk central lines in pediatric intensive care unit patients: a nurse-driven intervention to raise awareness and reduce central line associated bloodstream infections	45	Clinical Research / Critical Care 2	5:35 PM	6
Namara, George, Marta	ACCM Confocal Microscope Core	16	Basic Science 2	5:49 PM	2
Noren, Henry	Early prediction of neurologic injury in pediatric ECMO patients	43	Clinical Research / Critical Care 2	5:21 PM	6
Olberding, Valerie	RNA and DNA methylation signatures are globally distributed in the neonatal pig brain	28	Basic Neuroscience 2	5:28 PM	4
Patel, Vedant	The effect of endothelin-1 on skeletal muscle function by regulating miR-133b expression	07	Basic Science 1	4:27 PM	3
Quiroga, Diego	Sexual dimorphisms present in downstream elements of AGO-2/miR-181c pathway.	13	Basic Science 2	5:28 PM	2
Romer, Lew	Directing multicellular organization by varying the aspect ratio of soft hydrogel microwells	08	Basic Science 1	4:34 PM	3
Sah, Nirnath	Novel glucose-dendrimer targets hyperexcitable neurons	29	Basic Neuroscience 2	5:35 PM	4

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Sankara, Shomari	Feasibility of social work intervention in older adults before non-cardiac surgery	82	Quality Improvement	4:34 PM	9
Santino, Chelsey	Functional performance and loss of independence in older patients with heart failure with preserved ejection fraction undergoing non-cardiac surgery	42	Clinical Research / Critical Care 2	5:14 PM	6
Sieber, Frederick	Multidisciplinary geriatric care in the PACU: a quality improvement initiative	79	Quality Improvement	4:13 PM	9
Simmons, Samantha	Epidural analgesia for labor: continuous infusion versus intermittent bolus	73	Pain	4:34 PM	7
Sims, Harrison	The perceptions of a novel syringe organizational device following implementation and its impact on operating room workflow during a surgical case.	75	Quality Improvement	3:45 PM	9
Sowers, James	Bioenergetic failure and tryptophan metabolism perturbations following traumatic brain injury in an experimental juvenile rabbit model	22	Basic Neuroscience 1	4:20 PM	2
Spears, Ian	Cerebral lipid metabolism in rabbits with central nervous system tuberculosis	20	Basic Neuroscience 1	4:06 PM	3
Stanislaus, Mellany	Identifying factors that contribute to disrespectful maternal care—an observational pilot	83	Quality Improvement	4:41 PM	9
Sun, Philip	Prevalence of delirium and its association with in-hospital outcomes in veno-venous extracorporeal membrane oxygenation in COVID-19 patients	48	Clinical Research / Critical Care 2	5:56 PM	6

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Tavarez, Tachira	Delayed IL-10 treatment targeted at microglia/macrophages after intracerebral hemorrhage	26	Basic Neuroscience 2	5:14 PM	4
Thomas, Ananda	Outcomes of patients who decline allogeneic blood transfusion	35	Clinical Research / Critical Care 1	4:06 PM	5
Thompson, Alexis	Midazolam effect on long-term outcomes in preclinical model of pediatric traumatic brain injury	17	Basic Neuroscience 1	3:45 PM	3
Tomobi, Oluwakemi	Pre-anesthesia counseling, consent, & professionalism	80	Quality Improvement	4:20 PM	9
Uniyal, Ankit (& Gerard Limerick)	Synergistic effects of peripherally restricted dual cannabinoid and mu-opioid receptor agonists in mouse model of neuropathic pain	67	Pain	3:52 PM	7
Vyas, Preeti	Systemic targeted monotherapy with D-DON results in microglial glutaminase inhibition and improvement in neurobehavioral scores in Mecp2-null and HET mice.	27	Basic Neuroscience 2	5:21 PM	4
Walpole, Joseph	Hypertension augments monocyte inflammatory response which impairs endothelial barrier function	12	Basic Science 2	5:21 PM	2
Wilkinson, Elizabeth	Dendrimer conjugation significantly improves brain pharmacokinetics and therapeutic efficacy of neutral sphingomyelinase 2 inhibitor DPTIP for treating Alzheimer's Disease	19	Basic Neuroscience 1	3:59 PM	3
Williams, Autumn	Simulated real-time EEG feature analysis for assessment of neurological injury post-cardiac arrest	62	Informatics & AI	5:28 PM	10

Presenter	Poster Title	Poster #	Category	Presentation Time	Monitor #
Yaache, Mira	Market trends and needs analysis of emergency response training and interest in a game-based learning tool to teach mass casualty preparedness	55	Education	5:42 PM	8
Young, Lisa	Assessing the need for a health equity curriculum for critical care fellows	56	Education	5:49 PM	8
Yuan, Yang	Effect of secreted frizzled-related protein 3 on neurogenesis and cognitive function in middle-aged mice model of Alzheimer's disease	30	Basic Neuroscience 2	5:42 PM	4
Zhang, Chi	scRNA-sequencing reveals subtype-specific transcriptomic perturbations in DRG neurons of PirtEGFPf mice in neuropathic pain condition	64	Informatics & AI	5:42 PM	10

Health Equity Honors

This year, we are launching the first cross-categorical recognition to highlight research that advances our departmental and institutional commitment to health equity. We believe that research in every domain of scientific discovery is crucial for advancing health equity in clinical care and outcomes. Understanding the mechanisms of disparity informs our collective ability to design healthcare that serves the unique needs of every patient. Submissions were selected for this honor if they explored any aspect of health equity, including:

- Characterizing mechanisms of disparity
- Investigating populations associated with inequities
- Evaluating interventions aimed at promoting equity / addressing disparities
- Advancing educational programs to disseminate information on equity

2022 Health Equity Honorees

Sex differences in vascular stiffening with age (Basic Science)
Martinez Yus, Marta; Wodu, Bulouere Princess; Smith, Logan; Wang, Huilei; Brady, Travis; Bauer, Maria; Nandakumar, Kavitha; Choi, Rira; Steppan, Jochen; Santhanam, Lakshmi

Sexual dimorphisms present in downstream elements of AGO-2/miR-181c pathway (Basic Science)
Quiroga, Diego; Roman, Barbara; Das, Samarjit

Population-based study of inpatient and outpatient encounters following pediatric drowning in Maryland (Clinical Research / Critical Care)
Macmillan, Katherine; Hoops, Katherine; Kudchadkar, Sapna; Gielen, Andrea; McDonald, Eileen; Pritchett, Laura; Nasr, Isam; Ryan, Leticia

Outcomes of patients who decline allogeneic blood transfusion (Clinical Research / Critical Care)
Thomas, Ananda J.; Adegboye, Janet; Myers, Emmarie; Sekaran, Anjana; Stanislaus, Mellany; Frank, Steven M

Variation in clinical outcomes for hospitalized children related to childhood opportunity index (Clinical Research / Critical Care)
Garg, Anjali; Sochet, Anthony; Stockwell, David

Discrepancies in hypoxemia detection by race and ethnicity in ECMO-supported patients (Clinical Research / Critical Care)
Kalra, Andrew; Shou, Benjamin; Zhao, David; Wilcox, Christopher; Keller, Steven; Whitman, Glenn; Kim, Boo Soo; Cho, Sung-Min

COVID-19 pediatric respiratory care educational training program for healthcare workers in Lesotho: An Observational Study (Education)
Joseph, Kristen S; Lekhela, Tiiso D; Rose, Michael R; Gersz, Lawrence; Mahachi, Nyikadzino; Mungati, More; Shoba, Matsosane; Montsi, Sello; Leluma, Sebaki F; Oyewusi, Lawrence; Mirembe, Justine; Shilkofski, Nicole; McCollum, Eric D

Assessing the need for a health equity curriculum for critical care fellows (Education)
Young, Lisa; O'Conor, Katie J; Banks, Michael C; Torres, Crisanto M; Toy, Serkan; Laytin, Adam D

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Perioperative opioid tapering in patients on methadone medication-assisted treatment (MAT) for opioid use disorder (OUD) (Pain)
Leon, David; Jaremko, Kellie; Speed, Traci; Shechter, Ronan; Hanna, Marie

Identifying factors that contribute to disrespectful maternal care—an observational pilot (Quality Improvement)
Stanislaus, Mellany; Lawson, Shari; Beach, Mary Catherine; Jones, Miranda; Ahmed, Saiffudin; Toy, Serkan

Multidisciplinary geriatric care in the PACU: a quality improvement initiative (Quality Improvement)
Sieber, Frederick; Wang, Nae-Yuh

Pre-anesthesia counseling, consent, & professionalism (Quality Improvement)
Tomobi, Oluwakemi; Lee, Jay; Tran, Tina; Schiavi, Adam; Akca, Ozan; Chari, Asha; Azefor, Tangwan; Sampson, John

Feasibility of social work intervention in older adults before non-cardiac surgery (Quality Improvement)
Sankara, Shomari; Brown, Charles IV; Goeddel, Lee

Ultramini Abstracts

Basic Science - 1

The adenosine A2A receptor regulates miR-181b expression in aorta: therapeutic implications for large artery stiffness	
Akiyoshi, Kei; **Fujimori, Tomonari**; Fu, Xiuping; Shah Aparna P.; Yamaguchi, Atsushi; Steenbergen, Charles; Santhanam, Lakshmi; Berkowitz, Dan; Baraban, Jay M.; Das, Samarjit	Inhibition of the translin/trax (TN/TX) RNase has emerged as a candidate therapeutic strategy for combatting Large Artery Stiffness (LAS). In this study, we show that stimulation of the adenosine A2A receptor (A2AR) facilitates the formation and activation of the TN/TX RNase complex in vascular smooth muscle cells.
Targeting LOXL2 in angiotensin II-induced hypertension	
Martinez Yus, Marta; Wang, Huilei; Brady, Travis; Choi, Rira; Nandakumar, Kavitha; Smith, Logan; Jang, Rosie; Wodu, Bulouere Princess; Rastogi, Shivam; Stoddart, Laila; Kim, Deok-Ho; Steppan, Jochen; and Santhanam, Lakshmi	Hypertension, a major risk factor for cardiovascular diseases, accelerates arterial stiffness with aging. It is of clinical interest to test therapeutic targets against vascular stiffness in hypertensive patients. In this study, we discovered that depletion of LOXL2, a key enzyme in matrix remodeling, is protective against hypertension induced arterial stiffening.
Increased amino acid utilization by the lung vasculature in pulmonary hypertension	
Philip, Nicolas; **Gadkari, Mahin**; Zhang, Cissy; Huetsch, John; Yun, Xin; Harlan, Rob; Graham, David; Shimoda, Larissa; Le, Anne; Santhanam, Lakshmi; Suresh, Karthik; Steppan, Jochen	Serum from the right and left ventricles of SuHx rats and healthy controls show an increase in oxidized glutathione across the lungs and reduced levels of glutamine in the RV. These results imply that glutamine consumption by the lung microvasculature may be driven by using glutamine to produce reduced glutathione.
Resistin is a critical regulator of inflammasome activation in macrophages	
Kariyawasam, Udeshika; Skinner, John; Lin, Qing; Johns, Roger	hResistin/RELMα is a regulator of NLRP3 inflammasome complex activation, through HMGB-1 and BTK. The secreted IL-1β and IL-18 mediate the post-injury innate responses, to induce vascular remodeling over time for PH development. It may also explain their role of hResistin in diseases such as atherosclerosis, cardiac remodeling/failure and LPS sepsis.
Effect of ECM and mechanical strain on vascular cell plasticity	
Brady, Travis; Santhanam, Lakshmi; Gerecht, Sharon	Age-related vascular stiffening is, in part, due to decreased enzyme-mediated turnover of collagen-I by VSMCs. Stiff substrates and growth factors such as TGF-β2 can drive pathological phenotype changes in ECs. Screening for specific MMP activity in both cell types may reveal mechanisms of remodeling and responding to stiff environments.
Macrophage-targeted Dendrimer-Tesaglitazar therapy for atherosclerosis	
Almodiel, Diego; Rangaramanujam, Kannan; Kannan, Sujatha; Santhanam, Lakshmi	Atherosclerosis is a multicellular disease that affects not only immune cells, but smooth muscle cells and endothelial cells of arteries. Using dendrimer conjugated Tesaglitazar (D-Tesa), we investigate if targeting macrophages in plaque is sufficient to ameliorate atherosclerosis in apolipoprotein E deficient mice on a high fat diet.

The effect of Endothelin-1 on skeletal muscle function by regulating miR-133b expression	
Patel, Vedant; Fujimori, Tomonari; Das, Samarjit.	Endothelin-1 upregulates miR-133b in skeletal muscle, causing insulin resistance and exercise intolerance during heart failure. As a therapeutic intervention, blocking the effect of Endothelin-1, miR-133b expression can be maintained to get protection against insulin resistance and exercise intolerance.
Directing multicellular organization by varying the aspect ratio of soft hydrogel microwells	
Gayatri J. Pahapale; Jiaxiang Tao; Milos Nikolic; Sammy Gao; Giuliano Scarcelli; Sean Sun; **Lewis H. Romer**; David H. Gracias	A new mode of cell organization by migration in response 3D geometry on soft substrates is presented and is controlled by tuning the aspect ratio, independent of chemical patterning and curvature. Parameters that regulate this cell organization are elucidated and used to investigate fundamental questions relevant to tissue development.

Basic Science - 2

Sex differences in vascular stiffening with age	
Marta Martinez Yus, Marta; Wodu, Bulouere; Smith, Logan; Wang, Huilei; Brady, Travis; Bauer, Maria; Nandakumar, Kavitha; Choi, Rira; Steppan, Jochen; Santhanam, Lakshmi.	Increased arterial stiffness is a significant contributing factor for cardiovascular disease (CVD). The risk of CVD augments with age in humans, with significant risk acceleration in post-menopausal women. In this study, we showed that key physiological features of sex differences in vascular stiffening are recapitulated in the C57BL/6J mouse model.
hResistin regulates pulmonary smooth muscle cell activation and proliferation through macrophages	
Kariyawasam, Udeshika; Skinner, John; Lin, Qing; Johns, Roger;	hResistin has an important regulatory role in macrophages to induce pro-proliferative environment, specially via IL-1β and IL-18 secretion that induces post-injury innate responses and SMC proliferation to induce vascular remodeling over time for PH development. Blocking hResistin would be a good therapeutic target to prevent inflammation driven vascular remodeling and PH.
B cells are regulated by RELMα in pulmonary hypertension	
Kariyawasam, Udeshika; Skinner, John; Lin, Qing; Johns, Roger.	RELMα/hResistin recruits B cells to the lung in pulmonary hypertension and regulates the pro-inflammatory function of B cells, which is an important mechanism of the RELMα/hResistin-induced vascular inflammation and remodeling in PH. These findings shed more light on the development of novel treatment or prevention of pulmonary hypertension associated with inflammatory diseases.
Hypertension augments monocyte inflammatory response which impairs endothelial barrier function	
Walpole, Joseph; Dante, Siddhartha; Wang, Huilei; Nandakumar, Kavitha; Khoury, Elizabeth; Tucker, Elizabeth W.; Santhanam, Lakshmi; Kannan, Sujatha	Patients with systemic inflammatory conditions experience increased morbidity and mortality. We present in vitro data demonstrating a monocyte mediated mechanism for endothelial barrier disruption that is exaggerated by comorbid obesity and hypertension which may play a role in vasculopathies associated with acute infection.

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Sexual dimorphisms present in downstream elements of AGO-2/miR-181c pathway.	
Quiroga, Diego; Roman, Barbara; Das, Samarjit	Premenopausal females have a lower risk for cardiovascular disease, the mechanisms are poorly understood. The present study tested the hypothesis that AGO-2 play an important role in the sexual dimorphism of heart.
Effect of maternal inflammation on arterial stiffness in early age	
Almodiel, Diego; Liu, Kristen; Kannan, Sujatha; Santhanam, Lakshmi	Studies on the effect of maternal inflammation on cardiovascular development have been hindered due to the small size of rat and mouse pups. Using rabbit kits, we have developed a model to investigate aortic properties at young ages and compare baseline data to kits subjected to inflammation in-utero.
The role of the unfolded protein response and LOXL-2 in heart failure with preserved ejection fraction	
Bauer, Maria; Martinez Yus, Marta; Nandakumar, Kavitha; Azarcon, Philip J; Brady, Travis; Almodiel, Diego; Gadkari, Mahin; Steppan, Jochen; Santhanam, Lakshmi	The critical molecular mechanisms underlying heart failure with preserved ejection fraction (HFpEF) have not been fully elucidated. Our experiments have shown that our in vivo and in vitro models are suitable to investigate the role of the unfolded protein response and LOXL-2 in the development of HFpEF.
ACCM Confocal Microscope Core	
McNamara, George; Mintz, Cyrus David	The ACCM Confocal Microscope is a Leica SP8 scanhead DMi8 inverted microscope (Ross 910). 4 laser lines and 2 HyD photon counting hybrid detectors, available 24/7 to trained users. This microscope can enhance your research, translational and clinical work.

Basic Neuroscience - 1

Midazolam effect on long-term outcomes in preclinical model of pediatric traumatic brain injury	
Thompson, Alexis; Ramprasad, Manisha; Saraswati, Manda; Mathena, Paige; Jantzie, Lauren; Mintz, C. David; Robertson, Courtney	In previous histological studies, TBI-sedation rats showed reduction in inflammation and neuronal cell death suggesting neuroprotective properties of midazolam. This finding did not translate into improvements in cognitive function. Ongoing studies will use ex vivo brain MRI to measure tissue loss in our pediatric TBI model.
Clinical and telemetric electroencephalographic seizure monitoring in a neonatal piglet model of hypoxic-ischemic encephalopathy and therapeutic hypothermia	
Javdan, Cameron; Primiani, Christopher; O'Brien, Caitlin; Chen, May; Kulikowicz, Ewa; Adams, Shawn; Lester, Bailey; Rivera-Diaz, Natalia; Olberding, Valerie; Niedzwiecki, Mark; Ritzl, Eva; Habela, Christa; Koehler, Raymond; Lee, Jennifer; Martin, Lee	We have developed a neonatal gyrencephalic large animal model in piglets that can be used to study neuropathology and therapeutics related to hypoxic-ischemic-encephalopathy (HIE).

Dendrimer conjugation significantly improves brain pharmacokinetics and therapeutic efficacy of neutral sphingomyelinase 2 inhibitor DPTIP for treating Alzheimer's Disease	
Wilkinson, Elizabeth; Sharma, Anjali; Pal, Arindom; Tallon, Carolyn; Wu, Ying; Thomas, Ajit; Yoo, Seung-Wan; Haughey, Norman; Rais, Rana; Rangaramanujam, Kannan; Slusher, Barbara.	Here we describe the synthesis and characterization of a PAMAM dendrimer-drug conjugate (D-DPTIP) for improving the oral delivery of DPTIP for treating Alzheimer's Disease. In Alzheimer's Disease mice, D-DPTIP boosts the brain pharmacokinetics and therapeutic efficacy, boding well for future translation.
Cerebral lipid metabolism in rabbits with central nervous system tuberculosis	
Spears, Ian; Kim, John; Erice, Clara; Tressler, Caitlin; Tucker, Elizabeth	Glycerophospholipid, sphingolipid, and cholesterol derivatives were decreased in young rabbit brains with CNS TB compared to unaffected rabbits. Different lipids were increased in the lesion compared to the hemisphere without lesions, highlighting lipids' spatial heterogeneity. These lipids provide potential targets for CNS TB treatment.
The effect of secreted frizzled related-protein 3 (sFRP3) and Wnt signaling on cognitive behavior after traumatic brain injury	
Allende Labastida, Javier; El Demerdash, Nagat; Shi, Yanrong; Avery, Brooklyn; Yuan, Yang; Koehler, Raymond C; Han, Xiaoning	An essential area of traumatic brain injury research uses the repair potential of stem cells. The inhibition of the secreted Frizzled Related-Protein 3, an inhibitor of Wnt signaling, regulates activity-dependent neural stem cell proliferation and maturation. The sFRP3-mediated modulation of neurogenesis after injury could provide an avenue for functional recovery.
Bioenergetic failure and tryptophan metabolism perturbations following traumatic brain injury in an experimental juvenile rabbit model	
Sowers, James; Liyange, Wathsala; Sah, Nirnath; Kannan, Rangaramanujam; Kannan, Sujatha	We report significant perturbations in tryptophan and bioenergetic metabolites including kynurenine, kynurenic acid, quinolinic acid, glucose, N-acetyl aspartate, creatine, urate and NAD+/NADH at one day and three days after injury in a juvenile rabbit traumatic brain injury model. The influence of microglial activation on these pathways was subsequently studied.
Transcranial photoacoustic imaging of middle cerebral artery occlusion stroke model in neonatal piglets in vivo	
Kang, Jeeun; Yang, Zeng Jin; Wei, Liwen; Graham, Ernest M.; Boctor, Emad M.; Koehler, Raymond C.	We present a transcranial photoacoustic imaging of middle cerebral artery cauterization model in neonatal piglets in vivo, which has high translational feasibility towards non-invasive perinatal brain monitoring application in clinics.

Basic Neuroscience - 2

The Effect of J147 as a Novel Therapeutic on Apoptosis in Hippocampus with Neonatal Hypoxic-Ischemic Encephalopathy	
Li, Qun; Li, Fengying; Gao, Rachel; Cyrus, Mintz.	Neonatal hypoxic-ischemic encephalopathy (HIE) occurs around birth time and leads to neurologic disorders. Currently, there is no pharmacologic treatment available for HIE. J147, an experimental drug against Alzheimer's disease, ameliorates apoptosis in hippocampus of mouse HIE model. Our long-term goal is to position J147 for a clinical trial for HIE.

White matter injury in a pediatric rabbit model of CNS TB	
Damiba, Nelly; Sah, Nirnath; Erice, Clara; Kim, John; Kannan, Rangaramanujam; Kannan, Sujatha; Jain, Sanjay; Tucker, Elizabeth W	Neuroinflammation secondary to CNS TB causes white matter injury and decreased density which could explain the neurobehavioral deficits seen clinically. Our preliminary data suggest that dendrimer-NAC (D-NAC), an anti-inflammatory/antioxidant that crosses the BBB, rescues white matter injury and increases its density in CNS TB-infected rabbits compared to those treated with dexamethasone.

Delayed IL-10 treatment targeted at microglia/macrophages after intracerebral hemorrhage	
Tavarez, Tachira; Shi, Yanrong; Koehler, Raymond.	Microglia/macrophage (M/MΦ) assists with hematoma clearance and angiogenesis post-ICH. IL-10 works on M/MΦ enhancing hematoma clearance in the acute phase. Phosphatidylserine containing liposomes (PSL) conjugated with IL-10 (PSL-IL10) is a promising IL-10 vehicle. This study investigates effects of PSL-IL10 administration in mice with ICH on behavioral outcomes, neuroinflammatory responses, angiogenesis.

Systemic targeted monotherapy with D-DON results in microglial glutaminase inhibition and improvement in neurobehavioral scores in Mecp2-null and HET mice.	
Vyas, Preeti; Fowler, Amanda; Sah, Nirnath; Liu, Jinhuan; Khoury, Elizabeth; Sharma, Anjali; Thomas, Ajit; Rais, Rana; Slusher, Barbara; Rangaramanujam, Kannan; Kannan, Sujatha.	Our work explored potential of a multi-pronged therapy targeting mechanisms of injury (glutamate excitotoxicity, oxidative stress, inflammation) in RTT. We combined strengths in dendrimer nanotechnology, neuropharmacology, neurodevelopmental and translational research and provided evidence for dendrimer-based D-DON therapy to alleviate behavioral symptoms in RTT via inhibition of glutaminergic-pathway in glial cells.

RNA and DNA methylation signatures are globally distributed in the neonatal pig brain	
Olberding, Valerie; Amrein Almira, Adriana; Javdan, Cameron; K. Lee, Jennifer; J. Martin, Lee	Epigenetic patterns in piglets with encephalopathy were assessed for aberrancy. Data shows that salient epigenetic markers and their regulatory mechanisms have broad distributions and neuronal and glial cell nuclear enrichment throughout neonatal pig brain gray and white matter regions are potentially poised for acquired injury-induced rewriting of the epigenetic landscape.

Novel glucose-dendrimer targets hyperexcitable neurons	
Sah, Nirnath; Sharma, Anjali; Salazar, Sebastian; Rangaramanujam, Kannan; Kannan Sujatha;	Neuronal hyperexcitability and excitotoxicity is a common pathology across multiple neurological disorders that necessitates neuron-specific therapeutics. We report a novel glucose dendrimer that targets hyperexcitable neurons and can be used to conjugate anti-epileptic drugs to treat seizures.

Effect of secreted frizzled-related protein 3 on neurogenesis and cognitive function in middle-aged mice model of Alzheimer's disease	
Yuan, Yang; Wan, Jieru; Alibilli, Amrutha; Labastida, Javier Allende; Koehler, Raymond C. ; Han, Xiaoning	Alzheimer's disease is a neurodegenerative disease. The depletion of Secreted frizzled-related protein 3 (sFRP3), an antagonist of Wnt signaling pathways, has been shown to promote neurogenesis under physiological conditions. Inhibiting sFRP3 gene expression may improve neurogenesis and cognitive function in the mouse model of Alzheimer's disease.

ACCM Cellular, Molecular & Biomarker Discovery Initiative	
Heller, Nikki; Das, Sam	The ACCM Cellular, Molecular & Biomarker Discovery Initiative provides a jump-start for new basic and translational collaborative discovery projects and grants within ACCM. Have an idea for a research project or grant but don't know where to begin? We can help. Contact Nikki Heller nheller@jhmi.edu and Sam Das sdas11@jhmi.edu.

Clinical Research - 1

Population-based study of inpatient and outpatient encounters following pediatric drowning in Maryland	
Macmillan, Katherine; Hoops, Katherine; Kudchadkar, Sapna; Gielen, Andrea; McDonald, Eileen; Pritchett, Laura; Nasr, Isam; Ryan, Leticia.	In three years, there were 541 pediatric patients who sought medical care following a drowning event in Maryland, with 47 patients requiring admission. Race-related risks were identified when stratified by age, with minority children accounting for 62% of visits in the 10-19 years group.

Plasma biomarkers as prognostication in patients receiving extracorporeal membrane oxygenation	
Kapoor, Shrey; Premraj, Lavien; Ahmad, Ameen; Muquit, Siam; Everett, Allen; Zhu, Jie; Cho, Sung-Min	Plasma biomarkers are increasingly utilized to aid clinical decision-making. We identify three biomarkers, GFAP, Tau and NFL, with life-saving potential for neuromonitoring of acute brain injury and hemorrhagic events on extracorporeal membrane oxygenation (ECMO) support. We strongly recommend further research to identify which novel biomarkers has highest clinical yield.

Clinical methods & results of mass spectrometric examination of exhaled aerosol samples in intubated ICU patients for early identification of pulmonary infection via proteomics	
Crasta, Melanie; Chen, Dapeng; Chen, Shuo; Devin, Alese; Haddaway, Caroline; Caton, Emily; Bryden, Wayne; McLoughlin, Michael; Mirski, Marek.	Exhaled breath samples of intubated patients were spectrometrically analyzed to isolate truncated proteoforms indicative of respiratory tract infections (RTI). 6 proteoforms representing either proteolytic enzymes or lung structure proteins, were statistically different between patients with and without RTI. This non-invasive and rapid diagnosis of RTI in critically ill patients may lead to expeditious deployment of focused antibiotics.

Outcomes of patients who decline allogeneic blood transfusion	
Thomas, Ananda J.; Adegboye, Janet; Myers, Emmarie; Sekaran, Anjana; Stanislaus, Mellany; Frank, Steven M.	In this study, we examined obstetric patients who decline blood transfusions. We analyzed 124 deliveries (88 patients) and collected information about comorbidities, delivery methods, maternal/fetal outcomes, and blood management techniques. This study aims to identify and analyze patient care strategies in managing obstetric bleeding while avoiding transfusion for these patients.
Peripheral and arterial blood gas oxygen saturation levels are discordant in various ECMO cannulation configurations	
Kalra, Andrew; Shou, Benjamin; Zhao, David; Wilcox, Christopher; Keller, Steven; Whitman, Glenn; Kim, Boo Soo; Cho, Sung-Min.	Pulse oximetry overestimates SaO2 in peripherally-cannulated VA-ECMO patients, and this may be accredited to differential hypoxia during peripheral-cannulation and vasopressors/inotropes. Pulse oximetry overestimates SaO2 in single-lumen more than double-lumen cannulated VV-ECMO patients, and this may be due to hemolysis due to greater resistance of blood flow in the single-lumen.
Variation in clinical outcomes for hospitalized children related to childhood opportunity index	
Garg, Anjali; Sochet, Anthony; Stockwell, David C	In this large, multicenter study, COI was associated with worsened clinical outcomes. Mortality, PICU admission, MV, and LOS varied by COI with lower COI associated with higher mortality, increased likelihood of PICU admission and increased LOS. These observed represent gaps for public health initiatives to establish equitable healthcare.
Organ dysfunction recovery in pediatric ECMO patients	
Huang, Justin; Roem, Jennifer; Bembea, Melania	In patients with HFpEF undergoing non-cardiac surgery, the combination of poor functional performance and decreased exercise capacity was associated with for loss of independence after surgery. The pre-operative identification of these patients may help to risk stratify those at highest risk of post-operative loss of independence.
Overtransfusion is common in patients receiving massive transfusion	
Adegboye, Janet; Thomas, Ananda; Cruz, Nicolas; Frank, Steven.	Of patients who received ≥10 units of red blood cell transfusions, 65% had a discharge hemoglobin above 8 g/dL, 35% above 9 g/dL, and 18% above 10 g/dL. These findings reveal an opportunity to reduce unnecessary blood usage by recognizing when to stop giving blood to patients receiving massive transfusion.

Clinical Research – 2

Discrepancies in hypoxemia detection by race and ethnicity in ECMO-supported patients	
Kalra, Andrew; Shou, Benjamin; Zhao, David; Wilcox, Christopher; Keller, Steven; Whitman, Glenn; Kim, Boo Soo; Cho, Sung-Min.	Skin pigmentation biases pulse oximetry measurements in ECMO patients, with SpO2 overestimating SaO2 consistently in Asian, Black, and Hispanic ECMO patients. This discrepancy was greater in VV-ECMO than in VA-ECMO, and there may be further biological and physiological explanations for this SpO2-SaO2 discrepancy that should be investigated with granular data.

Implementation of consistent medical direction consults during pediatric critical care interhospital transport	
Bhatia, Pooja; Costabile, Philomena; Devlin, Bridget; Harkins, Lauren; Frederick, Christina; Klein, Bruce; Noje, Corina	Johns Hopkins Pediatric Transport implemented consistent transport medical direction for all incoming pediatric critical care transports. Consistent transport medical consultation is feasible, impacts patient care en route, and generates revenue. QI efforts are ongoing, as our team strives for 100% compliance and further assessment of its impact on patient outcomes.
Functional performance and loss of independence in older patients with heart failure with preserved ejection fraction undergoing non-cardiac surgery	
Santino, Chelsey; Goeddel, Lee	In patients with HFpEF undergoing non-cardiac surgery, the combination of poor functional performance and decreased exercise capacity was associated with for loss of independence after surgery. The pre-operative identification of these patients may help to risk stratify those at highest risk of post-operative loss of independence.
Early prediction of neurologic injury in pediatric ECMO patients	
Noren, Henry; Mishra, Disha; Prathima, Priyamvada; Lu, Yuzhi; D'Souza, Valentina; Miao, Yang; Sun, Valentina; Overby Taylor, Casey; Greenstein, Joseph; Leung, Dennis; Bembea, Melania	Time-series data on lab measurements and the administration of blood products during ECMO are better predictors of the onset of neurologic injury in pediatric ECMO patients than pre-ECMO data. This time-series prediction model could improve pediatric ECMO patient outcomes through early identification of those at high risk for neurologic injury.
Time burden of high intracranial pressure (ICP) in patients with acute brain injury and the need for an early ICP crisis detection system	
Mathur, Rohan; Dziedzic, Peter; Stevens Robert D; Leek, Jeff; Suarez, Jose I.	In 198 brain-injured ICU patients undergoing intracranial pressure (ICP) monitoring, we describe: demographics, underlying etiologies, and outcomes of interest including development of ICP crisis, mortality, lengths of stay, and need for permanent CSF diversion. We describe the total time burden of high ICP in 29 patients with intraparenchymal monitors.
High risk central lines in pediatric intensive care unit patients: a nurse-driven intervention to raise awareness and reduce central line associated bloodstream infections	
Morgenstern, Stephanie N.; Kitlas, Jessica A.; McIlquham, Taylor J.; Booth, Lauren D.; Thompson, Katherine L.; Fleischmann, Laura E.; Milstone, Aaron M.; Bernier, Meghan L.; Sick-Samuels, Anna C.	We developed a novel screening tool to identify patients at high risk for central line-associated bloodstream infections (CLABSI) in our PICU. The weekly screening tool was associated with reduced CLABSI rates from 1.83 to 1.15 per 1000 catheter days with improved clinician awareness and implementation of CLABSI prevention strategies.
Neuropathological findings in COVID-19 vs non-COVID-19 acute respiratory distress syndrome - a matched case control study	
Humayun, Mariyam; Zhang, Lucy; Zaikos, Thomas D; Kannapadi, Nivedha, Nyquist, Paul, Cho, Sung-Min	We looked at differences in neuropathology between 10 COVID-19 and 20 age and sex-matched non-COVID ARDS patients. The frequency of overall ABI (70% vs 55%), infarct (30% vs 30%), ICH (50% vs 35%), HIBI (30% vs 35%), and CMB (20% vs 5%) between the two groups was similar (p values >0.05).

The association of oxygen delivery on cardiopulmonary bypass and postoperative delirium	
Chen, Mengkun; Brown, Charles H.	In patients undergoing cardiac surgery on cardiopulmonary bypass (CPB), lower oxygen delivery (DO2) level and longer time under DO2 threshold is significantly associated with higher risk of postoperative delirium, independent of potential confounders. These findings support the role of impaired oxygen delivery on CPB in the development of postoperative delirium.
Prevalence of delirium and its association with in-hospital outcomes in veno-venous extracorporeal membrane oxygenation in COVID-19 patients	
Sun, Philip; Fanning, Jonathon; Peeler, Anna; Shou, Benjamin; Caturegli, Giorgio; Whitman, Glenn; Cha, Stephanie; Kim, Bo; Cho, Sung-Min.	In our retrospective review of severe COVID-19 ARDS patients requiring VV-ECMO at Johns Hopkins, we found that delirium occurred in nearly all patients with assessable neurologic exam. Non-survivors had significantly more delirium-unassessable days on VV-ECMO and total VV-ECMO days, indicating their complicated medical course, fatal neurologic complications, and heavy sedation.

Education

A novel case-based echocardiography teaching platform for critical care medicine trainees	
Ghobrial, Mina; Goeddel, Lee	Point-of-care Transthoracic Echocardiography (POC TTE) is a crucial adjunct in the management of acutely ill patients. A multidisciplinary team of physicians at JHH created a novel, online, asynchronous, case-based application that focuses on key aspects of POC TTE image interpretation and the corresponding clinical decisions that would be most appropriate.
PCCM fellow-led procedure curriculum for pediatric residents	
Grindy, Anna; McCaw, Julie; Brigham, Elizabeth; Gardner-Yelton, Sarah; Nadkarni, Anisha; Schreiber, Hilary; Levin, Amanda	Responding to a need for increased procedure teaching in the pediatric residency program, we developed an educational curriculum in which Pediatric Critical Care Medicine fellows teach pediatric residents to perform lumbar punctures, bag-mask ventilation, IO placement, and peripheral IV placement. Residents demonstrated competency and subjective confidence in those procedures.
Teaching fellows to teach: impact of novel fellows as educators curriculum on fellow procedural teaching	
Anna Grindy, Yasamin Sanii, Diana Steppan, Brittany Badesch, Serkan Toy, Nicole Shilkofski, Amanda Levin	We are conducting an observational study on PCCM fellows' use of the five microskills of teaching. Following an educational workshop, preliminary data suggest that PCCM fellows increased their use of the teaching skills during procedural teaching sessions for pediatric residents.
Evaluation of a simulation curriculum to improve nursing-led early physical rehabilitation of critically ill children	
LaRosa, Jessica M.; Lenker, Hallie; Brown, Kristen; Shilkofski, Nicole; Kudchadkar, Sapna R.	We developed a nurse-targeted simulation curriculum aimed at mobilizing critically ill children. We then conducted a pre-post interventional study to evaluate implementation of the curriculum. Our study demonstrated that hands-on early mobility education for nurses improves self-efficacy, knowledge, and clinical skills mobilizing critically ill children.

COVID-19 pediatric respiratory care educational training program for healthcare workers in Lesotho: an observational study	
Joseph, Kristen S; Lekhela, Tiiso D; Rose, Michael R; Gersz, Lawrence; Mahachi, Nyikadzino; Mungati, More; Shoba, Matsosane; Montsi, Sello; Leluma, Sebaki F; Oyewusi, Lawrence; Mirembe, Justine; Shilkofski, Nicole; McCollum, Eric D	Knowledge of transmission, symptoms, testing, and management of pediatric COVID-19 is low among healthcare workers in Lesotho despite two years of pandemic care. Dedicated training demonstrated improvement in knowledge base across cadres of healthcare workers necessary for appropriate management of pediatric patients as new variants of COVID-19 emerge.
An educational quality improvement project for the first pediatric anesthesiology resident rotation: a microlearning-based curriculum intervention	
Beiene, Zodina; Schwengel, Deborah	The challenge of delivering a uniform learning experience for all trainees, and one that is feasible for faculty, is an educational quality improvement challenge that can be addressed using microlearning. This project describes the creation of a mechanism to address this challenge.
Market trends and needs analysis of emergency response training and interest in a game-based learning tool to teach mass casualty preparedness	
Yaache, Mira; Greenberg, Robert; Divito, Anthony; Schwengel, Deborah	Mass casualty preparedness is a challenge for hospitals. Game-based learning may provide a time-effective opportunity to teach preparedness. Market analysis suggests that hospitals need time- and cost-effective options for training. Our game-based learning tool, Influx!, should be marketable.
Assessing the need for a health equity curriculum for critical care fellows	
Young, Lisa; O'Conor, Katie J; Banks, Michael C; Torres, Crisanto M; Toy, Serkan; Laytin, Adam D	Inequities are increasingly recognized in all aspects of healthcare, yet there are no standard curricula for health equity education. In a needs assessment among critical care faculty and fellows, participants reported minimal prior education on health equity and prioritized key health equity topics. Developing a curriculum focused on health equity in critical care may enhance professional development and promote strategies for improving health equity.
An educational quality improvement project for NICU nursing staff: using cognitive aids to improve understanding and management of neonatal epidurals	
Maheshwari, Raj; Schwengel, Deborah	Neonatal ICU nursing staff have limited experience caring for neonates with epidurals. Cognitive aids can provide clear, relevant information about physiology of neonatal epidurals and troubleshooting information. This project explores the utility of a cognitive aid and whether it improves competency and comfort with neonatal epidurals in the NICU.

Informatics and AI

Prediction of lactate concentrations after cardiac surgery using machine learning and deep learning approaches	
Kobayashi, Yuta; Peng, Yu-Chung; Bush, Brian; Jung, Youn-hoa; Goeddel, Lee; Whitman, Glenn; Brown, Charles; Venkataraman, Archana	Various machine learning frameworks were trained to predict a patient's maximum lactate concentration up to 24 hours after cardiac surgery. The inclusion of minute-by-minute intraoperative data consistently improved the predictive performance of the models, suggesting that valuable information may be captured in the evolving dynamics of the intraoperative data.

A novel algorithm to calculate target preoperative hemoglobin for patients declining allogeneic transfusion	
Cruz, Nicolas; Guinn, Nicole; **Adegboye, Janet**; Thomas, Ananda; Hsiao, Joyce; Lo, Brian; Chaturvedi, Shruti; Resar, Linda; Frank, Steven.	We describe a novel algorithm, derived from the allowable blood loss formula, used to calculate the ideal target preoperative hemoglobin for patients who do not accept blood products. By using this algorithm to guide preoperative optimization, patients can avoid clinically significant postoperative anemia and the need for allogeneic blood transfusion.
More than words: language patterns indicative of unrecognized shock in children undergoing interhospital transfer	
Chowdhury, Nabila; Badaki Makun, Oluwakemi; Ryan, Leticia; Klein, Bruce; Costabile, Philomena; Noje, Corina	In this pilot sample, referring providers used discretely identifiable terms to describe patients with unrecognized shock (URS) compared to those with recognized shock (RS). Compared to the clinically unambiguous term ("shock") used to describe patients with RS, providers describing patients with URS more frequently used ambiguous descriptors of patient presentation.
Early monitoring of neurological recovery using Poincaré analysis index of heart rate variability - a potential biomarker for asphyxial cardiac arrest related brain injury	
Agarwal, Prachi; Geocadin, Romergryko; Thakor, Nitish V	We investigated heart rate variability (HRV) based on the Poincaré analysis method during the hyperacute recovery period after resuscitation in male Wistar rats. Correlation of NDS scores with the neurological outcomes indicated that the early sympathovagal changes at 30-min are as good an indicator as NDS obtained after 4 hrs.
Simulated real-time EEG feature analysis for assessment of neurological injury post-cardiac arrest	
Williams, Autumn; Guo, Yu; Li, Ziwei; Geocadin, Romergryko; Thakor, Nitish.	Primary Result: Describes an innovative method to automatically segment EEG by applying cross-disciplinary methods from control theory and discrete event analysis to signal processing algorithms. Translational Implication: Provides a framework for future real-time neurological monitoring of unconscious patients. Clinical Implication: Increased capability for diagnosis of neurological injury.
Development of a Stata command for pediatric risk of mortality (PRISM) calculation	
Azamfirei, Razvan; Mennie, Colleen; Fackler, James C.; Kudchadkar, Sapna R.	We developed a Stata command (prismscore) that performs PRISM III/IV score calculations, adding error-proofing, the ability to use both SI and US laboratory value units, and a graphical user interface. The tool improves the reproducibility of research involving the scores and streamlines data analysis for pediatric critical care datasets.
scRNA-sequencing reveals subtype-specific transcriptomic perturbations in DRG neurons of PirtEGFPf mice in neuropathic pain condition	
Zhang, Chi; Hu, Ming-Wen; Wang, Xue-Wei; Cui, Xiang; Liu, Jing; Huang, Qian; Cao, Xu; Zhou, Feng-Quan; Qian, Jiang; He, Shaoqiu; Guan, Yun	Single-cell RNA-sequencing unraveled cell subtype-specific transcriptomic changes in both injured and uninjured primary sensory neurons after nerve injury and demonstrated transcriptomic sexual dimorphism. These findings may help in development of neuron subtype-specific and sex-specific therapies for neuropathic pain treatment.

RNA-sequencing analysis of mice dorsal root ganglion neurons reveals pain-related gene regulations by HC-HA/PTX3	
Zhang, Chi; Huang, Qian; C. Ford, Neil; N. Raja, Srinivasa; Guan, Yun; He, Shaoqiu	We identified changes in distinct gene networks and transcriptional signatures functioning in DRG neurons after HC-HA/PTX3 treatment. The differentially expressed genes are centered around neurochemical mechanisms of pain and may be crucial targets for pain treatments.

Pain

Spinal cord stimulation attenuates paclitaxel-induced peripheral neuropathic pain and gait impairment by modulating macrophage-mediated neuroinflammation in peripheral nerves	
Bakare, Ahmed Olalekan; Stephens, Kimberly; Sanchez, Karla; Raja, Srinivasa; Guan, Yun; Sivanesan, Eellan.	In adult male tumor-bearing RNU rats, spinal cord stimulation (SCS) inhibited chemotherapy-induced peripheral neuropathic pain, partially normalized gait impairment, and attenuated nerve fiber injury via modulation of inflammatory cytokines and macrophage-mediated neuroinflammation, and gene expression mediating anti-inflammatory cytokines, neuronal outgrowth, and ion transport in peripheral nerves.
Synergistic effects of peripherally restricted dual cannabinoid and mu-opioid receptor agonists in mouse model of neuropathic pain	
Uniyal, Ankit; **Limerick, Gerard**; Ford, Neil C; Grenald, Shaness; He, Shaoqiu; Cui, Xiang; Guan, Yun; Raja, Srinivasa N*	Systemic co-administration of peripherally restricted cannabinoid and mu-opioid receptor agonists synergistically inhibit the mechanical hypersensitivity in nerve-injured mice. Targeting cannabinoid and mu-opioid receptors in PNS using a low-dose pharmacological regimen could provide an efficacious and safer therapeutic approach for the treatment of neuropathic pain.
Peripheral nerve stimulation-induced adenosine A3 receptor (A3R) signaling contributes to the inhibition of lamina I NK1R-GFP neuron synapses in neuropathic mice	
Ford, Neil C.; He, Shaoqiu; Cui, Xiang; Zhang, Chi; Xu, Qian; Zhu, Guangwu; Dong, Xinzhong; Raja, Srinivasa N.; Guan, Yun.	Presynaptic A3R signaling mediates the inhibition of C-eEPSCs at NK1R-GFP neuron synapses produced by 50 Hz PNS of Aβ-fibers, which suggests the inhibition of ascending transmission of pain signals and thus pain perception. Our results highlight the clinical potential of PNS as a safe opioid-sparing treatment for neuropathic pain.
Activation of spinal adenosine 3 receptors contributes to spinal cord stimulation-induced pain inhibition in rats after nerve injury	
Xiang, Cui; Neil C., Ford; Shaoqiu, He; Chi, Zhang; Jing, Liu; Qichao, Wu; Guangwu, Zhu; Srinivasa N, Raja; Yun, Guan.	Activation of adenosine 3 receptor (A3R) signaling contributes to the inhibition of spinal nociceptive transmission by spinal cord stimulation (SCS) in rats after nerve injury, and SCS analgesia may be enhanced by targeting spinal A3R.
The effects of intraoperative methadone on postoperative pain control in pediatric patients: a systematic review	
Azamfirei, Razvan; Procaccini, Dave; Lobner, Katie; Kudchadkar, Sapna R.	Methadone usage in pediatric patients reduced postoperative opioid consumption, was non-inferior to other opioids in reported pain scores and had a similar frequency of adverse events. The quality of evidence was low highlighting the need for large, well-designed RCTs to evaluate the efficacy of intraoperative methadone in pediatric surgical populations.

Effectiveness of single-shot erector spinae blocks on perioperative opioid requirements and length of stay after Nuss procedure	
Aranda-Valderrama, Paola; Greenberg, Robert S., Vecchione, Tricia M.; Vanderhoek, Samuel M.	In pediatric patients undergoing the Nuss procedure for pectus excavatum, addition of single-shot ESP blocks to the perioperative analgesic regimen is safe, effectively decreases perioperative opioid requirements and facilitates earlier hospital discharge.
EZH2 in primary sensory neurons contributes to the development of neuropathic pain	
Jing Liu, Xiang Cui, Chi Zhang, Guangwu Zhu, Shaoqiu He, Yun Guan	Deletion of Ezh2 in DRG neurons prevented heat and mechanical hypersensitivities in nerve-injured mice, where the underlying mechanism may be through the function of H3K27me3 and downstream TRPV1 channels.
Epidural analgesia for labor: continuous infusion versus intermittent bolus	
Simmons, Samantha	Patients undergo many physiologic changes during pregnancy that increase their risk for local anesthetic systemic toxicity. Current literature shows that programmed intermittent boluses result in more extensive spread of local anesthetic in the epidural space, which ultimately reduces the total drug consumption and improves maternal safety.
Perioperative opioid tapering in patients on methadone medication-assisted treatment (MAT) for opioid use disorder (OUD)	
Leon, David; Jaremko, Kellie; Speed, Traci; Shechter, Ronan; Hanna, Marie	Engagement with Acute Pain Service (APS) in-patient and enrollment in Perioperative Pain Program (PPP) clinic post-operatively for patients on methadone for MAT, has shown to help these patients wean off, or stop altogether, from non-methadone opioids.

Quality Improvement

The perceptions of a novel syringe organizational device following implementation and its impact on operating room workflow during a surgical case.	
Sims, Harrison; Biro, Joshua; Shaik, Sabour; Rastogi, Sagar; Lusk, Connor; Woodward, Jeffrey; Neyens, David; Catchpole, Ken; Abernathy III, James	A simple syringe organizational hub was found to significantly reduce syringe movement. Provider acceptance of the device varied.
Standardizing front-line provider handoff in the pediatric intensive care unit	
Booth, Lauren D; Wieczorek, Beth; Ruddy, Theresa; Levin, Amanda; Robertson, Courtney; Tschudy, Megan M.; Bernier, Meghan.	The aim of this QI project was to standardize front-line provider (FLP) written handoff communication by using an EMR standardized script in a handoff tool. Written handoff compliance improved from 0% to 90% (median and mean), sustained for 8 months. An EMR script improved compliance of structured communication between FLPs.
Increasing pediatric interhospital transport efficiency: a quality improvement intervention	
Costabile, Philomena; Bhatia, Pooja; Devlin, Bridget; Harkins, Lauren; Frederick, Christina; Klein, Bruce; Tschudy, Megan; Noje, Corina	Johns Hopkins Pediatric Transport changed its transfer process by developing a dedicated intake-RN role, staffed by a transport nurse not providing direct patient care. While transport times did not decrease post-intervention, we believe this was largely due to the surge in critical care transports, compounded by historic ICU capacity challenges.

Utilizing an Ethiopian ICU registry to identify opportunities for quality improvement	
Laytin, Adam; Sultan, Menbeu; Zewdie, Ayalew; Hansoti; Bhakti; Checkley, William; Berenholtz, Sean	ICU registries collect data about epidemiology, processes of care and clinical outcomes for research and QI purposes. In Ethiopia, a context-appropriate ICU registry was piloted, and demonstrated a high burden of illness and commensurate high mortality rates. Improving early recognition of critical illness and triage protocols may improve ICU survival.
Multidisciplinary geriatric care in the PACU: a quality improvement initiative	
Sieber, Frederick; Wang, Nae-Yuh	The purpose of this pilot is two- fold: to fine tune our protocol which incorporates elements of hospital based multidisciplinary geriatric care (MGC) into current post-anesthesia recovery room (PACU) practice; to determine whether implementing a PACU based MGC model of care will decrease postoperative delirium in frail older surgical patients. Preliminary findings suggest that implementing a PACU-MGC program leads to a decrease in early postoperative delirium.
Pre-anesthesia counseling, consent, & professionalism	
Tomobi, Oluwakemi; Lee, Jay; Tran, Tina; Schiavi, Adam; Akca, Ozan; Chari, Asha; Azefor, Tangwan; Sampson, John.	A more structured informed consent process can help patients understand the roles of the anesthesiologist and other team members, increase risk recall for general anesthesia, elicit cooperation with and understanding of pre-oxygenation, and improve on perceptions of the specialty. The shared decision-making domain had greater benefit than the other domains.
Improving efficacy of provider communication during pediatric rapid response team calls	
Beal, James; Levin, Amanda; Jeffers, Justin; Shilkofski, Nicole	We designed an educational curriculum for pediatric resident physicians focused on pediatric emergency management and communication with emergency handoff using ABC-SBAR (airway, breathing, circulation, situation, background, assessment, recommendation). Surveys collected after pediatric rapid response team events were used to determine the efficacy of the educational intervention.
Feasibility of social work intervention in older adults before non-cardiac surgery	
Shomari Sankara, Charles Brown IV MD MHS, Lee Goeddel MD MPH	Psychosocial risk factors are increasingly associated with postoperative outcomes in vulnerable patients. We evaluated the feasibility of a social work intervention in older adults prior to surgery. In our first cohort of 96 patients 49 (51%) of patients were evaluated. We documented interesting early trend in the data collection and barriers to improve the function of the intervention.

Identifying factors that contribute to disrespectful maternal care—an observational pilot	
Stanislaus, Mellany; Lawson, Shari; Beach, Mary Catherine; Jones, Miranda; Ahmed, Saiffudin; Toy, Serkan	This observational pilot utilizes a survey to identify variables related to disrespectful maternal care. The study aims are to compare demographic data, clinical outcomes and survey responses between minority and non-minority patients; identify challenges of survey administration in the postpartum period; and estimate the incidence of perceived disrespectful maternal care.

Full Abstracts

The adenosine A2A receptor regulates miR-181b expression in aorta: therapeutic implications for large artery stiffness

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The identification of large-artery stiffness (LAS) as a major, independent risk factor for cardiovascular disease (CVD)-associated morbidity and mortality has focused attention on identifying therapeutic strategies to combat this disorder. As genetic manipulations that delete or inactivate the translin/trax (TN/TX) microRNA (miR)-degrading enzyme confer protection against aortic stiffness induced by chronic ingestion of high-salt water (HSW; 4%NaCl in drinking water for 3 weeks) or associated with aging, interventions capable of inhibiting TN/TX RNase activity may have therapeutic efficacy in LAS. Previous studies conducted in neurons have demonstrated that TX, but not TN, is associated with the C-terminus of adenosine A_{2A} receptors ($A_{2A}R$) and that stimulation of these receptors triggers dissociation of TX. As vascular smooth muscle cells (VSMCs) express $A_{2A}R$, we investigated whether stimulation of $A_{2A}R$ on VSMCs may lead to increased TN/TX complex activity. We found that treatment of A7r5 cells with the $A_{2A}R$ agonist, CGS21680, increases association of TX with TN. Furthermore, this treatment decreases levels of pre-miR-181b, a target of TN/TX, and mature miR-181b. To check whether $A_{2A}R$ activation might contribute to HSW-induced aortic stiffening, we assessed the impact of daily treatment with the selective $A_{2A}R$ antagonist, SCH58261, in this paradigm. We found that this treatment blocked aortic stiffening induced by HSW. Further, we confirmed that the age-associated decline in aortic pre-miR-181b/miR-181b levels observed in mice also occurs in humans. Taken together, these findings suggest that further studies are warranted to evaluate whether blockade of $A_{2A}Rs$ may have therapeutic potential in treating LAS.

Targeting LOXL2 in angiotensin II-induced hypertension

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Introduction: Hypertension is one of the major risk factors for cardiovascular diseases, including coronary artery disease, cardiac hypertrophy, atrial fibrillation, stroke, heart failure, and renal failure. Hypertension also accelerates arterial stiffening noted with natural aging. Aortic stiffness has been shown to be both a cause and a consequence of isolated systolic hypertension. Increased pulse pressure elevates pulsatile aortic wall stress, which escalates elastin degradation that normally occurs with aging and causes aortic stiffening. Thus, it is of high clinical interest to target arterial stiffening in the context of hypertension.
We have previously identified lysyl oxidase-like 2 (LOXL2) as a potential therapeutic target for treating vascular stiffening. LOXL2 is a key enzyme in the extracellular matrix (ECM) that catalyzes matrix deposition and remodeling. In a previous study, we showed that LOXL2 depletion decelerates arterial stiffening during natural aging by modulating matrix stiffness and smooth muscle cell (SMC) stiffness and contractility. In this study, we determined if LOXL2 depletion is also protective against hypertension induced arterial stiffening, via the established angiotensin II (Ang II) infusion model of experimental hypertension in LOXL2+/- mouse model.

Methods and Results: Ang II pumps were implanted in LOXL2+/- and WT mice for a 3-week treatment. Blood pressure and pulse wave velocity were measured noninvasively at different time points to assess hypertension and aortic stiffness. Results corroborated that Ang II infusion induces hypertension in both WT and LOXL2+/- mice, and that arterial stiffening is ameliorated in LOXL2+/- mice even when Ang II-induced hypertension is present. These results were supported by Western blotting. Then, uniaxial tensile testing was used to test the elastic properties of the aortic rings, and wire myography was used to test vasoconstriction and relaxation response. These experiments showed that the increase in arterial stiffness due to Ang II-induced hypertension is driven by both matrix remodeling and VSMC response. Histology analysis supported these findings, showing increased aortic wall thickness, interlamellar distance and collagen deposition in mice with Ang II infusion. Elevated heart weight in mice with Ang II infusion and qPCR results showed induced cardiac hypertrophy, which was not protected by LOXL2 knockdown. Then, human aortic SMC and endothelial cells (HAEC) were cyclically stretched, to show that the overexpression of LOXL2 in the aorta under Ang II-induced hypertension is upregulated by cyclic strain.

Conclusion: Arterial stiffening is increased with Ang II infusion; however, it is ameliorated in LOXL2+/- mice compared to WT mice when Ang II-induced hypertension is present. This rise in arterial stiffness is driven by both matrix remodeling and VSMC response. Cardiac hypertrophy occurred with Ang II infusion, and LOXL2 knockdown was not protective against it. Future studies will continue to 1) elucidate the mechanisms involved in the regulation of LOXL2 expression in response to Ang II-induced hypertension, 2) investigate the sex differences in in vivo stiffness and vasoreactivity, and 3) study LOXL2 as a potential therapeutic target against cardiac hypertrophy.

Increased amino acid utilization by the lung vasculature in pulmonary hypertension

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Background: Pulmonary arterial hypertension (PAH) is characterized by narrowing of the pulmonary arteries, endothelial cell dysfunction, and an increased proliferation of smooth muscle cells and fibroblasts. Moreover, there is distinct shift in metabolic activity, called the glycolytic shift, during which glucose molecules are shunted towards anaerobic respiration and production of critical macromolecules. This decreases the available glucose that can be used as a fuel in the tricarboxylic acid cycle. To compensate for the lack of metabolites due to the glycolytic shift, there is an increase in the use of non-glucose fuels - such as amino acids and fatty acids. However, the effect of this shift on other metabolic pathways is still unknown. In this study, we investigated the metabolic gradient that exists across the pulmonary circulation to define the metabolic shift that cells undergo during PAH.

Material and Methods: We carried out metabolomic analysis on serum samples taken from the right and left ventricles (RV and LV) of rats with PAH (SU5416/Hypoxia model: SuHx) and healthy controls.

Results: Induction of PAH resulted in increased pulmonary artery pressures and RV hypertrophy. Metabolomics of serum collected from the RV were different in PAH versus controls. This was driven by lower metabolite levels of several amino acids, including valine, glutamine, proline, alanine, phenylalanine, isoleucine, and tryptophan. Comparing the LV/RV ratio in our paired serum samples revealed that increased oxidized glutathione was a major determinant of the difference between the SuHx and control LV/RV metabolite ratios.

Conclusion: Our data shows decreased levels of amino acids in the RV serum of SuHx animals, this may be driven by an increased consumption in the pulmonary vasculature. Moreover, given that glutamine levels in the RV are decreased, while we observe a positive oxidized glutathione gradient across the pulmonary vasculature in our experiments. We hypothesize that glutamine consumption in the lung microvasculature may be driven in part by the use of glutamine to produce reduced glutathione. These results provide the basis for a mechanistic study aimed at understanding how interrupting glutathione and/or branched-chain amino acid metabolism in pulmonary vasculature contributes to PAH.

Resistin is a critical regulator of inflammasome activation in macrophages

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Introduction: Human resistin (hResistin) and its rodent homolog resistin-like molecule (RELM)-α are proinflammatory molecules, which activate immune cells and promote the secretion of other proinflammatory cytokines. Increasing evidence showed elevated levels of hResistin appear as a connecting link between multiple diseases including insulin resistance, diabetes, atherosclerosis, cardiovascular diseases (CVD), pulmonary hypertension (PH), autoimmune disease, malignancy, asthma, inflammatory bowel disease and etc. NLRP3 inflammasome was recently suggested to play a pivotal role in the occurrence of vascular inflammation leading to PH. However, the precise functional and mechanical roles of hResistin/ RELM-α, on NLRP3 inflammasome activation in immune cells are not yet fully understood. Hence, we aimed to study the detailed mechanism of how hResistin/ RELM-α regulates NLRP3 inflammasome in macrophages. We have previously reported RELM-α as a binding partner and activator of Bruton's Tyrosine Kinase (BTK) and one of the activators of high-mobility group box-1 (HMGB1). Since, both HMGB1 and BTK are regulators of the NLRP3 inflammasome we hypothesized hResistin regulates the priming and activation stages of the NLRP3 inflammasome through HMGB-1 (priming) and BTK (activation) in immune cells.

Methodology: The regulation of NLRP3 inflammasome activation pathways by hResistin/ RELM-α was investigated using both in-vitro and in-vivo studies. Human macrophages were stimulated with recombinant hResistin protein with or without inhibitors of hResistin, BTK and HMGB1. The NLRP3 inflammasome priming and activation pathways were determined in hResistin treated immune cells. To confirm the BTK driven NLRP3 activation, co-localization of NLRP3 and BTK was checked in lung sections of WT and RELMα-K/O mice kept in 4 days of hypoxia.

Results: Similar to the previously published data, we observed binding of hResistin to human BTK. hResistin upregulated the expression and secretion of HMGB1 in the human macrophages. hResistin induced the expression of NLRP3, pro-casase-1 and pro-IL-1β in macrophages, which were prevented by the hResistin blocking antibody (hResistin ab) or HMGB1 antagonist Box-A. hResistin also induced the activity of caspase-1 in human macrophages, which was prevented by the BTK inhibitor ibrutinib and hResistin ab. Moreover, hResistin induced the BTK-dependent IL-1β secretion in human macrophages. Consistently, hypoxia induced the RELMα-dependent upregulation of BTK and NLRP3 in the mouse lung tissues in vivo. Interestingly, the observed co-localization of NLRP3 and BTK in 4 days of hypoxic WT-mice was significantly reduced in RELMα-K/O mice, further confirming the fact that RELMα is a critical regulator of NLRP3 inflammasome activation.

Conclusion: This study confirms the novel concept of regulation of priming and activation stages of NLRP3 inflammasome through hResistin/RELMα. hResistin/ RELM-α regulates the priming and activation stages of the NLRP3 inflammasome through HMGB-1 and BTK in macrophages. Thus, the secreted IL-1β and IL-18 mediate the post-injury innate response and the transition to adaptive immunity, which is the mechanism of how hResistin/RELMα amplifies and sustains inflammation to induce vascular remodeling over time for PH development. It may also explain their role of hResistin in diseases such as atherosclerosis, cardiac remodeling/failure and LPS sepsis.

Effect of ECM and mechanical strain on vascular cell plasticity

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Authors have requested to not include the abstract for distribution.

Macrophage-targeted dendrimer-Tesaglitazar therapy for atherosclerosis

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Background: Atherosclerosis is a leading contributor to cardiovascular disease, the number one cause of death globally. Although atherosclerosis is increasingly being recognized as an inflammatory disease, with innate and adaptive immunity involved in the disease's progression, it is clearly a multicellular disease that also affects endothelial cells (ECs) and smooth muscle cells (SMCs) of arteries. Our goal is to determine if targeting immune cells in atherosclerosis is sufficient in halting, or even regressing plaque accumulation. Peroxisome proliferator activated receptors (PPARs) located in macrophages present a promising therapeutic target as PPAR-α and PPAR-γ agonists have been shown to improve lipid metabolism and inhibit macrophage foam cell formation. We target anti-atherogenic pathways in immune cells using D-Tesa, a dendrimer conjugate of a dual PPAR-α/γ agonist, Tesaglitazar.

Methods: 25-week-old, male, apolipoprotein E knockout ($ApoE^{-/-}$) mice were fed high fat diet (HFD) for 16 weeks to induce atherosclerosis. After 16 weeks on HFD, mice were randomized into two groups: 1) treatment group: D-Tesa for 6 weeks (20μg/kg twice weekly by oral gavage (n=8) and 2) (Sham) controls (n=9). D-cy5, a fluorescently labeled dendrimer that uses the same dendrimer as D-Tesa, was injected into a control mouse to determine uptake in plaque using confocal microscopy. Pulse wave velocity was measured by dividing the distance between two points along the descending aorta by the time taken for a cardiac pulse to transverse the determined distance. Blood pressure was taken via tail cuff measurement using a CODA Scientific noninvasive blood pressure system. Body weight measurements were also taken throughout the experiment. Aortic lipid deposition was quantified with Oil Red O staining and processed in ImageJ.

Results: Immunofluorescence staining and confocal microscopy revealed that the dendrimer used in D-Tesa was able to enter atherosclerotic plaque of $ApoE^{-/-}$ mice. Our study showed that after 6 weeks, D-Tesa decreased pulse wave velocity in treated versus untreated atherosclerotic mice (5.9±0.7 vs 3.5±0.4 m/s) with no alterations to blood pressure. Mice treated with D-Tesa also experienced a significant decrease in weight, despite HFD. Additionally, D-Tesa treated mice showed significantly less plaque accumulation when compared to untreated mice (51.6±5.3 vs 41.6±10.2 percent lesion area).

Conclusion: D-Tesa therapy ameliorates arterial stiffening and plaque deposition in an $ApoE^{-/-}$ model of atherosclerosis. It offers the surprising benefit of weight loss despite the continuation of a high fat diet. Further research will be conducted to investigate any sex differences and to see if macrophage targeting can have secondary benefits, such as improving endothelial dysfunction, to ameliorate atherosclerosis.

The effect of endothelin-1 on skeletal muscle function by regulating miR-133b expression

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Heart failure (HF) is extremely prevalent among the American populace, accounting for a large portion of mortalities. Recent studies suggest that insulin resistance (IR) and exercise intolerance (EI) are closely related to HF; however, the underlying mechanism connecting the three is unclear.

MicroRNAs (miRs) are small, non-coding RNA molecules that enact post-translational transcript regulation through genetic silencing of messenger RNAs (mRNAs). miRs play a significant role in skeletal muscle function and metabolism.

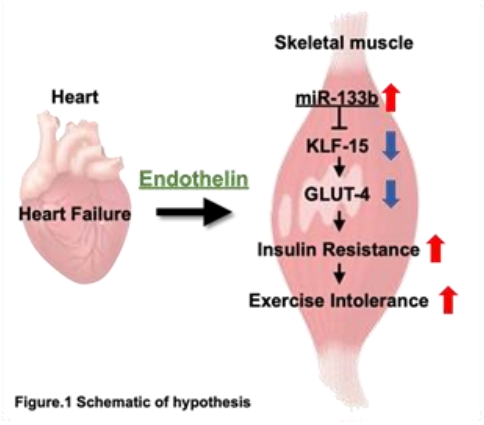

Figure.1 Schematic of hypothesis

Our primary goal is to understand the molecular mechanism of miR-mediated energetic abnormalities in skeletal muscle and verify their effects on EI in HF.

Our preliminary research suggests Endothelin-1 (ET-1) caused increased expression of miR133b in skeletal muscle, as well as downregulation of KLF15 and GLUT4 expression. Thus, we hypothesize that ET-1 mediates the expression of miR-133b in skeletal muscle and causes insulin resistance and finally leads to EI in HF.

Our two aims to test this hypothesis are: (1) to validate the effect of ET-1 on the development of IR in skeletal muscle (in vitro) and (2) to determine whether in HF, the lack of miR-133b expression protects against IR and EI in skeletal muscle (in vivo).
We will use a mouse with transverse aortic constriction (TAC) as an HF model. To test the effect of miR-133b, we will generate knockout mice, which will allow for comparison between the mice with and without miR-133b.

Our long-term goal for this project is to treat skeletal muscle dysfunction selectively and contribute to the improvement of EI in HF, targeting miR-133b. These experiments will allow us to determine if ET-1 and miR-133b are viable therapeutic targets to do so.

Directing multicellular organization by varying the aspect ratio of soft hydrogel microwells

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Multicellular organization with precise spatial definition is essential to various biological processes, including morphogenesis, development, and healing in vascular and other tissues. Gradients and patterns of chemoattractants as guides of multicellular organization are well-described, but the influence of three-dimensional geometry at physiological stiffnesses is less well defined. We present the discovery of a new mode of endothelial cell self-organization guided by a combinatorial effect of stiffness and three-dimensional geometry (microwells), independent of protein or chemical patterning. Endothelial cells in 2 kPa soft hydrogel microwells are approximately 30 times more likely to migrate to the microwell edge to organize in ring-like patterns than in stiff 35 kPa microwells. Furthermore, this self-organization is independent of curvature. Instead, we observe a quantitatively striking dependence on microwell aspect ratio (perimeter/depth) when cells are growing on soft 2 kPa hydrogels. Ring-like self-organization is significantly more pronounced in microwells with aspect ratio < 25. Experimental insights gained using Brillouin microscopy, quantitative epifluorescence/confocal microscopy, and pharmacological studies combined with mathematical modeling revealed that this ring-like self-organization results from the balance between tangential cytoskeletal tension, cell-cell, and cell-substrate adhesion. In addition to affecting multicellular organization in periodic microwells, we further show that this new mode of self-organization can be used to program reproducible cell patterning in customized CAD-designed microwell shapes, such as the letters of the word “CELL” simply by providing appropriate topological and mechanical cues. Our findings highlight the importance of the combinatorial effects of geometry and stiffness in complex cellular self-organization. We anticipate that this discovery can be leveraged to facilitate the engineering of bionics and integrated model organoid systems with customized nutrient vascular network.

Sex differences in vascular stiffening with age

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Introduction: Throughout the lifetime of humans and animals, large compliance vessels suffer changes in function and structure, becoming stiffer with aging. Increased arterial stiffness is a significant contributing factor in the cardiovascular system deterioration. During this aging process, the risk of cardiovascular disease (CVD) augments in both men and women, and even though pre-menopausal women are relatively protected from CVD, women suffer a significant risk acceleration after menopause. Studies have shown that older women present higher aortic stiffness compared to men, with a further increase in blood pressure, diastolic dysfunction, and left ventricular remodeling. Consequently, female prevalence of several diseases such as isolated systolic hypertension, refractory hypertension, and heart failure with preserved ejection fraction (HFpEF), is presumed to be strongly related to this increase in arterial stiffness.
Over the past decades, scientists have substantially advanced in the understanding of gender disparities in cardiovascular factors and outcomes, however, the mechanistic differences and manifestations of arterial stiffness in men and women require further investigation. It is crucial to better understand the sex variability in vascular stiffening and aging to help identify and develop novel risk assessment tools and therapeutic targets, and ultimately fulfil the goal of improving women's health. In this study, we determined if the key physiological features of sex differences are recapitulated in the C57BL/6J mouse model using indices of vascular stiffening.

Methods and Results: Male and female C57Bl/6J mice were used at 3-4 months old (premenopausal) and at 18-20 months old (postmenopausal). Pulse wave velocity (PWV), the gold-standard index of in vivo arterial stiffening, and blood pressure (BP) were measured noninvasively. Results showed a markedly increase in PWV with age in females compared to males, while BP remained the same in all groups. Tensile testing was measured to test the elastic properties of the aorta, which revealed that both intact and decellularized aorta from old mice were significantly stiffer than that of young mice in both male and female. Wire myography was used to test the vasoreactivity and relaxation response. Results corroborated that α1-adrenoreceptor-mediated vasoconstriction decreased with age significantly in females and not in males, and endothelial dysfunction was more striking in females. RT-qPCR revealed that estrogen receptor 1 (ESR1) expression decreased with age in females, and androgen receptor (AR) expression was elevated in post-menopausal females but not significantly.

Conclusion: Vascular stiffness is exacerbated in post-menopausal females compared to age-matched males. Older females' aorta also presents lower vasoconstriction and larger endothelial dysfunction compared to males. This study proves that the C57BL/6J mouse model is a robust and reliable pre-clinical model in which to study sex differences in vascular aging, because it recapitulates the sex differences observed in humans regarding indices of in vivo vascular stiffness. Future studies will continue to 1) elucidate the molecular mechanisms underlaying increased arterial stiffness in females after menopause, 2) identify and test novel targets to stop and/or reverse this increase in arterial stiffening, and 3) investigate the effect of elevated AR expression in older females in arterial aging.

hResistin regulates pulmonary smooth muscle cell activation and proliferation through macrophages

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Introduction: Human resistin (hResistin) is a cysteine rich secretory molecule that promotes the secretion of other proinflammatory cytokines from immune cells. High levels of circulating hResistin appear as a connecting link between multiple diseases including pulmonary hypertension (PH). Inflammasome activation is an emerging area of inquiry in PH research. However, the role of hResistin, in inflammation driven human pulmonary artery smooth muscle cells (PASMCs) proliferation and subsequently vascular remodeling in PH is not yet known. Since, the regulation of macrophages is required for a pro-proliferative microenvironment in the PH developing lung, our aim is to understand how hResistin regulates activation and proliferation of PASMCs through macrophages.

Method: Human THP-1 derived macrophages were treated with 20nM hResistin. After 24hrs incubation, media was collected. PASMCs were starved for 24 hours and were treated with macrophage conditioned media, with or without neutralizing IL-1β or IL-18 antibodies. After 30 minutes, phosphorylation of AKT and ERK1/2 were analyzed in western blot. Similarly, in another plate, after 24hrs, proliferation of PASMC, were further confirmed, with cell count and BrdU assay. To further confirm the effect of hResistin on SMC migration and proliferation through macrophage derived IL-1 β and IL-18, levels of matrix metalloproteinases (MMP-1) were also analyzed in western blot.

Results: Conditioned media from hResistin treated macrophages induced the proliferation of PASMCs. Interestingly, blocking IL-1β or IL-18 in PASMCs, caused significantly reduced cell proliferation. Moreover, phosphorylation of AKT and ERK1/2, which are key indicators of proliferation, was induced by the above conditioned media and prevented by blocking IL-1β or IL-18. Direct stimulation of the same dose of hResistin failed to induce PASMC proliferation. Similarly, MMP-1 was induced by hResistin treated conditioned media and were significantly reduced by blocking IL-1β or IL-18.

Conclusion: Our study shows hResistin plays an important role in regulating macrophages to induce pro-proliferative environment, specially via IL-1β and IL-18 secretion that induces post-injury innate responses and PASMC proliferation to induce vascular remodeling over time for PH development. However, the exact mechanism of hResistin-regulated inflammasome activation for vascular remodeling and PH needs further investigation.

B cells are regulated by RELMα in pulmonary hypertension

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Introduction: Abnormalities in B cell function have been linked to immune dysregulation and PH pathogenesis. Resistin-like molecule (RELM) α, the rodent homolog of human resistin (hResistin), is the most hypoxia-upregulated gene in mouse lung, and RELMα/Hresistin are implicated in PH development. However, the interaction between RELMα/hResistin and B cells in PH has not been reported. Bruton's tyrosine kinase (BTK) is a key component of B-cell-receptor (BCR) signaling. We previously identified BTK as a critical binding partner of RELMα/hResistin that mediates chemokine actions on macrophages, B cells and bone marrow cells. Here we suggest a role of RELMα/hResistin in regulating B cell signaling in PH.

Methods: We used a chronic hypoxia model of PH in wild-type (WT) and RELMα gene knock-out (KO) mice with parallel normoxia controls to determine RELMα-regulated B cell signaling in vivo. We also examined the functions of hResistin-stimulated human B cells in vitro.

Results: Gene array analysis showed that the BCR component CD79b is one of the top downregulated genes in the RELMα-KO hypoxic lung compared to WT control, indicating that RELMα activation remarkedly upregulates BCR signaling. Using the anti-RELMα/hResistin therapeutic antibody, we further revealed that RELMα activation induces the recruitment of B cells to the hypoxic PH-developing lung. Intriguingly, stimulation of RELMα recombinant protein facilitated B1 polarization of the primary B cells isolated from mouse lung. In vitro, hResistin protein treatment induced the BTK-dependent migration of human B cells. Moreover, hResistin induces the production of BTK and HMGB1 (the key DAMP molecule) in human B cells.

Conclusion: RELMα/Hresistin recruits B cells to the lung in PH. RELMα/hResistin also regulates the pro-inflammatory function of B cells, which is an important mechanism of the RELMα/Hresistin-induced vascular inflammation and remodeling in PH.

Hypertension augments monocyte inflammatory response which impairs endothelial barrier function

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Department of [1]Anesthesiology and Critical Care Medicine, [2]Biomedical Engineering, [3]Center for Nanomedicine, and [4]Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD 21287

Introduction: Inflammatory vasculopathies in the setting of acute infection increase morbidity and mortality as was seen in critical SARS-CoV-2 infection. Comorbidities associated with systemic inflammation, including hypertension and obesity, are noted to increase the risk of critical illness. Here we investigate the inflammatory response of healthy donor and hypertensive donor monocytes as a mechanism of endothelial barrier disruption.

Methods: Cytokine release by CD14+ monocytes from two Caucasian males (one healthy and one with obesity and hypertension) was compared at baseline and after exposure to SARS-CoV-2 recombinant spike protein receptor binding domain (S-protein-RBD) by multiplex ELISA. Next, human lung microvascular endothelial cells (HLMVECs) from a healthy donor were exposed to control media, S-protein-RBD or monocyte conditioned media (MCM) collected in the first phase. Endothelial barrier function was measured by electric cell-substrate impedance sensing. Finally, western blotting was used to investigate S-protein-RBD internalization within endothelial cells exposed to MCM from healthy and hypertensive/obese monocytes exposed to S-protein-RBD or control media.

Results: Hypertensive/obese-subject monocytes exhibited exaggerated IL-6, IL-8, IL-12p70, TNF-α, and IL-10 secretion following exposure to S-protein-RBD. Further, MCM from hypertensive monocytes was sufficient to disrupt HLMVEC barrier integrity both with and without exposure to S-protein-RB (Figure). When treated with MCM from healthy monocytes, HLMVEC barrier integrity was maintained and, even following stimulation with S-protein-RBD, capable of barrier recovery. Notably, HLMVECs exposed to S-protein-RBD alone demonstrated no change in barrier activity. Additionally, S-protein-RBD internalization was increased by exposure to MCM from hypertensive/obese-subject monocytes stimulated by S-protein-RBD.

Conclusion: In vitro data demonstrate a link between systemic inflammatory states (obesity and hypertension) and potentiation of monocyte mediated cytokine release capable of disruption endothelial barrier integrity. Further, when stimulated with SARS-CoV-2 S-protein-RBD this effect was enhanced such that monocytes from a donor with obesity and hypertension disrupted endothelial barrier integrity to a greater degree and limited barrier recovery. These findings suggest a link between systemic inflammatory states and an immune mediated mechanism of endothelial damage that is exacerbated in acute infection.

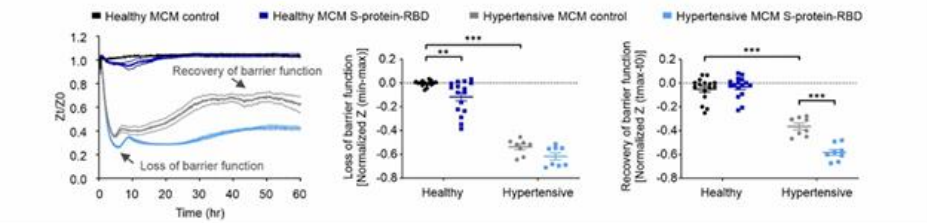

Figure: Normalized endothelial barrier impedance (Z_t/Z_0) as a function of time (Left) demonstrates loss of barrier function (Center) and impaired recovery (Right) when treated with MCM from hypertensive monocytes.

Sexual dimorphisms present in downstream elements of AGO-2/miR-181c pathway

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MicroRNAs (miRNAs) perform critical functions in normal physiology and disease by associating with AGO2 and downregulating partially complementary messenger RNAs (mRNAs). It has been shown that the obesity results in overexpression of one of these miR, miR-181c, and can lead to heart failure by translocating the AGO2-miR-181c complex to the mitochondria, decreasing mt-COX1 protein (target of miR-181c) and stimulating reactive oxygen species (ROS). As a key player in these mechanisms, AGO2 and phosphorylation of Ago2 at S387, generated by Akt, facilitates the interaction with GW182 and their localization to cytoplasm. In this way, the phosphorylation of AGO2 at serine residue 387 inhibits the translocation of the AGO2-miR-181c complex to the mitochondria, reducing the production of ROS by preventing the decrease of mt-COX1. In the other hand, premenopausal females have a lower risk for cardiovascular disease, the mechanisms are poorly understood. The present study tested the hypothesis that AGO2 play an important role in the sexual dimorphism of heart.

We found that miR-181c was significantly decreased in mitochondria from the hearts of female mice compared to those of male mice. Furthermore, we detected that AGO2 phosphorylation at serine 388 (serine 387 analog in humans) in female mice and serine 387 AC16 cells treated with estradiol was significantly increased. Also, downstream elements of the AGO2-miR-181c pathway, such as Sp1 and MICU1, were significantly increased in female mice hearts compared to male mice hearts.

These data suggest that higher levels of AGO2 activation play an important role in female cardioprotection.

Effect of maternal inflammation on arterial stiffness in early Age

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Inflammation in utero can have adverse consequences on fetal development, causing long-term effects on resulting offspring. The maternal inflammatory response has well documented detriments on the fetus such as neurodegenerative diseases. The in-utero environment can impact the future health of offspring-a theory known as fetal origins of adult disease. However, little is known about the effect of maternal inflammation on the cardiovascular system. We hypothesize that impairments prompted by fetal exposure to inflammation in utero affect arterial development. Mechanistic studies are hindered because mouse/rat pups are very small and standard arterial measurements are not possible in early, postnatal age. Therefore, we developed and used a rabbit model to study arterial aging in the neonatal to adolescent age range. To this end, we measured arterial stiffness in rabbits from post-natal day 1 to 60. Tensile testing (electromechanical puller) was used to examine the mechanical properties of aortic rings. Briefly, force-displacement data acquired from the electromechanical puller were converted to stress-strain curves using sample dimensions (wall thickness, length, and lumen diameter) determined using microscopy. We found that there is an age dependent increase in aortic stiffness due to structural properties mediated by both elastin and collagen. The diameter and wall thickness of aorta also increased with age. We then evaluated if maternal exposure to inflammation shifts the time trajectory of arterial stiffening in early age. Pregnant rabbits 28 days into gestation, were given intrauterine injections of LPS. Labor was induced two days later (gestational day 30) to deliver kits that were subjected to intrauterine inflammation. 1- and 3-day old rabbit kits exposed to LPS in utero did not display a significant difference in aortic stiffness when compared to age matched control kits. At day 7, we saw a definitive increase in stiffness in endotoxin kits. Further work will be conducted at older age groups to determine if the difference in aortic stiffness increases with age. Our data on the passive vessel stiffness of untreated kits provides the groundwork for identifying the impact of intrauterine inflammation in the cardiovascular space as well as a baseline for treatment.

The role of the unfolded protein response and LOXL-2 in heart failure with preserved ejection fraction

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Background
The fundamental mechanism that leads to heart failure with preserved ejection fraction (HFpEF) is incompletely understood. Unfolded protein response (UPR), an adaptive cellular defense mechanism that is activated in response to endoplasmic reticulum stress (ER), has been implicated as a causative mechanism; however, the critical molecular pathways that lead to the development of HFpEF remain unclear. Our hypothesis is that LOXL-2 plays a central role in UPR dysregulation and subsequent apoptosis and matrix remodeling in HFpEF, and its blockade will ameliorate or reverse the effect of ER stress on matrix remodeling.

Methods
We used 1. A7R5 cell culture to trigger the unfolded protein response by exposing the cells for 24 hours to hypoxia, hyperthermia at 40°C, and their combination, and 2. an established ZSF1 rat model to interrogate the mechanism in vivo. LOXL2 expression in the cell cultures was determined by Western blotting, and the in vivo development of HFpEF was assessed by cardiac pulsed wave Doppler echocardiography in lean and obese ZSF1 rats.

Results
1. Both hypoxia and hyperthermia induced cell death in the cell cultures; concomitant exposure resulted in fewer cell death than exposure to hyperthermia alone. 2. LOXL2 expression was increased in the treatment groups relative to the controls. 3. The obese ZSF1 rats demonstrated echocardiographic evidence of diastolic dysfunction at baseline compared to heathy lean rats. The interim assessment showed worsening diastolic dysfunction in the obese cohort.

Conclusions
1. Both hypoxia and hyperthermia are physiologic stressors that induce apoptosis in A7R5 cells. 2. Hypoxia is protective against the detrimental effects of hyperthermia. 3. The ZSF1 rat model is suitable to recapitulate the clinical and echocardiographic features of HFpEF.

ACCM Confocal Microscope Core

George McNamara[1,2], Cyrus David Mintz[1,3]

[1]ACCM Confocal Microscope Core, [2]Ross Fluorescence Imaging Center, Division of Gastroenterology, [3]Division of Anesthesiology and Critical Care Medicine, Department of Medicine, Johns Hopkins School of Medicine

Leica DMi8 inverted microscope with SP8 spectral confocal scanhead with two HyD *photon counting* Detectors and a full range of laser lines (405, 488, 552, 638 nm).

Rates

- $27/hour for fully trained **expert** users, **during** JHMI business hours (Mon-Fri 9am-5pm).
- $20/hour for fully trained expert users, **outside** JHMI business hours (outside Mon-Fri 9am-5pm).
- $120/hour for Dr. McNamara to operate the confocal microscope for users who need an operator.

ACCM has bought substantial user time on this microscope and will distribute it to departmental researchers based on need and scientific merit, please contact Dr. Mintz (cmintz2@jhmi.edu) to request a grant of user hours.

Features

- Ross Bldg 910 scan card access for all fully trained users, **available 24/7** trained users**.**
- Leica DMi8 inverted microscope, automated XY stage, Z-focus, up to 8192x8192 pixels.
- Two HyD photon counting detectors è better sensitivity and quantitation than PMTs.
- HyVolution2 GPU enabled deconvolution (‘near instant gratification’, improved contrast).
- 5x/0.15 NA dry objective lens = large field of view (1.0 Airy unit, 666 nm XY pixel size).
- 20x/0.75 NA dry objective lens (1.0 Airy unit, 120 nm XY pixel size).
- 63x/1.40 NA oil immersion objective lens:
  - for 1.0 Airy unit pinhole size, we recommend 60 nm XY pixel size.
  - for 0.6 Airy unit pinhole size, we recommend 50 nm XY pixel size (1.2x increased resolution; use with HyVolution2 GPU deconvolution).
- Emission spectra scanning 9rarely needed).
- Spectral and channels unmixing.
- Leica NAVIGATOR tile scanning available.
- ACCM confocal Microscope Core is directed by Prof. Cyrus David Mintz.
- Managed by Dr. McNamara (31 years professional microscopist) in conjunction with Ross Fluorescence Imaging Center (FIC), Director. Bin Wu, single molecule imaging expert, single molecule RNA FISH, biophysicist and neuroscientist. FIC microscopes are all available to ACCM staff (Olympus FV3000RS confocal, FISHscope, etc).
- Dr. McNamara is now also manager of High Throughput Phenotypic Screening Core (Jeff Mumm, PI), able to screen zebrafish larvae, brain organoids, tumor spheroids.

iLab Scheduler https://johnshopkins.corefacilities.org/equipment/345585
Information http://confocal.jhu.edu/current-equipment/leica-sp8-confocal-microscope

Midazolam effect on long-term outcomes in preclinical model of pediatric traumatic brain injury

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Introduction

TBI is one of the leading causes of disability and death in the pediatric population. The most critically ill are admitted to the pediatric intensive care unit where they are exposed to necessary sedative medications and in often escalating doses. Benzodiazepines, which in preclinical studies have been shown to impair neurodevelopment and cognitive outcomes, are often used as an adjunctive class of sedatives in the care of these patients. We hypothesized that early exposure to midazolam following TBI would worsen outcomes in a pediatric pre-clinical model.

Methods

Male Sprague-Dawley rats (postnatal day, PND 17) were divided into four groups: naive (n=5), naive with sedation (n=9), TBI (n=12), and TBI with sedation (n=12). TBI groups underwent controlled cortical impact (CCI). Starting on post-injury day (PID) 1, sedation groups received 12 hours per day of sedation, using intra-peritoneal injections of midazolam, given at intervals to maintain sedation based on a standard rating scale. The rats were divided into short term, mid-term, and long-term groups and were sacrificed on post-injury day 4, 28 and 60-100 respectively. In our long-term behavioral studies, the rats underwent behavioral testing with visual discrimination touchscreen task, open-field and gait analysis. After completion of behavior tests, the rats were then sacrificed and ex-vivo brain MRI analysis was completed.

Results

Previous works have shown short-term sedated rats following TBI had less neuro-inflammation and apoptotic cell death. On visual discrimination analysis, TBI-sedation rats had higher failure rates, committed more errors, and required more correction trials. With open field testing, TBI-sedation rats spent less time in the center of the field and had more deficits on gait analysis. MRI analysis is ongoing and includes measurements of total tissue loss, white matter volume loss and brain subregion injury analysis.

Conclusion

In our previous short-term histological studies, TBI-sedation rats had reduced microglial activation and reduced apoptotic activity compared to injured rats without sedation. These findings suggested potential neuroprotective properties of midazolam. However, this reduction in inflammation and neuronal cell death did not translate into improvements in cognitive function. Ongoing studies will use ex vivo brain MRI to measure tissue loss in our pediatric TBI model.

Clinical and telemetric electroencephalographic seizure monitoring in a neonatal piglet model of hypoxic-ischemic encephalopathy and therapeutic hypothermia

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Neonatal hypoxic-ischemic encephalopathy (HIE) is a risk factor for seizure disorders. No clinically relevant large animal model exists for modeling perinatal brain damage, therapeutic hypothermia, progression of electrical seizure activity and associated motor phenotypes, and single-cell neuropathology in combination. A gyrencephalic neocortex is necessary to better model human neonatal neuropathology and epileptogenesis. We sought to develop such a model. Neonatal piglets received hypoxia-ischemia (HI)+normothermia (n=9), HI+overnight hypothermia (n=6), sham+normothermia (n=6), or sham+overnight hypothermia (n=6). Piglets were sedated, intubated, anesthetized subjected to 45 min hypoxia (FiO_2 0.1), followed by 5 min room air, and then 8 min asphyxia. Piglet resuscitation was achieved with 50% oxygen, chest compressions, and epinephrine. Some piglets, before the HI protocol, were instrumented with sterile epidural 4-lead electrode telemetry arrays. Secure and permanent electrode placement was done by craniotomy and micromanipulation of contact screw insertion precisely onto the dura mater. The transmitter was placed subdermally in a neck pocket with the antenna exiting posteriorly. Piglets had continuous electroencephalography (EEG) during recovery and overnight manual video recording. All piglets were unmedicated. Piglets that developed intractable seizures were euthanized. Piglet survival was 2-7 days. Piglets were perfused with 4% paraformaldehyde for electrode placement verification as epidural and brain paraffin processing, sectioning, and hematoxylin & eosin neuropathology. Clinical seizures usually emerged 24 hours after extubation. They often appeared during sleep, consisting of sudden arousal, repetitive rooting, and orofacial twitching and then clonic movement. Clonic movements spread from the head region to the shoulder and forelegs appearing as more generalized tonic clonic seizures. Some piglets ultimately developed fictive running movements using forelegs and hindlegs and advanced to apparent status epilepticus. Continuous EEG confirmed the presence of seizures in some piglets as seen by rhythmic spike-wave complexes appearing in specific areas of neocortex and then generalizing to other areas of neocortex. Seizures were seen in HI piglets with and without hypothermia. The neuropathology in neocortex was topographically organized and ranged from selective neuronal injury, laminar necrosis, to pan-laminar necrosis. Subcortical areas were also damaged. We thus have developed a unique gyrencephalic large animal model that comprehensively integrates clinically relevant neonatal HIE, a therapeutic standard of care, continuous EEG, survival, a neurologic phenotype, and cellular neuropathology.

Dendrimer conjugation significantly improves brain pharmacokinetics and therapeutic efficacy of neutral sphingomyelinase 2 inhibitor DPTIP for treating Alzheimer's Disease

Elizabeth Wilkinson, Anjali Sharma, Arindom Pal, Carolyn Tallon, Ying Wu, Ajit Thomas, Seung-Wan Yoo, Norman Haughey, Rana Rais, Kannan Rangaramanujam, Barbara Slusher

Hydroxyl terminal PAMAM dendrimers (PAMAM-OH) have shown significant potential for targeting activated microglia and neuroinflammation in preclinical models and in humans, with positive implications for many CNS diseases. In the case of Alzheimer's Disease (AD), which constitutes a growing health concern, increased microglial inflammatory activity is a prominent pathological feature. The extracellular vesicles (EVs) that traffic cargo such as pro-inflammatory cytokines, amyloid β protein, and tau protein to neurons have an active role in the progression of AD. The enzyme neutral sphingomyelinase 2 (nSMase2) is, in part, responsible for regulating this biosynthesis, and nSMase2 downregulation has been shown to reduce EV secretion and subsequently slow tau propagation, plaque formation, and ultimately improve cognition in mouse models of AD.

Using a high throughput screening of over 365,000 compounds, 2,6-dimethoxy-4-(5-phenyl-4-(thiophen-2-yl)-1H-imidazol-2-yl) phenol (DPTIP) has emerged as a highly promising candidate for the inhibition of human nSMase2. DPTIP is potent, selective, elicits a dose-dependent reduction of EV release *in vitro,* and in an IL-1β induced mouse model of brain injury when administered intraperitoneally. As DPTIP directly targets disease progression, it constitutes a novel treatment unlike any of today's symptom-based approaches. Despite its potency, DPTIP exhibits low oral bioavailability ($F<5\%F<5\%$), moderate brain uptake, and a short half-life ($t_{1/2}<0.5\ \mathrm{hr}$) when administered orally in its free form. Consequentially, we have conjugated DPTIP to PAMAM-OH to promote targeted delivery to activated microglia and enhance the oral pharmacokinetics. Here, we describe the synthesis and characterization of the novel G4 PAMAM-OH dendrimer-drug conjugate D-DPTIP. We synthesized D-DPTIP, using a scalable methodology. *In vitro*, D-DPTIP is chemically stable at extracellular pH 7.4, releasing <20% of the drug payload over 3 weeks, while >90% DPTIP releases at intracellular pH 5.5 over 2 weeks. *In vivo*, oral administration of D-DPTIP to PS19 mice expressing mutant human tau increases the plasma clearance time (to 4h from 24h), half-life (50h vs 4h) in the brain, and brain:plasma ratio (4.9 vs 0.26) relative to free DPTIP. Additionally, D-DPTIP inhibits EV release for 48h and attenuates nSMase2 activity while free DPTIP showed no significant effects when administered perorally to mice with IL-1β induced brain inflammation. In the future, similar strategies may be employed to significantly improve the therapeutic effect of drugs that may otherwise be deemed unsuitable for *in vivo* administration.

Cerebral lipid metabolism in rabbits with central nervous system tuberculosis

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Background: Central nervous system (CNS) tuberculosis (TB) is the most dangerous and fatal form of extrapulmonary TB. While CNS TB comprises only 2% of cases, a majority impacts those under 2 years old. Current treatment relies on complex antimicrobial regimens and corticosteroids which are not uniformly effective, therefore novel therapeutic targets are needed. Studies in pulmonary TB showed infection sites undergo upregulation of lipid metabolism and sequestering with high levels of cholesterol ester (CE), cholesterol (CHO), and triacylglycerol (TAG). It is believed that reorganization of host lipid metabolism is one way *Mycobacterium tuberculosis* evades the host immune system and obtains nutrients. The role of glycerophospholipids (GPL), phospholipids, and sphingolipids (SL) and their metabolisms have not been thoroughly explored in CNS TB, even less so in a pediatric rabbit model. Matrix Assisted Laser Desorption Imaging (MALDI) mass spectrometry was performed to compare TB-infected and uninfected rabbit brains to identify potential lipid targets.

Methods: Rabbits with and without experimentally induced CNS TB via parenchymal injection of *M. tuberculosis* (TB-infected, n=1) or saline (uninfected, n=1). Infection incubated for 3 weeks prior to harvest and fixation. Brains were cryosectioned (at 10µm) onto indium tin oxide coated slides and sprayed with 40 mg/mL DHB in 50% acetonitrile. MALDI imaging was performed in reflection positive mode with 100µm spatial resolution. Data was imported into SCiLS Lab for analysis and ROC was used to determine significant differences. The m/z values were used in the LMSD Database to obtain the lipid identities.

Results: Several lipids related to cholesterol metabolism were decreased in the TB brain compared to the uninfected brains. Notable metabolites included cholesterol precursor 7-dehydrocholesterol-d7 (390.977 m/z), cholesterol ester CE 20:4 (672.416 m/z) which were the only mammalian cerebral lipids that were obtained with the search. Additional significant peaks and their most likely lipid identities: 369.344 m/z (GPL/SL) 566.993 m/z (GPL), 706.528 m/z (GPL), 707.513 m/z (GPL), 728.507 m/z (GPL), 732.525 m/z (GPL), 733.536 m/z (GPL), 755.515 m/z (GPL), 751.55 m/z (GPL), 782.576 m/z (GPL), and 783.56 m/z (GPL). Two peaks, 360.058 m/z and 378.072 m/z, were likely to be cholesterol derivatives but have not yet been confirmed. The CNS TB brain was further analyzed to compare the hemisphere with the lesion to the hemisphere with no lesion and we found that lipid levels were increased in the lesional hemisphere. Notable peaks included: 329.006 m/z (SL), 350.985 m/z (SL), 369.344 m/z (GPL/SL), 703.575 m/z (GPL), 704.559 m/z (GPL), 725.554 m/z (GPL), 726.565 m/z (GPL), 742.529 m/z (GPL), 742.503 m/z (GPL), 743.541 m/z (GPL), and 807.535 m/z (GPL). Finally, notable potential cholesterol derivatives included: 360.058 m/z and 400.343 m/z.

Conclusions: Our investigation in rabbits with CNS TB showed lipid content was spatially heterogeneous with decreased host lipids in the TB-infected brains compared to uninfected, but areas of higher concentration in the TB lesions. Further MS/MS analysis using silver nitrate matrix is planned to confirm the identities of these peaks.

The effect of secreted frizzled related-protein 3 (sFRP3) and Wnt signaling on cognitive behavior after traumatic brain injury

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Traumatic brain injury (TBI) is a major cause of death and disability, with an incidence of approximately 64-74 million cases occurring worldwide each year. An important avenue of research in TBI has been the use of stem cells for repair after injury. Wnt signaling modulates diverse cellular processes, including stem cell proliferation, differentiation, regeneration, and inflammation, through the canonical Wnt/β-catenin and the noncanonical Wnt/calcium pathways. Recent studies have revealed that inhibition of the secreted Frizzled Related-Protein 3 (sFRP3), an inhibitor of Wnt signaling, regulated neural stem cell quiescence and increased activity-dependent proliferation and maturation in the hippocampus. Nevertheless, the role of sFRP3/Wnt in neurogenesis after brain injury remains unclear. Here, we examine the effect of sFRP3 deletion on neurogenesis in the subgranular and subventricular zones after TBI. We assess whether sFRP3 depletion promotes functional recovery four weeks after TBI. We used 10-12 weeks old male C57BL/6 and homozygous sFRP3 knockout mice. The mice were randomly assigned to three groups: TBI, sham (craniotomy), and naïve. TBI was induced by controlled cortical impact (1.0mm depth, 3.0m/s at 15° impact angle). TBI causes a significant increase in righting reflex and modified neurological severity score. sFRP3 depletion improves the neurobehavioral outcome of learning and memory assessed by novel object recognition 4 weeks after TBI. Immunohistochemical analysis is currently underway to quantify the effects of sFRP3 inhibition on neurogenesis after TBI, assessing survival, differentiation, and maturation, in correlation with the described functional effects.

This work was supported by NIH grant R01NS105894.

Keywords: behavioral function, cognition/learning/memory, stem cells, neurogenesis

Bioenergetic failure and tryptophan metabolism perturbations following traumatic brain injury in an experimental juvenile rabbit model

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In this study, we report results of metabolic changes from a juvenile rabbit traumatic brain injury model using a controlled cortical impact injury. Metabolic changes were determined using a mass spectrometry-based metabolomics approach where post-natal day five rabbit kits were injured. Ipsilateral brain regions to the impact site were collected one and three days after injury and compared to sham controls. Six biological replicated samples were analyzed per experimental condition. At one day and three days post injury, several tryptophan metabolites were elevated and in particular, kynurenic acid, a metabolite of the kynurenine pathway that is reported to be neuroprotective, as much as ten times relative to sham animals. Additional perturbations in bioenergetic metabolites including glucose, N-acetyl aspartate, creatine, urate (ATP/GTP degradation product) and NAD+/NADH were found one day after injury. Three days after injury, NAD+ and NADH continued to decrease. Currently, the only known endogenous de novo synthetic pathway of NAD+/NADH is via tryptophan metabolism/the kynurenine pathway. Much of the perturbations in the kynurenine pathway are thought to derive specifically from microglial cells, the primary immunomodulatory cell of the central nervous system. Therefore, additional metabolic analysis of microglial cells both in vitro and in vivo were conducted to determine their influence on tryptophan metabolism and contribution towards bioenergetic perturbations. Our results help improve our understanding of the temporal evolution of metabolic changes and the immune response during injury and repair after TBI in the hopes of identifying novel therapeutic strategies and targets.

Transcranial photoacoustic imaging of middle cerebral artery occlusion stroke model in neonatal piglets in vivo

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*Both authors contribute equally to this work.

Early differential diagnosis of perinatal ischemic stroke from global hypoxia-ischemia is often difficult, which prevents an accurate decision making for the best follow-up treatment. In this study, we tested the ability of a transcranial photoacoustic (PA) imaging probe to non-invasively detect embolic stroke induced by a single-side cauterization of middle cerebral artery (MCA) within 1 h of onset in a gyrencephalic piglet brain. The area of stroke lesion, where oxyhemoglobin (HbO2) concentration is lower than 30%, was measured over the 25 mm2 area in the first 1 mm brain tissue depth for a comparative evaluation between MCA cauterization and control groups (n = 4 each). In the 0.2-mm interval, the spectroscopic PA images of the MCA cauterization group showed decreasing trend from wider stroke region at the surface (i.e., {2.21±2.69, 1.38±1.88, 1.25±1.51, 1.10±1.23, 0.7±0.82}), which was not presented in the control group (i.e., {0.80±0.86, 0.77±0.80, 0.72±1.12, 0.46±0.44, 0.92±1.12}). The maximal difference is presented at the brain tissue surface with up to 2.74 times wider area. The regional brain injury due to the single-sided MCA cauterization was validated by 24 h post-stroke cerebral infarction confirmed in the triphenyltetrazolium chloride (TTC)-stained images. The results indicate the capability of transcranial PA imaging to identify embolic stroke model with MCA cauterization, which is consistent with our previous results to identify global hypoxia and thrombotic stroke.

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The effect of J147 as a novel therapeutic on apoptosis in hippocampus with neonatal hypoxic-ischemic encephalopathy

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Background. Neonatal hypoxic-ischemic encephalopathy (HIE) occurs in interruption of oxygenated blood supply to brain in the period surrounding birth, which leads to nerve cell death resulting in brain damage. Infants who survive HIE often have clinically apparent cognitive impairment or neurologic disorders. Currently, there is no FDA-approved pharmacologic treatment available for HIE. J147 ($C_{18}H_{17}F_3N_2O_2$) is an experimental drug against Alzheimer's disease and aging in mouse models. J147 ameliorates dysfunction of intercellular calcium metabolism and ATP synthesis, which leads neurotoxicity and cell death. In this study, we are looking to determine whether J147 may reduce specifically neuronal apoptosis in HIE mice. This would further demonstrate the potential of J147 as a treatment for HIE.

Methods. Two cohorts of C57BL6 mice were used: (1) for immunohistochemistry (IHC) and (2) for Western blot (WB). Hypoxic-ischemic (HI) was performed at P10. Briefly, under 1.5% isoflurane anesthesia, the right common carotid artery was permanently blocked with a cautery. After 1 h recovery, animals were exposed to 8% oxygen with balance nitrogen for 45 min. Sham animals did not undergo carotid artery blockage and hypoxic exposure. After HI, mice were daily fed by oral gavage with J147 dissolved in corn oil or oil only as vehicle (Veh). For both cohorts, animals were divided into three groups: Sham; HI+Veh; and HI+J147. Mice for IHC were given J147 in a series of doses (0.5mg/kg; 1mg/kg; 5mg/kg; 10mg/kg; 25mg/kg) at P10-P14 and perfused with 4% paraformaldehyde at P14. Brain sections were immuno-stained for NeuN, caspase-3, or TUNEL. NeuN+ area in hippocampus was measured and numbers of caspase-3+ or TUNEL+ cells were counted with ImageJ. Animals in cohort (2) received 10mg/kg J147 until sacrifice at P11, P14, or P17. Hippocampus tissue was removed and WB was conducted for caspase-8 (early apoptosis marker), caspase-9 (mid-phase marker), and Parp-1 (late marker).

Results. (1) IHC. 0.52 mm^2 NeuN+ area per section in Sham, 0.32 mm^2 in HI+Veh ($p<0.01$), and 0.45 mm^2 in HI+J147 ($p<0.05$ to HI+Veh) were observed. Number of TUNEL+ cells per section in HI+Veh was dramatically increased than Sham (372.7 vs. 36.3, $p<0.0001$) and J147 partially reversed this number (208.2, $p<0.01$). For per section, very little caspase-3+ cells were seen in Sham (3.5) and HI+Veh induced apoptosis (120 cells; $p<0.0001$). Different doses of J147 decreased this number. 104.8 cells ($p>0.05$) were seen in mice with 0.5mg/kg J147; 94.5 cells ($p>0.05$) in 1mg/kg group; 38.3 cells in 5mg/kg group ($p<0.01$); 28.8 cells in 10mg/kg ($p<0.001$); and 20.67 cells in 25mg/kg group. (2) WB. Immunoreactivity of caspase-8 over standard marker was enhanced in HI+Veh and reduced in HI+J147 in all timepoints [**P11:** 87.4% vs. 136.7% ($p<0.01$) vs. 95.5% ($p<0.05$); **P14:** 79.5% vs. 145.4% ($p<0.001$) vs. 103.4% ($p<0.05$); **P17:** 88.9% vs. 141.9% ($p<0.01$) vs. 89.8% ($p<0.01$)]. Caspase-9 intensity in Sham was less than in HI+Veh and J147 reversed this effect [**P11:** 25.3% vs. 51.1% ($p<0.01$) vs. 36.3% ($p>0.05$); **P14:** 28.6 vs. 93.6 ($p<0.0001$) vs. 72.3 ($p<0.05$); **P17:** 7.5% vs. 56.7% ($p<0.0001$) vs. 19.6% ($p<0.0001$)]. HI+Veh elevated the level of Parp-1 and J147 partially ablated this effect [**P11:** 55.4% vs. 88.4% ($p<0.05$) vs. 78.2% ($p>0.05$); **P14:** 70.5% vs. 106.6% ($p<0.01$) vs. 75.9% ($p<0.05$); **P17:** 67.2% vs. 110.6% ($p<0.001$) vs. 78.6% ($p<0.05$)].

Conclusion. J147, as neuroprotective reagent, significantly ameliorates the apoptosis in hippocampus, which was induced by common carotid artery blockage in a neonatal HIE mouse model. These results support our long-term goal to position J147 for a clinical trial for HIE.

White matter injury in a pediatric rabbit model of CNS TB

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Background and Aim: Central nervous system (CNS) tuberculosis (TB) is the most devastating form of extrapulmonary TB, especially in children and immunocompromised hosts. Even with the current standard-of-care antimicrobial treatment, mortality and morbidity remain unacceptably high, emphasizing the need to optimize treatment. Although infection control is important, neuroinflammation secondary to infection leads to neuronal and white matter or myelination injury and is thought to be a principal contributor to poor outcomes. The current standard of care interventions – host-directed therapy, adjunctive corticosteroids (i.e., dexamethasone) – do not significantly improve neurobehavioral outcomes and novel therapeutics are urgently needed. N-acetyl cysteine (NAC) is an anti-inflammatory and antioxidant but can be toxic at high doses and does not cross the blood-brain barrier (BBB) easily. However, when conjugated to dendrimer delivery devices, dendrimer-NAC (D-NAC) crosses the BBB, targets activated microglia, reduces white matter injury and improve outcomes in animal models of neuroinflammation. We previously developed a pediatric rabbit model of CNS TB causing neuroinflammation and suspected white matter injury contributing to neurobehavioral deficits. Here we propose using our established pediatric CNS TB rabbit model to test the ability of D-NAC to reduce CNS TB-induced white matter injury.

Method: Young New Zealand White rabbits (post-natal day 5) received an intraparenchymal injection of PBS (uninfected control, n = 2) or live *Mycobacterium tuberculosis* H37Rv (TB-infected, n = 3). After 3 weeks, CNS TB-infected rabbits received treatment with D-NAC (n = 2) or dexamethasone (n = 1) for 2 weeks before brain tissue was harvested. Brains were fixed with 16% PFA, paraffin embedded, sectioned to 10 µm and stained with luxol fast blue to identify myelinated axons and Nissl bodies. White matter area was then quantified with ImageJ.

Results and Conclusions: The density of white matter in the brains of CNS TB-infected rabbits was higher in those treated with D-NAC compared to dexamethasone and approached the density of healthy, uninfected control rabbits. Although preliminary, these results are consistent with the improved neurobehavior score we saw with D-NAC treatment compared to untreated rabbits in earlier studies. These preliminary data demonstrate that D-NAC is a promising anti-inflammatory and antioxidant for treatment of CNS TB. However, additional studies in combination with antimicrobial regimens would be beneficial to validate these findings.

Funding Source
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Delayed IL-10 treatment targeted at microglia/macrophages after intracerebral hemorrhage

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Spontaneous intracerebral hemorrhage (ICH) is a devastating disease with high morbidity and mortality. Despite improvements in mortality, ICH-associated disability adjusted life years (DALYs) lost are a startling 1.2 million annually in the United States. Given the increasing number of young and middle-aged individuals with ICH, the economic and health implications of this disease are of great concern. Supportive care is the mainstay of management of patients with ICH, and surgical interventions to mitigate the primary and secondary mechanisms of ICH-associated injury have not been proven to be beneficial. The lack of interventions to improve morbidity and mortality has resulted in increased interest in finding alternative neuroprotective therapies that target the mechanisms of ICH-associated injury.

The pathophysiology of ICH is complex and many of the mechanisms of injury and recovery associated with this condition are not fully elucidated. Blood components and mechanical forces from the hematoma onto the surrounding tissue provoke a neuroinflammatory cascade with microglia and macrophages (M/M Φ) being the earliest cells to participate. Activated M/MΦ take on a pro-inflammatory or anti-inflammatory phenotype through polarization. The M2 phenotype M/MΦ play a key role in hematoma clearance, angiogenesis, and tissue repair. These cells secrete Interleukin 10 (IL-10), which has been shown to be a promising therapy in several neurologic conditions, including ICH. However, IL-10 delivery presents a challenge due to its large size and short half-life. Phosphatidylserine containing liposomes (PSL) conjugated with IL-10 (PSL-IL10) are a promising vehicle for IL-10 delivery targeted directly to M/MΦ. Phosphatidylserine is a molecule found in the inner membrane of the cell lipid bilayer and serves as a ligand for phagocytic cells. Unpublished work from Dr. Koehler's lab demonstrated accelerated hematoma clearance and improvement of acute neurologic outcomes of young male mice with ICH after PSL-IL10 administration 30 minutes post injury. They were able to confirm direct M/MΦ uptake of the PSL-IL10, making this a promising delivery system.

Other characteristics that may impact the response to IL-10 and functional outcomes have yet to be explored. Specifically, the impact of age can potentially influence the response to IL-10. We know that our innate immune system experiences physiological changes as we age. Furthermore, IL-10 may promote brain repair independent of accelerating hematoma clearance. Here, we will delay initiation of PSL-IL10 administration until 7 days after ICH, a time when most of the hematoma is cleared in the mouse model. The overall objective of this study is to investigate the effects of daily administration of PSL-IL10 at 7-14 days after ICH in middle-aged mice on 1) neurocognitive and emotion-based behavioral outcomes, 2) the neuroinflammatory response, and 3) angiogenesis as a necessary process for brain repair. If results are promising, this method of treatment can be potentially translated into therapies for patients with ICH.

Systemic targeted monotherapy with D-DON results in microglial glutaminase inhibition and improvement in neurobehavioral scores in MeCP2-null and HET mice.

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Rett Syndrome (RTT) is a progressive neurodevelopmental disorder, caused by mutations in the gene encoding for methyl-CpG binding protein 2 (MeCP2). It affects 1 in 10,000 to 15,000 live female births and is associated with seizures, non-purposeful stereotypical hand movements, motor dysfunction, and intellectual disability. Although therapies are being explored for symptomatic management, there are currently no therapies that modify the course of disease progression in RTT. Recent work with MeCP2 deficient mouse models has demonstrated a major role for glutamatergic pathways, specifically microglial-produced glutamate, due to upregulation of glutaminase in the pathology of RTT. The glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) broadly blocks glutamine-utilizing reactions and is a potent inhibitor of glutaminase, however it is also associated with poor brain penetration and systemic toxicities, most of which are gastrointestinal-related (e.g. nausea/vomiting, diarrhea, mucositis). Therefore, we have used a hydroxyl dendrimer nanoparticle platform (~4 nm, non-toxic) that targets activated/dysregulated glia and astrocytes in Mecp2-deficient mice, but not in WT from systemic administration**.** Our study explored that targeted monotherapy of a dendrimer-conjugated DON (D-DON) can result in microglial glutaminase inhibition and improvement in neurobehavioral scores in Mecp2-null and HET mice while eliminating the peripheral toxicity of free DON. We observed an increase in glutaminase activity in 5-6 weeks old Mecp2 KO/Saline treated mice in comparison to the treated groups. The D-DON treatment resulted in selective glutaminase inhibition in the isolated microglia from Mecp2-null mice. Furthermore, the HET mice were treated biweekly for 8 weeks with saline, DON at 1 mg /kg or D-DON 1 mg/kg i.p. (on a DON basis) beginning at 6 months of age (when HET animals show consistently symptomatic phenotype with an average neurologic score of ≥3). D-DON treated HET mice showed significant improvement in phenotype severity with improved neurobehavior score, particularly paw-clench, while DON and saline groups did not. Other neurobehavioral and motor assessments like open field and contextual fear conditioning etc. are also being carried out to access the pre and post treatment phenotypic differences in these groups. Our study provides evidence for D-DON therapy to alleviate behavioral symptoms in RTT via inhibition of glutaminergic pathway in glial cells.

Keywords: Rett syndrome; Glutaminergic pathway; D-DON; Neurobehavioral studies

RNA and DNA methylation signatures are globally distributed in the neonatal pig brain

Valerie Olberding, Adriana Amrein Almira, Cameron Javdan, Jennifer K. Lee, and Lee J. Martin

Epigenetic mechanisms could contribute to the delayed neural degeneration, neural network dysfunction, and long-term cognitive disabilities in children that have experienced neonatal hypoxia-ischemia. However, the distributions and cellular localizations of epigenetic writers, erasers, readers, and signatory markers in different brain regions of clinically relevant large animal models of neonatal encephalopathy have not been studied. In neonatal pig brain, we studied using western blotting and immunohistochemistry the distributions of: nucleolar protein-Sad1/UNC84 domain protein 2 (NSUN2), a methyltransferase that catalyzes methylation of various RNAs; N6-methyladenosine (m6A), the most abundant mRNA modification; and 5-methylcytosine (5mC), a methylated form of the DNA base cytosine. The NSUN2 antibody detected a highly specific protein at ~ 90 kDa in western blots of piglet brain homogenates. By immunohistochemistry, NSUN2 was highly enriched in the nucleus of neurons and glia throughout the brain. Granule neurons in the cerebellum, but not in hippocampal dentate gyrus, were the exception by having low NSUN2 immunoreactivity. m6A immunoreactivity, fully abolished by competition of antibody with purified m6A and diminished by RNase treatment, was also localized to the nucleus of neurons and glia throughout the brain. m6A immunoreactivity was particularly enriched in glial white matter cell nuclei and in cells of the ganglionic eminence. 5mC immunoreactivity had an abundant global distribution in neurons and glia and was discretely localized to fine strands throughout the nucleus of neurons and in larger neuronal intranuclear formations. RNA and DNA epigenetic patterns in piglets with encephalopathy are being assessed for aberrancy. These data show that salient epigenetic markers and their regulatory mechanisms have broad distributions and neuronal and glial cell nuclear enrichment throughout neonatal pig brain gray and white matter regions and are potentially poised for acquired injury-induced rewriting of the epigenetic landscape.

Novel glucose-dendrimer targets hyperexcitable neurons

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Neuronal hyperexcitability can cause abnormal brain function and often leads to neuronal death in diseases like epilepsy and traumatic brain injury. Targeting the select populations of hyperexcitable neurons to restore their spiking activity can rescue neurons from excitotoxicity and cell death, thus avoiding cascading effects of secondary injury propagation. However, delivering drugs selectively to hyperexcitable neurons has not been achievable, let alone at relevant doses. Here, we report a novel nanoparticle, glucose-dendrimer (GD2), that can target hyperexcitable neurons in primary culture, ex-vivo acute cortical brain slices, and in-vivo mouse models of seizure. Pharmacology experiments in ex-vivo brain slices suggest GD2 uptake in neurons is mediated through glucose transporters (GLUT and SGLT). Inspired by these findings, we conjugated GD2 with a potent anti-epileptic drug, valproate (GD2-VPA), for efficacy studies in the pilocarpine-mouse model of seizure. When delivered intranasally, GD2-VPA significantly decreased the seizure-induced freezing behavior. We conclude that glucose-dendrimer selectively targets hyperactive neurons and GD2-drug conjugates can be used for neuron-specific therapies.

Effect of secreted frizzled-related protein 3 on neurogenesis and cognitive function in middle-aged mice model of Alzheimer's disease

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Background: Secreted frizzled-related protein 3 (sFRP3) is one of the antagonists of Wnt canonical and noncanonical signaling pathways. Wnt signaling regulates multiple cellular processes including proliferation, neuroinflammation and neurodegeneration. Previous studies have shown that sFRP3 depletion promotes neurogenesis in the hippocampus under physiological conditions. However, it is unclear the role of sFRP3/Wnt signaling in cerebral diseases. Alzheimer's disease is characterized by progressive loss of the learning and memory. The neurogenesis declines sharply in the hippocampus of patients with Alzheimer's disease. This study is to investigate whether inhibiting sFRP3 gene expression improves hippocampal neurogenesis and cognitive function in the mouse model of Alzheimer's disease.

Methods and Results: APP/PS1 mice and sFRP3 homozygous knock out ($sFRP3^{-/-}$) mice were mated to generate APP^{+} $sFRP3^{-/-}$ mice. Cognitive and memory tests including Y-maze spatial recognition test, novel object recognition test and Morris Water-maze test were performed in middle-aged $APP^{+}sFRP3^{-/-}$ mice, with age-matched APP/PS1 mice and C57BL/6 mice. We found that APP^{+} $sFRP3^{-/-}$ mice showed a potential trend of improving cognitive behavior and memory. We investigated the expressions of EdU, NeuN and immature neuronal marker protein (DCX) to evaluate neurogenesis in the hippocampus. The expression of EdU showed an increasing trend in the hippocampus of APP^{+} $sFRP3^{-/-}$ mice. Currently, we are addressing the levels of Iba1 and CD68 by immunostaining. The activation of Wnt signaling pathway will be tested by western blot or RT-PCR.

Conclusions: sFRP3 deficiency may promote the neurogenesis in the hippocampus and improve the cognitive function in the mouse model of Alzheimer's disease. sFRP3 deficiency may decrease microglial activation and neuroinflammation in the mouse model of Alzheimer's disease. Inhibition of sFRP3 may be a potential treatment target for Alzheimer's disease.

ACCM Cellular, Molecular & Biomarker Discovery Initiative

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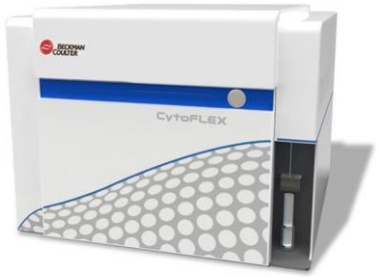
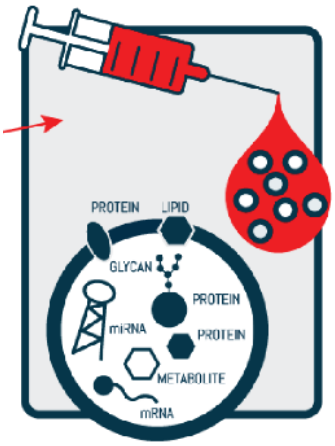
Our Mission: answering clinical questions with basic and translational science expertise towards discovery and patient care





Removing barriers to basic and translational science

Methodologies and Capabilities
- immune and non-immune cell profiling, characterization
- soluble mediator quantification and biomarker discovery
- live cell and organoid functional assays
- exosome quantification, characterization
- cell-specific exosomes capture from various biofluids
- single-cell analyses, large dataset analysis, high throughput assays

Scientific Expertise
- lung and cardiovascular diseases
- immune system and inflammation
- cellular functional imaging
- exosomes and non-coding RNA function
- biomarker discovery by liquid biopsy (cell-specific exosome capture and cargo analysis)
- large dataset analysis, e.g. RNA-Seq

Instrumentation and data analysis
- CytoFLEX 3-laser, 13-color cytometer, 96-well plate loader
- IncuCyte S3 Live Cell Imaging System with scratch wound and spheroid assay modules
- Kaluza flow cytometric analysis software
- Fully automated RNA handling robots
- Quant Studio 5 Real-time PCR
- QIAcuity Digital PCR

Getting started
- One-on-one consult for feasibility, study design, and small pilot experiment(s)
- Application for StAAR Awards, Core or Investigator; Core Coins
- Data collection, analysis, and manuscript preparation
- Partnering on grant proposals

Contact the Leads: Nikki Heller nheller@jhmi.edu | Sam Das sdas11@jhmi.edu

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Population-based study of inpatient and outpatient encounters following pediatric drowning in Maryland

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Background: Drowning is a cause of significant pediatric morbidity and mortality. Prior studies show that males, young children, and Black children are at particular risk. Our objective is to evaluate these trends in a state-wide cohort and determine associations with inpatient hospitalization to inform prevention strategies.

Methods: This is an IRB-approved retrospective cohort study using the publicly available Health Services Cost Review Commission database, which contains patient-level data on all inpatient and outpatient visits (including emergency department) in Maryland, reflecting 700,000 inpatient and 5.7 million outpatient visits annually. We used ICD-10 codes to identify patients 0-19 years with a hospital visit for a drowning event between 2016-2019. Extracted data included sex, age, race (minority status defined as non-white), patient zip code (rural or urban status defined per state-level maps), insurance and type of encounter (inpatient or outpatient). Descriptive statistics and univariate/multivariable logistic regression were used to summarize the data and evaluate associations with inpatient encounters, as a measure of higher severity.

Results: Of 541 medical visits for drowning, 47 were inpatient and 494 were outpatient. There were 536 nonfatal and 5 fatal outcomes. Overall, most patients were male (59%), 0-4 years (52%), white (54%) and lived in an urban setting (83%); 40% had public insurance and 45% had commercial insurance. White children accounted for 66% of visits amongst those 0-4 years whereas minority children accounted for 62% of visits among those 10-19 years. Overall, there were no significant differences between children with and without inpatient hospitalization based on sex, race, residence or insurance. Adolescents (10-19 years) were more likely than younger children to require admission (OR 3.3, 95% CI = 1.7-6.7). Minority patients accounted for the highest proportion of inpatient admissions in the 5-9 year age group (82%, p = 0.006).

Discussion: Although most drowning-related hospital visits occurred in young children, adolescents were more likely to be hospitalized. Race-related risk varied by age group. These patterns merit further study and can guide specific interventions to prevent drowning in Maryland children.

Plasma biomarkers as prognostication in patients receiving extracorporeal membrane oxygenation

Shrey Kapoor, Lavien Premraj, Ameen Ahmad, Siam Muquit, Allen Everett, Jie Zhu, Sung-Min Cho

Introduction

Neurological complications in VA-ECMO beget a 7-15% mortality rate; however, existing literature demonstrates that neuromonitoring reduces the rate of complications. Current methods of neuromonitoring are lifesaving, and there is an increasing need for easily measured, accurate markers that can predict neurological injury. We propose that plasma biomarkers such as Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NFL), and Tau can be utilized for prognostication of neurologic outcomes on ECMO. We hypothesized that patients with higher levels of inflammatory biomarkers will be at higher risk for neurologic complications.

Methods

In this pilot prospective, cohort study, patients were consented within 24 hours of cannulation and followed over the duration of their VA-ECMO course. Peak concentrations of plasma biomarkers were used for analysis. Samples were taken daily for first 7 days and every other day afterwards as long as patient remained in the ICU. We utilized a multiplex analytical platform for candidate brain and endothelial injury biomarkers on SECTOR Imager 6000 reader plates using commercially available antibodies and calibrant proteins. Outcomes were determined by the modified Rankin Scale (mRS) with a favorable outcome of mRS <4. All data was managed by REDCAP. Statistical analyses included calculating the Area Under ROC curves to determine the biomarkers with highest sensitivity and specificity and were performed with STATA v17.

Results

20 patients were enrolled. Median age was 48.5 (41.5-62 IQR) years, and patients were 55% female. The median peak concentration values of GFAP, NFL, and Tau were 382.3 pg/ml (100.8-5,516.4), 8,306.7 pg/ml (2,338.9-13,577.2), and 1,278.4 pg/ml (318.7-3,447.4), respectively. There were 15 patients (75%) with unfavorable neurologic outcome at discharge, 17 patients had acute brain injury (85%), 10 patients had thromboembolic events (50%), and 14 patients had hemorrhagic events (70%). In prognostication of acute brain injury in patients, the plasma biomarkers GFAP, NFL and Tau achieved an AUC of 0.84, 0.73, and 0.73 respectively. Furthermore, GFAP, NFL and Tau achieved an AUC of 0.70, 0.81, and 0.70 for prediction of hemorrhagic events on ECMO.

Conclusion

We identify three key plasma biomarkers, GFAP, Tau and NFL, that have the groundbreaking potential to assist critical care medics in their prognostication of acute brain injury and hemorrhagic events on ECMO. Plasma Biomarkers can play a vital role in neuromonitoring and prognostication; thus, we strongly recommend further research to identify feasibility and utility of novel biomarkers in the context of VA-ECMO and neurological complications to understand which combination of plasma biomarkers has the highest clinical yield.

Clinical methods & results of mass spectrometric examination of exhaled aerosol samples in intubated ICU patients for early identification of pulmonary infection via proteomics

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Introduction: Early coverage of focused antibiotics has been shown to be important in the reduction of patient morbidity & mortality. Optimal management of ICU respiratory tract infections (RTI) is currently hindered by substantial delay in pathogen identification. Rapid diagnostic approaches to nonvolatile breath compounds have been well described, whereas timely screening of aerosolized material – rich in pathogenic markers – has been more challenging. In this study, our research team developed a new non-invasive method for the characterization of processed, truncated proteoforms from aerosol samples collected from intubated ICU patients. Major clinical methodological challenges involved obtaining concentrated, aerosolized, exhaled patient breath samples and prompt post-collection processing for subsequent spectroscopic proteoform analysis.

Methods: Upon receiving informed consent, 70 mechanically ventilated patients were recruited from the NCCU and MICU. The BreathBiomics™ device was connected to the exhalation limb of ventilator circuit for four hours. The collected breath samples were gas sterilized before spectrometric analysis. Additional data related to medical history and microbiology lab results of all enrolled patients were collected. Patient recruitment was impeded by the often unavailability of legally appointed representatives to provide consent. Technical barriers to breath sampling included condensation of fluid in the collection filter and disruption of sampling times due to clinical interventions for the patient. Truncated proteoforms were identified using top-down proteomics in which intact proteoforms are characterized by high-resolution mass spectrometry. Quantitative differences in truncated proteoforms between the two groups were identified, and multiple logistic regression analysis was used to predict RTI.

Figure 1 – In-line ventilator circuit sampling tubing with proprietary filter [lower right]

Results: Usable exhaled aerosol samples were collected from 47 intubated patients; 25 with microbiologically diagnosed RTI, and 22 without RTI. Following analysis, 6 truncated proteoforms, representative of either proteolytic enzymes or lung structure proteins, were statistically different between intubated patients with and without RTI. Specifically, the truncated proteoforms of collagen type VI alpha three chain protein, matrix metalloproteinase 9, and putative homeodomain transcription factor 2 were found to be independently associated with RTI.

Conclusions: The investigative team encountered only minor clinical methodological difficulties in obtaining isolated exhaled breath samples of sufficient quality to perform discriminative, truncated proteoform analysis. This pilot study describes a non-invasive method that may lead to an efficient and rapid method to diagnose RTI in critically ill intubated patients.

Outcomes of obstetric patients who decline allogeneic blood transfusion

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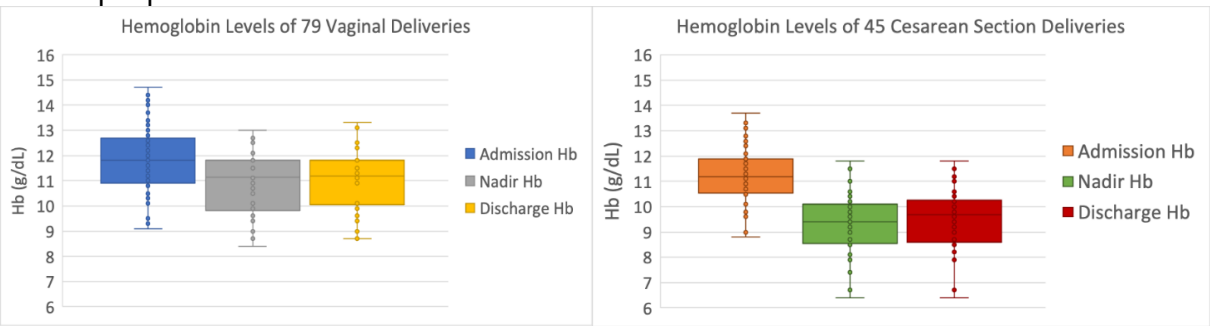
Background: Obstetric bleeding is a major risk both during and after delivery and postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality nationally. In patients who decline blood products for religious or personal reasons, management of postpartum bleeding can be especially challenging without the option to transfuse. Since the inception of the Bloodless Medicine and Surgery program ten years ago, The Johns Hopkins Hospital has provided obstetric care to hundreds of Jehovah's Witness patients. This study aims to identify and analyze patient care strategies and outcomes in this population.

Methods: We conducted a retrospective chart review of obstetric patients presenting to Labor & Delivery from 2012-2022 and identified 88 patients (124 deliveries) who declined allogeneic blood transfusions. Information about comorbidities, delivery methods, maternal/fetal outcomes, and blood management techniques were analyzed.

Results: The median age of our cohort was 30 years, and the median BMI was 33. Comorbidities for PPH included obesity (64%), labor augmentation with oxytocin (53%), hypertensive disorders of pregnancy (35%), diabetes (11%), and uterine overdistension from polyhydramnios, macrosomia, or twin gestation (10%). Of the 100 patients with prenatal anemia (81%), 53 were treated with oral iron, 16 with intravenous iron, and 12 with vitamin B12 or folate. Among the 124 deliveries, 79 (64%) were vaginal deliveries and 45 (36%) were cesarean sections. The median blood loss was 300 mL for vaginal deliveries and 800 mL for cesarean sections. In total, 18 cesarean deliveries (15%) met the criteria for PPH, defined as blood loss greater than 1000 mL. There were no vaginal deliveries with greater than 1000 mL of blood loss. All 124 patients received oxytocin in the peripartum period. Additional peripartum strategies to control bleeding included additional uterotonics (44%), intraoperative cell salvage present (25%), and tranexamic acid (5%). From admission to discharge, the average hemoglobin decreased from 11.7 to 11.0 g/dL for vaginal deliveries, and from 11.2 to 9.4 g/dL for cesarean sections. There were no hysterectomies and no peripartum mortalities.



Conclusion: Our hospital's Bloodless Medicine program has optimally managed Jehovah's Witness obstetric patients for the past decade with no mortalities. Patient blood management techniques such as prenatal optimization with iron and vitamin B12/folate, utilization of second-line uterotonics, cell salvage, or tranexamic acid, and careful monitoring of bleeding are crucial in managing obstetric bleeding while avoiding transfusion for these patients.

Peripheral and arterial blood gas oxygen saturation levels are discordant in various ECMO cannulation configurations

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Introduction: Disagreements between SpO_2 and SaO_2 have been studied, but insufficient data exists on how different cannulation strategies influence the discrepancy in venoarterial (VA) and venovenous (VV) ECMO patients.

Methods: A retrospective, observational study was conducted at a tertiary care center using Bland-Altman analyses to obtain the mean difference (SpO_2–SaO_2) and comparing the SpO_2–SaO_2 difference by generating p-values (Wilcoxon rank-sum and Kruskal-Wallis tests).

Results: We analyzed 16,352 SpO_2-SaO_2 pairs that were concurrently measured (≤ 10 minutes) with ≥ 70% saturation level from 141 VA-ECMO and 59 VV-ECMO patients.
In VA-ECMO, pulse oximetry underestimated SaO_2 in centrally-cannulated patients (-0.15%) and overestimated SaO_2 in peripherally-cannulated patients (0.52%, p<0.0001). Patients without post-cardiotomy shock (PCS) had a greater mean difference (0.40%) than those with PCS (0.018%, <0.0001). Patients who were required to use vasopressors/inotropes during ECMO also had a greater mean difference (0.28%) than those without vasopressors/inotropes (0.12%, p<0.001). Most PCS patients were centrally-cannulated, and the majority of patients who required vasopressor/inotrope were peripherally-cannulated.
In VV-ECMO, pulse oximetry overestimated SaO_2 in single-lumen (1.7%) and double-lumen cannulated patients (1.1%, p<0.0001). The mean difference for patients with LDH levels <500, 500-1000, and >1000 units/L was 0.75%, 1.6%, and 1.8%, respectively (p<0.0001).

Conclusions: Pulse oximetry overestimates SaO_2 in peripherally-cannulated VA-ECMO patients, and this may be attributed to differential hypoxia during peripheral-cannulation and vasopressors/inotropes. Pulse oximetry overestimates SaO_2 in single-lumen more than double-lumen cannulated VV-ECMO patients, and this may be attributed to hemolysis due to greater resistance of blood flow in the single-lumen.

Variation in clinical outcomes for hospitalized children related to childhood opportunity index

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Authors have requested to not include the abstract for distribution.

Organ dysfunction recovery in pediatric ECMO patients

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In a recent survey, family members and healthcare providers ranked duration of organ dysfunction (OD) as the third most important outcome in a hypothetical interventional trial for critically-ill children. Rates of OD recovery on and post-ECMO are currently unknown. In this retrospective cohort study, we investigated rates of OD during the 14 days prior to and up to 28 days following ECMO initiation, using the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) criteria. We included 226 children (<18 years) supported on ECMO from 2011 to 2020 at one quaternary care center. Median age was 3.3 months (IQR 0.1-45.1) and 43% were female. All patients experienced at least 1 day of OD during the study period, with median 2 (IQR 1-3) OD/day in the 14 days prior to ECMO start, 4 (IQR 3-5) OD/day during ECMO, and 2 (IQR 1-3) OD/day following ECMO. Among survivors to hospital discharge (n=98), endocrine dysfunction showed the greatest recovery from ECMO day 0 to hospital day 28 (90% to 16%), followed by cardiovascular (100% to 34%), hepatic (79% to 17%), and hematological dysfunction (83% to 23%). Recovery rates were lower in patients who died in the hospital (n=128), with endocrine recovery from 88% to 32%, cardiovascular from 100% to 60%, hepatic from 83% to 63%, and hematological from 84% to 36%. Immune dysfunction rates increased in both groups. Further characterization of OD trajectory is needed for family counseling and for early identification of patients most likely to benefit from supportive treatment.
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Overtransfusion is common in patients receiving massive transfusion

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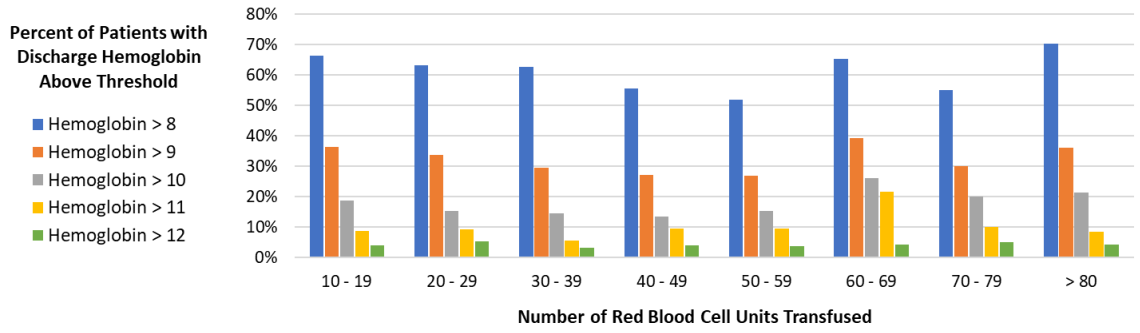
Background: Although there are several validated criteria used to trigger a massive transfusion protocol, there are no specific guidelines for when to stop. Overtransfusion can increase morbidity through electrolyte abnormalities, acid/base disorders, fluid overload, or acute lung injury. Also, blood is a valuable and limited resource, so the decision to transfuse each unit should be made judiciously. Our goal was to assess the massive transfusion practices at our hospital to test the hypothesis that a substantial number of these patients were overtransfused.

Methods: In this retrospective cohort study, patients were included if they received at least 10 units of red blood cells during their hospitalization from 2016 to 2022. Our exposure was the number of red blood cell units transfused, and our outcome was the percentage of patients who were discharged with their hemoglobin above a certain threshold (either 8, 9, 10, 11, or 12 g/dL). We expected that patients who received more transfusions would have higher hemoglobin measurements at discharge.

Results: We analyzed 2,953 hospitalizations where the patient received at least 10 units of red blood cells. Of these encounters, 1,922 patients (65%) were discharged with a hemoglobin above 8 g/dL, 1,033 patients (35%) above 9 g/dL, and 527 patients (18%) above 10 g/dL. The highest discharge hemoglobin was 18.1 g/dL. Overall, there was no association between the number of units transfused and the percentage of patients discharged with a hemoglobin above 8, 9, 10, 11, or 12 g/dL ($p = 0.13$, $p = 0.33$, $p = 0.44$, $p = 0.40$, and $p = 0.85$, respectively).

Conclusions: Of the patients who received at least 10 units of red blood cells during their hospitalization, about 2/3 had a discharge hemoglobin above 8 g/dL, 1/3 above 9 g/dL, and 1/5 above 10 g/dL. Patients were similarly overtransfused, regardless of the number of units received. These findings reveal an opportunity to reduce unnecessary blood usage by recognizing when to stop giving blood to patients receiving massive transfusion.

Figure 1: Percentage of patients with their discharge hemoglobin above a certain threshold (8, 9, 10, 11, or 12 g/dL), based on the number of red blood cell units transfused.



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Discrepancies in hypoxemia detection by race and ethnicity in ECMO-supported patients

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Introduction: The inaccuracy of pulse oximetry in different races/ethnicities has been studied in various cohorts, but limited data exist in ECMO patients.

Methods: In a retrospective, observational, tertiary care center study, we performed Bland-Altman analyses to determine the mean difference (SpO_2–SaO_2), linear mixed-effects modeling (LMM) to calculate SpO_2–SaO_2, adjusting for age, sex, vasopressor/inotrope, cannulation strategy, and time-dependent laboratory variables, and ROC analyses using 88%, 92%, and 95% SaO2 thresholds.

Results: Of 141 venoarterial (VA) and 59 venovenous (VV) ECMO patients, we examined SpO_2-SaO_2 pairs (16,352) that a) were measured within 10 minutes of each other and b) reflected saturations $\geq$ 70%. Overall, the SpO_2–SaO_2 discrepancy was greater in VV-ECMO (1.3%) vs. VA-ECMO (0.27%).

In VA-ECMO, pulse oximetry overestimated SaO_2 in Asian (0.2%), Black (1.03%), and Hispanic (0.03%) patients and underestimated White (-0.06%) and non-specified race (-0.80%) patients. In LMM, SpO_2 underestimated SaO_2 by -11.38% in non-specified race patients (95% CI=-22.4% to -0.37%, p=0.043).

In VV-ECMO, pulse oximetry overestimated SaO_2 in Asian (1.0%), Black (2.9%), Hispanic (1.1%), and White (0.36%) patients and underestimated SaO_2 in non-specified race patients (-0.53%). In LMM, SpO_2 overestimated SaO_2 by 0.19% in Black patients (95% CI=0.045% to 0.33%, p=0.023).

In all ECMO patients, the AUC for SpO_2 to accurately estimate SaO_2 was highest at the 88% threshold and lowest at the 95% threshold.

Conclusions: Pulse oximetry overestimates arterial gas oxygen saturation in Asian, Black, and Hispanic ECMO patients compared to White patients, and this discrepancy is larger in VV-ECMO than in VA-ECMO.

Implementation of consistent medical direction consults during pediatric critical care interhospital transport

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Purpose/Objectives: Johns Hopkins Pediatric Transport coordinates all incoming pediatric transfers to our quaternary center. Pediatric intensivists serve as medical control physicians (MCPs). There is significant heterogeneity within the medical direction process, with communication between transport team members and MCP occurring on an as-needed basis (with no communication for some calls). We aimed to implement consistent transport medical direction via audio telecommunication systems for all incoming critical care transports (CCTs), provide appropriate documentation in the electronic medical record (EMR), and facilitate billing for all direction provided. We hypothesized that: 1) this QI effort would lead to a more consistent, reliable, and comprehensive medical direction process; and 2) timely access to medical direction during transport might improve quality metrics and, importantly, patient outcomes.

Design/Methods: The new process implemented on 8/1/2021 required the team to initiate a formal consult with the MCP after assuming care of the patient at the referring institution and, as needed, for additional medical direction before and during patient retrieval. Subsequently, the MCP would document in our institution's EMR utilizing a prefilled note template and bill using the appropriate transport medical consult code(s) (99485 for acute patients ≤24 months old, first 30 minutes; 99486 add on for acute patients ≤24 months old, additional 30 minutes; 99288 for non-acute or patients >24 months). Pre-implementation, we provided training to the MCPs and transport personnel, including education on the new transport workflow and information regarding billing and transport medical control requirements. Subsequently, we performed a retrospective review of all pediatric CCTs performed six months pre- and six months post-intervention to assess compliance with the new medical direction process (including documentation and billing) and compare transport quality metrics.

Results: Our team performed 827 pediatric CCTs during the study period: 356 pre- and 471 post-intervention. The post-intervention cohort was younger and included more patients triaged to the ICU, but transport logistics were not different between groups. Of the 471 post-intervention CCTs, 437 were eligible for medical direction consult; of these, 432 (98.9%) received medical consults and 87.5% of them (378/432) were documented in the EMR. These 378 documented consults had 387 associated billing codes (99288: 218, 99485: 159, and 99486: 10), resulting in $38,700 in charges and $22,653 in payments. When compared to pre-intervention, the post-intervention CCTs had higher compliance with in-transport temperature monitoring (90.7% vs. 66.7%, p=0.017), glucose documentation (92.6% vs. 80%, p=0.003), and pain assessment (98.3% vs. 94.1%, p=0.002). When compared to pre-intervention, post-intervention CCTs received more transport interventions (60.1% vs. 39.6%, p<0.001) but had a longer median (IQR) bedside time: 24 (16-32) vs. 20 (14-26) min, p<0.001.

Conclusion/Discussion: Consistent transport medical consultation is feasible for pediatric critical care transports, impacts patient care en route, and generates revenue. QI efforts are ongoing, as our team strives for 100% compliance and further assessment of its impact on patient outcomes.

Functional performance and loss of independence in older patients with heart failure with preserved ejection fraction undergoing non-cardiac surgery

Chelsey Santino, MD, MS, Lee Goeddel, MD, MPH

Background: Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and is associated with increased morbidity and mortality. Exercise intolerance is a primary clinical manifestation of HFpEF, often assessed pre-operatively with subjective determination of exercise capacity per patient report. An objective determination of a patient's functional performance can be assessed via Edmonton Frail Scale and may add additional information to the perioperative assessment. Loss of independence is an important patient-centered outcome measure that has been associated with postoperative readmissions and even death after discharge. The association between exercise capacity, functional performance, and loss of independence in patients with HFpEF has not been studied. We evaluated the relationship between functional performance, exercise capacity, and loss of independence in patients with diagnosed HFpEF undergoing non-cardiac surgery at a single tertiary academic center.

Methods: We performed a retrospective analysis of patients presenting to our perioperative optimization clinic who were scheduled to have non-cardiac surgery and had an ICD-10 diagnosis of heart failure. Heart failure with preserved ejection fraction was confirmed with TTE evidence of preserved LVEF within one year of planned surgery. Patients were further screened for completion of Edmonton Frail Scale (EFS) assessment and anesthesiologists' assessment of subjective exercise capacity prior to surgery. Functional performance and exercise capacity scores were then compared to loss of independence which was defined as discharge to rehabilitation or skilled nursing facility with evidence of loss of functional performance and/or activities of daily living on formal postoperative physical and occupational therapy evaluation.

Results: Of the 4000 patients who presented to our perioperative optimization clinic and completed an Edmonton Frail Scale assessment, 120 (3%) had an ICD-10 diagnosis with TTE confirmation of HFpEF. Agreement between exercise capacity and functional performance was40%, kappa statistic was 0.1228 with a p value of 0.0086. Of the 120 confirmed HFpEF patients, a total of 21 had loss of independence. Nine of the 21 patients with loss of independence had pre-operative assessments of the lowest exercise capacity and poorest functional performance. Three of the patients had intermediate functional performance but lowest exercise capacity assessment. Two of the patients had intermediate exercise capacity assessment but poorest functional performance.

		HFPEF (n=120)		
Loss of independence	**Functional Performance (lower number is better)**			
Exercise Capacity (higher number is better)	2	1	0	Total
<1 met	9 (41%)	3 (20%)	1 (25%)	13 (32%)
1-4 mets	2 (12%)	3 (14%)	2 (6%)	7 (10%)
>4 mets	1 (100%)	0	0	1 (14%)
Total	12 (30%)	6 (15%)	3 (7%)	

Conclusions: In patients with diagnosed HFpEF undergoing non-cardiac surgery, the combination of poor functional performance via Edmonton Frail Scale and decreased anesthesiologist-determined exercise capacity appear to be associated with increased risk of post-operative loss of independence. The addition of functional performance to pre-operative evaluation may help to determine HFpEF patients undergoing non-cardiac surgery who are at highest risk of loss of independence.

Early prediction of neurologic injury in pediatric ECMO patients

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Objective: Extracorporeal membrane oxygenation (ECMO) is used to provide life support for critically ill children with severe, refractory cardiopulmonary failure. Despite its life saving potential, mortality in children requiring ECMO support is high (40%). This is partially attributed to high risk of acute neurologic injury because of the delicate balance between clotting and bleeding that exists during ECMO. The objective of this study was to develop prediction models for the onset of neurologic injury using machine learning methods, using data from the multicenter Pediatric ECMO Outcomes Registry (PEDECOR).

Methods: Data were split in training and testing data sets (70/30). A baseline static model was built using only pre-ECMO patient demographic and medical history features. Then a dynamic Random Forest model using pre-ECMO features as well as time-series features, including daily laboratory (including coagulation) and blood product administration features, was built to identify patients at high risk of neurologic injury, prior to onset of injury. This process was iterative, with those no longer at risk (decannulated from ECMO or already developed injury), removed from further prediction of injury for the following day of ECMO.

Results: The PEDECOR cohort included 1350 patients <18 years of age (53% male, median age 0.31 years, IQR [0.02, 3], median ECMO duration 4 days, IQR: [2,8]). Of the 1350 patients, 185 (13.7%) suffered intracranial hemorrhage, ischemic stroke, or both, with a mean time to injury of 4.3 days (median: 2, IQR: [1,5]). The pre-ECMO models resulted in low AUC < 0.5, which is no better than a random no-skill classifier, and the dynamic models resulted in notably higher AUC at each day of prediction (ECMO day 1: 0.78, day 2: 0.86, day 3: 0.79). The sensitivity and specificity of the time series model was greater than 0.70 and 0.64 respectively for the first three days of predictions, with an average precision of 0.29.

Conclusions: These results suggest that models that incorporate time series data on daily lab measurements and blood product administration outperform models trained on exclusively pre-ECMO features in the prediction of neurologic in pediatric ECMO patients. The time-series prediction model provides clinicians with at least one day of early warning for neurologic injury onset for the majority of patients at high risk. The key limitation of this study is the low precision of the model, making the predictive power of this model a key focus of future investigation with larger pediatric ECMO data sets.

Time burden of high intracranial pressure and the need for an early ICP crisis detection system

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Acute traumatic and non-traumatic brain injuries trigger mechanisms that cause delayed secondary brain injury, of which sustained elevated intracranial pressure (ICP) is a major such mechanism. Patients at high risk for elevated ICP are monitored using invasive ICP monitors that generate a continuous calibrated ICP waveform from which a mean ICP value is continuously generated. Current guidelines recommend initiation of treatment when the mean ICP crosses a threshold of either 20mmHg or 22mmHg. However, these treatments can often take minutes to hours to exert their effect in reducing ICP, thereby exposing the patient to risk of injury while the ICP remains high.

We identified and characterized a retrospective cohort of 198 patients that underwent ICP monitoring, of whom 100 developed ICP crisis. In a sub-analysis of 29 patients undergoing monitoring with intraparenchymal monitors only, we describe the total time the patients spend with an elevated ICP while being monitored. We also describe our future goals to develop a near-real-time ICP crisis detection system, including the use of an automated algorithm for ICP waveform analysis, and a machine learning based algorithm for ICP waveform segmentation and classification.

Table 1. Baseline Characteristics of all patients included in our data set
( ) is % of total, and ± reflect standard deviation

Characteristic	**ICP Crisis (n)**	**No ICP Crisis (n)**
Number of Patients	100	98
Mean Age	50.1 ± 17.3	52.9 ± 16.6
Number of Men	53 (53.0)	45 (45.9)
Number of Women	47 (47.0)	53 (54.1)
Type of ICP monitor		
# of EVDs	74 (74.0)	88 (90)
# Intraparenchymal Monitors	29 (29.0)	8 (8)
#Lumbar Drains	2 (2.0)	2 (2)
Initial Etiology of Brain Injury		
IVH (all causes)	56 (56.0)	47 (47.9)
Non-Traumatic ICH	32 (32.0)	34 (34.7)
Aneurysmal Subarachnoid Hemorrhage	31 (31.0)	33 (33.7)
Brain Tumors	14 (14.0)	25 (25.5)
TBI	19 (12.0)	6 (6.0)
Large Territory Ischemic Stroke	6 (6.0)	5 (5.1)
Other	19 (19.0)	31 (31.0)
Secondary Outcomes of Interest		
Number of Deaths	48 (48.0)	12.0 (12.2)
Mean ICU LOS in days	19.2 ± 16.9	16.4 ± 12.7
Median ICU LOS in days	16.0	13.0
Mean Hospital LOS in days	31.5 ± 56.2	37.7 ± 56.4
Mean duration ICP monitoring (Days)	14 ± 14,1	9 ± 8.6
Median duration ICP monitoring (days)	11	7
Permanent CSF Diversion (VPS or VAS)	26 (26.0)	9.0 (9.2)

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High risk central lines in pediatric intensive care unit patients: a nurse-driven intervention to raise awareness and reduce central line associated bloodstream infections

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Background and Aim:
Comprehensive guidelines assessing pediatric critical care patients' risk for developing central line-associated bloodstream infections (CLABSI) are lacking. Despite our pediatric intensive care units' (PICU) >90% compliance to institutional CLABSI prevention process measures, we observed CLABSI rates above national benchmarks. We aimed to identify clinically relevant factors increasing patients' CLABSI risk, design and implement a screening tool based on identified risk factors, and improve clinician awareness and management of CLABSI risk factors.

Method:
After reviewing patient factors from historic CLABSIs from our 36-bed quaternary PICU and published risk factors for our patient population, we developed a novel CLABSI risk screening tool with actionable mitigation strategies. Starting in December 2020, this tool was applied weekly to all PICU patients with a central venous access device (CVAD). We compared pre- and post-implementation data for CVAD utilization rates, CLABSI rates, and surveyed clinicians for effect on clinical practices.

Results:
Over 12 months, 758 patients were screened weekly revealing 186 high risk lines. CVAD utilization rates (device days per patient days) decreased from 0.60 and 0.68 in the two quarters preceding implementation to 0.54 for 2021. CLABSI rates decreased from 1.83 (per 1000 catheter days) in 2020 to 1.15 in 2021. Post-intervention, clinicians reported improved awareness of CLABSI risk, strategies to reduce CVAD entries, prompt CVAD removal, and adherence to prevention processes.

Conclusions:
Implementation of our novel screening process and decision support tool proactively identified patient specific CLABSI risk factors. It allowed targeted risk mitigation strategies associated with decreased CLABSIs and device utilization rates with improvement in clinician CVAD practices of maintenance and removal.

Neuropathological findings in COVID-19 vs non-COVID-19 acute respiratory distress syndrome - a matched case control study

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Rationale:
Acute respiratory distress syndrome (ARDS) is often associated with acute brain injury (ABI) including ischemic infarct, intracranial hemorrhage (ICH), and hypoxic ischemic brain injury (HIBI). A brain autopsy study showed that two-third of non-COVID-19 ARDS patients had ABIs. Currently, sparse data exist if COVID-19 carries a higher risk of ABI compared to those with non-COVID-19 in ARDS patients.

Objective:
To identify differences in ABI and neuropathology findings between COVID-19 and non-COVID ARDS patients.

Design:
We identified autopsy patients with COVID-19 ARDS between March 2019 to June 2022 at a single tertiary center from a retrospective autopsy registry. Each COVID-19 ARDS case was age and sex matched to non-COVID ARDS autopsy cases, also identified from the retrospective institutional registry. Demographics, past medical history, and hospital data were collected and compared.

Results:
Ten patients with COVID-19 ARDS and 65 patients with non-COVID ARDS had brain autopsy shortly after their ARDS course, resulting in 20 non-COVID-19 and 10 COVID-19 age- and sex-matched pairs. The median brain weight was similar for both groups. The frequency of overall ABI (70% vs 55%), ischemic infarct (30% vs 30%), ICH (50% vs 35%) and HIBI (30% vs 35%) between COVID-19 ARDS and non-COVID-19 ARDS patients was similar (all p values >0.05). Hemorrhage subtypes included subarachnoid (30% vs 5%), subdural (0% vs 5%), intraparenchymal (0% vs 10%), petechial (0 vs 10%) and microbleeds (20% vs 5%). Gliosis was seen in 50% of COVID-19 vs. 10% of non-COVID-19 patients (p=0.03).

Other baseline demographics were comparable between the two groups including the ratio of arterial oxygen partial pressure to fractional inspired oxygen (p=0.54). Median age for the sample was 64.5(IQR 57-79) years with 70% males. Length of ICU stay (median [IQR] 11.5 [7-17] vs 11 [6-19.5] days) and duration of mechanical ventilation (median [IQR] 8[2.5-15] vs 8 [2-14] days) was similar for COVID-19 and non-COVID-19 cohorts, respectively.

Conclusion:
Our study did note a higher frequency of acute brain injury on autopsy in COVID-19 ARDS compared to non-COVID ARDS, though not statistically significant. Given the small sample size of the study, further research is needed to compare differences in neurological injury between these populations.

The association of oxygen delivery on cardiopulmonary bypass and postoperative delirium

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Introduction Inadequate oxygen delivery (DO_2) on cardiopulmonary bypass (CPB) has been associated with acute kidney injury. Delirium may result from inadequate oxygen delivery and impaired cerebral perfusion, but no prior studies have investigated the association of impaired DO_2 on CPB with postoperative delirium.

Methods There were 124 patients undergoing cardiac surgery included in this analysis, whose oxygen delivery status on CPB was adequately monitored and recorded during surgery. According to previous literature, DO_2 was calculated every operative minute using the following equation: DO_2 [ml/min/m^2] = pump flow (L/min) × (Hemoglobin [g/dL] × 1.36 × 100% + 0.003 × Arterial Oxygen Tension [mmHg]) × 10 / body surface area (m^2). Five metrics of DO_2 were derived per individual participant: 1) the nadir value of DO_2; 2) the average of DO_2; 3) the moving average of DO_2 in each 5-min window; 4) the total time (minutes) under DO_2 threshold (225 [ml/min/m^2]); 5) the area under the curve (AUC) for DO_2 threshold. Postoperative delirium was assessed on postoperative days 1, 2, and 3, using the 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM). The comparison of DO_2 metrics between the group of patients with delirium and those without was tested using the student t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution). The association of DO_2 metrics and incident postoperative delirium was examined using multivariable logistic regression models.

Results Compared to non-delirious patients, DO_2 metrics were significantly different in patients who developed delirium (see **Table**, all comparison *p*-values<0.05). Specifically, the nadir, average, and moving average of DO_2 were negatively associated with delirium, while the total time or AUC below the DO_2 threshold were positively associated with delirium. Moreover, multivariate logistic models revealed postoperative delirium was associated with lower average DO_2 and higher total time under the DO_2 threshold, independent of potential confounders (p<0.05).

Conclusions Lower DO_2 level and longer time under DO_2 threshold during CPB are significantly associated with higher risk of postoperative delirium in cardiac surgical patients. These findings support the role of impaired oxygen delivery on cardiopulmonary bypass in the development of postoperative delirium.

Table: DO_2 metrics and postoperative delirium.

	No Delirium (n=111)	Delirium (n=13)	Comparison *p*-value	Odds Ratio†
Nadir DO_2, ml/min/m^2	143.1 (87.0, 199.5)*	77.0 (68.7, 128.4)	0.042	0.995 (0.985, 1.005)
Average DO_2, ml/min/m^2	325.2 (55.3)	278.8 (43.6)	0.004	**0.983 (0.969, 0.997)**‡
Moving average of DO_2, ml/min/m^2	235.2 (191.4, 281.5)	198.7 (160.4, 239.3)	0.044	0.996 (0.986, 1.005)
Total time of DO_2 <225, min	2.0 (1.0, 9.0)	9.0 (2.0, 42.0)	0.024	**1.027 (1.002, 1.052)**‡
AUC of DO_2 <225, ml/m^2	374.9 (93.3, 1438.6)	1761.3 (326.0, 8261.7)	0.031	1.000 (1.000, 1.000)

* DO_2 metrics data were represented in median (interquartile range), except for average DO_2, which was represented in mean (standard deviation).

† Odds ratio in multivariable logistic regression models which were adjusted by age, bypass time, preoperative hemoglobin, and log EuroSCORE.

‡ *p*-value<0.05.

Prevalence of delirium and its association with in-hospital outcomes in veno-venous extracorporeal membrane oxygenation in COVID-19 patients

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Background & Purpose: Delirium in intensive care unit (ICU) portends unfavorable outcomes. Veno-venous extracorporeal membrane oxygenation (VV-ECMO) has been used in COVID-19 acute respiratory distress (ARDS). We aim to assess the characteristics of delirium and describe associated factors in this group.

Methods: We retrospectively reviewed adult patients on VV-ECMO for severe COVID-19 ARDS on Johns Hopkins Hospital ECMO registry in 2020-2021. Delirium was assessed by the Confusion Assessment Method for the ICU performed every 4 hours, with the exclusion of those who were sedated/unarousable based on Richmond Agitation-Sedation Scale score of -4/-5. Primary outcomes were the prevalence and duration of delirium. Secondary outcomes included use of sedatives since the onset of delirium and in-hospital mortality.

Results: Forty-seven eligible patients had the median age of 51 years (IQR=15) and ECMO duration of 31 days (IQR 41.5). Laboratory parameters included pre-cannulation P/F ratio of 63 (IQR=14.5), PaCO2 of 65mmHg (IQR 18), pH of 7.27 (IQR 0.15), lactate of 2.3mmol/L (IQR 1.5), and IL-6 of 422pg/ml (IQR 1339). Significant events included secondary pneumonia in 38 (81%), systemic thromboembolism in 14 (30%), intracranial hemorrhage in 11 (23%), tracheostomy placement in 43 (91%), and death in 26 (55%). Excluding 6 persistently comatose patients, 40 of the remaining 41 patients (98%) had ICU delirium during ECMO support, diagnosed on 9.5 days (IQR=16) from ECMO cannulation, with total delirium days of 9 (IQR 17.25) afterward. Proportion of delirium days did not correlate with ECMO duration or mortality (p=0.36). Sedating agents since delirium onset included benzodiazepine (n= 39), opioids (n=40), haloperidol (n=2), quetiapine (n=35), dexmedetomidine (n=33), ketamine (n=38), and propofol (n=33). Average daily dosage of these analgo-sedatives and antipsychotics on ECMO days were not significantly different between survivors vs. non-survivors. Non-survivors had significantly longer delirium-unassessable days on VV-ECMO with RASS of -4/-5 (median days 17 vs. 23, p=0.03) and total VV-ECMO days (median days 27 vs. 44.5, p=0.04).

Conclusion: Delirium occurred commonly in our VV-ECMO patients and is multifactorial from sedation and complicated hospital course. Avoiding heavy sedation may help reduce delirium days and allow for earlier evaluation of neurologic complications and better patient outcomes.
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A novel case-based echocardiography teaching platform for critical care medicine trainees

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Point-of-care transthoracic echocardiography (POC TTE) is among the most crucial adjuncts in the evaluation and management of critically ill patients in the Emergency Department and Intensive Care Unit (ICU). Numerous studies have demonstrated a routine role for POC TTE in these settings.[1,2] A consensus statement by the American Society of Echocardiography (ASE) and the American College of Emergency Physicians published in 2010 referred to POC TTE as a fundamental tool and recommended its use for a variety of clinical scenarios.[3]

POC TTE changes management decisions in acutely ill patients and improves care. Ferrada et al. published a randomized trial demonstrating that patients who were evaluated with POC TTE in their initial evaluation in the trauma bay received a lower volume of intravenous fluids, had a reduced time from the trauma bay to the operating room, and had higher rates of ICU admission.[4] Another investigation by Ferrada et al. showed that POC TTE directly changed the management plans in 96% of hypotensive patients greater than 65 years of age.[5] Finally, Kanji et al. demonstrated reduced 28-day mortality and lower administration of intravenous fluids when intensivists used POC TTE to guide early resuscitation for patients admitted to the ICU with vasopressor-dependent hypotension.[6]

Ultrasound instruction is expanding and has now been incorporated into the curriculum of multiple clinical training programs.[7] However, despite its acknowledged growing importance, there is no consensus training guideline among professional societies and a standardized program proven to develop requisite competency among trainees is lacking.[7] A combination of bedside instruction and web-based teaching modules has shown promise as one possible approach to adequate POC TTE education. Studies have shown that incorporation of online teaching platforms are time-saving and effective for instruction of image interpretation.[8]

In addition to in-person instruction, a novel, web-based POC TTE teaching platform has been incorporated into the education curriculum for critical care medicine fellows at Johns Hopkins Hospital (JHH). A multidisciplinary team including cardiac anesthesiologists, a critical care medicine fellow, and an anesthesiology resident collaborated to create an online, asynchronous, case-based application that focuses on key aspects of POC TTE image interpretation and the corresponding clinical decisions that would be most appropriate. Each of the cases were obtained from real-life clinical scenarios in ICUs at JHH. Trainees receive a transthoracic echocardiography (TTE) video series and complete a 22-item multiple choice form that simulates what an individual may assess for using bedside ultrasound and what decisions could be made based on the images provided. Each question has a corresponding explanation that describes specific aspects of the case TTE as well as reviews recommendations from the American Society of Echocardiography. Subsequently, discussions are held with the trainees and experts in echocardiography to review the case. While participants have conveyed positive reflections and demonstrated strong clinical competency with POC TTE utilizing this platform, future studies are needed to evaluate its efficacy and generalizability in different clinical settings, training programs, and geographic regions.

PCCM fellow-led procedure curriculum for pediatric residents

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The American Board of Pediatrics and ACGME require graduates of pediatric residency programs to be competent in certain procedures, including bag-mask ventilation (BMV), lumbar punctures (LP), intraosseous catheter (IO) placement, and peripheral IV (PIV) placement. Nationally, pediatric trainees are experiencing a decrease in opportunities to perform procedures. The pediatric residency program at our institution relies heavily on the PICU rotation for procedural teaching. Previous resident evaluations of the PICU rotation reported inadequate exposure to these procedures. The goal of this study is to demonstrate the efficacy of fellow-led teaching of common pediatric procedures through objective and subjective measures.

We developed a standardized curriculum for BMV, LPs, IO placement, and PIV placement that consisted of brief didactics and hands-on practice using task trainers. We adapted existing validated assessment tools to assess competency for BMV, LPs, and IO placement. No validated assessment tool for PIV placement was available. Off-service fellows provided hour-long, weekly procedure teaching sessions and assessed the residents' skills on the task trainers at the end of each session. Residents also self-assessed their competency for each procedure using a Likert scale 1-5.

A total of 51 residents completed self-assessments and were observed performing the above procedures. BMV accounted for 21 of the total assessments (41%), IO placement 10/51 (19%), LPs 9/51 (18%), and peripheral IV placement 11/51 (22%). Mean self-assessment for BMV was 4.2/5 (range 3-5), 4.5/5 (range 4.2-5) for LP, 4.3/5 (range 2-5) for PIV placement, and 4/5 (range 2-5) for IO placement. Mean objective assessment score was 17.2/19 correct (90%) for BMV, 10.9/11 (99%) correct for LP, 11.3/12 (94%) correct for peripheral IV placement, and 15/16 (94%) correct for IO placement.

Fellow-led procedure teaching for pediatric residents in the PICU results in both objectively assessed competence and subjective confidence in performing four crucial procedures required by the American Board of Pediatrics and ACGME.

Teaching fellows to teach: impact of novel fellows as educators curriculum on fellow procedural teaching

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Teaching trainee physicians to be educators is a rapidly advancing field in medical education; however, the majority of the literature focuses on residency curricula and faculty development with only a few articles specifically targeting subspecialty fellowship training. The scant literature indicates that fellows want to teach and learn to become better educators, that residents want to learn from fellows, and that fellows teaching residents improves both fellow and resident satisfaction.

We created a novel Fellows as Educators curriculum that focused on providing PCCM fellows with the skills to teach pediatric residents how to perform procedures that the American Board of Pediatrics and ACGME denote as entrustable professional activities (EPAs), specifically, lumbar punctures, bag-mask ventilation, intraosseous catheter placement, venipuncture, and intravenous catheter placement. Previous resident evaluations of the PICU rotation had reported variable levels of satisfaction with the quality of teaching received from PICU fellows and noted that resident exposure to those required procedures was inadequate.

From August 2021 to February 2022, study team members observed fellows teaching residents how to perform the above procedures using task trainers. We collected resident evaluations of the fellows and fellow self-evaluations adapted from the Stanford Faculty Development Tool, fellow evaluations of the residents' procedural skills using validated checklists for four of the five procedures, and observer checklists of the fellows' use of the Five Microskills of Teaching. In March 2022, fellows participated in a 3-hour Fellows as Educator Bootcamp during which they learned the framework for the Five Microskills of Teaching, participated in three teaching simulations (two procedural and one clinical), and listened to an expert panel on giving feedback. Following the bootcamp, fellows continue to provide procedural teaching to the pediatric residents, and the same subjective and objective measures are being collected.

To date, 15 fellows have participated in the pre-workshop data collection and 11 have participated in post-workshop data collection. Overall, residents evaluate the fellows very favorably with mean scores on each question ranging from 4.7 – 4.9. Fellows reported that they were least confident in their ability to give constructive feedback (mean score 3.8 out of 5 on Likert scale). While we have not yet collected enough post-workshop data to be sufficiently powered to detect a statistical significance, preliminary data suggests that the fellows overall use more of the microskills following the workshop compared to before (7.4/10 vs 6.8/10), and there was a notable increase in the number of fellows who ask the residents what they know about the procedure following the workshop (8/11 or 73%) compared to before (10/15 or 67%).

This preliminary data indicates that the residents value teaching from the fellows and the fellows increased the use of microskills following the Fellows as Educators workshop, yet there is still room for improvement when it comes to fellows' teaching skills. Completion of post-workshop data collection and expansion to include clinical teaching observations of PCCM, pediatric emergency medicine, and NICU fellows is ongoing.

Evaluation of a simulation curriculum to improve nursing-led early physical rehabilitation of critically ill children

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Objectives: Early pediatric intensive care unit (PICU) mobilization is safe and associated with improved clinical outcomes. Nurses are the sole PICU staff involved in the majority of mobilizations. Nursing-specific mobility training is desired, improves ICU mobilization compliance, and increases nursing confidence in mobilizing higher-risk patients. Simulation is superior to traditional instruction methods for teaching clinical skills. Thus, the aim of this study is to design and implement a nurse-targeted, simulation-based early mobility curriculum to determine if it improves nurse self-efficacy, knowledge, and skills.

Methods: We conducted a pre-post interventional study of PICU nurses. We developed and deployed a half-day simulation curriculum. The educational strategy included group simulations, debriefing sessions, and didactic sessions. The early mobility self-efficacy assessment was on a Likert scale from 1 (not confident) to 4 (very confident). The knowledge assessment was a 20-question test. Individual skills were assessed using a 25-item rubric during Observed Structured Clinical Examinations (OSCE).

Results: Data was compiled from 11 PICU nurses who participated in a half-day simulation-based early mobility curriculum. The nurses who participated had a median of 2 years (Interquartile Range [IQR], 0.7-3) of nursing experience and 1.5 years (IQR, 0.7-2.5) of PICU experience. Participation in the curriculum improved the early mobility self-efficacy score from a median of 2.7 (IQR 2.67-3) to a median of 3.6 (IQR 3.1-3.7; p-value 0.001). Knowledge assessment test scores also improved from a median of 14 (IQR 12-16) questions correct to a median of 17 (IQR 16-18) questions correct (p-value 0.001). Additionally, nurses completed more clinical skills during the OSCE with an improvement from a median of 14 (IQR 13.5-16) items to 18 (IQR 17-19) items (p-value 0.002).

Conclusions: Development of a simulation-based early mobility curriculum is feasible. Hands-on early mobility education for nurses improves self-efficacy, knowledge, and clinical skills mobilizing critically ill children.

COVID-19 pediatric respiratory care educational training program for healthcare workers in Lesotho: an observational study

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Objectives: To develop and implement COVID-19 pediatric care training for healthcare workers in Lesotho
Design: Prospective pre-post training evaluation
Setting: Three hospitals in Lesotho, Berea District Hospital, Mafeteng Regional Hospital, and Queen Mamohato Memorial Hospital (QMMH), all of which have limited capacity in oxygen delivery for pediatric patients. Only QMMH has pediatricians available.
Participants: Pediatricians, general physicians, nurses, nursing assistants, and other healthcare workers
Interventions: Three one-day offsite trainings on March 31 – April 1, 2022 which covered epidemiology, pathophysiology, clinical presentation, and treatment of pediatric COVID-19 infection.
Outcome measures: Participants completed a fifteen-question multiple choice examination immediately before and after the one-day training. Examinations included questions on transmission, symptoms, testing, and basic management. Differences in pre- and post-training examination scores were evaluated across sites and healthcare worker cadres. One question was excluded form analysis due to a lack of question clarity.
Results: 82 participants completed the pre-test and 79 completed the post-test. Nurses comprised 56/82 (68.3%) of the participants while doctors comprised 14/82 (17.1%), and 12/82 (14.6%) were other healthcare workers. The mean score on the pre-examination was 6.3/14 (45.1%, Standard Deviation (SD) 15.3%). Four participants received the lowest score of 3/14 and only 2/82 participants scored >80%. Doctors scored highest on the pre-participation examination with a mean of 7.5/14 (53.6%, SD 10.8%) while nurses scored on average 5.5/14 (39.1%, SD 9.8%). On post-training examinations, 39 participants scored >80% and 9 participants scored 100%. Six participants scored <50%. The mean post-training score was 10.8/14 (76.8%, SD 17.7%). Doctors continued to have the highest mean score of 11.5/14 (81.9%, SD 16.9%) with nurses having a mean score of 10.7/14 (76.6%, SD 18.9%). Comparison of pre- and post-training examination performance using paired *t*-tests are ongoing.
Conclusions: Despite two years of pandemic exposure to COVID-19, knowledge of transmission, symptoms, testing, and management of pediatric COVID-19 remains low among healthcare workers in Lesotho. Dedicated training demonstrated improvement in a critical knowledge based needed to adequately care for pediatric patients with COVID-19.

An educational quality improvement project for the first pediatric anesthesiology resident rotation: a microlearning-based curriculum intervention

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Problem statement and needs assessment: Learning in residency education is fraught with time constraints and clinical work assignments, creating the challenge of delivering a uniform learning experience for all trainees. Notwithstanding, the ACGME expects all trainees to have reliability and uniformity in their training, resulting in competence demonstration in 23 Milestones. The current curriculum consists of a series of resource materials and early morning case conferences and neither are trackable events, nor are they necessarily comprehensive or containing content validation by numerous faculty.

Goal/Aim: To improve uniformity and knowledge gains in resident learning through the first pediatric subspecialty rotation. A secondary goal is to improve the teaching process, making consistent content delivery easier for faculty.

Scope: All residents of the JHU ACCM program

Intervention: Creation of a new curriculum based on microlearning modules to standardize the resident learning experience in terms of medical knowledge.

Metrics: Assessment of learning using pre- and post-tests and survey assessment of satisfaction of the residents and the faculty teachers.

Rationale: Microlearning in health education involves creating small, easily digestible modules of information that are high-yield for the novice learner and reduce the intrinsic cognitive load burden. When coupled with interactive and digital technology, the flexibility, ease of accessibility, and on-demand nature promotes learner motivation and long-term retention.

Methods: Step one (currently underway) includes survey creation and deployment to pediatric anesthesiology faculty (based on the ABA Content Outline) to identify consensus on foundational topics in junior level pediatric anesthesiology training. Step two involves development of microlearning packets. Step three is implementation of the new curriculum. Step four is assessment of learning using pre- post-tests and assessment of satisfaction with surveys.

Keywords:
Microlearning, digital learning, health education, pediatric anesthesiology, cognitive load

Market trends and needs analysis of emergency response training and interest in a game-based learning tool to teach mass casualty preparedness

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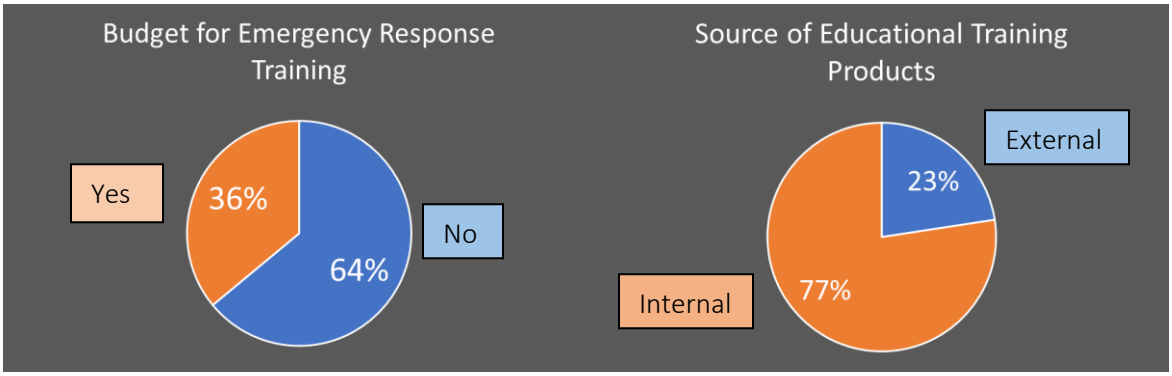
Introduction: We are a multi-disciplinary group of faculty and staff at Johns Hopkins Medicine within the department of Anesthesiology & Critical Care Medicine that have developed a game-based, training tool which teaches intra-hospital mass casualty incident response principles, to help hospitals elicit a rapid and coordinated inter-professional response, with the goal of saving the maximum number of lives with minimal resources available: this training tool is called *Influx!*

Methods: To understand the market trends and needs, we conducted market research in May through April 2022 with 30 participating hospitals that shared information in 30-minute interviews by answering 16 structured questions.

Results: Some of the insights derived were that most hospitals do conduct annual disaster training exercises and use homegrown internal training tools as they do not have an allotted budget for emergency response training. Training practice priorities were ranked:
1. Time to train (61%)
2. Validated training techniques (48%)
3. Cost of the training tool (55%).

In reflecting on their COVID-19 response, issues with communication as it relates to the clarity and accuracy of information disseminated and available was the most recurring theme and shortfall. This was a good proof of concept for our training tool which requires effective communication for players to achieve goals and advance to the next round**.**



Discussion: These market results support evidence in the literature that institutions need help providing adequate training and preparedness. Furthermore, *Influx!* should be marketable.

Assessing the need for a health equity curriculum for critical care fellows

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Background: Inequities in healthcare delivery and outcomes are increasingly recognized within all practice areas. Factors like implicit bias and social determinants of health (SDoH) contribute to health disparities, stratified among race, gender, socioeconomic status, and most other demographic categories. In medical education, formal training in implicit bias, SDoH, diversity, equity, and inclusion (DEI), and other fundamental health equity concepts can enhance trainee knowledge and approach to equitable healthcare. Accordingly, the ACGME requires these concepts to be included in training programs. However, most residency and fellowship graduate medical education programs do not have a standardized curriculum and often do not dedicate time in the academic curriculum to health equity education. Trainees at all levels may thus have inadequate knowledge of these important topics. To date, few needs assessments have been conducted regarding health equity curriculum in U.S. fellowship programs, and none have been conducted in anesthesiology or critical care fellowship programs.

Aim: This study aims to assess critical care faculty and fellows' knowledge of health equity concepts and ability to integrate health equity concepts into patient care and mentee education, in order to inform the development of a curriculum on health equity in critical care.

Methods: An anonymous needs assessment was administered to critical care faculty and fellows at Johns Hopkins University School of Medicine. The questionnaire was composed of Likert-scale ranking and free-response questions for participants to self-assess knowledge of and comfort in practicing and teaching health equity concepts. The needs assessment form was developed by a panel of health equity education leaders and piloted by sampled faculty and residents. The protocol was acknowledged as exempt by the institutional review board.

Results: Data collected from 26 critical care faculty and 7 fellows (85%, anesthesiology/critical care; 14%, burn surgery) indicated that 45% of survey respondents reported observing or experiencing health inequity in patient care on a weekly basis. Thirty-six percent reported observing or experiencing bias from patients or colleagues against healthcare personnel weekly. Seventy-eight percent of respondents reported believing that fellows received either little or no exposure to health equity during medical school and residency. Most fellows surveyed reported they would not feel at all confident teaching medical students and residents on 11 out of 14 key health equity topics. The highest-rated educational method by faculty was guided group discussions and debriefs, and by fellows was interactive lectures by community members and activists. The majority of faculty rated implicit bias the most important topic to address; the highest-rated topic to fellows was healthcare personnel mental health and burnout.

Conclusion: Health equity remains under-emphasized in undergraduate and graduate medical curricula. This study demonstrates the need for improved health equity education in graduate medical education in order to mitigate and address health disparities in care. These findings were used to inform the development of a curriculum on health equity in critical care.

EDUCATION

An educational quality improvement project for NICU nursing staff: using cognitive aids to improve understanding and management of neonatal epidurals

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Problem statement and needs assessment: Management of neonates in the ICU setting demands vigilance, frequent assessment, and more dedicated nursing staff to identify acute changes in presentation and how that may affect a patient's dynamic management plan. Time constraints among NICU nursing staff make it difficult to introduce new information on top of clinical obligations that staff already have. Since the placement and management of neonatal epidurals is not performed routinely, there is limited exposure to this modality of pain control. Amongst NICU nursing staff, there exist gaps in understanding the fundamentals of how a neonatal epidural works and the tenets of basic troubleshooting when encountering a problem.

Goal/Aim: To achieve improved understanding of how a neonatal epidural works and improved competency in troubleshooting a neonatal epidural when encountering a technical or mechanical issue. A secondary goal is to make additional resources for neonatal epidural management immediately available to NICU nursing staff who should need it.

Scope: NICU nursing staff of JHU ACCM program

Intervention: Creation of a brochure style cognitive aid outlining physiology and benefits of neonatal epidurals, troubleshooting techniques, and resources for management.

Metrics: Assessment of learning and competency using identical, de-identified quizzes before and after distribution of cognitive aids

Rationale: Neonatal epidurals are being used with more frequency at major academic centers and other institutions in the appropriate patient population. Although this is an excellent modality of pain control, limited exposure to NICU nursing staff is a potential barrier to caring for neonates who had an epidural placed. Succinct, readily available information that outline the fundamentals of neonatal epidural physiology and troubleshooting techniques are invaluable to a NICU nurse who might have limited experience in managing them. A cognitive aid is an ideal educational tool to accomplish this goal of disseminating information.

Methods: 1) Creating and distributing pre-quiz and cognitive aid to NICU nursing staff. 2) Administering post-quiz. 3) Distribution of cognitive aids to strategic locations within NICU where they can continue to be used in management of neonatal epidurals. 4) Assessment of learning using pre- and post-tests.

Prediction of lactate concentrations after cardiac surgery using machine learning and deep learning approaches

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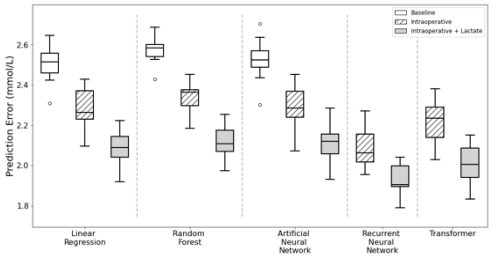
Abstract

Hyperlactatemia after cardiopulmonary bypass has been consistently associated with postoperative morbidity, increased duration of intensive care stay, and mortality. However, existing prediction models in cardiac surgery often ignore minute-by-minute data available on key cardiopulmonary bypass parameters, limiting their predictive power. Here, we report the use of machine learning frameworks to predict a patient's maximum lactate concentration up to 24 hours after cardiac surgery. We considered three classes of predictive models: (1) static models using baseline preoperative variables, (2) augmentation of the static models with intraoperative statistics, and (3) a dynamic approach that integrates preoperative variables with intraoperative time series data. The machine learning models were trained on baseline patient characteristics and intraoperative minute-by-minute monitoring data from electronic health records of over two thousand cardiac surgeries. The prediction errors for five different models are shown in Figure 1, with the best model having a prediction error of 1.90 mmol/L (IQR 1.89, 2.0). We found that the inclusion of dynamic intraoperative data consistently improved the predictive performance of machine learning models, compared to models that only utilized baseline or static intraoperative characteristics. These results imply that valuable information may be captured in the evolving dynamics of the time series data. Moreover, we used Shapley additive values (SHAP) to identify which features most strongly contributed to lactate prediction and found that intraoperative lactate, baseline anemia, and weight were the strongest and most consistent features. The machine learning models with the highest predictive performance relied on a combination of key baseline and intraoperative features to make predictions.



Legend: Plots showing mean absolute error in predicting maximum lactate concentrations in the first 24 hours after surgery. The results of five different machine learning models are shown, with separate models based on included variables (only baseline variables, baseline and intraoperative variables, baseline and intraoperative variables and all intraoperative lactate values). The linear regression, random forest, and artificial neural network models use summarized statistics of intraoperative data, while the recurrent neural network and transformer models incorporate time-series intraoperative data.

A Novel algorithm to calculate target preoperative hemoglobin for patients declining allogeneic transfusion

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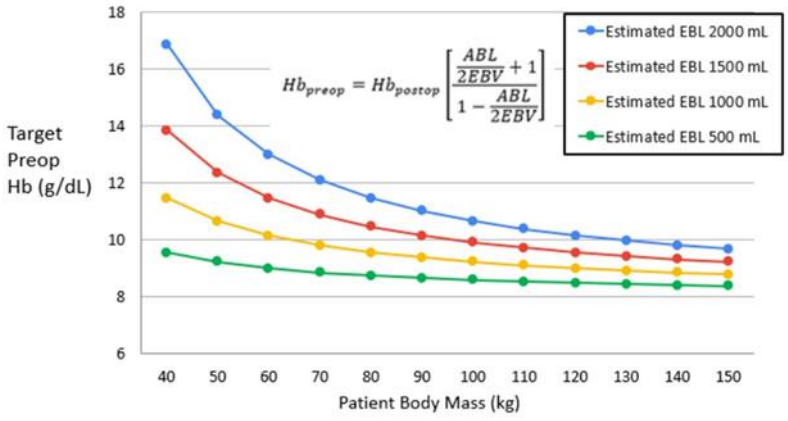
Background: Providing care to patients who decline blood transfusions can be challenging, especially for procedures where patients may lose large amounts of blood. In these types of cases, optimizing preoperative hemoglobin to account for predicted blood loss is essential. We describe a novel algorithm, derived from the allowable blood loss formula, that is based on body mass and expected blood loss. The formula allows for the calculation of the ideal target preoperative hemoglobin.

Methods: Between 2017 to 2021, we coordinated perioperative care for 25 spine surgery patients who declined allogeneic blood transfusions for religious reasons. We applied the algorithm to this cohort of patients to calculate their ideal target preoperative hemoglobin and to guide their preoperative anemia treatment. Hemoglobin concentrations were assessed before anemia treatment, after anemia treatment, immediately after surgery, and at the time of discharge.

Results: Using our algorithm, the ideal target preoperative hemoglobin ranged from 8.2 to 11.9 g/dL. Preoperative anemia was treated with oral iron in 7 patients (28%), intravenous iron in 10 patients (40%), and erythropoietic stimulating agents in 3 patients (12%). After anemia treatment, the mean hemoglobin concentration increased by 1.5 g/dL, and the majority of patients exceeded their target preoperative hemoglobin goal. Intraoperatively, just over half of patients received tranexamic acid, and only 3 patients had enough blood loss to allow for salvaged blood reinfusion. Postoperatively, the mean hemoglobin concentration decreased by 1.7 g/dL, and the lowest hemoglobin upon discharge was 6.7 g/dL. There were no in-hospital mortalities.

Conclusion: This algorithm was useful in calculating the target preoperative hemoglobin required to safely allow surgery, while avoiding clinically significant postoperative anemia. Using this algorithm along with best practice intraoperative blood management methods allows safe practice and good outcomes for patients who decline blood transfusion.



More than words: language patterns indicative of unrecognized shock in children undergoing interhospital transfer

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Background: Eighty-nine percent of pediatric emergency department (ED) visits in the United States occur in general rather than specialized pediatric EDs. Children in shock initially evaluated at general EDs are at increased risk of misdiagnosis prior to transfer to a tertiary or quaternary care pediatric center, resulting in increased mortality and morbidity. One means of detecting early predictive indicators of shock in this patient population is through the analysis of the verbal communication between clinicians from the referring and accepting hospitals during transfer request calls using natural language processing (NLP). The aim of this pilot study was to identify specific terms frequently used by referring providers during the transfer request call to describe pediatric patients with unrecognized shock (URS) compared to recognized shock (RS).

Methods: Transcripts of transfer request calls were obtained for patients aged ≤21 years who were transferred to the Johns Hopkins Children's Center (JHCC) between January 1, 2015 and December 31, 2021 with the primary diagnosis of shock upon evaluation at JHCC. The referring facility's diagnosis was compared to the diagnosis at JHCC to determine if shock was recognized vs unrecognized at the referring institution. Transcripts were reviewed to identify descriptive terms most frequently used by referring providers. Data were analyzed using STATA/SE 17.0. Continuous variables were summarized using medians and interquartile ranges (IQR). A two-sample test of proportions was used.

Results: Twenty-three transcripts (11 URS and 12 RS) were analyzed. Median age (IQR) of patients with URS and RS was 13 (0-204) months and 42 (9-177) months, respectively. Compared to the RS cohort, patients with URS had longer hospitalizations (median (IQR): 9 (5-30) vs. 3.5 (2-6.8) days, p=.01). The term **"shock"** was used in 91.7% of RS vs. 0% of URS transcripts (p<.001). The term **"appearing"** was used in 45.5% of URS vs. 0% of RS transcripts (p=.004). Terms that approached statistical significance in being used more frequently to describe patients with URS vs. RS: **"pale"** (36.4% URS vs. 8.3% RS, p=.05), **"tired"**, **"sick"**, **"mottled"**, **"fast breathing"** (18.2% URS vs. 0% RS, p=.06 each).

Conclusion: In this pilot sample, there were discretely identifiable terms that referring providers used to describe patients with URS compared to those with RS. Compared to the clinically unambiguous term ("shock") used to describe patients with RS, providers describing patients with URS more frequently used ambiguous descriptors of patient presentation (e.g. overall appearance, coloration, mental status and respiratory patterns). Analysis of additional qualifying transcripts is expected to reveal more statistically significant differences between URS and RS transcripts. NLP methodology will then leverage these distinct identifying terms to create prediction models for shock in children undergoing interhospital transfer.
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Early monitoring of neurological recovery using Poincaré analysis index of heart rate variability - a potential biomarker for asphyxial cardiac arrest related brain injury

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Heart rate variability (HRV) is influenced by autonomic nervous system including subcortical structures such as brainstem. We hypothesized that HRV would reflect graded response to hypoxic ischemic brain injury after cardiac arrest (CA). We investigated HRV based on the Poincaré analysis method during the hyperacute recovery period after resuscitation to define its role in assessing neurologic recovery.

Adult male Wistar rats (360±20g) were subjected to 7-min of asphyxial CA and grouped based on neurologic recovery - good (n=17) and bad (n=16), assessed at 4 hr post-return-of-spontaneous circulation (rosc) using a standardized Neurological Deficit Scale (NDS). A good outcome (GO) was defined as a NDS sub score (arousal+brainstem) of 36-40 and bad outcome (BO) as 23-35, with 40 as good and 0 as brain dead. A Poincaré plot showing successive heart rate intervals was developed and analyzed on 5-min ECG segments (first 1 hr) owing to the nonstationary HRV patterns during early recovery period. Machine learning models were trained to assess the results from the standard deviations (SD1, SD2), to decipher the parasympathetic and sympathetic activities. Both groups showed statistically different NDS at 4 hr post rosc (GO : 39.65±0.99; BO : 30±2.65) ($p<0.01$). GO group exhibited an immediate increase post resuscitation in SD1 (0.55±0.23) and SD2(0.67±0.29) with a gradual decrease ~1 hr, SD1 (0.20±0.12) and SD2(0.13±0.09). No significant differences in early Poincaré parameters (SD1(0.30±0.14) and SD2(0.28±0.16)) vs after 1 hr of recovery (SD1(0.29±0.08), SD2(0.30±0.16)) were observed across BO group. For GO, all parameters indicated a faster return to baseline values, showing a better recovery of the cardiac autonomic control, in agreement with the evolution of NDS. Logistic regression and naïve Bayes performed best with SD2, giving an accuracy of 72% (AUC:0.75) and 75%(AUC:0.88) for recovery prognostication in 5-fold cross validation. Unlike previous studies to find biomarkers for CA related brain injury focused on cortical assessment, our results indicate that the novel HRV method can fill the gap in assessing subcortical injury after CA.

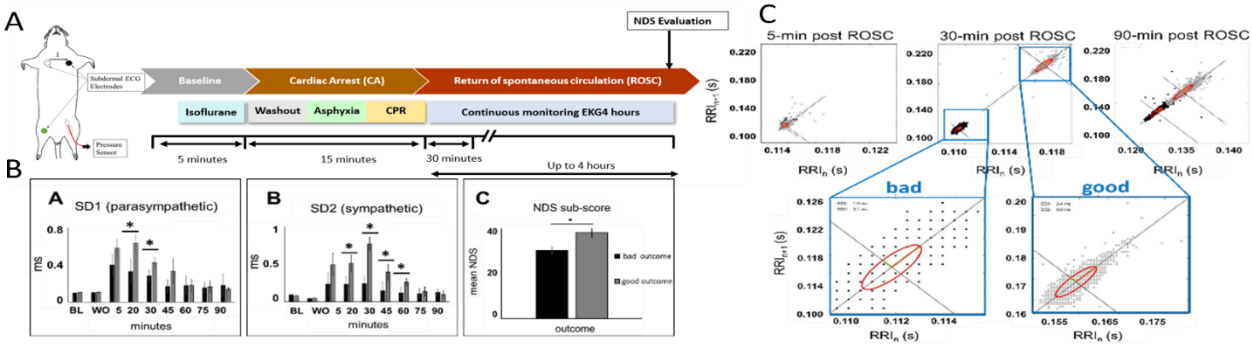

Fig A. Timeline of cardiac arrest experiment. Isoflurane anesthesia is washed out over 5 min, CA is induced by turning off the ventilator for 7 min period. CPR is administered until ROSC. Functional outcome is determined by 4-hr post-ROSC NDS testing.
Fig B. (A) Mean SD2 and (B) Mean SD1 during the experimental process (BL- baseline, WO- washout) and first hour post rosc. (C) NDS sub-scores for the two recovery outcomes. Significance is denoted as *P<0.05.
Fig C. Poincaré plots for different recovery modes at different times post rosc in 2 rats. Loss of RRI variability can be seen by the very narrow clustering of points in the group 1 at 30-min. The points clustered in the ellipse are very sparse in the BO group when compared to the other as seen in the zoomed-in figure. No remarkable changes were seen between the groups at 5 and 90-min.

Simulated real-time EEG feature analysis for assessment of neurological injury post-cardiac arrest

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Over 80% of patients are unresponsive on first examination post-cardiac arrest, often leading to neurological impairment with high morbidity and mortality. Following return of spontaneous circulation during resuscitation, patient EEG must progress from isoelectric to continuous. During this transition, EEG is characterized by alternating patterns of aperiodic waveforms (bursts) and minimal activity (suppression). Features of this burst-suppression period can aid in prognosis of neurological outcome; however, current standards of feature segmentation involve time-intensive human visual analysis. Algorithms for automated segmentation have seen limited clinical translation as they are designed for post-hoc, population-based analysis, or for neurophysiological patterns specific to pharmacological agents. We present an innovative control theoretic approach to address these deficiencies, targeted to real-time use in EEG monitoring of individual patients with cerebral injury resulting from asphyxial cardiac arrest. This model treats each EEG measurement as a discrete event and determines overall system state using state observers that monitor independent attributes: entropy progression, pattern duration, voltage amplitude, and waveform phase history. The entropy progression state observer identifies the patient as in an isoelectric or continuous state, while the latter three observers deterministically identify whether the neurophysiological signal is currently presenting a burst or suppression state based on a confluence of their individual observations. Parameters of interest for each of these attributes were sourced from standard clinical practice guidelines but can be modified based on prevailing patient neurophysiological activity. Development of the system utilized EEG collected from eight male Wistar rats who underwent a 7-minute asphyxial cardiac arrest and resuscitation following an established experimental protocol. This protocol has been validated to closely reflect pathophysiological conditions and neurological functional recovery of human patients. EEG was monitored continuously using two epidural screw electrodes for up to four hours post-cardiac arrest. Two independent systems then reviewed the EEG in strict forward temporality, with overall state decision made through a weighted voting process. Subsequent versions of this software will perform review in real-time on live signals.

Development of a Stata command for pediatric risk of mortality (PRISM) calculation

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Introduction/Hypothesis: PRISM scores have been used in pediatric research to estimate mortality risk and control for illness severity. A major barrier to the usage of this score is the complexity of the calculation and the lack of publicly available implementations. The single publicly available calculator is inconsistently accurate depending on units used and supports data entry for only one patient at a time. Usage of the score over large datasets requires developing custom code to assign scores to physiological variables and calculate the probability of mortality, a resource-intensive and error-prone process. Custom implementations duplicate efforts and are not guaranteed to be accurate. Here we describe the development of a STATA command that calculates PRISM III and PRISM IV scores.

Methods: A STATA command that performs PRISM III and PRISM IV score calculations was developed on STATA/MP 17.0. The command implemented the scoring described in the original papers while adding robust error-proofing, data validation, the ability to use both SI and US laboratory value units, and a graphical user interface. Command validation was accomplished by performing unit tests and calculating scores based on deidentified data. Spot checks were performed to ensure the accuracy of the calculations. The command was additionally tested by generating datasets of 10,000,000 simulated patient records containing random realistic data with predetermined PRISM scores and comparing the command output with the predetermined score. To test the run-time of the command, the command was run over 5 distinct datasets using STATA/MP 17.0 2-cores.

Results: The STATA command achieved 100% accuracy on both the spot checks and the generated data. The median run-time for PRISM III calculations over 10,000,000 simulated patient records is 50.48 seconds (IQR 46.74 - 50.83). The median run-time for PRISM IV calculations over 10,000,000 simulated patient records is 51.52 seconds (IQR 50.46 - 53.44).

Conclusions: The prismscore STATA command performs PRISM III and PRISM IV calculations accurately and efficiently over datasets of all sizes. The tool improves the reproducibility of research involving the scores, streamlines data analysis for pediatric critical care datasets, and offers significant time and resource savings to the research community.

scRNA-sequencing reveals subtype-specific transcriptomic perturbations in DRG neurons of *Pirt*^{EGFPf} mice in neuropathic pain condition

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Abstract

Functionally distinct subtypes/clusters of dorsal root ganglion (DRG) neurons may play different roles in nerve regeneration and pain. However, details about their transcriptomic changes under neuropathic pain conditions remain unclear. Chronic constriction injury (CCI) of the sciatic nerve represents a well-established model of neuropathic pain, and we conducted single-cell RNA-sequencing (scRNA-seq) to characterize subtype-specific perturbations of transcriptomes in lumbar DRG neurons on day 7 post-CCI. By using *Pirt*^{EGFPf} mice that selectively express an enhanced green fluorescent protein in DRG neurons, we established a highly efficient purification process to enrich neurons for scRNA-seq. We observed the emergence of four prominent CCI-induced clusters and a loss of marker genes in injured neurons. Importantly, a portion of injured neurons from several clusters were spared from injury-induced identity loss, suggesting subtype-specific transcriptomic changes in injured neurons. Moreover, uninjured neurons, which are necessary for mediating the evoked pain, also demonstrated cell-type-specific transcriptomic perturbations in these clusters, but not in others. Notably, male and female mice showed differential transcriptomic changes in multiple neuronal clusters after CCI, suggesting transcriptomic sexual dimorphism in DRG neurons after nerve injury. Using *Fgf3* as a proof-of-principle, RNAscope study provided further evidence of increased *Fgf3* in injured neurons after CCI, supporting scRNA-seq analysis, and calcium imaging study unraveled a functional role of *Fgf3* in neuronal excitability. These findings may contribute to the identification of new target genes and the development of DRG neuron cell-type-specific therapies for optimizing neuropathic pain treatment and nerve regeneration.

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RNA-sequencing analysis of mice dorsal root ganglion neurons reveals pain-related gene regulations by HC-HA/PTX3

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Background: HC-HA/PTX3, which is purified from the human amniotic membrane, demonstrated pain-inhibitory effects in the clinic. However, the molecular basis underlying this therapeutic effect is poorly understood. Dorsal root ganglia (DRG) neurons transmit peripheral sensory inputs to the spinal cord. Here, we sought to identify changes in distinct gene networks and transcriptional signatures functioning in DRG neurons after HC-HA/PTX3 treatment.

Methods: We performed RNA-sequencing (RNA-seq) of cultured mouse DRG neurons after incubating with HC-HA/PTX3 (15 µg/ml) or vehicle for 24 hours. Differential gene expressions were identified with the R packages. The variations between data sets due to technical differences were adjusted with the ComBat-seq. Protein-protein interaction (PPI) analysis was applied to identify the networks of the pain-related genes.

Results: Compared to vehicle, HC-HA/PTX3 induced 1996 differentially expressed genes (DEGs) which were centered on the neuroactive ligand-receptor interaction pathway. PPI analysis revealed that over 50 DEGs are closely related to pain and analgesia, suggesting that these genes may be essential for HC-HA/PTX3-induced pain inhibition. In particular, the pro-opiomelanocortin (POMC) pathway, which affects opioid analgesia, was enhanced by HC-HA/PTX3. Functionally, this change contributed to HC-HA/PTX3-induced neuronal inhibition.

Conclusions: Our RNA-seq study showed that HC-HA/PTX3 induced profound gene expression changes in primary sensory neurons. These changes center around various neurochemical mechanisms of pain and analgesia. Current findings may help uncover the molecular mechanisms of pain inhibition by HC-HA/PTX3, as well as identify new targets for pain treatment.

Keywords: RNA-sequencing, dorsal root ganglion, HC-HA/PTX3, ligand-receptor interaction, POMC, pain, bioinformatics.

Spinal cord stimulation attenuates paclitaxel-induced peripheral neuropathic pain and gait impairment by modulating macrophage-mediated neuroinflammation in peripheral nerves

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Introduction: Chemotherapy-induced peripheral neuropathic pain is a debilitating chronic pain condition associated with dose-dependent treatment with taxanes (e.g., paclitaxel). Increased macrophage-mediated pro-inflammatory activities are widely reported to mediate the development and maintenance of hypersensitivity of sensory neurons. Here, we examine the effects of conventional spinal cord stimulation (SCS) on inflammatory cytokines and macrophage-mediated neuroinflammatory transcripts in the sciatic nerve.

Method: Adult male tumor-bearing RNU rats were used for this study examining paclitaxel (PTX)-treatment (total 8mg/kg i.p.), non-squamous cell lung carcinoma (NSCLC), and SCS (during and after PTX administration). Reflexive (mechanical, heat) pain behaviors, gait (catwalk), and sciatic nerve morphology were assessed. Pro- and anti-inflammatory cytokines, and differential gene expression in sciatic nerves were examined using bead-based multiplex immunoassay and bulk RNA-sequencing techniques, respectively. Infiltration of macrophages was investigated through immunohistochemical examination of CD206, CD68, CX3CL1, CX3CR1 and S100B.

Result: SCS reduced mechanical hypersensitivity, and partially normalized the gait disturbance noted in the PTX-treated groups. There was a significant reduction in axon diameter in PTX-treated rats that received sham-SCS, as compared with that in SCS group. Multiplex immunoassay showed higher concentrations of IL10 (an anti-inflammatory cytokine) and MIP3A in the sciatic nerve of PTX-treated rats that received SCS, compared with that in sham-SCS group. RNAseq unraveled differential gene expression after SCS, with 607 (59.2%) genes up-regulated while 418 (40.8%) genes were down-regulated, as compared to sham-SCS group. Notably, genes related to anti-inflammatory cytokines (e.g., Osm, Il1rn, tgfb1, IL10ra) and those regulating neuronal growth and ion transport (e.g., Ephb2, KCNQ3, and Aqp1) were up-regulated, while others were down-regulated (e.g., Maob and Scn8a) in the SCS group. Immunohistochemistry studies showed differences in macrophage infiltration and polarization between groups, with corresponding changes in the expression of CX3CR1, CX3CL1, CD68, CD206, and S100B.

Conclusion: Our findings suggest that SCS inhibited CIPN pain-related behavior, partially normalized gait impairment, and attenuated nerve fiber injury partially via modulation of inflammatory cytokines and macrophage-mediated neuroinflammation, and gene expression mediating anti-inflammatory cytokines, neuronal outgrowth, and ion transport in peripheral nerves.

Synergistic effects of peripherally restricted dual cannabinoid and mu-opioid receptor agonists in mouse model of neuropathic pain

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Neuropathic pain (NP) affects about 7-10% of the global population, but most pharmacological therapies currently in use are effective in less than 50% of patients and are limited by their non-specific binding to the central nervous system (CNS) targets, resulting in adverse effects. Targeting the peripheral nervous system (PNS) may provide safer therapies for NP, devoid of deleterious CNS effects. We have previously reported that activation of peripheral opioid receptors produced analgesia in rodent models of neuropathic pain, but repeated administration results in tolerance. Here, we aim 1) to determine in a mouse model of NP whether co-administration of peripherally restricted agonists, CB13 (dual CB1 and CB2 cannabinoid receptor agonist) and DALDA (mu-opioid receptor agonist) results in additive or synergistic attenuation of NP, and 2) evaluate the CNS-associated side effects and the development of tolerance. A spared nerve injury model (section of common peroneal and sural nerves with intact tibial nerve) was performed in C57BL/6 mice and the effects of CB13 and DALDA co-administration were determined on the paw withdrawal to mechanical stimuli, using the von-Frey test. Conditioned place preference (CPP) was performed to study the spontaneous ongoing pain component in animals. The receptor colocalization was studied using RNAscope and the cellular basis of cannabinoid and mu-opioid receptor interactions in DRG are being studied in our lab. RNAscope analysis revealed the co-expression of CB1 and mu-opioid receptors in the DRG neurons. The separate administration of CB13 and DALDA inhibits mechanical hypersensitivity and spontaneous ongoing pain in nerve-injured mice. Importantly, systemic co-administration of both compounds produced significant analgesia and isobolographic analysis suggested the synergistic effect of the combination. Further studies are ongoing in the lab to determine the effect of the combination on spontaneous ongoing pain and CNS safety profile. Our preliminary findings indicate that systemic co-administration of CB13 and DALDA synergistically attenuate mechanical hypersensitivity in nerve-injured mice. We conclude that dual targeting of peripheral cannabinoid and mu-opioid receptors may present a novel, potent and safe strategy to treat neuropathic pain.

Peripheral nerve stimulation-induced adenosine A3 receptor (A3R) signaling contributes to the inhibition of lamina I NK1R-GFP neuron synapses in neuropathic mice

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Background: Peripheral nerve stimulation (PNS) is an emerging candidate for effective opioid-sparing pain treatment. The Gate Control Theory asserts that spinal pain signal transmission is gated by inhibitory interneurons which can be activated by Aβ-fiber impulses. However, the detailed mechanisms that contribute to synaptic inhibition after PNS, such as 50 Hz Aβ-fiber stimulation, remain partially understood. Although adenosine A3 receptors (A3Rs) are expressed in the spinal cord, their roles in PNS-induced inhibition of spinal projection neuron synapses were unclear.

Methods: We used a multidisciplinary approach to investigate the influence of PNS-induced A3R signaling at in lamina I NK1R-GFP neuron synapses, ~80% of which are projection neurons. Moreover, we examined the impact of endogenous adenosine metabolism modulation on PNS-induced synaptic inhibition. *NK1R-GFP* knockin mice were developed to facilitate the identification of NK1R+ neurons in the spinal cord. Neuropathic pain was induced by tibial spared-nerve injury (SNI-t) to the left hindlimbs of NK1R-GFP mice. Immunohistochemistry, RNA scope, and western blot analysis were used to investigate A3R expression in NK1R+ neurons in the spinal cord from naïve and neuropathic mice. Patch-clamp electrophysiology was used to elucidate the influence of A3R signaling and 50 Hz PNS on C-fiber-evoked excitatory post-synaptic currents (C-eEPSCs) in NK1R-GFP neurons.

Results: NK1R-GFP+ neurons in lamina I express A3Rs, and SNI-t significantly increased the level of A3R protein in the spinal cord. In addition, A3R agonists significantly inhibited C-eEPSCs in NK1R-GFP neurons, suggesting that endogenous A3R-mediated pain inhibition may counteract the development of pain hypersensitivity after nerve injury. Importantly, 50 Hz PNS inhibited C-eEPSCs, which was significantly attenuated by bath-application of A3R antagonist MRS1523 (30 nM). In contrast, blocking the adenosine deaminase-dependent conversion of adenosine to inosine with bath-applied deoxycoformycin (dCF; 1 μM) significantly increased the synaptic inhibition of NK1R-GFP neurons by 50 Hz PNS.

Conclusion: Nociceptive transmission in lamina I NK1R-GFP neurons may be dampened by 50 Hz PNS through activation of A3R. Moreover, inhibiting adenosine deaminase which would increase the level of adenosine accumulated in the synapse enhanced the overall synaptic inhibition produced by 50 Hz PNS. Thus, A3R activation may serve as a key mechanism for the synaptic inhibitory effects of 50 Hz PNS, the effects of which can be amplified with enzyme inhibitors to increase its clinical efficacy for the management of neuropathic pain.

Activation of spinal adenosine 3 receptors contributes to spinal cord stimulation-induced pain inhibition in rats after nerve injury

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Background: Mechanisms of pain inhibition from spinal cord stimulation (SCS) remain partially known. Activation of adenosine 3 receptors (A3Rs) may induce analgesia, but its role in SCS-induced pain inhibition is unclear.

Methods: In a tibial nerve spared injury (SNI-t) model of neuropathic pain, we conducted RNAscope *in situ* hybridization, immunofluorescence staining, and Western blot to examine the expression of *adora3* mRNA and A3R protein in the spinal cord. Moreover, we recorded the local field potentials (LFPs) *in vivo* at the lumbar (L4-5) spinal segments and investigated the roles of A3Rs in the inhibition of C-fiber input-evoked LFP (C-LFP) by SCS.

Results: RNAscope and immunofluorescence staining demonstrated that both *adora3* mRNA and A3R protein were highly expressed in the activated microglial cells labeled by CD68, but little on neurons and astrocytes in the spinal cord dorsal horn. Although the expression of A3R was decreased at day 14 after SNI-t, spinal topical application of 2-CI-IB-MBCA, a selective A3R agonist, dose-dependently attenuated C-LFP evoked by a high-intensity test pulse (5 mA, 2 ms) at the sciatic nerve. Importantly, conventional epidural SCS (50 Hz, A-plateau intensity, 0.2 ms, 5 min) at T13-L1 spinal level also significantly decreased C-LFP, and this effect was blocked by spinal topical application of MRS1523 (200 nM), a selective A3R antagonist.

Conclusion: Our findings unraveled an important role for spinal A3R in SCS-induced pain inhibition after nerve injury, and hence enhancing endogenous A3R signaling, especially in microglia, may be a promising strategy to potentiate SCS-induced pain inhibition.

Keywords: spinal cord stimulation, adenosine, nerve injury, microglia, neuropathic pain.

The effects of intraoperative methadone on postoperative pain control in pediatric patients: a systematic review

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Inadequate perioperative pain control has deleterious effects on children's development and can lead to heightened pain experiences and the avoidance of future medical procedures. Reports of perioperative use of methadone in children are increasing, as it has a favorable pharmacodynamic profile; however, the effectiveness of methadone in reducing postoperative pain has not been systematically reviewed. We, therefore, aimed to compare the effect of intraoperative methadone versus other opioids on postoperative opioid consumption, pain scores, and adverse events in pediatric patients. We identified studies in PubMed, Scopus, Embase, and CINAHL databases from inception to July 2022. Postoperative opioid consumption, pain scores, and adverse events were extracted for analysis. We screened 1783 studies, of which 79 studies were selected for full-text review. Six studies were included in the final synthesis. Postoperative opioid consumption was decreased overall in children who received methadone compared to those who did not. Additionally, methadone was non-inferior to other opioids in reported pain scores, and the frequency of adverse events was similar between the groups. Although the data reviewed infers the benefit of perioperative methadone in pediatric patients, the overall quality of evidence was low per GRADE criteria and we cannot make strong recommendations for the regular use of methadone in the perioperative setting at this time. Our results highlight the need for large, well-designed randomized trials to fully evaluate the safety and efficacy of intraoperative methadone in diverse pediatric surgical populations.

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Effectiveness of single-shot erector spinae blocks on perioperative opioid requirements and length of stay after Nuss procedure

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Authors have requested to not include the abstract for distribution.

EZH2 in primary sensory neurons contributes to the development of neuropathic pain

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Background: Neuropathic pain is a challenging clinical problem that responds poorly to current pain treatments. Identifying its molecular determinants is essential for developing new mechanism-based therapies. Epigenetic reprogramming in sensory neurons is involved in the transition from acute to chronic pain after injury, of which EZH2 regulates histone methylation and may be a promising target for pain treatment. However, roles of EZH2 in the dorsal root ganglion (DRG) neurons, which are primary sensory neurons, in the development of neuropathic pain remain unclear.

Methods: Western blotting was performed to examine changes in the expressions of EZH2 protein and its catalytic H3K27 trimethylation (H3K27me3) in lumbar DRGs and spinal cord in mice after tibia nerve spared injury (SNI-t) or chronic constriction injury (CCI) of the sciatic nerve. RNAscope multiplex fluorescent assay was conducted to investigate the distribution of *Ezh2* mRNAs in different subpopulations of DRG neurons. In vitro calcium imaging was conducted to examine the excitability of cultured DRG neurons. To determine the functional roles of peripheral neuronal EZH2 in neuropathic pain, we developed *Pirt* $^{cre/+}$; *Ezh2*$^{fl/fl}$ conditioning knockout (cKO) mice in which *Ezh2* was selectively deleted in most of primary sensory neurons. Hargreaves and von Frey tests were then conducted to examine thermal and mechanical sensitivity, and Catwalk was used to assess the gait changes after injury.

Results: SNI-t significantly upregulated EZH2 expression in lumbar DRGs and spinal cord of WT mice at day 3 post-injury. There was a trend that EZH2 expression was also increased in DRGs after CCI. RNAscope study revealed the co-localization of *Ezh2* mRNA with both large-diameter (NF200+) and small-diameter non-peptidergic (IB4+) and peptidergic (CGRP+) DRG neurons. Strikingly, the development of heat and mechanical hypersensitivities after SNI-t was significantly attenuated in *Pirt* $^{cre/+}$; *Ezh2*$^{fl/fl}$ cKO mice, as compared to *Ezh2*$^{fl/fl}$ control mice. Both genotypes showed similar gait impairment after SNI-t. Calcium imaging showed that the average peak response of DRG neurons to the bath application of capsaicin (0.5 μM), a potent TRPV1 agonist, was also decreased in *Pirt* $^{cre/+}$; *Ezh2*$^{fl/fl}$ cKO mice. The expression of H3K27me3 in lumbar DRGs was upregulated in WT mice, but not in *Pirt* $^{cre/+}$; *Ezh2*$^{fl/fl}$ cKO mice at day 3 after SNI-t.

Conclusion: Our findings suggest that deletion of *Ezh2* selectively in DRG neurons prevented the development of neuropathic heat and mechanical hypersensitivities. The underlying mechanism may involve changes in H3K27me3 function and downstream TRPV1 channels.

Key words: Epigenetic, Ezh2, dorsal root ganglion, neuropathic pain, mice.

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Epidural analgesia for labor: continuous infusion versus intermittent bolus

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Epidural analgesia is the ideal method for providing adequate pain relief during labor while minimally effecting maternal and fetal physiology. Local anesthetic spreads horizontally and longitudinally throughout the epidural space where it bathes nerve roots and diffuses into the cerebrospinal fluid to achieve analgesia. The epidural space also contains blood vessels, which introduces the risk of inadvertent absorption of local anesthetic into the systemic circulation. If large amounts of local anesthetic reach the systemic circulation, supratherapeutic blood levels can cause toxicity. Patients undergo many physiologic changes during pregnancy that increase their risk for local anesthetic systemic toxicity, therefore, the lowest possible dose of local anesthetic should be used. The purpose of this project is to synthesize the results of four clinical trials that examine the effect of epidural administration techniques on total local anesthetic consumption. To seek evidence related to programmed intermittent epidural boluses for labor analgesia, the following PICOT was developed: In laboring patients, how do programmed intermittent epidural boluses compared to continuous epidural infusions affect total local anesthetic consumption during the first and second stage of labor? Although the continuous infusion technique is the standard of care throughout North America, current literature shows that programmed intermittent boluses result in more extensive spread of local anesthetic in the epidural space, which ultimately reduces the total drug consumption and improves maternal safety.

Perioperative opioid tapering in patients on methadone medication-assisted treatment (MAT) for opioid use disorder (OUD)

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Introduction:
The Perioperative Pain Program (PPP) at Johns Hopkins was created to address aspects of pain management and opioid use across the continuum of the perioperative period with the goal of personalized treatment plans that combine 1) multimodal pain management, 2) an opioid-tapering strategy, and 3) multidisciplinary care. A previous pilot study of 251 patients, including patients undergoing treatment for OUD with methadone or buprenorphine, showed that the majority (73-82%) were able to have their opioid oral morphine milligram equivalents (MME) decreased between initial and final PPP appointments. Within the MAT subset, acute postoperative pure opioid agonist doses across the course of PPP treatment were significantly decreased in 46.4% of the preliminary cohort and 35.7% were tapered completely off acute opioids. This project is aimed at further elucidating the natural history of opioid use throughout the perioperative period, including hospitalization, in a larger methadone treated cohort and investigate the effect of PPP enrollment on opioid tapering.

Materials and Methods:
In this IRB approved retrospective chart review pilot study, we used a previously compiled dataset of individual and perioperative characteristics of PPP patients (2017-2021). Inclusion criteria was defined as documented methadone treatment for OUD, surgery requiring inpatient stay >24 hours, in addition to attendance at a minimum of 2 PPP visits related to that surgery with at least one postoperatively. The perioperative period was defined as the entirety of inpatient hospitalization and included pre-operative PPP visits for up to 2 months prior to surgery (when applicable), as well as all transitional pain management visits at the PPP for up to 2 years postoperatively. Outcome measures include each patient's non-MAT opioid dosage in MME throughout their perioperative course, as well as any changes in their methadone dose.

Results:
Initial dataset screening revealed a group of 31 patients on methadone MAT for OUD, who fit inclusion criteria. The group was mainly Caucasian (61%), with similar gender distribution (45.2% male), median age of 45, average hospital length of stay of 6 days, and a heterogeneous mixture of surgery types including orthopedic (29%), neurosurgical (16%), vascular (12.9%) and trauma (12.9%). Chart review is ongoing and has been completed for 10 patients with 77% noted to be on preoperative non-MAT opioids at admission. In this pilot cohort, 70% were tapered off non-methadone opioids at PPP completion (range of 2-27 appointments). For patients not fully weaned from opioids their MME at the last PPP visit was lower than at hospital discharge, with a mean drop in daily MME of 87. Early engagement with inpatient acute pain service (90%) yielded an average MME decrease of 240 +/- 119 from POD0 to last PPP visit, while maintaining methadone for MAT. Again, a consistent trend of decreased MME was seen in all cases over time in PPP. Notably methadone dosages were altered in 40% of patients reviewed thus far.

Discussion:
Early review of OUD PPP patients on perioperative methadone appears to demonstrate substantial non-MAT opioid weaning. Further analysis will explore pain severity changes, the impact of methadone dose changes, and potential predictors of PPP non-compliance or weaning failure. Future work is aimed at analysis of buprenorphine MAT patient outcomes enrolled in PPP.

The perceptions of a novel syringe organizational device following implementation and its impact on operating room workflow during a surgical case

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One of the most common medication errors in the delivery of anesthesia is a “syringe swap,” in which an unintended medication is selected and delivered to the patient (Orser et al., 2001). In a previous study we designed a syringe organizational hub to address syringe swaps and evaluated it through a four-step process consisting of 1) studying the work as done, 2) studying syringe motion 3) prototyping a syringe organizational hub, and 4) evaluating the syringe organizational hub through data from a survey sent to clinicians who based their perceptions off a one-minute video clip of the hub in use. To give providers a more accurate representation of the device and to determine how it impacts the operating room workflow, we found it necessary to test the device in practice. The objectives of this study were to observe the hub in use in operating rooms to investigate both the impact of a syringe organizational hub on the work practices and provider perceptions of the hub’s impact on the work practice.

To assess the impact of the syringe organizational hub on the work practice, we performed in-situ observations of anesthesia residents using the device at a large academic hospital in the Mid-Atlantic United States. To assess provider perceptions of the device after use, we surveyed providers using the Technology Acceptance Model (TAM) and compared their scores with scores of participants who only viewed the video (in a previous study). We observed a total of 25 cases and obtained a total of 10 complete survey responses which can be compared to the 21 responses which were previously gathered from residents.

Linear regression analysis of the syringe motion data revealed that cases where the hub was used had significantly less syringe movements per hour (M=10.39, SD=5.77) than cases where the hub was not used (M=16.65, SD=6.05) ($p<.05$). TAM data after use was compared to TAM data generated from our prior video-based survey to determine if using the hub during a case changed perceptions of use. While there was an increase in the average response score for perceived usefulness (3.18 v 3.44), attitude towards use (3.33 v 3.63), and behavioral intent (3.17 v 2.67), these differences were not significant as determined by a linear regression model.

Through this study, we continued our analysis of the acceptance of a previously designed syringe organizational hub. The results of the observation data reveal that the implementation of the syringe organizational hub significantly reduced syringe motion ($p<.05$). These results suggest that the device was successful in reducing syringe motion and consolidating the location of drug delivery. This shows that a relatively simple device can have a significant impact on the operating room workflow. Changes in the survey data following use generally reflect the positive impact on the workflow, though these differences were not significant (potentially due to small sample size). When coupled with the syringe movement data, these results suggest that the organizational hub shows a lot of promise when it comes to improving the anesthesia workflow, but this does not guarantee a significant increase in acceptance. In this study, the quantitative approach to measuring perceptions of use led to ambiguous results, and future work will explore attitudes towards adoption from a qualitative approach to further investigate perceptions of use. Future work should also look deeper into if use of this device actually leads to a reduction of syringe swaps and medication errors.

Standardizing front-line provider handoff in the pediatric intensive care unit (PICU)

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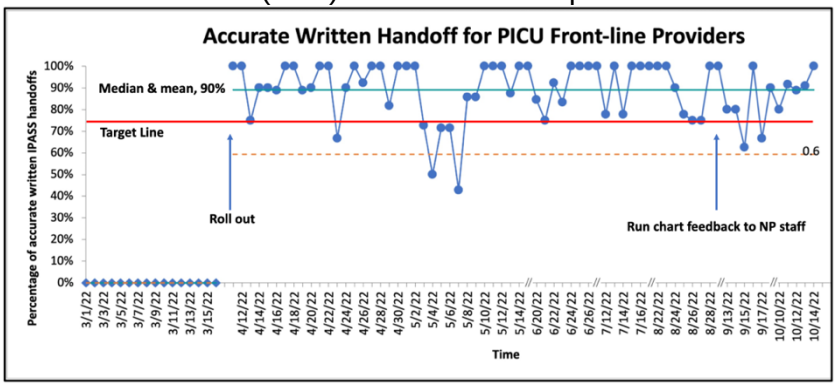
Aim: Published guidelines for structured handoff communication provide shared expectations and responsibilities for senders and receivers of patient information. We recognized a lack of written handoff for front-line providers (FLP) of pediatric intensive care unit (PICU) patients. Therefore, the aim of this quality improvement (QI) project was to standardize FLP written handoff communication to include patient one-liner, illness severity, and daytime events in at least 75% of the electronic medical record (EMR) handoff tool within a three-month period.

Methods: We did a mixed-methods QI project including:
Pre-intervention Survey: We disseminated a web-based survey to nurse practitioners (NP)/hospitalist, attendings, and residents to assess perceptions of the written handoff practices and use of a handoff tool. Open-ended free text comments were analyzed thematically by two researchers. Disagreements were resolved by consensus.
Intervention: PICU clinicians developed 2 EMR standardized scripts for use in the tool. Education was provided to PICU attending, FLP, and resident staff.
Evaluation: We collected nominal data (yes, no) for the inclusion of all three written components: patient one-liner, illness severity, daytime events. We performed data collection nightly after handoff for 16 days pre-intervention, five weeks post-intervention, and then one week per month. We compiled nominal data into a control chart.

Results Pre-Intervention Survey: Response rate was 69.2% (n = 78). A third of participants did not use the handoff tool and 94% of these participants reported they were interested in using the tool if it included up to date information. We conducted content analysis of free text responses to open ended question with 49 discrete units of analysis, 25 codes, and 4 themes: lack of standardization (41%), barriers to effective handoff (31%), facilitators to effective handoff (18%), desire for helpful handoff (10%).

S-chart: Nominal data with target line (75%), median (90%), and mean (90%) over an 8-month period.



Conclusion
The use of an EMR standardized script within a handoff tool improved compliance of structured communication between FLP PICU providers.

Increasing pediatric interhospital transport efficiency: a quality improvement intervention

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Purpose/Objectives: Johns Hopkins Pediatric Transport (JHPT) coordinates all incoming pediatric transfers to our quaternary center and utilizes a dynamic staffing model. With our recent growth in transport volume, our staffing model of one pediatric transport nurse – who also served as the intake nurse (iRN) – could result in delays and inefficiencies in transport. Therefore, JHPT implemented a change in its transfer intake process by developing a dedicated iRN role, staffed by a pediatric transport nurse not providing direct patient care. The iRN's responsibilities include: 1) triaging transfer referral calls; 2) communicating with sending and receiving providers; and 3) coordinating the entire transport process from dispatch to patient retrieval. We hypothesized that this quality improvement effort would increase transport process efficiency, reliability, and consistency, potentially leading to improved patient outcomes.

Design/Methods: We performed a retrospective review of patients aged ≤21 years transferred to our children's center three months pre-intervention (5/1/2021-7/31/2021) and three months post-intervention (8/1/2021-10/31/2021). We then compared pre- and post-intervention times to answer the referral call, accept the patient, and mobilize the team.

Results: We reviewed 1,402 charts with available transport information: 646 in the pre-intervention and 756 in the post-intervention group. Compared to the pre-intervention group, the post-intervention group had 17% higher call volume, 36.6% increase in critical care transports (CCTs), and 100% increase in COVID-19/MISC transports, more days with ≥90% intensive care unit (ICU) occupancy rates (90% vs. 74%), and more patients unable to be accommodated due to lack of hospital capacity (113 vs. 41). While the times to answer the referral call and accept the patient were not different between groups, the post-intervention group had slightly longer transport mobilization time. There was a similar trend for the CCT subgroups, with no differences in time to answer the call (median [IQR]: 3 [2-7] vs. 4 [3-6] minutes) and acceptance time (13 [6-33] vs. 10 [6-24] minutes), but a longer post-intervention mobilization time (52 [25-117] vs. 34 [19-69] minutes, $p<0.001$). Mobilization improved when team was available, yet remained longer post- vs. pre-intervention (38 [22-70] vs. 28 [18-52] minutes, $p=0.007$). There were 68 CCTs performed on days with <90% ICU occupancy: 25 post-intervention (2.8 CCTs/day) vs. 43 pre-intervention (1.8 CCTs/day). The transport team was available for 17 (68%) post- vs. 39 (90.7%) pre-intervention CCTs ($p=0.041$). For this subgroup, the average daily acceptance time was shorter post-intervention, yet not statistically significant (median [IQR]: 9 [6-14] vs. 20 [8.3-37] minutes, $p=0.362$); mobilization times improved when team was available, but were not different between groups (36 [22-44] post- vs. 28 [17-49] minutes pre-intervention, $p=0.522$).

Conclusion/Discussion: While transport times did not decrease post-intervention, we believe this was largely due to the surge in CCTs, compounded by historic ICU capacity challenges. Acceptance time reflected the critically low ICU capacity, while mobilization time was impacted by transport volume, by team availability, and likely by infection control measures.

Utilizing an Ethiopian ICU registry to identify opportunities for quality improvement

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Introduction:
The global burden of critical illness disproportionally affects low- and middle-income countries (LMICs), and the outcomes of critical ill patients are significantly worse in those settings. Quality improvement efforts in LMICs are hampered by the lack of robust data about the burden of critical illness or the quality of care in LMIC ICUs. ICU registries are valuable tools that have been implemented in high-income countries to describe the epidemiology, processes of care and clinical outcomes in ICUs, laying the groundwork for effective research and QI projects.

Methods:
We implemented a novel, resource-appropriate ICU registry using an online platform developed by Crit Care Asia to collect data about the demographics, illness patterns, processes of care and clinical outcomes of critically ill patients admitted to two tertiary ICUs in Addis Ababa, Ethiopia. Clinical data were collected and inputted by specially trained data clerks. The first two months of patient data were extracted and analyzed descriptively.

Results:
In June and July, 2021, 83 patients were admitted to the ICUs at St. Paul Hospital and Millennium Medical Center and the Addis Ababa Burn, Emergency and Trauma Hospital. Median age was 35 years (IQR 24-52) and 61% were male. 49% of patients were admitted post-operatively, with 68% of those following emergency surgery. On the day of ICU admission 77% required ventilator support and 17% required vasoactive support. Mean Apache II score was 24.1 (SD 4.1). By July 31, 47% of patients were transferred from the ICU alive, 33% had died in the ICU and 20% remained in the ICU. Standardized mortality ratio was 1.02. Mean length of stay (8.2 days) was similar for survivors and non-survivors.

Conclusions:
This report demonstrates the feasibility of collecting surveillance data in Ethiopian ICUs using the Crit Care Asia platform, and the importance of ICU registries to understand ICU case-mix, processes of care and clinical outcomes in ICUs. These ICUs treat a high burden of critical illness. In this preliminary analysis, the high observed mortality rate is explained by the severity of illness being treated. Improving early recognition of critical illness and triage protocols may be important strategies to improve ICU survival.
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Multidisciplinary geriatric care in the PACU: a quality improvement initiative

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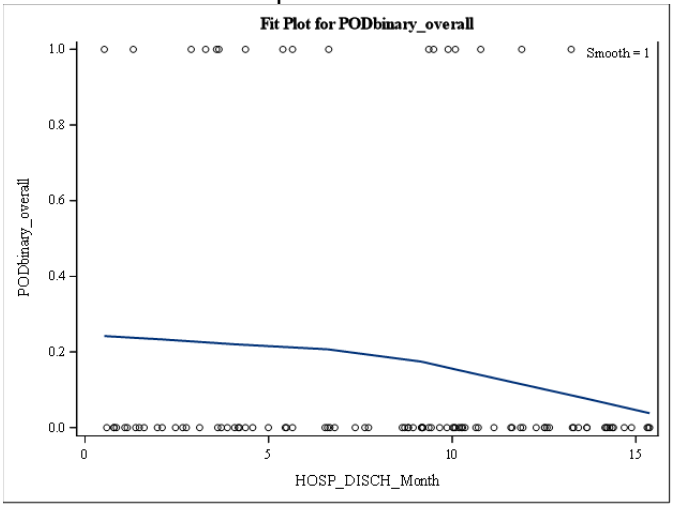
Introduction: Frailty is common in older surgical patients and is associated with higher rates of postoperative delirium. Hospital based multidisciplinary geriatric care (MGC) plans include simple non-pharmacologic approaches developed to decrease delirium in geriatric populations and have demonstrated success in diverse settings. In the surgical setting, MGC care plans have been instituted postoperatively on the ward following post-anesthesia care unit (PACU) transfer. However, onset of postoperative delirium primarily occurs within the first 24 hours. Thus, the PACU provides an opportunity for earlier MGC implementation during the time of highest cognitive risk in frail surgical patients. The purpose of this pilot is two- fold: to fine tune our protocol which incorporates elements of hospital based MGC into current post-anesthesia recovery room (PACU) practice; to determine whether implementing a PACU based MGC model of care will decrease postoperative delirium in frail older surgical patients.

Methods: Following IRB approval, this project studied subjects $\geq$ 65 years undergoing elective surgery not requiring ICU stay. Additional eligibility criteria included a preoperative Edmonton frailty score $\geq$ 6. The PACU-MGC model incorporates literature supported elements of hospital based MGC care for delirium prevention into current PACU practice. Delirium was assessed with the 4 A's test (4AT; www.the4at.com). The 4AT has been validated on the hospital ward and in the PACU as an excellent screening instrument for delirium with high specificity and sensitivity. The primary outcome was binary: 4AT score of $\geq$4 (delirium) at any time postoperatively on the surgical wards or 4AT score <4 (no delirium) at all postoperative assessments. Lowess smoothing was used to examine changes in delirium risk as determined by postoperative 4AT scores with ongoing development and implementation of the PACU-MGC model of care.

Results: 99 patients were studied from 7/20-10/21. Loess smoothing during the study time period shows continuous improvement in delirium rates in this frail population. intervention (see figure).



Conclusion: Preliminary findings suggest that implementing a PACU-MGC program leads to a decrease in early postoperative 4AT scores. In addition, an MGC care program is feasible to implement in the PACU setting. Further study is warranted to determine the effects of the PACU-MGC program on outcomes in frail surgical patients.

Pre-anesthesia counseling, consent, & professionalism

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Introduction: The anesthesia consent form has become a standard before surgery. However, there has been little examination regarding verbal aspects of anesthesia consent and of the value of the discussion that should take place prior to surgery. Similarly, lack of understanding of the duties and responsibilities of anesthesiologists is damaging to the broader professional status of the field. This study used patient pre-anesthesia discussions and post-operative questionnaires to examine their understanding of general anesthesia, duties and responsibilities of the anesthesiologist, and the role of the anesthesiologist within the operating room.

Methodology: The study design was a single-blinded, randomized controlled trial where patients were assigned to a control or intervention group. with 174 patient participants and their anesthesia care team members enrolled in the study at a major academic teaching center (n=82 in the intervention group, n=92 in the control group) and 59 participants enrolled at a hybrid academic/community hospital (n=29 in the intervention, n=30 in the control groups). The control group had their pre-operative discussion performed by an anesthesia team member (attending anesthesiologist, resident anesthesiologist, or nurse anesthetist) in a manner commensurate with their routine for preoperative discussion. The intervention group had their pre-operative discussion performed by one of the intervention group anesthesiologists with knowledge of specific material that must be addressed in the domains of consent, patient autonomy, and professionalism. All patients underwent a postoperative interview within three days after surgery. Both groups completed post-operative questionnaires and results were analyzed with descriptive statistics and the Mann-Whitney U Tests.

Results: Participants in the intervention group were significantly more likely to rate the discussion as very detailed (mean = 4.90/5 vs 4.45/5; p=0.0002), slightly more likely to recall which type of anesthesia they were consented for (99.2% vs 93.4%, p=0.332), significantly more likely to understand why pre-oxygenation was important (64.5% vs 11.6%; p<0.00001), more likely to report a reduction in preoperative anxiety compared to the control group (3.83/5 vs. 3.33/5; p=0.008), more likely to correctly recall a discussion of one or more anesthesia risks (88% vs 60%, p = 0.01), and more likely to know the roles of the members of their anesthesia care team (48.3% vs 24.6%, p<0.0001), despite recognition that anesthesia team members in both groups introduced themselves and their roles. There was no significant difference in patient satisfaction after the discussion (4.77 vs. 4.9; p = 0.23).

Conclusion: A more structured preoperative informed consent process can better help patients understand the roles of anesthesiologists and other team members, increase recall of risks for general anesthesia, elicit cooperation with and understanding of pre-oxygenation, and help improve on the status and perceptions of the specialty. Engaging patients in the shared decision-making domain appeared to benefit patients the most.

Improving efficacy of provider communication during pediatric rapid response team calls

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Communication errors and ineffective communication between medical providers has been recognized as a major determinant of medical errors and patient harm. Communication during acute emergencies and patient decompensations becomes even more important as there is less time to convey critical information and concerns between providers. Emergency situations on pediatric inpatient units are managed by pediatric resident physicians until the arrival of a rapid response team (RRT). Such events are typically high in acuity but occur at low frequency. Pediatric residents may not have significant experience to gain the skills and confidence to manage pediatric emergencies and to give effective emergency handoff to RRT members. The communication between pediatric residents and the RRT needs to be focused and succinct, but the communication and shared mental model at RRT events can be poor between the two teams. Additional training on how to manage pediatric emergencies and communicate effectively with emergency handoff is needed.

We proposed that implementing an educational curriculum for pediatric resident physicians focused on: 1) RRT event emergency management 2) standardization of communication through ABC-SBAR 3) utilization of an ABC-SBAR cognitive aid, and 4) simulations to practice critical information synthesis and effective communication will result in improved communication between pediatric residents and RRT members. Ultimately, improving the communication in these emergency situations can potentially prevent delays in care, provide more efficacious patient care, and reduce medical errors.

Post RRT event surveys were collected from pediatric resident physicians, pediatric critical care fellows, and nursing shift coordinators to assess for the quality of communication and emergency handoff during RRT events in the Johns Hopkins Hospital Bloomberg Children's Center. Data was collected during three different time periods: pre-intervention (n=53), intervention rollout (n=63), and post intervention (n=87). Data collection was deemed post intervention after greater than 75% of the pediatric residency cohort had exposure to the educational curriculum and formal ABC-SBAR training. Data collected from the surveys includes assessments of residents' emergency handoff, confidence scales to assess resident performance during RRT calls, and specific performance measures related to the use of ABC-SBAR. Data from the pre and post intervention periods will be compared to determine the efficacy of the educational curriculum and evaluate potential improvement in communication between providers during actual pediatric RRT events. Data collection is ongoing and will continue until January 2023 after one full year of survey collection has been completed. Preliminary data analysis is currently in process.

Feasibility of social work intervention in older adults before non-cardiac surgery

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Background:
Given that psychosocial risk factors are increasingly associated with postoperative outcomes in vulnerable patients, we aim to evaluate the feasibility of a social work-focused preoperative intervention in frail patients before surgery.

Methods:
In this preoperative intervention, a social worker met with patients who are identified by a score ≥ 6 on the Edmonton Frail Scale (EFS) prior to surgery in the center for preoperative optimization. The social worker then assesses patients in ten domains and performs a predetermined intervention. In this feasibility study, a sample of 96 targeted patients were analyzed to determine how many patients met with the social worker, and the categorization of these patients following social worker assessment. The first feasibility metric was greater than 40% of patients evaluated by the social worker.

Results:
In 96 patients, thirty-six patients had data collected within all ten categories. An additional thirteen patients (14% of target patients) met with the social worker but did not have a full ten category assessment. In total, 47 patients (48%) did not meet with the social worker, due to multiple reasons, such as being scheduled for an outpatient surgery, unable to be contacted via phone, and surgery being postponed.

We have found interesting patterns in the ten domains. In domain 1, which involves human social support for assistance with activities of daily living, some patients did not have a person identified for support following surgery (11.11%) or a person who is only able to commit to being available intermittently (25%). In domain 2, we found that 5.56% of patients lacked emotional support resources and 5.56% had occasional emotional support resources (11% in total). In the same domain, we also found that 11.11% of patients display inadequate stress management. Domain 3 suggested that financial concern was not an issue in this population.

Discussion:
Ideally, we would have wanted to have a higher percentage of our targeted patients evaluated but nonetheless met our feasibility metric. One reason targeted patients were not within the study include the form not being completed although meeting with the social worker. The social worker is crucial to this study, and it is important to assess how to best support our social worker in completing the form. We used this time point to address.

We used this intermediate assessment of feasibility to reinforce the data gathering instrument to better assess the feasibility and potential utility of this intervention.

Identifying factors that contribute to disrespectful maternal care—an observational pilot

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Background: Patient perceptions of respect and dignity have a significant impact on their experience while they are hospitalized. It is useful to explore these concepts in the obstetric population as numerous studies have highlighted stark racial and ethnic disparities within the outcome measure of severe maternal morbidity (SMM), with minorities having higher rates of adverse postpartum outcomes. Although SMM is related to the presence of clinical risk factors, there is an unexplained proportion of women whose outcomes are not solely attributed to the presence of comorbidities. This begs the question, what other non-clinical factors play a role in the development of SMM? Our hypothesis is that there is an association between perceived disrespectful maternal care and the inpatient de novo diagnosis of SMM, and that minority patients (self-reported non-white/Caucasian) have higher incidences of perceived disrespectful care. Due to the anticipated magnitude of this study, we propose use of a pilot study to first identify relevant variables that can help achieve our long-term aims.

The Johns Hopkins Hospital provides tertiary and quaternary care services to a racially and ethnically diverse obstetric population. Between 7/1/2021 and 6/30/22, a total of 2470 mothers gave birth. Of these, 196 mothers were diagnosed with SMM. The aims of this pilot study are to compare demographic data, clinical outcomes and survey responses between minority and non-minority patients; identify challenges of administering a survey in the immediate postpartum period; and to estimate the incidence of perceived disrespectful maternal care at Johns Hopkins main campus.

Methodology: All women who deliver between January 1, 2023 and June 30, 2023 at the Johns Hopkins Hospital Main/East campus (JHH) will be recruited to participate in a survey within 24 hours of their delivery. The survey is a revision of the Mothers on Respect Index (MORi)—adapted to query obstetric and anesthesia-related topics related to maternal experience. Recruitment for the survey will be performed by a postdoctoral fellow and a gift card will be provided for participation. The anticipated sample size for the pilot is 360 patients after applying exclusion criteria and with an anticipated 20% non-response survey rate. The charts of survey participants will be reviewed to obtain maternal and newborn demographics.

Significance/Conclusion: SMM is a significant public health concern that has far-reaching societal implications. The diagnosis is not always solely attributed to clinical risk factors. If there are non-clinical factors associated with the development of SMM, assuming one cannot control human behavior (bias, disrespect, etc.), there should be an objective tool like an EMR alert to identify high-risk mothers when they present for care in the postpartum period. However, determining an association between perceived disrespectful maternal care and SMM is a huge undertaking. A pilot study to identify associations between racial/ethnic groups and their maternal outcomes is a strategic first step.