13TH ANNUAL DEPARTMENT OF PEDIATRICS PEDIATRIC RESEARCH SYMPOSIUM

FRIDAY
APRIL 26, 2024
8:00 AM - 5:00 PM
Rady children’s Hospital Education & Office Building
Room 1800 and 1900
7960 Birmingham Drive
San Diego, CA 92123
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Abstracts

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8:00 AM  Welcome: Patrick Frias, MD  
President and CEO  
Rady Children’s Hospital-San Diego

8:05 AM  Welcome: Gabriel Haddad, MD  
Distinguished Professor of Pediatrics and Neurosciences  
Chairman of Pediatrics & Vice Dean, Children’s Academic Programs  
University of California, San Diego  
Physician-In-Chief & Chief Scientific Officer  
Rady Children’s Hospital – San Diego

8:20 AM  Keynote: Atul Butte, MD, PhD  
Introduction by Kelly Frazer, PhD  
Priscilla Chan and Mark Zuckerberg  
Distinguished Professor  
Director, Bakar Computational Health Sciences Institute  
University of California, San Francisco  
Chief Data Scientist, University of California Health

9:15 AM  Respiratory/Lung Center Session  
Session Moderated by Xin Sun, PhD

9:20 AM  T. Elizabeth Duong, MD  
Assistant Professor of Pediatrics  
Building a Molecular Roadmap of the Human Lungs, One Cell at a Time

9:40 AM  Sandra Leibel, MD MSc  
Associate Professor  
Elucidating Intrinsic Lung Epithelial Inflammatory Responses to Viral Infections Using Human Lung Organoids

10:00 AM  Eniko Sajti, MD, PhD  
Associate Clinical Professor  
Decoding Resilience: Unveiling Immune Pathways that Protect Against Premature Birth Associated Lung Disease

10:20 AM  Break (15 minutes)
10:35 AM Late-Breaking Science Session
Session Moderated by Tariq Rana, PhD

10:40 AM Gretchen Bandoli, PhD
Associate Professor, Pediatrics
Prenatal Cannabis and Infant Outcomes: An Update

11:00 AM Lori Broderick, MD, PhD
Assistant Professor, Depts. of Pediatrics and Molecular Biology
Through Thick and Thin: STAT4-driven Autoinflammation in Disabling Pansclerotic Morphea of Childhood

11:20 AM Nicole Coufal, MD, PhD
Adjunct Associate Professor of Pediatrics
Innate Neuroimmune Dysfunction as a Contributor to Pediatric Neurological Disease

11:40 AM Vira Kravetz, PhD
Assistant Professor, Pediatrics
Role of GLP1 Mediated Paracrine Communication in First Phase of Insulin Secretion and Insulitis Through the Lens of Network Analysis

12:00 PM Vivien Maltez, PhD
Assistant Professor
Hijacking suppression: Converting Regulatory T Cells into Th1 Effectors

12:20 PM Start: Poster Session 1
EOB 1900

12:20 PM Lunch
Outdoor Patio/Courtyard

1:50 PM End: Poster Session 1
EOB 1900
1:50 PM

**Keynote: Diana Bianchi, MD**

*Introduction by Tina Chambers, PhD, MPH*

Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

2:45 PM

**Host Microbe Session**

*Session Moderated by Manuela Raffatellu, MD*

2:50 PM

**Alejandro Chavez, MD, PhD**

Associate Professor of Pediatrics

*Identifying Broadly Active Protease Inhibitors through Multiplex Chemical Screens*

3:10 PM

**Ronnie Fang, PhD**

Associate Professor of Pediatrics

*Designing Cell Membrane-Coated Nanoparticles for Antibacterial Vaccination*

3:30 PM

**Fabian Rivera-Chavez, PhD**

Assistant Professor, Depts. of Pediatrics and Molecular Biology

*Molecular Remodeling of Gut Metabolism by Cholera Toxin*

3:50 PM

**Karsten Zengler, PhD**

Professor in the Depts. of Pediatrics and Bioengineering and the Program in Materials Science and Engineering at UC San Diego

*Targeted alteration of the microbiome*

4:10 PM

**Closing Remarks + Awards**

4:30 PM

**Start: Poster Session 2**

EOB 1900

5:30 PM

**End: Poster Session 2**

EOB 1900
Atul Butte, MD, PhD is the Priscilla Chan and Mark Zuckerberg Distinguished Professor and inaugural Director of the Bakar Computational Health Sciences Institute (bchsi.ucsf.edu) at the University of California, San Francisco (UCSF). Dr. Butte is also the Chief Data Scientist for the entire University of California Health System (health.universityofcalifornia.edu), the tenth largest by revenue in the United States, with 20 health professional schools, 6 medical schools, 6 academic health centers, 10 hospitals, and over 1000 care delivery sites. Dr. Butte has been continually funded by NIH for 20 years, is an inventor on 24 patents, and has authored nearly 300 publications, with research repeatedly featured in the New York Times, Wall Street Journal, and Wired Magazine. Dr. Butte was elected into the National Academy of Medicine in 2015, and in 2013, he was recognized by the Obama Administration as a White House Champion of Change in Open Science for promoting science through publicly available data. Dr. Butte is also a co-founder of three investor-backed data-driven companies: Personalis (IPO, 2019), providing medical genome sequencing services, Carmenta (acquired by Progenity, 2015), discovering diagnostics for pregnancy complications, and NuMedii, finding new uses for drugs through open molecular data. Dr. Butte trained in Computer Science at Brown University, worked as a software engineer at Apple and Microsoft, received his MD at Brown University, trained in Pediatrics and Pediatric Endocrinology at Children's Hospital Boston, then received his PhD from Harvard Medical School and MIT.
Diana W. Bianchi is the Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Dr. Bianchi oversees an annual budget of approximately $1.7 billion in support of NICHD’s mission to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all. Dr. Bianchi is also head of the Prenatal Genomics and Therapy Section for the Medical Genetics Branch at the National Human Genome Research Institute.

Dr. Bianchi received her M.D. from Stanford University School of Medicine and her postgraduate training in Pediatrics, Medical Genetics and Neonatal-Perinatal Medicine at Boston Children’s Hospital and Harvard Medical School. Dr. Bianchi’s research focuses on prenatal genomics with the goal of advancing noninvasive prenatal DNA screening and diagnosis to develop new therapies for genetic disorders that can be administered prenatally.

Prior to coming to NICHD, she spent 23 years at Tufts Medical Center, where she was the founding Executive Director of the Mother Infant Research Institute, as well as the Natalie V. Zucker Professor of Pediatrics, Obstetrics, and Gynecology at Tufts University School of Medicine. Dr. Bianchi also was the Vice Chair for Pediatric Research at the Floating Hospital for Children, Boston, and served for a time on the NICHD advisory council. She is a Past President of the International Society for Prenatal Diagnosis and the Perinatal Research Society. She is a former member of the Board of Directors of the American Society for Human Genetics and a former council member of both the Society for Pediatric Research and the American Pediatric Society. She was elected to membership in the National Academy of Medicine (formerly the Institute of Medicine) in 2013.

Dr. Bianchi has received multiple awards, including the 2015 Neonatal Landmark Award from the American Academy of Pediatrics, the 2016 Maureen Andrew Award for Mentorship from the Society for Pediatric Research, and the 2017 Colonel Harland Sanders Award for lifetime achievement in Medical Genetics from the March of Dimes. In 2020, she received an honorary doctorate from the University of Amsterdam and received the Health Public Service Visionary Award from the Society for Women’s Health Research. Dr. Bianchi was a finalist for the Samuel J. Heyman Service to America Medal in 2022 and honored as a Forbes 50 over 50 awardee.
Building a Molecular Roadmap of the Human Lungs, One Cell at a Time

T. Elizabeth Duong, MD
Assistant Professor of Pediatrics

Dr. Elizabeth Duong is a Pediatric Pulmonologist and physician scientist. She applies single-cell genomic technologies and computation biology to identify lung cell populations regulating lung development, homeostasis, and disease.
Elucidating Intrinsic Lung Epithelial Inflammatory Responses to Viral Infections Using Human Lung Organoids

Sandra Leibel, MD MSc
Associate Professor

Dr. Sandra Leibel is an Associate Professor in the Department of Pediatrics at the University of California, San Diego (UCSD), a Neonatologist and lung biology researcher. Her research is focused on human lung development and lung epithelial disease. She received her Masters of Science degree in Lung Physiology from the University of Toronto after being recruited into the Physician Scientist program at the Hospital for Sick Children. There, she developed a novel stem cell derived human lung organoid model to study genetic surfactant disease. These function as a human ‘mini-lung’ in a dish and have yielded many insights into the mechanisms of lung development and injury. She has expanded her research interests into developing higher level human model systems and studying the impact of viral and fungal pathogens on lung homeostasis. She has published extensively and is currently funded by CIRM and the NIH to study the effects of SARS-CoV-2 and coccidioidomycoses on the human lung.
Decoding Resilience: Unveiling Immune Pathways that Protect Against Premature Birth Associated Lung Disease

Eniko Sajti, MD, PhD
Associate Clinical Professor

Dr. Eniko Sajti is a board-certified pediatrician and neonatologist at Rady Children's Hospital-San Diego. She is also an associate professor of pediatrics at UC San Diego School of Medicine. She received her medical and doctoral degrees from Utrecht University in the Netherlands. As an awardee of the Dutch Royal Academy of Sciences, she completed a postdoctoral fellowship in pulmonary medicine at the University of California, San Francisco. After completing her pediatric residency and neonatology fellowship at Harvard Medical School/Boston Children's Hospital, she was recruited to UC San Diego Department of Pediatrics.

The Sajti lab's primary interests are to understand the molecular and cellular mechanisms controlling the development of the neonatal innate immune system. Current projects focus on determining the genetic and epigenetic signature of specialized innate immune cells in the neonatal lung and brain. To understand the relative contribution of various subtypes of innate immune cells to premature birth-related lung disease and impaired neurodevelopmental outcomes, Dr. Sajti employs genome-wide approaches and computational analyses to identify transcriptional and epigenetic mechanisms unique to each cell type. By elucidating disease and cell-type-specific gene regulatory networks, she hopes to develop new targeted therapies tailored to the needs of individual patients.
Prenatal Cannabis and Infant Outcomes: An Update

Gretchen Bandoli, PhD
Associate Professor, Pediatrics

Gretchen Bandoli is an Associate Professor in Pediatrics, and is Director of the Center for Population Research and Scientific Methods at ACTRI, and co-Director of the UCSD-SDSU Doctoral Program in Epidemiology. As a perinatal epidemiologist, her research focuses on exposures in pregnancy, including cannabis, alcohol, and chronic conditions.
Dr. Lori Broderick is a board-certified allergist/immunologist at Rady Children's Hospital-San Diego and Associate Professor of Pediatrics at UC San Diego, with specific interests in disorders of pediatric immunity.

At UC San Diego, Dr. Broderick leads a research program consisting of complementary projects focusing on the genetics of rare diseases and dysregulation of the immune system, with a focus on the molecular mechanisms and clinical impacts of inborn errors of immunity. Her translational work strives to better understand disorders of immune dysregulation at both ends of the immune spectrum through novel gene identification, investigations of molecular mechanisms, and discovery of new therapeutic approaches. She has characterized the genetic etiology behind rare disorders of immune dysregulation, including the role of complement Factor I in Acute Hemorrhagic Leukoencephalitis, mutations in the essential gene topoisomerase IIb (TOP2B) as the cause of a novel B cell-restricted immunodeficiency with dysmorphism, and most recently identified STAT4 as a therapeutically targetable genetic etiology for disabling pansclerotic morphea of childhood.
Innate Neuroimmune Dysfunction as a Contributor to Pediatric Neurological Disease

Nicole Coufal, MD, PhD
Adjunct Associate Professor of Pediatrics

Dr. Coufal is a physician scientist with training in pediatric critical care and a research interest in neuroimmunology. The goal of her lab is to understand the contribution of innate immunity to neurodevelopmental and pediatric neurodegenerative diseases. By understanding the interaction between the brain environment and cellular ontogeny on macrophage function, the lab strives to understand the molecular and cellular mechanisms underlying innate immune dysfunction to ultimately identify novel therapeutic targets in untreatable pediatric diseases. Her lab utilizes a combination of translational, patient-specific pluripotent stem cell and genome-wide approaches to identify cellular mechanisms in common neurodevelopmental and rare pediatric neurodegenerative disorders.
Role of GLP1 Mediated Paracrine Communication in First Phase of Insulin Secretion and Insulitis Through the Lens of Network Analysis

Vira Kravets, PhD
Assistant Professor, Pediatrics

Dr. Vira Kravets obtained her Ms. Sci in Physics, with specialty “Photonics” from the Kyiv National University of Ukraine. She then moved to Colorado, USA to obtain her Ph.D. in Physics. Her thesis focused on Plasmonic nano materials for bioimaging and biosensing applications. Dr. Kravets applied her knowledge of optics, spectroscopy, and computational modelling to study the function of living pancreatic tissue from healthy and diabetic donors. As a Postdoctoral Fellow at the Anschutz Medical Campus of the University of Colorado, Dr. Kravets studies the role of heterogeneity of the insulin-producing cells in the formation of the neuro-endocrine networks in pancreatic islets. She discovered a “first-responder” cell population, which drives micro-organs’ response to blood glucose. Dr. Kravets is a recipient of career awards from Burroughs Wellcome Fund: “Careers at Scientific Interfaces”, as well as from NIH (NIDDK): “Emerging Leaders in Type 1 Diabetes”.
Hijacking suppression: Converting Regulatory T Cells into Th1 Effectors

Vivien Maltez, PhD
Assistant Professor

Vivien Maltez, PhD, is an Assistant Professor in the Division of Allergy, Immunology, and Rheumatology within the Department of Pediatrics at the University of California San Diego. A California native, she majored in Molecular Biology at Scripps College in Claremont, California, and then jumped coasts when she was selected to join the 2nd cohort of UNC Chapel Hill’s Postbaccalaureate Research Education Program (PREP). She chose to stay and earned her Ph.D. in Microbiology and Immunology studying bacterial pathogenesis, innate immunity, and cell death. Dr. Maltez then transitioned to the National Institutes of Health and was selected for the Postdoctoral Research Associate Training Program to fund her cancer research. She then successfully competed for the MOSAIC K99/R00, a career transition award with an emphasis on improving diversity at the faculty level. She has now returned to her home state as part of the UCSD FIRST Faculty program to head her own laboratory focused on decoding the cellular interactions that dictate tumor responsiveness to immunotherapy. She will primarily leverage a suite of imaging techniques that retain crucial spatial information while providing single cell resolution.
Identifying Broadly Active Protease Inhibitors through Multiplex Chemical Screens

Alejandro Chavez, MD, PhD
Associate Professor of Pediatrics

Dr. Chavez is an Associate Professor in the Department of Pediatrics at the University of California San Diego. His laboratory focuses on the development of high-throughput genome engineering and screening technologies to speed the rate of discovery, with a particular interest in applying these tools to the fields of neurodegeneration and infectious disease. Dr. Chavez is the recipient of various awards including the NIH New Innovator Award, Career Award for Medical Scientists from the Burroughs Wellcome Fund and grants from DARPA, DoD, Chan-Zuckerberg Initiative, NIH and the Silicon Valley Community Foundation.
Dr. Ronnie H. Fang is currently an Associate Professor in the Department of Pediatrics at the University of California San Diego, USA. As a member of Professor Liangfang Zhang’s nanomedicine research group at the University of California San Diego, Dr. Fang participated in the development of the first cell membrane-coated nanoparticles (CNPs). Cell membrane coating nanotechnology provides a facile and effective means of functionalizing synthetic nanoparticles, enabling them to circulate for longer and to better interface with various biological substrates. Dr. Fang’s current research focuses on the continued development of CNPs, with a particular emphasis on designing next-generation platforms through genetic engineering approaches for drug delivery, vaccination, and detoxification applications.
Molecular Remodeling of Gut Metabolism by Cholera Toxin

Fabian Rivera-Chavez, PhD

Assistant Professor, Depts. of Pediatrics and Molecular Biology

Fabian Rivera-Chávez completed his B.S in Molecular, Cell, and Developmental Biology at the University of California, Santa Cruz, and received his Ph.D. in Microbiology from the University of California, Davis, under the supervision of Prof. Andreas Bäumler. He went on to pursue postdoctoral research at Harvard Medical School in the laboratory of Prof. John Mekalanos before starting his lab at UC San Diego in 2020.
Targeted alteration of the microbiome

Karsten Zengler, PhD

Professor in the Depts. of Pediatrics and Bioengineering and the Program in Materials Science and Engineering at UC San Diego

He has more than 30 years of experience in the fields of microbiology and systems biology. After receiving his Ph.D. at the Max Planck Institute for Marine Microbiology (Bremen, Germany), he worked for seven years in the biotechnology industry where he led a team of scientists to pioneer the high-throughput cultivation for the isolation and recovery of previously unculturable microorganisms. His work has focused on understanding the interactions of microorganisms with their environment and their hosts. He spearheaded the field of community systems biology where he combined his knowledge in microbial physiology and molecular biology with computational modeling to discover new physiological capabilities, regulatory effects, and novel multidimensional interspecies interactions. His lab has been on the forefront of developing new approaches to determine and to quantify the role of the microbiome in health and disease. Moreover, his group has invented approaches to selectively alter complex microbiomes. This interdisciplinary approach allows for a deeper understanding of microbial interactions and for determining causality and mechanisms. Dr. Zengler has authored more than 200 publications and patents and is the cofounder of several companies. He serves on the advisory board of different companies and institutions.
ABSTRACTS

Implementation of the Quality Incentive Pool Program To Measure And Improve Preventative Care Quality Metrics in a Small Academic General Pediatrics Practice

Joshua Rothman, Vanessa Scott, Heather Irwin, Amy Sitapati

BACKGROUND: The California Department of Health Care Service implemented a Medi-Cal managed care Quality Incentive Pool (QIP) program that incentivizes effective, affordable care. University of California, San Diego (UCSD) Academic General Pediatrics (AGP) is a small academic pediatrics practice that utilizes evidence-based guidelines, however quality metrics were previously not tracked. In this study, we implemented QIP metric reporting for Medi-Cal managed care patients and assess quality improvement (QI) initiatives to increase care delivery.

METHODS: From 2021-2023 Medi-Cal managed care patients assigned to UCSD AGP were evaluated on QIP metrics in 8 domains: 1) Child and Adolescent Well Care Visits (WCV), 2) Childhood Immunization Status (CIS10), 3) Developmental Screening in the First Three Years of Life (QDEV), 4) Immunizations for Adolescents (IMA), 5) Lead Screening in Children (LEAD), 6) Weight Assessment & Counseling for Nutrition and Physical Activity for Children & Adolescents (WCC), 7) Well-Child Visits in the First 30 Months of Life (W30), 8) Preventive Care and Screening: Depression Screening and Follow-Up Plan (CDF). Several QI projects were implemented during the measurement period. Two proportion z-tests were used to measure differences in rates between years.

RESULTS: From 2021-2023 rates improved in all domains: WCV (46.67% to 53.64%, p<0.05); CIS10 (15.85% to 46.04%, p<0.05); QDEV (43.16% to 70.03%, p<0.05); IMA (10% to 30.23%, p<0.05); LEAD (57.32% to 76.60%, p<0.05); WCC in BMI%ile documented (65.08% to 89.91%, p<0.05), Nutrition Counseling (61.43% to 71.88%, p<0.05), and Physical Activity Counseling (60.00% to 69.60%, p<0.05); W30 in the first 15 months (41.51% to 76%, p<0.05), and 15 months to 30 months (64.81% to 69.70%, p<0.05); and CDF (66.33% to 74.60%, p<0.05).

CONCLUSIONS: Assessment, QI initiatives, and reporting of QIP metrics for Medi-Cal managed care patients assigned to UCSD AGP resulted in increased measures in 8 out of 8 domains. Further QI initiatives should be pursued.

Sexual abuse screening in children with neurodevelopmental differences

Lauren Gist, MD, MPH, Nicole Stadnick, PhD, MPH, Amy Machado, MA, BCBA

BACKGROUND: Prior literature has shown that children and teens with a neurodisability are more likely to experience sexual abuse compared to neurotypical peers. The American Academy of Pediatrics outlines the role of healthcare workers as mandated reporters, but there is limited literature identifying current screening rates or practices amongst pediatricians.

METHODS: Through a community partnership formed through the Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program, a needs assessment was conducted at SEEDS Therapy group who focused on sexual education for neurodiverse populations. Based on the needs assessment done, 11 key informant pediatric providers were interviewed on their screening practices and rates using a standard list of questions. Interview questions and responses were utilized to generate a Microsoft Teams survey, then sent out to all UCSD/Rady Children Hospital pediatricians and trainees. Data was collected from December 2023 through Jan 2024.

RESULTS: 47 pediatric providers, fellows and residents completed the survey. Approximately 50% reported specifically screening for sexual abuse in their practice. In regards to screening methods, screening with verbal history was more often utilized as compared to a written questionnaire, lab testing, or exam. Children are screened less often than teens. Non-speaking patients are screened less often than their speaking peers. Survey takers overall reported less comfort initiating a conversation and discussing sexual health in neurodiverse patients.

CONCLUSIONS: Currently there are no clear standardized guidelines with practical recommendations or tools in order to facilitate sexual abuse screening for medical providers. There is work to be done in regards to standardizing practices, promoting provider education on sexual health and risk of abuse in neurodiverse populations and support in normalizing the topic as part of a routine health encounter.
**ABSTRACTS**

*Allergy, Immunology, and Rheumatology*

**GSDME Promotes PAD4 Activation and DNA Externalization from Apoptotic Neutrophils**


**BACKGROUND:** Neutrophil extracellular traps (NETs) neutralize bacterial and fungal pathogens but can also promote thrombosis, autoimmunity, and sterile inflammation. The presence of citrullinated histones, generated by the peptidylarginine deiminase 4 (PAD4), is synonymous with NETosis and is considered independent of apoptosis. However, non-apoptotic cell death signaling pathways mediated by MLKL and GSDMD can also engage PAD4 in neutrophils to trigger NET formation. Additionally, while PAD4 is hypothesized to neutralize charge on histones to facilitate chromatin decondensation, a genetic deficiency in Padi4 fails to prevent chromatin decondensation but does prevent NET formation following MLKL activation. Together, these data suggest more complex roles for PAD4 in the extrusion of nuclear DNA. Here we explored the role of GSDME – another pore-forming protein activated by apoptotic caspases – in controlling PAD4 activation, DNA externalization, and NET formation in apoptotic neutrophils.

**METHODS:** Cell viability was quantified by flow cytometry and live-cell imaging using Hoechst, Cell Tracker Green, Annexin V, and propidium iodide. Histone citrullination was studied at the population level by immunoblot, at the single cell level by lattice SIM super-resolution microscopy, and at the molecular level by an in-situ ChiP-Seq methodology CUT&Tag. Calcium signaling linked to PAD4 activation was monitored by flow cytometry. Ultrastructural changes occurring in the absence of PAD4 and GSDME were investigated by transmission electron microscopy and super-resolution microscopy.

**RESULTS:** Intrinsic and extrinsic apoptosis promote GSDME-dependent calcium mobilization and membrane permeabilization, leading to histone H3 citrullination (H3Cit), nuclear DNA extrusion, and cytoplast formation. H3Cit distribution on chromatin is developmentally controlled by PAD4 in neutrophils, with H3Cit found concentrated at promoter regions during neutrophil development. Lattice SIM super-resolution microscopy revealed clustered distribution of H3Cit in the nuclei of neutrophils, reflecting a unique spatial organization and coordination of multiple promoter elements in neutrophils. Following apoptotic stimulation, H3Cit redistributes in a coordinated process from promoter to intergenic and intronic regions. Loss of GSDME prevents nuclear and plasma membrane disruption of apoptotic neutrophils, but also blocks calcium signaling that activates PAD4, ultimately preventing NET formation. During apoptosis in GSDME-deficient neutrophils, early-apoptotic cellular changes to the chromatin and cytoplasmic granules are prolonged, generating highly atypical cellular states that fail to extrude nuclear DNA.

**CONCLUSIONS:** Apoptotic signaling engages PAD4 in neutrophils, establishing a cellular state that is primed for NETosis, but that occurs only upon membrane disruption by GSDME, thereby redefining the end-of-life for neutrophils.

**ASSOCIATING CHANGES IN KAWASAKI DISEASE PREVALENCE WITH WIND PATTERNS IN JAPAN**

*Charles D. Copeland, Laurel L. Dehaan, Chisato Shimizu, Jennifer A. Burney, Daniel R. Cayan, Jane C, Burns*

**BACKGROUND:** Kawasaki disease (KD) is an acute pediatric vasculitis of unknown etiology, though immunological and epidemiological evidence suggest an immune reaction to an inhaled triggering agent. Past studies have proposed that distinct geographic patterns of incidence could be explained by the wind-blown transport of a triggering agent. In Japan, recent years have observed significant year-to-year variations in KD prevalence that further provoke the search for an environmental explanation.

**METHODS:** We compared the prevalence of KD in five regions of Japan with modeled wind patterns and likely air source regions from 2010-2019. We defined average seasonal cycles of KD prevalence and seasonal wind patterns in order to compare periods of anomalously high or low KD prevalence with seasonally-anomalous wind. We also compared year-to-year variations in KD prevalence with interannual variability in atmospheric features.

**RESULTS:** We found associations between variability in the wind and higher and lower rates of KD in Japan across different temporal and spatial scales. We found that year-to-year changes in seasonally-specific wind variables strongly correlated with subsequent KD prevalence, creating a possible environmental explanation for some of the pattern interannual variability observed in Japan in 2010-2019.

**CONCLUSIONS:** These results provide further evidence for a relationship between patterns of wind transport and KD prevalence, aiding in the search for an etiologic agent.
REDUCED CAPILLARY DENSITY IN THE MYOCARDIUM OF THE PATIENTS WITH KD HISTORY

CHISATO SHIMIZU, YUKI YOKOUCHI, TOSHIKI OHRASEKI, TAKEMASA ISODA, ELAINA BAO, STEVEN CAMPMAN, DENISE MALICKI, KEI TAKAHASHI, JANE BURNS

BACKGROUND: Endothelial dysfunction and reduced capillary density (capillary rarefaction) could lead to coronary microvascular dysfunction and myocardial ischemia. The histology of autopsies from adults who had KD in childhood revealed diffuse, bridging fibrosis in the myocardium, which was unlikely to be due to thrombosis of the epicardial coronary arteries. It is unclear how or why this fibrosis occurs. In the LCWE KD mouse model, reduced capillary density and increased fibrosis in the myocardium were reported long after induction of vasculitis. Electron microscopic study of endomyocardial biopsies from patients after KD showed dilated microvasculature with fresh thrombus suggesting disturbed microvascular circulation in these patients. To understand the etiology of myocardial fibrosis in KD patients, we studied capillary rarefaction in KD autopsies.

METHODS: To avoid the variability of capillary densities by myocardial region, we studied autopsies with the left-ventricular transverse sections (middle and apical levels). KD autopsies (n=14, age: 4m to 20y, interval from KD onset to autopsy: 10 days to 17 y, CA aneurysms n=10) and non-cardiac disease control cases (age: 2d to 1y) were studied. To reduce the influence of different fixation conditions, we tested antibodies to four different endothelial cell (EC) markers:CD31, CD34, thrombomodulin, and Factor VIII. Fields were chosen from three different areas: endocardium, epicardium, and middle (x200 magnification). Positively stained cells were counted using QuPath software.

RESULTS: In the myocardial sections from the KD autopsies, varying levels of inflammation and fibrosis were seen. Of the four antibodies tested, anti-thrombomodulin yielded the most consistent staining intensity and the highest specificity for EC. Staining with anti-thrombomodulin antibodies suggested diminished capillary density in KD myocardial sections compared to controls. Detailed capillary density analysis by myocardial region is in progress.

CONCLUSIONS: Investigation of capillary rarefaction in the myocardium from KD autopsies with different intervals between disease onset and death is in progress. Age-matched controls are also needed. These studies may shed light on the function of the myocardial microcirculation and the genesis of myocardial fibrosis following KD.

Phenotypic Differences in Monochorionic Diamniotic Twins with Chronic Granulomatous Disease


BACKGROUND: Chronic Granulomatous Disease (CGD) is an inborn error of immunity with defective NADPH oxidase activity leading to severe infections and hyperinflammation. We discuss different phenotypes in identical twin brothers with X-linked CGD.

METHODS: History and Physical - Twin A had a history of pneumonia, severe diaper dermatitis, and recurrent vomiting. Exam showed weight in the 10th percentile (%ile), length 0.1%ile, hepatosplenomegaly, inguinal lymphadenopathy and a non-healing inguinal wound. During his hospitalization, he was also noted to have bilateral glaucoma. Twin B had a history of meningitis, Serratia and Pseudomonas pneumonias, severe CMV and SARS-CoV-2 pneumonia complicated by pleural effusion, presumed Nocardia pulmonary abscess, severe diaper dermatitis, and recurrent vomiting. He was smaller than his brother (weight 0.5%ile, length 0.1%ile) with cervical and inguinal lymphadenopathy and splenomegaly.

RESULTS: Laboratory evaluation for Twin A revealed reduced activity (1%) on dihydrorhodamine (DHR) assay, persistent peripheral eosinophilia (600-5700 TH/uL) unresponsive to anti-parasitic treatment, elevated AST 45-768 U/L, ALT 31-1353 U/L and acute inflammatory markers. Serum CMV IgM was also positive. Imaging demonstrated diffuse mesenteric lymphadenopathy. Labs for twin B demonstrated reduced DHR activity (5%) and elevated acute inflammatory markers. He later also developed peripheral eosinophilia (500-3100 TH/uL) and elevated transaminases (AST 59-1564 U/L, ALT 48-1339 U/L) similar to that in his brother. Only CMV IgG was positive. Imaging demonstrated diffuse mediastinal and retroperitoneal lymphadenopathy. Esophagogastroduodenoscopy biopsies in both brothers revealed an eosinophilic abscess and duodenal eosinophilia without granulomas. Lymph node biopsies revealed numerous granulomas. Liver biopsies revealed chronic inflammation and fibrosis without granulomas.

CONCLUSIONS: Differences in timing, severity, and tissue involvement in identical twins highlight heterogeneous contributions to disease phenotype. The patients’ genetic mutation in a splice site may alter splicing patterns resulting in variation of mRNA expression that affects phenotype. Epigenetic changes from previous infections and microbiota diversity may also contribute to more differences.
ABSTRACTS

Patient-derived human induced pluripotent stem cell model to examine microglial dysfunction in Langerhans Cell Histiocytosis
Shivakumar Rajamanickam, Samantha Trescott, Samantha Mak, Anna Warden, Gabrielle Ramirez, Hilda Ding, Christopher K. Glass, Carl E. Allen, Nicole G. Coufal

BACKGROUND: Langerhans Cell Histiocytosis (LCH) is a rare pediatric disorder caused by somatic mutations in the MAPK/ERK pathway, commonly the B-Raf (BRAF) V600E missense mutation in hematopoietic stem cells, leading to an accumulation of abnormal histiocytes. Patients display a wide range of clinical symptoms; approximately 10% of LCH patients develop LCH associated neurodegeneration (LCH-ND), a severe progressive neurodegenerative condition that is poorly understood. Myeloid cells in the brain carrying somatic BRAFV600E mutations, either endogenous microglia or infiltrating cells that become microglia-like in the brain environment leading to heterogenous brain lesions that are not well modeled in mice. We hypothesize that LCH-ND can be modeled in a uniquely human approach utilizing patient derived stem cells differentiated to microglia like cells.

METHODS: We have generated the first human induced pluripotent stem cell model for LCH, with LCH patient derived stem cell lines carrying the BRAFV600E mutation and isogenic controls, differentiated into hematopoietic progenitors (iHPCs) and microglia. Next, utilizing a humanized mouse model for xenotransplantation of human hematopoietic progenitors into the murine brain, we find that BRAFV600E iHPCs causes LCH-ND like phenotype.

RESULTS: Transcriptional analysis of BRAFV600E microglia finds upregulation of inflammatory gene signatures with significant overlap with LCH-ND and recapitulates human CSF biomarker cytokines. BRAFV600E microglia exhibit an ameboid appearance with high infiltrating density in the brain. LCH engrafted brains display demyelination, astrogliosis, and reduced thickness of cortical layer 5. Additionally, BRAFV600E microglia express canonical markers of human LCH-ND including increased CD163, massive upregulation of antigen presentation such as HLA-DR. Brains of BRAFV600E iHPC engrafted mice also exhibit granuloma-like lesions with intense expression of HLA-DR and CD1A, similar to infiltrative peripheral lesions in human LCH-ND patients.

CONCLUSIONS: Our model that utilizes patient-derived pluripotent stem cells to generate BRAFV600E progenitors and microglia offers a valuable tool to elucidate the contribution of myeloid cells to the onset and progression of neurodegeneration. BRAFV600E microglia exhibit an inflammatory or activated phenotype, altered gene expression, release relevant cytokines, and cause changes to brain morphology reminiscent of LCH and LCH-ND disease in humans.

Loss of Myocyte Enhancer Factor 2C leads to human microglial dysfunction in vivo
Celina Nguyen, Emily Hansen, Bing Xia, Anna Warden, Chelsea Cates, Tali Nadav, Cristina Mora1, Mark Lopez Sanchez, Amanda Roberts, Christopher K. Glass, and Nicole G. Coufal

BACKGROUND: Microglia, the primary innate immune effector of the brain, have increasingly been found to impact brain maturation. Microglia function is intricately regulated by a network of environmentally dependent transcription factors, such as myocyte enhancer factor 2C (MEF2C). The role of MEF2C in neurodevelopment is notable because the loss of one allele results in a monogenetic autism spectrum disorder known as MEF2C haploinsufficiency syndrome (MHS). Patients with MHS exhibit a severe autism spectrum disorder characterized by intellectual disability, epilepsy, social and speech deficits. We hypothesize that human microglial MEF2C plays a crucial role in brain development and loss of MEF2C contributes to neurodevelopmental disorder-related phenotypes.

METHODS: Therefore, to study human microglial MEF2C in vivo, we generated CRISPR-mediated MEF2C genetic deletions in human induced pluripotent stem cells (hiPSCs). We xenotransplanted these human cell lines, creating chimeric mice with isogenic control and MEF2C knock-out hiPSC-derived microglia (termed xMGs).

RESULTS: Transcriptomic analysis suggests that loss of MEF2C up-regulates genes involved in microglial activation, cell migration and inflammatory response pathways and down-regulates genes involved in homeostasis, such as oxidative phosphorylation. Congruently, MEF2C knock-out xMGs demonstrate elevated levels of CD68, a classic marker of pro-inflammatory microglia, and are laden with lipid droplets. Furthermore, single-cell transcriptomic analysis of xMGs revealed that loss of MEF2C induced greater heterogeneity with increased presence of reactive microglia sub-types. These results indicate MEF2C is needed to restrain the microglial inflammatory response. To assess if dysregulated MEF2C knock-out xMGs might contribute to autism-relevant behaviors, we interrogated our chimeric mice in the juvenile play paradigm. Mice with MEF2C knock-out xMGs exhibited less interest in age-matched stranger mice when compared to mice engrafted with control xMGs.

CONCLUSIONS: In sum, our results demonstrate that MEF2C is a key regulator of microglia function and may be a potential therapeutic target for MHS and related neurodevelopmental disorders.
Intersection of environment and ontogeny on the microglial cell fate: diverse human macrophage progenitors in a murine model

Jing Wang, Michelle Du, Nathan Spann, Bing Xia, Mana Parast, Christopher K. Glass, and Nicole G. Coufal

BACKGROUND: Microglia are the brain-resident macrophages and play important roles in neurodevelopment and aging, including modulating neurogenesis, mediating synaptic pruning, and aiding myelination. Increasing evidence demonstrates that dysfunctional microglia contribute to diverse central nervous system (CNS) diseases, both neurodevelopmental and neurodegenerative. Generation of safe microglia replacements and elimination of toxic microglia is a promising but challenging and poorly developed approach to treat CNS disorders. A major hurdle is that microglia arise exclusively from primitive yolk sac hematopoiesis, which is distinct from other tissue resident macrophages that arise from the postnatal bone marrow. The majority of studies to date have utilized murine models, finding that transplanted peripheral macrophages lack microglia transcriptional patterns and fail to acquire key microglia characteristics. Our goal is to understand the unique human transcription factor networks underlying the ontological and environmental differences between microglia and peripheral macrophages, which could be therapeutically used for modifying or propelling towards to a microglial state.

METHODS: We have shown that human stem cell-derived hematopoietic progenitors (iHPC) transplanted into a humanized murine model deficient in resident microglia (Csf1rΔFIRE/ΔFIRE Csf1h/h Rag2-/- Il2rg-/-) closely replicates the yolk-sac derived fate of endogenous human microglia. We sought to compare these human microglial surrogates with human peripheral macrophages and identify the different ontological and environment effects on the microglial cell fate. We therefore transplanted CD34+ hematopoietic projector cells, umbilical cord blood (UCB)-derived monocytes, and iHPCs in the murine brain and liver. We characterized resulting brain resident macrophages by immunofluorescence, transcriptomics and epigenetic, finding that iHPCs, CD34+ cells and UCB-derived monocytes can migrate from the liver to the brain, differentiating into microglia/macrophages.

RESULTS: More macrophages expressing microglial markers are observed in the brain of iHPC engrafted than CD34+ and UCB-derived monocytes engraftment, and with brain versus liver engraftment. Interestingly, CD34+ projector cells have higher capability to differentiate into microglia-like cells than UCB-derived monocytes after engraftment in the brain. However, fewer macrophages are found in the liver after iHPC and CD34+ cells engraftment compared to UCB-derived monocytes transplantation, suggesting poor migration of monocytes to the brain and enhanced local hepatic engraftment.

CONCLUSIONS: This novel technique underlies robust brain engraftment of CD34+ projectors, UCB-derived monocytes after brain or liver engraftment with clear morphological differences in engrafted cells, suggesting transcriptional networks differences caused by the intersection of ontogeny and environment in microglial development.

Cyclosporine treatment in Kawasaki disease patients with coronary artery aneurysms or treatment resistance

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BACKGROUND: Kawasaki disease (KD) is an acute systemic vasculitis that can result in coronary artery aneurysms (CAA). 10–20% of patients fail to respond to standard treatment and require additional therapy to reduce the risk of CAA. Genetic studies have shown that polymorphisms in genes in calcium signaling pathways are associated with an increased susceptibility to KD and higher risk of CAA. Additionally, histopathological evaluation of KD CAAs has demonstrated T cell infiltration of the vessel wall. Given that cyclosporine A (CSA) inhibits calcineurin and T cell proliferation, CSA has been used to treat refractory KD patients.

METHODS: This single-center retrospective review examined 33 KD patients treated with CSA at Rady Children’s Hospital, San Diego, from 2013-2023, for CAA or treatment resistance. Demographics, laboratory studies, medications, adverse events, and echocardiographic data were analyzed.

RESULTS: Of the 33 KD patients treated with CSA, 25 patients received CSA for CAA and 8 for treatment resistance. Four patients received CSA intravenously initially, followed by oral therapy. Since 2014, all patients have exclusively received oral CSA. The target 2-hour post-dose level (300-600 ng/ml) was best achieved by 5 mg/kg/day orally divided BID. At the one-year follow-up, all patients who had been treated for CAA exhibited improved coronary artery Z-scores. Two patients experienced significant adverse events when treated with both IV steroids (2 mg/kg) and CSA. One patient developed posterior reversible encephalopathy syndrome (PRES) while the other developed an EBV lymphoproliferative syndrome. Discontinuation of CSA and steroids led to complete recovery in both cases.

CONCLUSIONS: CSA was generally well tolerated, though there were two adverse events with CSA together with steroids, which raises concern for using these medications in combination in KD patients. Our study contributes to the limited literature on CSA use in KD, providing insights for clinicians and advocating for cautious monitoring.
High Healthcare Utilization for Pediatric Asthma and Disparities in Air Pollution and Child Opportunity
Kelly Robinson, MD, Sweta Parjia, BS, Tatyana Mills, MD, Jacob Parker, BS, Manaswitha Khare, MD, Sydney Leibel, MD, MPH, Margaret Nguyen, MD

BACKGROUND: Asthma is a leading chronic condition in the pediatric population. It accounts for 2.3% of hospitalizations and $82 billion per year in costs in the United States alone. Among pediatric patients with asthma, those of a minority ethnicity and those who live under the federal poverty line, experience higher prevalence of asthma and increased morbidity and mortality compared to their peers. These disparities have persisted for decades despite extensive literature on this matter. We recognize that structural racism and systemic injustices have led to inequities in pollution burden and childhood opportunity which can impact asthma. Therefore, we aimed to assess for differences in pollution burden and childhood opportunity among the pediatric population with high healthcare utilization (HHU) for asthma within the Rady Children’s health system to identify potential areas for future intervention. We aim to 1) describe the proportion and geographic distribution of children with high healthcare utilization (HHU) for pediatric asthma within the Rady Children’s Health System, 2) compare air pollution and child opportunity between neighborhoods with and without HHU, and 3) evaluate for healthcare disparities within this population by stratifying patients by race, ethnicity, primary language, and insurance type.

METHODS: This is an ecological study of pediatric patients who were identified as having met the specific high healthcare utilization (HHU) criteria for asthma: 2 or more ED visits in the previous 6 months or 2 hospitalizations in the last 12 months. This study was limited to patients seen between 2015 and 2020 and with a residential address within the catchment area of San Diego, Riverside, and Imperial Counties. Pollution burden was assessed using the CalEnviro Score 4.0. The Child Opportunity Index (COI) provided an overall composite score across three domains: 1) education; 2) health and environment; 3) socioeconomic opportunities. We geocoded and aggregated patient addresses to the census tract level and used ArcGIS to map pollution and sociodemographic characteristics. We ran a Mann-Whitney U test to assess differences in pollution burden and COI composite score between census tracts and HHU asthma cases. We used a Kruskal-Wallis Test to assess for differences in the frequency of ED encounters and inpatient hospitalizations and the length of hospital stay within the population.

RESULTS: Of the 1,073 unique individuals who met the HHU criteria, 1,043 (97.2%) returned a valid address within the study area. The median for HHU asthma cases was 1.7 per 1000 children (IQR 0.9-3.1) across 408 census tracts. There were 733 census tracts with no cases of HHU asthma. Neither distribution of pollution burden nor COI composite score were similar on visual inspection. Pollution burden for census tracts with HHU asthma cases (mean rank = 612.4) was statistically significantly higher than for census tracts without HHU asthma cases (mean rank = 547.9 z = -3.2, p = .002). Similarly, census tracts with HHU asthma cases had significantly lower overall opportunity scores (mean rank= 464.8) than census tracts without HHU asthma cases (mean rank = 602, z = -6.9, p &lt;.001). There was a statistically significant difference in the number of ED visits by race, ethnicity, and insurance type. Black/African American patients on average had increased frequency of ED visits than their white counterparts despite only comprising 14.8% of the total population (p .002). Black/African American patients also averaged more hospitalization days than their peers, however this finding was not determined to be statistically significant. Hispanic patients had increased frequency of inpatient hospitalizations than non-Hispanic patients (p .043). Insurance type was shown to be associated with a statistically significant difference in the number of ED visits (p &lt;.001) and inpatient encounters (p .003). Patients with Medicaid/Medical insurance had higher frequency of ED visits compared to their peers with commercial insurance (p .001). There was no statistically significant difference in the number of hospital days by insurance type. There were no statistically significant differences between the number of ED encounters or inpatient hospitalizations, and number of hospital days by primary language.

CONCLUSIONS: We identified disparities in pollution and child opportunity among locations with pediatric asthma patients with HHU in Southern California. These disparities are associated with geographic location within San Diego county as well as race, ethnicity, and insurance type. These findings can inform efforts to mitigate factors that impact child health equity.
Computational and experimental assessment of preferential targeting of α-cell-rich regions of pancreatic islets in the early stage of type 1 diabetes
Nirmala V. Balasenthilkumaran, Jennifer C. Whitesell, Rachel Friedman, Vira Kravets

BACKGROUND: Type 1 Diabetes (T1D) is an autoimmune disorder characterized by the progressive destruction of insulin-secreting β-cells. The inflammation of an islet during T1D is known as insulitis. Insulitis (immune infiltration) is often heterogeneous, with initial infiltration present only on one side of the islet. We sought to understand what characteristics of these regions make them more prone to immune attack.

METHODS: To investigate this phenomenon, we applied network theory (a mathematical model that describes the relationship between a set of cells) to perform islet-level analysis on the non-obese diabetic mouse model of T1D. We created spatial networks to analyze proximities and quantify the interactions between α-, β-, T-, myeloid cells, and macrophages. Disease progression in each islet was assessed using T-/β- cell ratios, and the islets were classified as early, intermediate, or late-stage insulitis.

RESULTS: Firstly, we observed the presence of more immune cells in α-cell-rich regions of an islet. This was reinforced by comparison of experimentally-derived networks with computational modeling of islets with random positioning of immune cells. Secondly, upon quantifying the interactions between β-cells and immune cells, we observed that in the early stages of insulitis, T-cells and macrophages interacted significantly more with those β-cells situated in the proximity of α-cells (α-linked β-cells), than the β-cells lacking neighboring α-cells. Finally, we also observed increased association between T-cells and myeloid cells, and T-cells and macrophages in their interactions with β-cells.

CONCLUSIONS: Our findings indicate a non-random polarity in immune infiltration, with α-cell-rich regions of an islet being more susceptible to infiltration during peri-insulitis. Additionally, our findings also suggest that the α-linked β-cells could be killed first during insulitis Overall, our findings imply that α-linked β-cells or α-cells could be preferentially targeted by immune cells in the early stages of insulitis.

Real-time, multi-shot imaging improves image quality in an iCMR simulation study

BACKGROUND: Current iCMR relies on single-shot imaging, which uses the most recent MRI samples for image reconstruction. Adaptive radial k-space sampling (ARKS) enables multi-shot imaging by finding similar cardiac phases in real-time. However, the extent to which ARKS can improve iCMR image quality has yet to be explored.

METHODS: Twenty ECGs recorded during 4D flow imaging in non-sedated pediatric patients were analyzed with IRB approval. The median age was 12.9 years old (IQR: 11.5-14.7), the median heart rate was 75.7 bpm (IQR: 67.6-95.0), and the gender ratio was 50% female. We simulated iCMR imaging by using a 2D radial bSSFP acquisition sequence with TR = 2.6ms, with a duration of 110 seconds applied to the open-source ACDC cardiac MRI dataset. Single shot (SS) imaging with 15, 35, 65 spokes as well as ARKS reconstructions were implemented (Fig 1). We hypothesize ARKS has a higher Structural Similarity Index (SSIM) and a lower RMSE than the SS methods, especially SS-short (15 spokes) due to extreme undersampling.

RESULTS: RMSE of images acquired with ARKS was lower (p<0.05) than those generated with 15-spoke SS but higher (p<0.05) than 65-spoke SS. No difference (p>0.05) was observed between ARKS and 35-spoke SS. ARKS exhibited higher SSIM (p<0.05) than 15-spoke SS, but lower than 65-spoke SS and was no different than 35-spoke SS.

CONCLUSIONS: We have shown that multi-shot imaging can improve image quality relative to 15-spoke SS in an image simulation study. Image quality of the long single-shot method was higher than ARKS but may not take into account blurring of cardiac structures.
Closed-loop CMR acquisition improves 3D k-space acquisition and image quality during cardio-respiratory navigation

BACKGROUND: In CMR, pre-defined k-space acquisition schemes are cardio-respiratory binned for multi-shot reconstruction, leading to suboptimal k-space sample distribution. Closed-loop control of MRI sampling improves k-space data. Image quality of data distributed using this closed-loop approach remains unexplored. Here, we evaluate image quality of a closed-loop controlled 4D-flow acquisition via simulation.

METHODS: To Cardiac and respiratory signals from 16 pediatric patients (age 13.5±5.9 years, 10 males) were extracted from 4D-flow scans and were used to simulate two 4D-flow free-breathing schemes. Data were binned into 10 cardiac phases. First, a 3D predetermined, golden-angle based spiral phyllotaxis (GAsp) 4D-flow sequence was simulated. This trajectory was predetermined and accepted data were retrospectively binned. Second, a closed-loop GA-based spiral phyllotaxis 4D-flow sequence was simulated however the GA trajectory was played within each cardiac bin. ECG was continuously analyzed to identify the current physiologic bin via cross-correlation. This information was used to determine the next sample to be collected from a numerical phantom. Evenly distributed points in k-space were generated as reference. Data distribution uniformity was quantified based on the Delaunay radii (RDelaunay), which indicates the size of the gaps on the surface of a sphere. To assess the effect of k-space data distribution on image quality, in-silico phantom images were reconstructed using NUFFT. Image quality was evaluated using mean squared error (MSE) and multiscale structural similarity index (MS-SSIM).

RESULTS: The average heart of the 16 patients were 85.5±29.0 bpm. Data from adaptivesp were more homogeneous compared to GAsp. The data distribution achieved by adaptivesp was the same (p>0.05) to that in evenly distributed points. As simulations progressed, the MSE was lower (p<0.05) in adaptivesp compared to GAsp, with the two simulations and equidistant reference becoming equivalent from 80% of the scan duration onwards. MS-SSIM was higher (p<0.05) on adaptivesp at all time points compared to GAsp. Image quality equivalent to that of GAsp was reached by adaptivesp at 66% of the scan duration.

CONCLUSIONS: By integrating physiological information into closed-loop adaptive sequences, we demonstrate the potential for achieving a more uniform sampling of k-space. These methods may contribute to significantly reducing scan duration while preserving image quality.
ABSTRACTS

Bioinformatics and Systems Biology

DX2 as a Biomarker for Epithelial Damage in Inflammatory Bowel Disease
Daniella Vo, Sara McCoy, Debashis Sahoo

BACKGROUND: Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the lower GI tract affecting millions of people in the United States every year. One key factor for preventing IBD pathogenesis is maintaining a barrier between pathogens and the internal immune system, in which epithelial cells have a significant role. Caudal-related homeobox transcription factor 2 (CDX2) has a known role in regulating intestinal differentiation, homeostasis, and tumorigenesis. Although decreased CDX2 expression has been identified in IBD patients and CDX2 levels have been examined after various treatments, this has not translated into an actionable biomarker. Most studies only focus on the increase of inflammatory cells, but we are interested in looking specifically at the epithelial cells.

METHODS: We downloaded and analyzed publicly available IBD bulk RNA-seq and single cell RNA-seq datasets to examine how CDX2 expression changes in healthy vs IBD patients. We also performed immunohistochemistry staining in IBD patient samples with CDX2 to see how CDX2 changes along the colon crypts.

RESULTS: This paper summarizes the changes in CDX2 expression in various disease states by (1) performing extensive transcriptomic analysis of CDX2 expression in healthy versus IBD patients to show lower CDX2 levels in IBD patients, (2) showing the loss of CDX2 specifically in epithelial cells by utilizing single cell analysis and experimentally validating CDX2 loss in the epithelium in IBD patients using a new immunohistochemistry protocol and (3) showing that CDX2 can be used to predict therapeutic response during and before treatment.

CONCLUSIONS: We believe that CDX2 can be used as a biomarker for epithelial damage in inflammatory bowel disease because CDX2 was decreased in IBD cases, even when the epithelium was purified. In the single cell datasets, CDX2 is still lower in IBD patients compared to healthy patients when all cells except epithelial cells are filtered out, showing that CDX2 expression is lower in IBD patients and it is not only due to an increase in inflammatory cells.

Multi-omic QTL mapping in fetal-like pancreas reveals early developmental insights into obesity and diabetes etiology

BACKGROUND: The impact of early life events on the susceptibility to disease is an emerging area of research. In the pancreas, adverse events during fetal development can result in insulin resistance, impaired glucose metabolism, and the loss of beta cell function. These factors contribute to an increased risk of developing type 2 diabetes in adulthood. While current quantitative trait loci (QTL) datasets have been instrumental in characterizing genetic variants associated with disease, the crucial genetic contributions that occur during fetal development remain unclear as previous studies primarily focus on adult tissues.

METHODS: We generated paired RNA-seq and ATAC-seq data from 109 iPSC-derived pancreatic progenitor cells (PPCs) obtained from individuals with whole genome sequences and conducted both genome-wide expression QTL (eQTL) and chromatin accessibility (caQTL) analyses. We performed pair-wise colocalization between PPC eQTLs and those previously identified in adult pancreatic islets and adult whole pancreases to identify regulatory variants specific to early pancreas development. Finally, we colocalized the eQTLs with early developmental and adult metabolic traits.

RESULTS: We discovered 908 eQTL associations that were unique to the fetal-like PPCs and 4,604 that were unique to the adult. Notably, we found strong evidence linking 78 of these eQTLs to genome-wide association studies (GWAS) loci associated with type 2 diabetes, type 1 diabetes, and obesity-related traits. Among the fetal-associated type 1 diabetes loci were CDC37L1-DT and MEG3, neither of which have been previously explored in the fetal context. Additionally, we investigated the functional differences of genetic variants between the fetal-like and adult pancreas and identified 1,772 eQTLs that were active in both stages but associated with different eGenes. For instance, cholesterol-associated rs138349 impacted ADSL expression during pancreas development but affected ST13 expression in adulthood. We have successfully mapped caQTLs and are currently integrating them with eQTLs to better understand the regulatory mechanisms underlying both gene expression and disease risk.

CONCLUSIONS: Overall, we provide a valuable resource for the interpretation of regulatory variants fetal-like pancreatic progenitor cells. We uncovered insights into the roles of disease risk variants, which may operate specifically during early development or in adult stages. We also discovered pancreatic eQTLs that have altered regulatory functions between the two life stages. By characterizing causal variants across multiple contexts, we can begin to delineate the etiology of disease risk with a finer resolution.
Macrophages on the Run: Exercise-induced transitions in macrophage polarization states

Yotam Voskoboynik, Andrew McCulloch, Debashis Sahoo

BACKGROUND: Exercise plays a crucial role in maintaining and improving human health. However, the precise molecular mechanisms that govern the body’s response to exercise and periods of inactivity remain elusive. Current evidence appears to suggest that exercise exerts a seemingly dual influence on macrophage polarization states, inducing both pro-immune response M1 activation and cell-repair-focused M2 activation. To reconcile this apparent paradox, we leveraged a comprehensive meta-analysis of 75 diverse exercise and immobilization published datasets (2500+ samples), encompassing various exercise modalities, sampling techniques, and species.

METHODS: 75 exercise and immobilization expression datasets were identified and processed for analysis. The data was analyzed using boolean relationships which binary gene expression relationships in order to increase the signal to noise achieved from the data, allowing for the use of comparison across such a diverse set of datasets. We utilized a boolean relationship-aided macrophage gene model, to model the macrophage polarization state in pre and post exercise samples.

RESULTS: Our modeling uncovered a key temporal dynamic: exercise triggers an immediate M1 surge, while long term training transitions to a sustained M2 activation. These patterns were consistent across different species (human vs mouse), sampling methods (blood vs muscle biopsy), and exercise method (resistance vs endurance), and routinely showed statistically significant results.

CONCLUSIONS: These consistent patterns across all 75 studies examined suggest that the long term health benefits of exercise stem from its ability to orchestrate a balanced and temporally-regulated interplay between pro-inflammatory and reparative macrophage activity. Similarly, it suggests that an imbalance between pro-immune and cell repair responses could pave the way for disease development. Our findings shed light on the intricate molecular choreography behind exercise-induced health benefits.
ABSTRACTS

Cardiology

Analysis of Extubation Readiness Using Physiologic Time-series Data in a CTICU
Sarah Friedland, MD; Dana Mueller, MD; Edgar Alfaro, MD, MPH; Claire Merson; Mark Abcede; Nicole G Coufal, MD PhD; Rohit Rao MD MBA

BACKGROUND: The American Association for Thoracic Surgery endorses a class 1 level A recommendation for early extubation after congenital heart surgery. Currently, pediatric extubation readiness guidelines are inconsistent. Premature extubation can lead to extubation failure, increasing morbidity and mortality. This study evaluated the ability of a time-series data streaming platform to predict extubation readiness trial (ERT) outcomes.

METHODS: This is a retrospective single center analysis of ERT outcomes at a tertiary hospital from 3/2022-3/2023. Intubated patients undergoing ERTs in a pediatric CTICU were eligible for inclusion. A time-series platform (SickbayTM) was compared to conventional ERT, applying predetermined hemodynamic variations that determined ERT outcome. Conventional ERT assessed variations in respiratory rate, oxygen saturation, near-infrared spectroscopy (NIRS), heart rate, and blood pressure by 20% and ETCO2 change by ≥ 10 torr compared to baseline. Conventional ERT was measured as the percent change between baseline and ERT datapoints. The time-series baseline and ERT was the median of 3500 datapoints/hour. Conventional and time-series ERT outcomes were compared using these hemodynamic variations to evaluate for discrepancies in ERT outcome predictions.

RESULTS: 322 ERTs met inclusion criteria. Of the 211 conventional ERT failures, 69.7% time-series ERTs passed and 30.3% failed. Of the 111 conventional ERT passes, 55.9% time-series ERTs passed and 44.1% failed. In a multivariate non-parametric analysis, there was a significant variation in respiratory rate (p=<0.001) when time-series ERTs were compared to failed conventional ERTs. Otherwise, there were no statistically significant hemodynamic changes when time-series ERTs were compared to conventional ERTs (p=>0.05). Of the 39 patients extubated within 12 hours of passed conventional ERT, 21 (54%) passed and 18 (46%) failed per time-series ERT. Of the 6 re-intubated patients, 2 failed and 4 passed time-series ERT.

CONCLUSIONS: The study concludes that a time-series data streaming platform can be applied to predict ERT outcomes and compares favorably with conventional ERT. This platform may detect subtle hemodynamic variations. Future studies will utilize machine learning to build a predictive algorithm that predicts ERT outcomes.

Endarteritis in Silent PDA
Danielle Strah, MD, Stephen Dalby, MD, John Arnold, MD, Brent Gordon, MD

BACKGROUND: The patent ductus arteriosus (PDA) while essential for fetal life can cause problems if postnatal closure doesn’t occur. Audible PDAs are routinely closed due to hemodynamic concerns and potential for infective endarteritis (IE), however “silent” PDAs are believed to be lower risk without clear guidelines regarding indications for closure.

METHODS: N/A

RESULTS: We present a case of IE in a patient with silent PDA treated with prolonged antibiotic course and eventual transcatheter closure. A 5-year-old male with no known cardiac history presented with persistent fevers and respiratory distress despite completing multiple antibiotic courses over the preceding weeks for presumed pneumonia. Chest x-ray demonstrated focal consolidation consistent with pneumonia and mild cardiomegaly, for which an echocardiogram was performed, despite a normal cardiovascular exam. The echocardiogram demonstrated a small PDA with an echo-bright structure on the pulmonary artery end, concerning for vegetation. Chest CT demonstrated areas concerning for septic pulmonary emboli, while brain MRI and ophthalmologic exam were negative for paradoxical emboli. Multi-disciplinary discussion involving interventional cardiology and infectious disease allowed for formulation of a treatment plan as there are no standardized guidelines for this scenario. After completing a 6-week course of IV Ceftriaxone, there was resolution of the vegetation by echocardiogram and no evidence of ongoing bacteremia by lab tests. He then took daily prophylactic amoxicillin until undergoing successful transcatheter closure with 6 mm KA device, followed by 6 more weeks of amoxicillin. He remains free of bacteremia and endarteritis at one-year follow-up with plans to continue IE prophylaxis for foreseeable future.

CONCLUSIONS: This case highlights the risk of IE with a silent PDA, as well as the paucity of standardized treatment recommendations. It also demonstrates a successful treatment regimen for these rare cases. The necessity of lifelong bacterial endocarditis prophylaxis in this type of patient is also a matter for discussion as guidelines are lacking.
Novel Use of SpiderFX Embolic Protection System for Mechanical Thrombectomy in an Infant with Catheter-Associated Thrombosis

Henri Justino, MD, Danielle Strah, MD

BACKGROUND: Large, mobile intracardiac clots carry significant morbidity and/or mortality due to embolization and/or expansion. Options for transcatheter removal in small children are limited by need for large sheaths and potential blood loss. We present a novel catheter-based thrombectomy technique in an infant with a large right atrial and central venous thrombus.

METHODS: N/A

RESULTS: 2 weeks after removal of a left subclavian central venous line, a 3-month-old (4.4 kg) ex-premature infant was diagnosed with a large thrombus extending from the left innominate vein to the right atrium, adjacent to a large atrial septal defect (ASD), posing systemic embolization risk. To minimize systemic embolization risk during thrombectomy, temporary balloon occlusion of the ASD was performed via femoral venous access. A 7 mm SpiderFX embolic protection device was used to remove a large portion of the right atrial thrombus via a 4-Fr sheath in the right internal jugular vein (IJV). Echocardiogram revealed residual left innominate vein and superior vena cava thrombus with obstruction. Aspiration thrombectomy was attempted with a 5-Fr guide catheter, resulting in minimal clot extraction. The SpiderFX was used to remove the remaining thrombus via a 5-Fr sheath in the left IJV. Angiography and echocardiogram demonstrated no residual thrombus or obstruction. Blood loss was 15 cc (12 cc during ineffective aspiration thrombectomy). Follow-up at 20 months showed no recurrence of thrombus or obstruction.

CONCLUSIONS: The SpiderFX embolic protection system is designed to capture emboli to the carotid arteries during adult cardiovascular interventions in atherosclerotic vessels. It has never been described for thrombectomy. Current aspiration-based thrombectomy systems have limited utility in infants due to large sheath size requirement and risk of major blood loss. This case highlights the first use of an embolic protection device to successfully extract a large thrombus in a small infant using small sheaths with minimal blood loss.

A Clinical Tool to Relate Youth Risk Factors to Adult Cardiovascular Events and Type 2 Diabetes: The i3C Consortium

Jessica Haley, MD; Jessica G. Woo, PhD; David R Jacobs, Jr PhD; Lydia Bazzano, MD, PhD; Trudy Burns, PhD; Stephen Daniels, MD, PhD; Terry Dwyer, MPH, MD, MB, BS; Markus Juonala, MD, PhD; Olli Raitakari, MD, PhD; Alan Sinaiko, MD; Julia Steinberger, MD, MS; Alison Venn, PhD; Kara M. Whitaker, PhD; Elaine M. Urbina, MD, MS

BACKGROUND: Pediatric cardiovascular (CV) risk factor thresholds have been arbitrarily defined due to the lack of data linking childhood risk factors to adult CV events. This gap in knowledge has now been addressed with new analyses directly linking childhood risk factors and CV events and type 2 diabetes (T2DM). The aim of this study is to translate data relating childhood CV risk factors and adult CV disease and T2DM to clinically actionable values.

METHODS: A prospective observational study (n=38,589) in the International Childhood Cardiovascular Cohort (i3C) Consortium enrolled children aged 3-19 years in the 1970s and 1980s and followed them for over 30 years. Five childhood CV risk factors (smoking, body mass index (BMI), systolic blood pressure (SBP), triglycerides (TG), and total cholesterol (TC)) were measured and related to adult CV events. Secondary analyses in a subset included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose and insulin level. Age- and sex-specific z-scores were calculated for each risk factor, and a combined-risk z-score was calculated by averaging z-scores for the 5 key CV risk factors. Risk factor z-scores were back-transformed to natural units for clinical interpretation, with hazard ratios for adult CV events presented in color coded tables (green: no increased risk; orange: 1.4 to &lt;2.0-fold increased risk; red: at least doubling of risk). Risk levels for development of adult T2DM based on BMI, glucose and insulin were similarly calculated and presented.

RESULTS: Increased risk for CV events was observed at levels lower than currently defined abnormal clinical thresholds except for TC. Doubling of risk was observed at high normal levels, just below the clinical cut point for abnormality. Risk for adult T2DM began at levels of BMI and glucose currently considered normal.

CONCLUSIONS: Based on data showing significant relationships between childhood CV risk factors and adult CV events and T2DM, this study shows that risk in childhood begins below levels currently considered normal.
Quality Improvement Process to Improve Neonatal Cardiology Referrals in the Greater San Diego Area
Elizabeth E LaSalle, Juliana Gomez-Arostegui, Aamisha Gupta, Jose Silva Sepulveda

BACKGROUND: A referral guideline for neonates requiring outpatient cardiology evaluation was developed by a group of cardiologists at our institution to provide guidance for timing of referral and appropriate clinical testing for common cardiac diagnosis in the San Diego area.

METHODS: This guideline was sent by email to medical directors of 16 neighboring nurseries and neonatal intensive care units (NICUs). A survey was sent to care providers with the guideline to gauge its utility and respondent confidence with common cardiac diagnoses. Open-ended feedback was also elicited. The goal of this initial project was to increase provider comfort and guideline usage by 50% over 6 months.

RESULTS: Thirteen providers completed the entire survey. 79% respondents were from a single institution. 38% of participants were nurse practitioners, 25% newborn nursery attending physicians, and 6% (1/14) NICU fellow. 64% of respondents make 1-3 cardiology referrals weekly. 50% of respondents were aware of the guideline and 100% found it “somewhat helpful”. The majority reported using the guideline at least once per week 71% (5/7) and 86% (6/7) found it helped avoid contacting a cardiologist. Further evaluation showed that respondents reported feeling at least somewhat confident in managing ventricular septal defects (100%), atrial communications (92%), patent ductus arteriosus (84%), premature beats on ECG (76%), and less confident with right ventricular hypertension (46%) and prolonged QT intervals (31%). Respondents suggested incorporation of guidelines into echo reads and faster turnaround time for electrocardiogram reads.

CONCLUSIONS: This project is a work in progress. The initial survey gauges the use of our referral guidelines and provides feedback for improvement. The number of respondents was low and the majority are from a single location. Future directions include guideline revision and improving accessibility of the guidelines to better understand the cardiology needs of the community.

Reproducibility, and Accuracy of Echocardiographic Right Ventricular Function Assessments in Childhood Cancer Survivors at Risk for Heart Failure
Heidi Ostler, MD; Lin Liu, PhD; Khang Tong, MS; Maria Acuero, MAS; Juliana Gomez-Arostegui, MD, MPH; Seth Degner, RDMS; Fraser Golding, MD; Sanjeet Hegde, MD, PhD; Dennis J. Kuo, MD, MS; Hari K. Narayan, MD, MSCE

BACKGROUND: Our objectives were to assess the reproducibility and accuracy of conventional and newer echocardiographic (echo) measures of right ventricular (RV) systolic function in adolescent and young adult childhood cancer survivors treated with anthracycline therapy.

METHODS: In this prospective, cross-sectional, single-center study, echo and cardiac magnetic resonance imaging (MRI) were acquired a maximum of 12 weeks apart in childhood cancer survivors previously treated with anthracyclines. Echo and MRI measures of RV systolic function were performed by separate, blinded observers, with repeat measures in 10 echoes &gt;1 week apart to determine intra-observer reproducibility via coefficients of variation. For each echo measure, Spearman correlations with MRI RV ejection fraction (RVEF) and RV cardiac output were calculated.

RESULTS: Among 43 participants, three had RVEF &lt;50% (Table 1). Average analysis time was 100 seconds for fractional area change, 376 seconds for semi-automated strain, 27 seconds for automated strain without adjustments, 93 seconds for automated strain with manual adjustments, and 249 seconds for 3D analysis. Intraobserver coefficients of variation were 2.4%-11.4% and were lowest for tricuspid annular plane systolic excursion (TAPSE; 2.4%), tricuspid annular s’ (5.0%), uncorrected automated free wall longitudinal strain (5.2%), and 3D RVEF (5.2%). None of the echo measures were significantly correlated with MRI RVEF; TAPSE was correlated with MRI RV cardiac output (r=0.366, p=0.017; Table 2).

CONCLUSIONS: Echo strain and 3D measures of RV systolic function were feasible and reproducible in at-risk childhood cancer survivors, but they lacked significant associations with MRI-based RV function measures.
ABSTRACTS

Cardiology (cont.)

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CONCLUSIONS: Based on data showing significant relationships between childhood CV risk factors and adult CV events, this study shows that risk in childhood begins below levels currently considered normal.

Partial Anomalous Left Pulmonary Artery Supplying Left Upper Lobe: A Rare Pediatric Case with Angiographic Presentation
Jihyun Park, MD, Henri Justino, MD, Brian Pugmire, MD

BACKGROUND: Partial anomalous left pulmonary artery is a rare vascular anomaly that is often asymptomatic but can be associated with various cardiac anomalies or genetic syndromes. There are only 45 reported cases of PALPA in the English literature. Compared to left pulmonary artery (LPA) sling, PALPA does not cause significant tracheobronchial stenosis, even though it may be associated with other tracheobronchial anomalies. Interestingly, in most reported cases of PALPA the anomalous branch supplied the left lower lobe. We report a case of a full-term female with CHARGE syndrome who was found to have a partial anomalous left pulmonary artery arising from the proximal right pulmonary artery supplying the left lingula. Angiography, 2D CT imaging and 3D reconstruction of CT were employed to evaluate the PALPA and its relationship to the airway and aorta. This report also compares this case to previously reported cases and proposes to categorize this anomaly into further subtypes.

METHODS: Literature review of PALPA and retrospective case review

RESULTS: Our case is the first angiographic demonstration of the PALPA and the third reported case of PALPA supplying the left upper lobe in pediatric patients and second reported pediatric case in literature with the normal tracheal anatomy following a case reported in 2020. Even though the presence of PALPA often does not cause significant respiratory issues requiring surgical correction and thus far, and there is no significant clinical significance in different lobes being supplied by the anomalous LPA branch, it may be valuable to start further categorizing PALPA courses based on the lobes that it is supplying, as we may see more cases of the PALPA in following years.

CONCLUSIONS: PALPA is a rare anomaly that can present in isolation or in association with airway abnormalities. Although the vascular abnormality itself does not require management, familiarity with this condition is important to differentiate it from other vascular abnormalities that require correction.
Loss of ETS1 in coronary endothelium causes hypoplastic ventricular compact myocardium

Lu Wang, Paul Grossfeld

BACKGROUND: Jacobsen syndrome (JBS) is a rare chromosomal disorder caused by deletions in the long arm of human chromosome 11, resulting in multiple developmental defects including congenital heart defects (CHDs). Combined studies in humans and genetically engineered mice implicate that loss of ETS1 is the cause of CHDs in JBS. We have previously demonstrated that conditional deletion of ETS1 in all of the cardiac endothelial lineages (including endocardial and coronary endothelial cells) caused an hypoplastic ventricular compact myocardium in embryonic mouse hearts. In this study, we aimed to delineate the specific role of ETS1 in coronary endothelium in causing hypoplastic ventricular compact myocardium and to identify candidate secretory factors expressed by coronary endothelial cells that contributes to compact cardiomyocyte proliferation.

METHODS: ETS1 pan-endothelial-specific and coronary endothelial-specific knockout mice were used. Single-cell RNA sequencing and phenotypic assessments were performed together with expression analysis, immunofluorescence and RNAscope in situ hybridization to uncover phenotypic and transcriptomic changes in response to loss of ETS1.

RESULTS: Loss of ETS1 in coronary endothelial cells causes hypoplastic ventricular compact myocardium. Several secretory factors expressed by coronary endothelial cells, including Slit2 and Col18, were identified as potential candidates for promoting proliferation of compact cardiomyocytes.

CONCLUSIONS: These findings demonstrate the capacity of coronary endothelial cells to facilitate the proliferation of compact cardiomyocytes via the secretion of specific factors.
**Child Protection Service Reports in Children with Complex Chronic Conditions**

*Mallory McPhee, Jeannie Huang, Rebecca Rebbe, Natalie Laub*

**BACKGROUND:** Children with disabilities suffer higher rates of child maltreatment compared to healthy peers. Varying definitions of disability makes it difficult to determine which specific diagnoses place a child at increased risk of maltreatment. Children with complex chronic conditions (CCC) are a unique population and differ from broader groups of children referred to as “disabled” previously. This study aims to understand rates at which children with CCC are reported to child protective services (CPS) and what factors increase the risk of CPS reports.

**METHODS:** Retrospective review of a linked database of Rady Children’s Hospital Network (RCHN) encounters between 2016-2021 with birth and CPS records for children under 10y with a CCC diagnosis. Descriptive statistics and regression modeling were performed.

**RESULTS:** 47,896 children had a CCC diagnosis within RCHN. 55% were male, 52% had public insurance, and 64% were diagnosed with a CCC by age 4y. 43% identified as Hispanic, 36% as non-Hispanic White, and 5% non-Hispanic Black. The most common CCC types were cardiac, congenital/genetic defects, metabolic, and neurologic conditions. 10,104 children (21%) had at least one CPS report filed for maltreatment. Of the 10,104 children, 62% had more than one CPS report filed. The most common reason for first CPS report was general neglect at 44.5%. Regression analysis demonstrated increased risk for CPS reports in children with a neurologic condition (RR=1.38 [CI 1.31-1.45]), children on public insurance (RR 3.01 [CI 2.86-3.17]), and whose ethnicity was non-Hispanic Black (RR=1.58 [CI 1.47-1.70]) or non-Hispanic Native (RR 1.45 [CI 1.09-1.89]).

**CONCLUSIONS:** Nearly a quarter of children with CCC in the RCHN have been reported to CPS for child maltreatment. Increased risk of a CPS report includes children with public insurance or non-Hispanic Black and non-Hispanic Native race/ethnicity. These results highlight the vulnerability of this population and raise concerns regarding bias in reporting based on socioeconomic factors.

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**Social Media Facilitated Sexual Assault: The Dangers of Meeting Strangers Online**

*Miguel Cano MD, Amanda Dube MD, Natalie Laub MD, Shalon Nienow MD*

**BACKGROUND:** With the popularity and dependence on social media (SM) amongst adolescents, the dangers of online platforms are becoming more evident, including meeting sexual predators. Social media facilitated sexual assault (SMFSA) occurs when social media facilitates communication between a victim and perpetrator that leads to sexual assault. While prior literature suggests technology can play a role in facilitating sexual assaults, there is no specific literature on the prevalence of sexual abuse victims who report meeting their perpetrators via social media platforms such as Instagram. Our objective was to identify the prevalence of child sexual abuse victims who met their perpetrator on social media, and identify which SM platforms were reported most frequently.

**METHODS:** This is a retrospective cross-sectional study of children 10 to 18 years of age seen for sexual abuse evaluations at Rady Children’s Hospital Chadwick Center for Children and Families between 2018-2023. Data was analyzed via Stata using descriptive statistics and Chi Squared/Fisher’s exact Test.

**RESULTS:** Of the 1062 patients included, the mean age was 13y (SD 1.9), 89% were female, 36% White, and 19% Hispanic. The patient was related to alleged perpetrator 60% of the time. 80% of perpetrators were adult men. In the total population 7% reported SM was used to facilitate the sexual assault. When accounting only for victims with non-related perpetrators, there was a statistically significant increase in SMFSA at 12% (P value <0.0001). Snapchat followed by Instagram were the most common platforms used. There was no statistical significance in acquisition of sexually transmitted disease or physical injury between the two groups.

**CONCLUSIONS:** Social media platforms are being used to facilitate sexual assault in children between the ages of 10-18. Instagram and Snapchat are the two most common reported social media platforms. Further research is needed to understand how to keep children safe from predators on social media.
Temporal Association Between COVID-19 Infection and Retinal Hemorrhage in the Pediatric Population

Natalie Laub, Aaron T Zhao, Jocelyn He, Yinxi Yu, Gui-shuang Ying, Alyssa Spiller, Gil Binenbaum

BACKGROUND: Retinal hemorrhages (RH) are frequently seen in pediatric abusive head trauma. Recently SARS-CoV-2 (COVID-19) infection has been proposed in the medical-legal realm an alternative cause of retinal hemorrhage when a child abuse evaluation occurs. Case reports of RH in children with COVID-19 infection suggest COVID-19 could cause RH, but comparative data are lacking. We sought to evaluate the association between RH and COVID-19 infection in children.

METHODS: Retrospective cohort study of inpatient and outpatient children, 1 month to 18 years, with both COVID-19 testing and retinal exams, over a 46-month period. Association between COVID-19 and RH in 4 time periods (eye exams within 7, 14, 21, or 28 days of COVID-19 test) was evaluated with multivariable regression, adjusting for age and repeat COVID-19 testing.

RESULTS: Among 6,952 children studied (mean age 6.1 years), 3,496, 4,758, 6,887, 6,952 had retinal exams within 1, 2, 3, and 4 weeks of COVID-19 testing, respectively. Of these children 176 had RH and 249 had COVID-19. There were no association between COVID-19 and RH in any time period. Odds Ratio (OR) week one after positive COVID-19 test was 0.80 (95% CI 0.2-3.3); OR at 2 weeks 0.75 (95% CI 0.2-2.0); OR at 3 weeks 0.8 (95% CI 0.3-2.2); OR at 4 weeks 0.63 (95% CI 0.1-1.7).

CONCLUSIONS: In the only comparative study to date, COVID-19 was not associated with retinal hemorrhages at any time within 4 weeks of a positive test. A positive COVID-19 result should not be considered an alternative cause of RH in children, clinically or in legal proceedings.
**ABSTRACTS**

**Computer Science & Engineering**

**POSTER #31**

**Temporally-Aware Neural Networks For Cine MRI Reconstruction From Severely Undersampled Data**  

**BACKGROUND:** Interventional MRI (iMRI) requires both fast image acquisition which limits the number of samples available for reconstruction and also limits the computational complexity of the reconstruction process. We aim to exploit the temporal similarities of iMRI by using a convolutional-LSTM (convLSTM)--based framework that can quickly and accurately perform time-series forecasting on the iMRI sequence. We compare the reconstruction speed and quality of the convLSTM to MD-CNN, a 3D convolution based Neural Network that performs video-frame-interpolation using a sliding-window paradigm.

**METHODS:** The open-source Automated Cardiac Diagnosis Challenge (ACDC) dataset consists of cine MR images from 150 patients typically at ten different slice locations acquired during breath-holds. Images were undersampled using NUFFT. Ten golden angle radial spokes per frame were extracted to generate a time series of undersampled k-space data. Receiver coils were simulated by using Gaussian masks. This generated a multi-coil k-space time series, which was used as input for the Neural-Network. We propose a 3-component pipeline. First, a convLSTM interpolates missing k-space data in a coil-wise fashion. We convert this to image-space using IFFT. Finally we use a UNet to remove artefacts and generate a final prediction.

**RESULTS:** The convLSTM reduced the Floating-point OPERations (FLOPs) of the forward pass from 153.3B (billion) of the MD-CNN to 12.2B. MD-CNN takes 0.077 ± 0.003 seconds to reconstruct a frame (~13 FPS). The convLSTM method was 17 times faster (0.004 ± 0.0002 seconds per frame, ~226 FPS). Average SSIM of MD-CNN was (0.89 ± 0.03 higher) than that of convLSTMs (0.85 ± 0.04).

**CONCLUSIONS:** An LSTM-based approach enabled fast (>200 fps) image reconstruction from severely undersampled data, at a small tradeoff in SSIM as compared to MD-CNN.

**Spatial Transcriptomics to Resolve Macrophage Polarization along the Intestinal Crypt Axis**  
H M Zabir Haque, Daniella Vo, Sara Safa, Sahar Taheri, Mojgan Hosseini and Debashis Sahoo

**BACKGROUND:** Macrophages are an essential part of the immune system that work to maintain homeostasis. Previous work has studied various immune cells on stem cells at the bottom of the crypt, but macrophage polarization along the intestinal crypt is yet to be understood. The development of technologies such as spatial transcriptomics provides new modes of identifying differences in gene expression in varying parts of the tissue.

**METHODS:** We employed a novel technique using spatial transcriptomics data to identify differentially expressed genes in the intestinal crypt top and bottom. Using this data, we developed a model based on Boolean implications to specifically target differences in gene expression of macrophages in the top versus bottom of healthy intestine crypts.

**RESULTS:** We exclusively identified macrophages in the healthy intestine crypt top and the crypt bottom, named ICAM gene signature. ICAM exhibited that macrophages from adult samples were more reactive in the crypt top. Additionally, we found through the ICAM signature that macrophages are more active in diseased states than healthy ones. This highlights the spatial heterogeneity and functional differences within the intestine macrophage population.

**CONCLUSIONS:** A new spatial transcriptomics approach using Boolean implications identified differences in gene expression of intestinal crypt associated macrophage. This model provides insight into macrophage polarization along the intestinal crypt and provides a list of new potential biomarkers for targeting therapeutics.

**POSTER #32**

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**CONCLUSIONS:** A new spatial transcriptomics approach using Boolean implications identified differences in gene expression of intestinal crypt associated macrophage. This model provides insight into macrophage polarization along the intestinal crypt and provides a list of new potential biomarkers for targeting therapeutics.
Annotation of Epithelial Cell Types Along Human Colon Crypt Using Boolean Analysis

Sara S McCoy, Debashis Sahoo

BACKGROUND: Boolean analysis, characterized by its simplistic binary approach using values like 1/0 or high/low, has emerged as a valuable tool in delineating cellular differentiation states within both normal and cancerous tissues. While traditional clustering and differential analysis methods dominate biological data analysis, Boolean analysis offers a novel perspective. In this context, our study aims to demonstrate the efficacy of Boolean analysis in categorizing distinct cell types within human colonic crypts. Despite considerable efforts, the precise identification of colon crypt-maintaining cells remains elusive, with the majority of research in intestinal stem cell (ISC) biology focusing on the small intestine. Though two ISC populations—the +4 cells and the crypt base columnar cells—have been recognized, controversies persist regarding the true stem cells responsible for crypt maintenance. Our hypothesis posits that through an unbiased systems biology approach and mathematical modeling utilizing extensive patient-derived gene expression datasets, we can predict differentiation hierarchies and discern specific markers of stem and progenitor cells within human colon tissue. This innovative methodology holds promise for revolutionizing the field of intestinal stem cell biology.

METHODS: Data Collection and Processing: To investigate gene expression changes during normal differentiation steps, we initially gathered extensive cancer datasets encompassing thousands of patient-derived gene expression profiles. Specifically, we compiled a comprehensive collection of over 3500 publicly available colorectal cancer datasets. Boolean Relationship Analysis: Utilizing these datasets, we conducted Boolean relationship analysis, a methodological approach that offers insights into gene expression dynamics. For instance, we illustrated the Boolean relationship between KRT20 and CA1 in approximately 1330 colon cancer, 68 adenoma, and 170 normal colon samples. Notably, our findings revealed a distinct Boolean relationship in colon cancer, where high CA1 expression corresponds to high KRT20 expression. Interestingly, our analysis indicated that none of the examined colorectal cancer datasets displayed the gene expression profile of high CA1 and low KRT20, suggesting a universal rule within colon tissue physiology. Identification of Differentiation Markers: Given the remarkable correlation observed between normal and cancer tissues, we leveraged colon cancer datasets to unveil markers of differentiation in normal colon crypts based on Boolean principles. This approach allowed us to discern patterns indicative of differentiation states within the colon crypt environment. Advantages of Boolean Approach: In comparison to traditional computational methods, the Boolean approach offers distinct advantages in deciphering differentiation markers within colon tissue. Conventional methods typically involve cell type purification based on known surface markers expressed along the crypt gradient. However, analyses of human colon datasets utilizing surface markers such as EPHB2 and PTK7 demonstrated strong correlations between top crypt markers KRT20 and CA1. These correlations were observed in differential expression analyses between high/medium and low/negative samples, suggesting their utility in extracting top crypt markers from normal human colon tissue. Limitations and Considerations: While our approach offers valuable insights into differentiation markers, it is important to note certain limitations. For instance, datasets focused on goblet cell markers, such as MUC2 expression patterns, did not exhibit significant variations across different sample groups, indicating potential limitations in identifying goblet cell markers using the examined datasets. Overall, our methodological framework showcases the efficacy of Boolean analysis in elucidating gene expression dynamics and differentiation markers within normal colon crypts, offering novel insights into colorectal tissue biology and potential implications for cancer research.

RESULTS: Understanding the distinct roles of stem cells, progenitor cells, transiently amplifying cells, and terminally differentiated cells within the human colon crypt is essential for unraveling the underlying biology and pathogenesis of various human diseases, including cancer. Conventional methods such as immunohistochemical analysis and flow cytometry-based approaches have limitations, including antibody availability and loss of cellular structural organization. High-throughput assays provide valuable insights into average gene expression levels but lack direct correlation with quantitative modifications in cellular subpopulations. Furthermore, single-cell high-throughput assays introduce biases and inaccuracies due to RNA amplification, leading to random gene dropouts. However, our analysis revealed Boolean implication relationships between cell type markers in cancer datasets, which were consistently satisfied during differentiation pathways. Identification of Top-of-the-Crypt Markers: To identify markers specific to cells at the top of the crypt, we employed a Boolean relationship approach utilizing large patient-derived colon cancer datasets. We hypothesized that this approach could unveil universal rules of gene regulation, holding true throughout differentiation pathways. Notably, we discovered strong Boolean implications, such as X high =&gt; KRT20 high, indicative of genes expressed in the top crypt cells. Two candidate markers, HPGD and GUC2A2A, identified through this approach, were successfully validated by immunohistochemical analysis. Identification of Goblet Cell Markers: Similarly, we employed Boolean relationship analysis to identify markers specific to goblet cells within the colon crypts. By searching for Boolean relationships such as MUC2 low =&gt; X low, equivalent to X high =&gt; MUC2 high, we aimed to identify genes expressed in goblet cells. Through this approach, we identified candidate genes such as RAP1GAP, successfully validated by immunohistochemical analysis.

CONCLUSIONS: Our study showcases the effectiveness of Boolean analysis in elucidating gene expression dynamics and identifying cellular markers within the complex microenvironment of human colon crypts. By leveraging large patient-derived colon cancer datasets, we uncovered Boolean implication relationships that hold true not only in cancer tissues but also during differentiation pathways within normal colon crypts. Through this approach, we identified markers specific to distinct cellular subtypes, including those at the top of the crypt and goblet cells. The significance of this work lies in its potential to advance our understanding of the underlying biology and pathogenesis of various human diseases, particularly colorectal cancer. By deciphering the roles of stem cells, progenitor cells, transiently amplifying cells, and terminally differentiated cells, we lay the groundwork for future research aimed at developing targeted therapeutic interventions and diagnostic tools. Moreover, our findings highlight the limitations of conventional methodologies such as immunohistochemical analysis and flow cytometry-based approaches, underscoring the need for innovative computational approaches like Boolean analysis. By overcoming the challenges associated with data heterogeneity and cellular complexity, Boolean analysis offers a promising avenue for unraveling the intricacies of cellular differentiation and disease progression.
The Effect of a Modular Airway Training Program on Learning Acquisition and Intubation First-Pass Success Rates in the Pediatric Population

Jacob Hartung, Sandra Saw, Lisa Sacco

BACKGROUND: Advanced airway management including endotracheal intubation can be a lifesaving procedure. Specifically, the importance of first-pass success rate is critical given studies demonstrating that repeat intubation attempts increase incidence of adverse events. However, the relative rarity of pediatric tracheal intubations limits the opportunities for medical providers to become competent in the procedure which has likely led to the lower rate of first-pass success in pediatrics than in adults that is documented in studies. The Pediatric Airway Skills Training (PAST) program was created at Rady Children’s with the goal to improve provider airway knowledge, technical skills and overall first-pass success rate.

METHODS: Learners who rotate through the operating room at Rady Children’s for airway experience first participate in the PAST program. The program consists of three components. Prior to hand-on learning, learners complete online modules created by Childrens Hospital of Philadelphia that consist of three different modules: basic airway anatomy and assessment, bag-mask ventilation and endotracheal intubation. Learners then participate in a hands-on session that includes: pre and posttest, review of module main learning points and hands-on simulation including bag-mask ventilation, airway adjuncts, intubation and the use of video. Finally, learners are allowed into the operating room where they perform intubations under attending anesthesiologists' supervision.

RESULTS: As of April, 11th 2024, 417 intubation attempts in the operating room have been tracked by learners who first participated in the PAST program. The average first pass success rate was 83%. Learners' airway knowledge pretest score was 64.2% and post-test score was 77.5%.

CONCLUSIONS: Airway knowledge and skills of providers improved after completion of the PAST program, and first pass success rates were above national benchmarks reported for the pediatric population.
A Retrospective Study on the Demographics and Clinical Characteristics of Pediatric Androgenetic Alopecia

Danny Lee BA, BS, Dawn Eichenfield MD, PhD

BACKGROUND: Androgenetic alopecia (AGA) is clinically characterized by reduction in hair density, caliber and progressive balding. While AGA is a common cause of hair loss in the adults, it is underrecognized in the pediatric population. Little is known about the natural history, risk factors, and treatment in pediatric patients.

METHODS: This study was approved by Rady’s Children Hospital Institutional Review Board. A retrospective chart review from 1/1/2009 - 1/1/2023 was performed by evaluating demographics, family history, treatment, adverse effects, and reported outcomes.

RESULTS: Fifty-two patients were seen for androgenetic alopecia, of which 17 were female and 35 were male based on biological sex. There was one transgender female patient. Average age of initial presentation and reported age of onset were 15.58 and 14.02, respectively. Thirty-eight patients reported a family history of androgenetic alopecia, 13 had no family history, and 1 patient was adopted. Eleven patients were followed by endocrinologists. Dermatologists ordered various labs (e.g., DHEA-S, CBC) for 16 patients: 4 males to rule out secondary etiologies and 12 females for hyperandrogenism. Initial treatment prescribed included: minoxidil (43), triamcinolone (1), ketoconazole (2), finasteride (1), biotin (5), OCP (4), multivitamin (3), and active monitoring (7, 1 pt previously on OCPs). Twenty-five had follow-up with dermatology, with an average of 2.44 follow-up visits. 12 patients reported an improved course, 3 with a worsened outcome, and 10 unchanged. Out of those with follow-up, 10 patients reported adverse effects (e.g. dizziness caused by OCPs).

CONCLUSIONS: Our study shows that AGA is prevalent among adolescents and children. A majority of patients report a positive family history of androgenetic hair loss. A proportion was also seen by endocrinologists for related disorders such as PCOS. Prospective studies are needed to better define the relationship between AGA risk factors and outcome.
Defining Pediatric Laryngoscopy and Tracheal Intubation Airway Micro-skills with Standard Geometry Blades: A Delphi Study
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BACKGROUND: Pediatric intubation is a high-risk, low-frequency procedure in pediatric emergency departments. Given its low-frequency, opportunities for pediatric emergency medicine (PEM) fellows and faculty are rare. Breaking down a procedural skill into micro-skills can help develop mastery in that skill as a whole. However, there is sparse literature that defines the micro-skills that encompass pediatric direct laryngoscopy and endotracheal tube delivery, and therefore, identifying these component micro-skills can help to inform the future development of a formal airway curriculum for PEM physicians.

METHODS: We recruited twelve interdisciplinary airway experts from PEM, Pediatric Critical Care, and Pediatric Anesthesiology with seven institutions across the United States represented. Through multiple rounds of the Delphi method, our airway experts were tasked with reaching consensus on a complete list that defined the airway micro-skills utilized in pediatric direct laryngoscopy and tracheal intubation. During each round, experts scored each step on a 7-point scale, where 1 to 3 represented not important; 4-6 represented somewhat important; and 7 represented mandatory. Participants were able to suggest additional steps as needed, propose wording changes, suggest removal of steps that sounded similar, change the order of existing steps, and add free text comments to further qualify their rankings. The study coordinator calculated the median for each step and steps with a median ≤3.0 were removed for subsequent rounds. For subsequent rounds, each expert was provided the revised consolidated micro-skills list and an abstract of panel members’ comments from the previous round. This Delphi process was continued for a total of 4 rounds, at which point we reached ≥80% airway expert consensus that the airway micro-skill list was comprehensive. Cronbach’s Alpha was calculated as a inter-rater reliability measurement.

RESULTS: Four Delphi rounds were completed by all 12 multi-disciplinary pediatric airway experts. The pre-consolidated list after round one had 154 laryngoscopy items and 97 endotracheal tube delivery items. The post-consolidated list after round four had 16 laryngoscopy items and 22 endotracheal tube delivery items. Cronbach’s Alpha was calculated to be 85.9% at the completion of round four.

CONCLUSIONS: We successfully reached ≥80% airway expert consensus in the creation of our pediatric airway micro-skills list. This list can now be utilized to inform the future development of a formal airway curriculum for PEM physicians.

Low-Dose Intravenous Ketamine for Adolescents with Depression and Suicidal Ideation in the Emergency Department: A Randomized Placebo-Controlled Trial
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BACKGROUND: Suicide rates have increased over 20 years by ~60% among US adolescents aged 15-19 and 3-fold among those aged 10-14, making suicide the second leading cause of death. Sub-anesthetic ketamine has rapid anti-depressant effects, but no data exist on ketamine for depression and suicidal ideation (SI) in the pediatric ED.

METHODS: We enrolled a convenience sample of adolescents aged 12-17 in the ED with treatment-resistant depression requiring admission for acute SI in a double-blind randomized controlled trial of ketamine (0.2mg/kg IV, single dose over 2 minutes) versus saline placebo. Exclusion criteria included psychosis, substance use disorder, developmental delay, aggressive behavior, and medical contraindications to ketamine. Subjects completed a depression score, the Beck Youth Inventory (BYI), and the Suicidal Ideation Questionnaire (SIQ) at baseline and at 1 hour, 3 hours, 1 day, 3 days, and 7 days after treatment. We compared groups with Fisher exact and two-sided rank-sum tests.

RESULTS: The placebo (n=14) and ketamine (n=15) groups did not differ in demographic and clinical characteristics. There were no significant intergroup differences in BYI and SIQ scores at any time points after treatment. Adverse effects were more frequent in the ketamine group, most notably dissociation (7% vs 60%, p=0.004), with none after the 1-hour observation period.

CONCLUSIONS: The ED is an opportunity to provide rapid-acting antidepressant treatment for youth in mental health crisis. Although SI and depression did not significantly differ among groups, patients had reduction in overall SI and depression/anxiety scores over time. Further studies may determine a more effective dosing and route of ketamine for adolescents with SI in the ED.
Parental Perspectives of a SMS-based telemedicine asthma specialist care program following an emergency department visit

**Pade K, Ravandi B, Delgado R, Ramires-Sanchez E, Hall KM, Hall JE, Chang TP, Okelo SO**

**BACKGROUND:** Telemedicine video is increasingly used in ambulatory settings to improve access to pediatric specialist care. However, post-emergency department (ED) visits to primary care providers (PCPs) remains low among asthma patients. Short Message Service (SMS) text messaging is used ubiquitously but is an under-studied means of patient engagement following an asthma-related ED visit. The acceptability and appropriateness of a post-ED visit SMS text message-based asynchronous telemedicine asthma specialist care (ATM-ASC) program is unknown.

**METHODS:** This is a secondary analysis of data collected June, 2022 – May, 2023 in a randomized clinical trial of post-discharge telemedicine specialist care for children who presented to the emergency department for asthma care. SMS text message-based store-and-forward telemedicine care involved: 1) asthma severity assessment every 3 weeks; 2) automated treatment plans based on adherence to controller medicines and asthma severity; and 3) asthma specialist prescribing of controller medications (intervention only). We examined a variety of parent-centered outcomes regarding telemedicine asthma care and associated patient sociodemographic and clinical factors.

**RESULTS:** There were 145 participants (control = 68; intervention = 77), most of whom were male, Hispanic and on public insurance, without significant sociodemographic or clinical differences between treatment groups. There was significant asthma morbidity reported in the year prior to study enrollment: 84% reported one or more asthma exacerbations, while 64% reported two or more. Despite this, only 28% of all patients reported controller medication use and 19% reported prior asthma specialist care. At 3 months post-enrollment, nearly all parents (intervention and control) reported that telemedicine asthma care: was useful (93%), saved time (84%), was easy to use (96%), was simple to use (96%), met their needs (87.5%) and found it effortless (88.5%). On a 7-point Likert scale, the average satisfaction score for all families was 6.4.

**CONCLUSIONS:** SMS-based store-and-forward telemedicine asthma specialist visits are a strongly endorsed care model by parents of low socioeconomic and racial-ethnic minority children with uncontrolled asthma after an emergency department visit. The long-term benefits of this care model on improving clinical outcomes and in other patient populations are unknown.

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Analysis of Continuous Albuterol Dosing and its Effect on Nausea and Vomiting in the Pediatric Emergency Department

**Michael Gardiner, MD; Elise Zimmerman, MD; Brianna Irons, Jonathan Hermel, MD; Amy Bryl, MD; Kathy Hollenbach, Ph.D.**

**BACKGROUND:** Albuterol is a mainstay of treatment for children with acute asthma. Severe acute asthma is often treated in the pediatric emergency department (ED) with continuously nebulized albuterol. While albuterol is generally well tolerated, it has several known adverse effects including nausea/vomiting. The relationship between continuous albuterol dose and nausea/vomiting has not been well established.

**METHODS:** We performed a retrospective cohort analysis of ED patients treated between 7/2019 and 4/2021. We included patients <18 years of age treated with continuous albuterol. We excluded patients who were given ondansetron before albuterol, were immunosuppressed, or had cardiopulmonary disease other than asthma. We compared subjects who were given ondansetron in the ED to those who were not. We evaluated albuterol dosing, demographics, vital signs, Pediatric Asthma Score (PAS), other medications, hospital and ICU admission, and ED return visit within 72 hours.

**RESULTS:** Continuous albuterol was administered in 1944 encounters during the study period. 230 were excluded, resulting in 1714 encounters among 1416 subjects. Of these subjects 141 received ondansetron (8.2%, 95% CI 7.0 – 9.6). Subjects receiving ondansetron had lower oxygen saturation and higher maximum PAS; other demographics and vital signs were similar. Subjects given ondansetron received a higher initial dose of albuterol (p = 0.013). Among patients less than 40kg, those treated initially with 20mg/hr had a significantly higher rate of nausea/vomiting compared to those treated with 10mg/hr (9.2% vs. 4.0%, NNTH 19.2). Outcome measures were similar between groups.

**CONCLUSIONS:** Among 1714 ED encounters treated with continuous albuterol, subjects who were given ondansetron had higher PAS scores and lower oxygen saturation, indicating more severe illness. Among children weighing less than 40kg, those treated with 20mg/hr of albuterol had more frequent nausea/vomiting without differences in outcomes. Prospective study is needed to determine optimal treatment doses for these smaller patients.
**ABSTRACTS**

**Improving glycemic outcomes for children and adolescents with type 1 diabetes: A T1DX-QI Success Story.**

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**BACKGROUND:** Clinical outcomes continue to be less than ideal for children and adolescents with type 1 diabetes (T1D). Participation in learning collaboratives can support clinic-clinic benchmarking, improvement projects and use of the real world for system level changes. Targeted quality improvement (QI) projects can have a positive impact on glycemic outcomes. We aim to examine the impact of a single US center participation in a national T1D QI learning collaborative (T1DX-QI) on improving glycemic outcomes. Furthermore, we analyzed the changes in diabetes technology use.

**METHODS:** We evaluated glycemic outcomes and diabetes technology use from the single center prior and four years after joining T1DX-QI when robust QI projects were implemented to improve CGM and insulin pump access, increase diabetes clinic visit frequency, and to use care navigation outreach for at-risk patients. We included all patients with available data (n=1,450) aged 2 to 18 years with T1D diagnosed for at least 12 months. We compared data from 2018-2020 to 2021-2023 including mean HbA1c, diabetes technology use and the proportion of patients with an HbA1c<7% or >9%.

**RESULTS:** Baseline data showed mean age of 12.6 +/- 3.8 years, male sex was 53.9 %, 45.5 % had public insurance. In the four years after joining the network, CGM use increased from 59.7 % to 90.8 % (p<0.001), insulin pump from 29.1 % to 50.3 % (p<0.001), and mean HbA1c decreased from 8.7+/- 2% to 8.1+/- 1.9 % (p<0.001). There was an 11.3 % increase in the percentage of patient who achieved HbA1c<7% (p<0.001) and a 9 % decrease in the percentage with HbA1c>9% (p<0.001).

**CONCLUSIONS:** Adopting improvement science and sharing best practices like the T1DX-QI Collaborative can contribute to increased diabetes technology use and to improvement in glycemic outcomes.

**Experience with Gender Affirming Hormones and Puberty Blockers: A Qualitative Analysis of Sexual Function**

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**BACKGROUND:** Gender affirming hormone therapy (GAHT) is part of the transition for many transgender and nonbinary (TGNB) individuals. Additionally, it has become increasingly more common for TGNB youth to receive puberty blockers (GnRH agonist) to halt the pubertal progression. There have been few studies investigating sexual function and desire either during or after puberty blockers (PB) and/or GAHT. Our aim was to qualitatively evaluate the sexual experience of TGNB individuals during or following PB and/or GAHT, and outline any potential differences between the two groups.

**METHODS:** We performed an IRB approved two institutional study on the effect of PB and/or GAHT on sexual function and desire. The GAHT group (n=16): individuals who started GAHT (estrogen or testosterone) &gt;18 years. The PB+GAHT group (n=10): subjects with current or past GnRH agonist use +GAHT. All 26 enrolled subjects were interviewed using an open-ended topical guide. Qualitative analysis was performed by hand coding the interview transcripts using Constructivist Grounded Theory qualitative methods.

**RESULTS:** A total of 26 TGNB (20 assigned male at birth, 6 assigned female at birth: 18 transgender women, 5 transgender men, 3 non-binary) subjects ages 18-25y were interviewed about the effect of PB and/or GAHT on their sexual function and desire. Our analysis uncovered several themes that were consistent between groups (Table 1).

**CONCLUSIONS:** Themes were similar for both groups. Half the participants in each group reported feeling no regrets regarding hormone therapy, and the other half reported that they wished they had started hormones sooner. Two notable differences were identified between groups: those on PB+GAHT reported “less dysphoria” as a positive change in sexual desire, and the GAHT group reported more enjoyable sexual experiences since being on hormones. Interestingly, results did not reveal any significant differences between groups. The most prominent theme that arose in both groups was that the positive changes in sexual function and desire outweighed any negative changes that arose.
**Modelling T1D using syngeneic islet organoids and immune cells.**

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**BACKGROUND:** Type 1 diabetes (T1D) is an autoimmune disease thought to be caused by immune-mediated destruction of the insulin-producing β-cells in the pancreatic islets. Genetic evidence, including strong linkage to several MHC class II alleles, suggests that aberrant immune cell activity and increased β-cell sensitivity to stimulus-induced damage both contribute to T1D pathogenesis. Studying the mechanisms that underlie β-cell destruction in humans with T1D has been challenging because most of the key immunological events occur before diagnosis. Furthermore, while rodent models have been informative in defining some aspects of T1D etiology, there are fundamental differences between the rodent and human both in the pancreas with respect to islet architecture and vasculature, and with the immune system. Moreover, important aspects of human T1D pathology are not replicated in rodents. For example, massive insulitis is rarely detected in humans but is a common feature in the NOD mouse model of T1D. This observation has raised the question of whether immune cells play a lesser role in β-cell death in humans than in rodents. Thus, to fully understand human T1D pathophysiology, it is critical to develop new human models, where the interactions of all cells involved in the disease process can be studied in the context of normal islet architecture, vasculature, and extracellular matrix. Here, we report the establishment of an islet organoid model comprised of human pluripotent stem cell (hPSC) and human primary monocytes (Mo).

**METHODS:** First, we defined the media conditions for co-culturing human monocytes (Mo) with SC-islets. To obtain a highly pure Mo population, we used a group of markers, including CD11b, CD14, and MHC class II to isolate non-differentiated Mo from peripheral blood. A population of up to 95% purity was used to set up the co-culture with SC-islets. We next examined whether co-cultured Mo improve insulin secretion of SC-islets by degrading crinosomes and relieving stress from SC-β-cells and present immunogenic peptides to CD4+ T cells.

**RESULTS:** Performing dynamic GSIS on co-cultured SC-islets, we observed a strong reduction of insulin secretion and production in the presence of Mo and/or IFN-gamma. As Mo could function as an antigen presenting cells, we tested whether the SC-islet and Mo can express MHC class II in the co-culture. Consistent with the GSIS results, IFN-gamma induced the expression of MHC class II in insulin-negative cells. The presence of Mo did not affect MHC class II expression in co-cultured SC-islets. Further studies are needed to understand the identity of MHC class II expressing cells in SC-islets and their ability to present antigen to CD4+ T cells.

**CONCLUSIONS:** In this context, the new SC-islet organoids platform developed here provide a new in vitro model of human T1D that will aid in our understanding of the underlying basic mechanisms that drive T1D pathogenesis.

**Establishing a disease model for MODY1 using stem-cell derived pancreatic beta cells**

Winnie Gong, Kim-Vy Nguyen-Ngoc, Vivian Lin, Yesl Jun, Maike Sander

**BACKGROUND:** Maturity onset diabetes of the young type 1 (MODY1) is a form of monogenic diabetes clinically characterized by transient hyperinsulinemic hypoglycemia. Though MODY1 is known to be caused by a point mutation in the hepatocyte nuclear factor 4 alpha (HNF4a) gene, the disease mechanism behind MODY1 onset is not well-researched.

**METHODS:** In this study, CRISPR/Cas9-generated human embryonic stem cell-derived pancreatic beta cells carrying the R141X mutation in the HNF4a gene (HNFa R141X SC-islets) are successfully developed and used to study the biological mechanism behind MODY1 onset.

**RESULTS:** Consistent with the presentation of MODY1 in humans, our HNF4a R141X SC-islets demonstrate transient hyperinsulinemic hypoglycemia under glucose-stimulated insulin secretion. Notably, our HNF4a R141X SC-islets also show ~5% increased susceptibility to stress and undergo ~10% increased beta cell apoptosis. These effects can both be rescued back to baseline levels by treatment with alpha-1-antitrypsin, a well-researched anti-inflammatory agent within the context of chronic obstructive pulmonary disease.

**CONCLUSIONS:** In conclusion, this study offers the HNF4a R141X SC-islets as a controlled in vitro model to investigate biological mechanisms driving MODY1 onset and identifies beta cell apoptosis as one such mechanism. Given its potential for beta cell rescue, alpha-1-antitrypsin could be considered a target for the development of therapies to prevent or reverse beta cell death in MODY1.
Accelerating Colon Cancer Discovery with a Novel Vision-AI Approach
Mahdi Behroozikhah, Soni Khandelwal, Amitash Nanda, Atishna Samantaray, Arya Prabhudesai, Dharanidhar Dong, Debashis Sahoo

BACKGROUND: Colorectal cancer (CRC), also known as colon cancer, is the second most common cancer diagnosed in men and women annually in the United States. CDX2 is a crucial biomarker for colorectal cancer, and a thorough understanding of its expression pattern within the colon crypts is a significant factor in refining the diagnostic procedures and therapeutics for the disease. We have adopted a new staining process, demonstrating the differential expression of CDX2 in colon crypts. We performed a series of experiments throughout the investigation to validate the proposed hypothesis. We introduced an original work for gland instance segmentation using the novel mask-RCNN, which reveals a new gene expression pattern on the glandular epithelium cells.

METHODS: We used available microarray and RNA-Seq datasets in the NCBI Gene Expression Omnibus (GEO) database. The BooleanNet algorithm proposed by Sahoo et al. (2008) was used to find the Boolean relationship between ALCAM and CDX2 expression in the bulk tissue dataset. A novel method was proposed for the antigen retrieval part of the overall staining procedure. The proposed boiling method shows a differential expression of the CDX2 gene along the top and bottom of the crypt. We stained different slides and normal crypt regions were extracted and resized. Datasets were prepared using Reinhard normalization and divided into train, valid, and test sets. Gland segmentation was performed using the mask R-CNN and deployed models such as Resnet50-UNet, Resnet50-segnet, resnet101, FCN-8, FCN-32. Resnet50+FPN gave superior performance. We also used Yolo-based models to perform image segmentation. This led to an improvement of 10% in the IU score for U-crypt detection. Color variation detection analysis was performed on the crypts to justify the pattern.

RESULTS: We stained normal colon crypts obtained from 5 patient samples using CDX2, and surprisingly, we were able to capture this difference using IHC with this modified protocol. Our CDX2 staining result shows that the top of the crypt is enriched with brown stain, i.e., CDX2 high, whereas the bottom is enriched with blue stain, i.e., CDX2 low cells. As we increase time in the boiling protocol, the top and bottom of the crypt get the same staining and the same pattern as that of pressure cooking. These data suggest that CDX2 is differentially expressed in the colon crypt from top to bottom.

CONCLUSIONS: We have developed a computational approach and a new IHC method to show the differential expression of CDX2 along the colon crypts. An invariant Boolean relationship was found between CDX2 and ALCAM. CDX2 was identified as the earliest biomarker associated with cancer. The study introduces a novel deep-learning approach for epithelial gland segmentation in normal colon tissue. We have developed a new algorithm that integrates deep learning with the Boolean analysis framework to create a mathematical model of the human colon tissue. Our framework will improve the efficiency and accuracy of determining the appropriate treatment for the patient's diagnosis.
Lower rates of breastfeeding in mothers treated with chronically used anti-inflammatory medications
Essi Whaites Heinonen, Alec Todd, Diana L Johnson, Christina Chambers

BACKGROUND: Breastmilk is the recommended nutrition for first 6 months of life. Mothers requiring chronic medications may be advised or choose not to breastfeed due to lack of safety data. We aimed to determine if mothers treated with chronically used medications are less likely to follow breastfeeding recommendations than untreated mothers.

METHODS: Pregnant women from the US and Canada were enrolled in a prospective cohort study conducted by MotherToBaby between 2010 and 2022. Those with medications with potential to harm a breastfed infant were excluded. Exposure groups were defined as use of 1) selective serotonin reuptake inhibitors (SSRIs); 2) anti-inflammatory drugs; 3) asthma drugs and 4) no use of chronic medications at delivery. Outcomes were not breastfeeding and stopping breastfeeding before 6 months. The risk of not breastfeeding was compared between the medication groups and the unexposed with modified Poisson regression and the hazard of stopping before 6 months with Cox regression, adjusted for year enrolled, parity, SES, BMI, race and ethnicity.

RESULTS: The sample consisted of 293 SSRI exposed, 799 anti-inflammatory exposed, 217 asthma drug exposed and 4,439 unexposed. Rates of not breastfeeding were 3.1% in the SSRI group, 13.0% in the anti-inflammatory group, 5.5% in the asthma group and 3.0% in the unexposed. Mothers taking anti-inflammatory drugs were significantly more likely to not breastfeed (adjusted risk ratio 4.05; 95% confidence interval [CI] 3.12-5.26) and to stop breastfeeding before 6 months (adjusted hazard ratio 1.75; CI 1.30-2.35). Point estimates for other comparisons were also elevated but the CIs included 1.

CONCLUSIONS: Women treated with anti-inflammatory drugs were more likely to not breastfeed and to stop breastfeeding before 6 months than unexposed. Many therapeutics for chronic inflammatory diseases have been approved without adequate safety data in lactation. Timely development of safety data is needed to support clinical decision-making on breastfeeding.

The Impact of Maternal Mental Health on Human Milk Oligosaccharide Composition
Hannah Riedy BA, Kerri Bertrand MPH, Christina Chambers PhD, MPH, Gretchen Bandoli PhD, MPH, MBA

BACKGROUND: Human milk oligosaccharides (HMOs) are a set of diverse carbohydrates abundant in human breast milk. They provide numerous health benefits to infants, such as helping form the gut microbiome and altering immune responses. There are over 200 types of HMOs, and HMO composition varies significantly among women. Though prior studies have identified factors contributing to this variation, no groups have evaluated the potential impact of maternal psychological health on HMOs.

METHODS: Data originated from the UC San Diego Human Milk Biorepository. HMO profiles consisting of 19 prevalent HMOs were assayed in 926 samples. Maternal depression (Edinburgh Postnatal Depression Scale, EPDS), anxiety (State Trait Anxiety Inventory, STAI), and stress (Perceived Stress Scale, PSS) were assessed by self-reported measures. HMOs were assessed individually and summarized by principal component analysis (PCA), each of which was stratified by Secretor status. Associations between each HMO or principal component and maternal psychological state were analyzed using multivariable linear regression adjusted for maternal and infant age, infant sex, race, and exclusive breastfeeding.

RESULTS: The analytic sample consisted of those who completed the EPDS (n=562), STAI (n=567), and/or PSS (n=561). Of those with complete HMO profiles and psychological scales, 60 (10.7%) had elevated depression, 76 (13.4%) had elevated anxiety, and 134 (23.9%) had elevated stress. After adjusting for multiple comparisons, the following HMOs were significant: LNFP III and LNH for Secretors with depression, DFLac and LNFP III for Secretors with stress, and 3FL, DFLNT, and DFLNH for non-Secretors with stress. No HMOs significantly varied by anxiety. In PCA, depression, anxiety, and stress were negatively associated with one to two components among Secretors, while only stress was negatively associated with a component among non-Secretors.

CONCLUSIONS: The concentrations of several HMOs varied with maternal psychological state. Additional studies are needed to understand whether this variation affects infant health.
Medications for nausea and vomiting of pregnancy: a prospective cohort study assessing the risk for preterm birth, small for gestational age and neonatal intensive care unit admissions
Laure Sillis, Essi Whaites Heinonen, Diana Johnson, Yunjun Luo, Veerle Foulon, Michael Ceulemans and Christina D Chambers

BACKGROUND: Nausea and Vomiting of Pregnancy (NVP) affects up to 80% of pregnant women. However, there is a considerable uncertainty surrounding the safety and efficacy of various NVP treatments.

METHODS: This study included live born singletons whose mothers participated in the MotherToBaby pregnancy studies between July 29, 2010, and April 9, 2021. Participants completed the Pregnancy-Unique Quantification of Emesis and Nausea questionnaire or provided general information about their NVP symptoms during the first trimester. The risks of preterm birth (PTB), the infant being small for gestational age (SGA) and neonatal intensive care unit (NICU) admissions were compared between women who were exposed to NVP medication, women with untreated NVP and women without NVP.

RESULTS: Data were analyzed from 603 women exposed to NVP treatment, 1568 women with untreated NVP, and 541 women without NVP. The rate of PTB did not significantly differ between pregnancies exposed to NVP medication (8.6%), pregnancies of women with untreated NVP (7.2%) and pregnancies of women without NVP (8.0%). Similarly, the rates of infants being SGA were 8.8%, 7.1%, and 7.2%, respectively, with no significant differences observed. All three groups had similar rates of NICU admissions, 11.0%, 10.4%, and 11.0%, respectively. The adjusted risk ratio for PTB among pregnancies exposed to NVP medication compared to the untreated NVP group was 1.20 (95% CI [confidence interval] 0.87-1.64) and 1.10 (95% CI 0.75-1.60) compared to the group without NVP. For SGA, the adjusted risk ratio was 1.28 (95% CI 0.93-1.77) compared to the untreated NVP group and 1.38 (95% CI 0.91-2.10) compared to the group without NVP. The adjusted risk ratios for NICU admissions were 1.07 (95% CI 0.82-1.40) and 1.06 (95% CI 0.75-1.48).

CONCLUSIONS: Our findings suggest that exposure to NVP treatment during pregnancy neither increases the risk of PTB nor the likelihood of the infant being SGA or requiring NICU admission.

Maternal exposure to social risk factors and adverse infant outcomes
Lucia Ferrer, BA; Christina Chambers, PhD, MPH; Annie Nguyen, PhD, MPH; Anup Katheria, MD; Gretchen Bandoli, PhD, MPH, MBA

BACKGROUND: Strong evidence exists demonstrating the association between social determinants of health and infant morbidity and mortality, though these data do not support conclusions about causality. We aimed to characterize the prevalence of prenatal ICD social code documentation, and to examine the association between maternal exposure to social risk factors and adverse infant outcomes.

METHODS: We conducted a retrospective cohort study of live-born births between 22 and 44 weeks’ gestation in California between 2007 and 2020. Maternal and neonatal data were collected from California Vital Statistics and hospital discharge records and linked. Maternal diagnosis of homelessness, inadequate housing, food insecurity, and unemployment were classified based on the presence of ICD social codes. Infant outcomes included preterm birth, low birthweight, small for gestational age, NICU admission, emergency department admission, rehospitalization and death. We estimated risk ratios using Poisson regression adjusted for maternal race, payer, and education.

RESULTS: 6,089,327 mother-infant pairs were included in analyses, 4,002 (65.7 per 100,000 live births) of whom had a documented health-related social need (HRSN). Infants with a maternal HRSN had a higher risk of prematurity (aRR 2.7, 95% CI 2.5, 2.9), low birthweight (aRR 2.7, 95% CI 2.5, 2.9), small for gestational age (aRR 1.5, 95% CI 1.4, 1.6), NICU admission (aRR 3.5, 95% CI 3.2, 3.8), and infant death (aRR 3.0, 95% CI 2.5, 5.9).

CONCLUSIONS: Social risk factor screening is poorly documented in hospital records and likely underestimates the true prevalence of HRSNs. Among those for whom documentation exists, infants with a maternal HRSN are at a significantly increased risk of morbidity and mortality.
Examining the Impact of Asthma, Monoclonal Antibody, and Selective Serotonin Reuptake Inhibitor Prescription Medications on Maternal Mental Health: A Focus on Depression, Anxiety, and Stress Screening Scores during Lactation

Kerri Bertrand, Alec Todd, and Christina Chambers

BACKGROUND: The use of prescription medications is a common concern for lactating individuals, particularly when they are necessary to manage chronic conditions. A recent study reported increased mental health diagnoses following the initiation of montelukast (Singulair) treatment. Data are sparse on how prescription drug therapies may be associated with an increase in adverse neuropsychiatric outcomes.[1] This study aimed to assess whether lactating individuals exposed to asthma medication, monoclonal antibodies (mAb), or selective serotonin reuptake inhibitors (SSRI) had higher scores on the Edinburgh Postnatal Depression Scale (EPDS), the state-trait anxiety inventory (STAI) or the perceived stress scale (PSS-10) compared to those without prescription medication exposure.

METHODS: Between August 2014 and January 2024, 3,423 lactating individuals from the U.S. and Canada were enrolled into Mommy’s Milk, a human milk research biorepository at the University of California, San Diego. Participants provided consent, completed a telephone interview about demographics, health history and medication and lifestyle exposures, and completed the EPDS, STAI and PSS-10 screening assessments online following their interview. Of those enrolled who completed the screening assessments, 24 women reported exposure to an asthma medication; 97 women reported exposure to a monoclonal antibody (mAb); 322 women reported exposure to a selective serotonin reuptake inhibitor (SSRI); and 1208 women reported no prescription medications. All exposures were mutually exclusive. Logistic regression compared critical scores (yes/no) on each assessment between exposed and unexposed groups, adjusting for maternal race, ethnicity, age and infant age. Statistical analyses were conducted using R.

RESULTS: The SSRI exposed group was 2.12 times more likely to have a high EPDS score and/or a positive suicidal ideation than the unexposed group (p=2.03e-6); 2.61 times more likely to have a high stress score than the unexposed group (p=8.29e-16). The mAbs exposed group had higher percentages of critical scores on all three assessments but they were not clinically significant.

CONCLUSIONS: SSRI exposure correlated with elevated mental health risks which is expected given the indications for these medications, monoclonal antibodies exhibited a protective effect, potentially indicating improved symptom management. The impact of asthma medication on maternal mental health remains unclear with non-clinically significant findings. More studies are needed.
Salma Iraqi, Dr. Shira Goldenberg, Dr. Hector Lemus, and Dr. Gretchen Bandoli

BACKGROUND: Although many have described better birth outcomes among foreign-born Latinas compared to US born women, few have assessed heterogeneity in risk by region of origin. We examined pregnancy and birth outcomes among individuals born in Latin American and the Caribbean (LAC-born) by region of origin and compared outcomes to individuals born in the US (US-born). Additionally, we investigated the role of social determinants of health as mediators.

METHODS: We used a retrospective cohort from the Study of Outcomes in Mothers and Infants (SOMI) compiled from California births between 2007 and 2020. We examined preeclampsia, gestational diabetes, preterm birth, and small for gestational age (SGA) as outcomes. We used logistic regression to calculate unadjusted and age-adjusted odds ratios for LAC-born nativity and region of origin compared to US-born individuals. Mediation analysis was performed to evaluate social determinants of health as mediators.

RESULTS: The odds of gestational diabetes were 1.6 (95% CI: 1.6-1.6) and 1.3 (95% CI: 1.3-1.3) times higher among those born in Mexico and Central America compared to US-born. Education mediated 23.5% and 18.8% of the observed associations. The odds of preterm birth were 1.2 (95% CI: 1.1-1.3) times higher among those born in the Caribbean, of which 19% was mediated by education. Lastly, SGA was positively associated with the Caribbean and Central America; health insurance mediated approximately 10% and 33% of the association.

CONCLUSIONS: There is heterogeneity in adverse pregnancy and birth outcomes among those born in LAC by region of origin. Among regions with an increased risk of adverse pregnancy and birth outcomes, education and health insurance should be further evaluated as intervention targets.
Surface Krt20+ Cells Regenerate Crypts Following DSS Colitis

Marie Gomez, Cambrian Liu, Nandini Girish, D. Brent Polk

BACKGROUND: Inflammatory bowel disease (IBD) is estimated to affect 3.1 million people in the U.S. IBD, which includes Crohn’s disease and ulcerative colitis, is characterized by repetitive cycles of injury and healing in the gastrointestinal tract. Although are treatments available to help suppress inflammation, there is a need for new therapies that directly target epithelial wound repair to enable mucosal healing and improve patient outcomes. However, little is known about the cellular origins of epithelial wound repair and their dynamic response to injury in the colon. Chemical injury induced by dextran sulfate sodium (DSS) leads to the loss of Lgr5+ cells, which act as stem cells under homeostatic conditions. It has been shown that in the absence of Lgr5+ cells, Lgr5-negative cells can contribute to the repopulation of crypts upon injury. Although several Lgr5-negative cells have been identified in the small intestine, it is not clear what cells contribute to regeneration in the colon.

METHODS: We have previously identified the emergence of a population of progenitor cells during wound repair, in which various epithelial cells throughout the depth of the injured mucosa can rapidly proliferate and regenerate crypts, including terminally differentiated Krt20+ cells. Using genetic lineage tracing studies in Krt20CreER::mTmG mice, we assessed the level of contribution from a population of surface Krt20+ cells during epithelial regeneration following acute injury. We also used organoid-formation assays to test whether organoids could be generated from Krt20CreER::mTmG mice to model reversion in vitro.

RESULTS: Under homeostatic conditions, labeled Krt20+ cells were observed after 2 days and these Krt20+ cells were then shed following normal turnover of the epithelium. However, following DSS injury, labeled Krt20+ cells repopulated crypts observed on day 35. This suggests that Krt20+ cells can de-differentiate and contribute to crypt recovery upon injury. Cells from Krt20CreER::mTmG mice treated with 4-hydroxytamoxifen contributed to organoid growth, budding, and maintained a long-term GFP signal, demonstrating that terminally differentiated Krt20+ cells are proliferative in culture.

CONCLUSIONS: We have shown that surface Krt20+ cells contribute to long-term labeling of repair epithelium and can proliferate in culture. These studies will help provide further insight into the cellular plasticity of the colonic epithelium during repair.
### SPINAL INVOLVEMENT IN CHARGE SYNDROME IMPLICATIONS FOR MANAGEMENT

**Adriana Gomes, Lynne Bird**

**BACKGROUND:** CHARGE syndrome (OMIM #214800) is an autosomal dominant disorder characterized by ocular coloboma, heart defects, atresia of the choanae, restriction of growth, genital hypoplasia, and ear malformations. Spinal anomalies have been reported occasionally in previous studies. In 2006, Blake et al. reported eleven out of 50 patients (22%) with CHARGE syndrome had hemivertebrae or scoliosis, and Jongmans et al. found scoliosis in six out of the 47 patients (13%), kyphosis in one, and abnormalities of the vertebral bodies in three (6%). In 2012, Tatten investigated the role of Chd7 in zebrafish by reducing Chd7 expression. They demonstrated that Chd7 is critical in primary axis development and vertebral mineralization. Chemical staining of the vertebrae revealed that the spine of Chd7-knockdown zebrafish had multiple skeletal anomalies, including smaller, irregular vertebral segments, wider intervertebral disc space, and smaller neural and hemal spines. The pedicles of the neural spines were, in some cases, missing or fused. Additionally, in some cases, a reduction in vertebral mineralization was noted.

**METHODS:** We reviewed the medical records of 41 individuals with CHARGE syndrome and gathered data regarding spinal anomalies. We described the spectrum of spinal anomalies and their clinical relevance.

**RESULTS:** We found 10 cases (24%) of spinal abnormalities, including incomplete segmentation of vertebral bodies and hemivertebrae, narrowing of inter-disk space, and spinal fusion defects. Incomplete bone mineralization and osteopenia were also seen in 10% of our cohort. We also found 2 cases of Os odontoideum, which can cause atlantoaxial instability and compression of the spinal cord, requiring a surgical approach.

**CONCLUSIONS:** Imaging is often required in CHARGE syndrome to evaluate the internal auditory canals; including the spine in this imaging can provide valuable information and guide management. The clinical impact of the spinal anomalies depends on factors such as degree of segmentation and concurrence with other structural abnormalities. Further evaluation of bone density should also be considered.

### A DIAGNOSTIC ODDESY OF TWO SIBLINGS WITH A NEURODEVELOPMENTAL DISORDER

**Kanika Parashar MBBS, Kristen Wigby MD**

**BACKGROUND:** Neurodevelopmental disorders (NDDs) are frequently seen in primary care pediatrics. Identifying the underlying genetic cause can improve prognosis, guide clinical management, and direct patients to tailored resources. Therefore, pursuing genetic testing is critical for accurate diagnosis and treatment.

**METHODS:** In this case review, we discuss two siblings who were referred to the Precision Medicine Clinic due to their unique facial features, including a long face, downward slant to palpebral fissures, wide mouth with gum hypertrophy, ears with prominent antihelices, and hypotonia. They also had speech apraxia and a low Body Mass Index. Since both siblings shared the same phenotype, we suspected that there was an underlying genetic etiology, possibly familial in nature. However, their initial testing, including Chromosomal oligo SNP (single nucleotide polymorphism) Microarray, Fragile X testing, and Metabolic evaluation, came back negative. Additionally, both siblings did not have any hearing loss, and the family history was insignificant.

**RESULTS:** Whole exome sequencing was proposed in the past but was denied by insurance. The result of Trio Whole Genome sequencing in the brother's sample showed one paternally inherited SNV (single nucleotide variant) in EMC10 gene, which was classified as a pathogenic variant, and a maternally inherited 35Kb deletion in Chr 19, which encompassed the EMC10 gene. The same results were obtained on Custom variant analysis by Sanger sequencing in the sister's sample.

Pathogenic variation in EMC10 gene is associated with autosomal recessive disorder: Neurodevelopmental disorder with dysmorphic features and variable seizures (NEDDFAS). This is an ultra-rare genetic condition with limited information for natural history of condition. After diagnosis, renal ultrasound for sister revealed mild-moderate unilateral pelivectasis, now being followed by nephrology.

**CONCLUSIONS:** This case review demonstrates the diagnostic impact of a genome-wide sequencing approach in identifying molecular etiology of NDDs
Microglial dysfunction contributes to cerebellar neurodegeneration in Friedreich's ataxia.

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BACKGROUND: Friedreich's ataxia (FRDA) is the most common inherited ataxia with an incidence of approximately 1 in every 40,000 individuals. This genetic disorder is caused by an abnormal GAA trinucleotide repeat expansion within the Frataxin (FXN) gene, leading to stalled transcription and thus severe reduction in FXN protein expression. FXN is a mitochondrial protein involved in iron-sulfur cluster biogenesis and iron homeostasis; its deficiency leads to a broad clinical phenotype including muscle weakness, ataxia, cerebellar perturbation, sensory loss, cognitive decline, and cardiomyopathy. Disease onset is between 5 to 15 years of age and within 10-15 years of symptom onset, patients are wheelchair-bound with no targeted treatment or cure currently available. The identification of new therapeutic targets may rely on an enhanced understanding of the cellular mechanisms by which FXN causes mitochondrial and cellular dysfunction in FRDA, as well as the cell type-specific contributions to neurodegeneration.

METHODS: Thus, we have generated induced pluripotent stem cells (iPSCs) from patients with FRDA, carriers and healthy controls, and differentiated them into microglia to query the microglial contribution to FRDA neuropathology. A potential therapeutic approach for FRDA involves autologous bone marrow transplant after dual-guide CRISPR mediated gene therapy to excise the GAA repeat expansion. Whether this approach ameliorates the neurodegenerative disease progression depends on the contribution of immune cells such as microglia to FRDA neuropathology. We therefore applied the dual-guide CRISPR approach to generate GAA repeat expansion corrected iPSCs and subsequently microglia.

RESULTS: Utilizing these unique approaches, we identified an altered transcriptomic signature and marked mitochondrial dysfunction in FRDA microglia. We found stark defects in the signaling between mitochondria and the endoplasmic reticulum in vitro, leading to attenuated Ca2+ activity in FRDA microglia. Of note, CRISPR correction appeared to rescue the microglial phenotype and improve mitochondrial efficiency. We then queried whether FRDA diseased microglia were sufficient to cause neuronal injury in healthy neurons and if so, by what mechanism. We co-cultured iPSC-derived microglia and healthy neurons and found that FRDA microglia interfere with neuronal activity and neuronal survival in vitro, a phenotype corrected with microglial CRISPR-mediated gene editing. Finally, we extended these findings to a murine xenotransplantation model wherein iPSC-derived microglial progenitors are transplanted into neonatal humanized mice genetically depleted for endogenous murine microglia. Intriguingly, xenotransplanted FRDA microglia perturbed the development and refinement of the cerebellar circuit, both the excitatory and inhibitory components, eventually leading to altered cerebellar Purkinje neuronal survival and Ca2+ homeostasis in vivo.

CONCLUSIONS: Altogether, these findings identify a critical role for microglia in the pathogenesis of neurodegeneration in FRDA and the potential for dual-guide gene editing to ameliorate this microglial-specific phenotype.
ABSTRACTS
Genetics (cont.)

Transplantation of wild-type hematopoietic stem and progenitor cells ameliorates disease locomotor dysfunction and organomegaly in a novel Sanfilippo Type C mouse model
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BACKGROUND: Mucopolysaccharidosis type IIIC (MPSIIIC) is a severe neurodegenerative lysosomal storage disease (LSD) caused by loss-of-function of the lysosomal transmembrane protein Heparan-α-glucosamine N-acetyltransferase (HGSNAT). MPSIIIC has no available treatment and is characterised by accumulation of glycosaminoglycans (GAGs) and presents with developmental delay and neuronal cell loss. Our lab has shown that transplantation of hematopoietic stem cells (HSPCs) rescue cystinosis, another LSD due to mutations in a transmembrane lysosomal protein. The mechanism of rescue involved lysosomal cross-correction from HSPC-derived macrophages to the disease cells via tunnelling nanotubes. We believe that the same principles could be used to treat MPSIIIC. We previously demonstrated that transplantation of syngeneic wild-type (WT) hematopoietic stem cell and progenitor cells (HSPC) could rescue cystinosis, another LSD also caused by loss of function of a transmembrane lysosomal protein14–17. We found that a major rescue mechanism involved lysosomal cross-correction from HSPC-derived macrophages to the disease cell via tunneling nanotubes18–20. We have also previously demonstrated that HSPC transplantation leads to long-term rescue in both a mouse model of Friedreich’s ataxia, a neurodegenerative disease, and in the 5xFAD Alzheimer’s disease mouse model (References). In both of these HSPCs engrafted and differentiated into microglia in the brain which led to the preservation of neuron, locomotor and neurological function as well as reduction of the AB plaque. Furthermore, we also previously shown that apart from neurological dysfunction HSPC transplantsations can also treat defects in multiple organs including the eye, muscle, heart, thyroid and spinal cord in cystinosis and Friedreich’s ataxia21,20,15. We believe that the same principle could be used to treat MPS IIIC as it also a multisystemic neurodegenerative lysosomal storage disease cause by mutation in a lysosomal transmembrane protein like cytosines with multiple organs affect like cystinosis and Friedreich’s ataxia. We aim to test the therapeutic efficacy of WT HSPC transplant in a new MPS IIIC mouse model we generated.

METHODS: HSPCs were isolated from bone marrow of WT GFP transgenic mice and transplanted into lethally irradiated MPS IIIC mice. Engraftment was assessed via flow cytometry. Behavioral tests included open field and Catwalk gait analyses. Tissue collection post-sacrifice involved measuring urine volume, organ weights, and histopathological analyses. Immunofluorescence staining assessed tissue engraftment. GAG and protein analyses utilized specific assays, while Western blotting examined LAMP1 expression. RNA extraction and real-time PCR determined gene expression. Statistical analysis employed ANOVA, Tukey’s multiple comparisons, unpaired t-tests, and multiple hypothesis corrections. All data were analyzed using GraphPad Prism, Python, and R statistical software.

RESULTS: A novel mouse model of MPS IIIC was created by disrupting the murine Hgsnat gene, leading to disease-specific carbohydrate accumulation. Transplantation of wild-type (WT) hematopoietic stem and progenitor cells (HSPCs) into MPS IIIC mice improved locomotor function. Despite partial restoration of Hgsnat expression and activity, GAG accumulation and lysosomal expansion persisted, albeit with reduced vacuolar presence following transplantation. WT HSPC transplantation also alleviated urine retention and organomegaly, and mitigated kidney pathology. Engrafted WT HSPCs differentiated into microglia-like cells in the brain and eyes, rescuing rod photoreceptor loss. Peripheral tissue analysis revealed engraftment of WT HSPCs as macrophage-like cells, decreasing inflammation markers. This study suggests the potential of WT HSPC transplantation for treating MPS IIIC, although challenges remain in fully restoring enzyme activity and reducing GAG accumulation.

CONCLUSIONS: This study explores the therapeutic potential of wild-type (WT) hematopoietic stem and progenitor cell (HSPC) transplantation for MPS IIIC, a lysosomal storage disease with limited treatment options. A novel mouse model of MPS IIIC was developed, displaying characteristic disease phenotypes. WT HSPC transplantation alleviated locomotor deficits, organomegaly, kidney pathology, urine retention, and neurobehavioral impairments. However, GAG accumulation and lysosomal expansion showed limited improvement post-transplantation, likely due to low Hgsnat expression in HSPC-derived cells. Despite this, decreased inflammation markers and tissue damage were observed, indicating potential therapeutic benefit. These findings suggest that WT HSPC transplantation could be a viable treatment strategy for MPS IIIC, particularly if strategies to enhance Hgsnat expression in HSPC-derived cells are developed.
Population-Based Study of Rare Epilepsy Incidence
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BACKGROUND: Rare epilepsies are a medically complex group of disorders often associated with refractory seizures and developmental disabilities. Epidemiologic estimates of incidence and prevalence are limited, sometimes to only counts worldwide. This study uses electronic health records and literature review to estimate incidence.

METHODS: We used electronic health record text search to identify children with 28 rare epilepsies in New York City (2010-2014). We estimated cumulative incidence and compared with literature.

RESULTS: Eight of 28 rare epilepsies had 5 or more prior estimates, and our measurements were within the published range for all. The most common were infantile spasms syndrome (1 in 2,920 live births), Lennox-Gastaut syndrome (1 in 9,690), and seizures associated with tuberous sclerosis complex (1 in 14,300). Fifteen of 28 had fewer than 5 prior estimates, and of these, we provided additional estimates for early infantile developmental and epileptic encephalopathy (1 in 32,700), epilepsy with myoclonic atonic seizures (1 in 34,100), Sturge-Weber syndrome plus seizures/epilepsy (1 in 40,900), epilepsy in infancy with migrating focal seizures (1 in 54,500), Aicardi syndrome plus seizures/epilepsy (1 in 71,600), hypothalamic hamartoma with seizures (1 in 225,000), and Rasmussen syndrome (1 in 450,000). Five of 28 rare epilepsies had no prior estimates, and of these, we provided a new estimate for developmental/epileptic encephalopathy with spike-and-wave activation in sleep and/or continuous spikes and waves during sleep (1 in 34,100). Data was limited for the remaining 12 rare epilepsies that were all genetic epilepsies.

CONCLUSIONS: We estimated the incidence of rare epilepsies using population-based electronic health record data and literature review. More research is needed to better estimate the incidence of genetic epilepsies with nonspecific clinical features. Electronic health records may be a valuable data source for studying rare epilepsies and other rare diseases, particularly as genetic testing becomes more widely adopted.
Access to Mental Health Care in Adolescent and Young Adults with Cancer: The Provider Perspective
Christina Ruiz, MD; Christina Baker, PsyD; Helen Giang, PsyD; Jason Schweitzer, MD; Paula Aristizabal, MD, MAS

BACKGROUND: Prevalence of anxiety and depression is increasing in Adolescent and Young Adults (AYA) with cancer, however there are limited resources to address unmet health needs. While AYAs undergo cancer treatment, they often require complex care, but systematic assessment of mental health needs is limited. Amongst the 118 guidelines published by the Children’s Oncology Group, there are no supportive care guidelines on supporting mental health during and after treatment despite an increasing rate of mental health disorders. We explored barriers and facilitators to access to mental health care for AYAs undergoing treatment for cancer at our institution.

METHODS: Our research team comprised of pediatric oncologists, psychiatrists, psychologists and anthropologists who adapted a 17-item survey from the Access to Tailored Autism Integrated Care (ATTAIN) instrument. Questions evaluated providers’ knowledge, attitudes, and behaviors related to mental health needs in AYA with cancer and barriers and facilitators to effective access mental health care. The survey was completed via REDCAP by physicians (18), nurse practitioners (2), clinical nurses (1), mental health providers (9) and other (4). Response rate was 49% (34/69).

RESULTS: Ninety percent of clinicians reported that &gt;25% of their patients had significant mental health concerns, with anxiety and depression being the most common. Almost half (46%) described that they refer &gt;25% of their patients to a mental health provider, however 78% reported they need help to determine when to refer, despite most (&gt;90%) noting that they feel comfortable interpreting screening results. Ninety-seven percent stated that they would be more likely to use screening instruments if they were tracked in the electronic health record over time. Scheduling appointments with mental health providers was recognized as a major barrier to effective access to mental health care, with &gt;90% of respondents expressing that patients and their families require additional help to schedule and attend mental health care appointments. They described months-long waits, insufficient resources, and healthcare fatigue as main obstacles. Ninety-four percent pointed out that a patient navigator to help schedule appointments would be a great facilitator to address mental health needs.

CONCLUSIONS: Systematic assessment of mental health needs for AYAs with cancer is lacking. Clinicians revealed they do not feel comfortable identifying when to refer patients for counseling or psychiatry, and described significant barriers to patients receiving the care needed. Further, clinicians observed that AYAs and their families require substantial help and support to effectively navigate the healthcare system and establish mental health care.

Atropisomeric pyrrolopyrimidine inhibitor selectively targets the RET tyrosine kinase in neuroblastoma
Ananya Bharathwaj, Erica A. Steen, Mariam Basilaia, Jeffrey Gustafson, Peter E. Zage

BACKGROUND: Increased RET expression is associated with poor prognosis in children with solid tumors such as neuroblastoma (NB), prompting an interest in RET inhibition. A number of kinase inhibitors currently in use for cancer patients have RET inhibitory activity, but these inhibitors also display activity against other kinases, resulting in unwanted side effects that limit their safety and efficacy. However, developing more specific RET inhibitors remains a drug design challenge due to high levels of conservation between kinase binding pockets. Using novel chiral chemistry leveraging atropisomerism, we have developed a novel RET inhibitor, getretinib, and have evaluated its potency and selectivity in vitro.

METHODS: Through a series of in-silico docking models, we turned a rapidly interconverting pyrrolopyrimidine (PPY) kinase inhibitor, a common class of multi-kinase inhibitors, into atropisomerically stable analogs by the strategic addition of two chlorine atoms at the ortho position. These synthesized R- and S-atropisomers were tested in increasing dosages against a panel of NB cell lines, which was assessed by continuous live cell imaging after 72 h of incubation. Treated cells were lysed and analyzed by western blot for total RET expression and RET phosphorylation.

RESULTS: R-getretinib reduced NB cell confluence in a dose-dependent manner, while S-getretinib had no significant effect on cell confluence over time. R-getretinib treatment of NB cells resulted in reduced phosphorylation of RET in a dose-dependent manner, while treatment with S-getretinib resulted in paradoxical increase in RET phosphorylation.

CONCLUSIONS: We present R-getretinib as an atropisomerically stable and potent inhibitor of RET and have shown its efficacy in in vitro models of NB. The high selectivity of R-getretinib towards RET has the potential to minimize unwanted side effects caused by off-target kinase binding, thereby increasing its potential for clinical utility.
ABSTRACTS
Hematology/Oncology (cont.)

Assessing Survival Outcomes in Pediatric Craniopharyngioma at the US-Mexico Border: A Cross-Border Neuro-Oncology Initiative
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BACKGROUND: Management of pediatric craniopharyngioma, requires complex, multidisciplinary care. Data on outcomes in low- and middle-income countries (LMIC) are lacking. To improve survival for children with brain tumors in the US-Mexico border, we established the Cross-Border Neuro-Oncology Program (CBNP) to facilitate access to high-complexity neuro-oncology for Mexican children.

METHODS: We retrospectively assessed clinical and surgical characteristics, progression-free survival (PFS), and overall survival (OS) in US and Mexican children who received neurosurgical intervention for craniopharyngiomas at Rady Children’s Hospital, San Diego (RCHSD) between January 2010 and December 2022. Patients received follow-up care at RCHSD (RCHSD cohort) or at Hospital General, Tijuana (HGT), Mexico (HGT cohort).

RESULTS: There were a total of 35 children with craniopharyngioma; 30 patients (mean age 8.7 years, 60% male) in the RCHSD cohort and five (mean age 14 years, 20% male) in the HGT cohort. The HGT cohort had longer symptom duration at presentation compared to the RCHSD cohort (24 weeks vs. 4 weeks, p=0.011). Pituitary dysfunction at diagnosis was observed in 20 (57%) patients, with growth hormone deficiency (n=17, 47%) being most common. Gross total resection was achieved in 94% of patients. Seven (23%) patients in the RCHSD cohort received adjuvant therapies, compared to 0 in the HGT cohort (p = 0.6). Endocrine treatment compliance was lower in the HGT vs. RCHSD cohort (50% vs. 100%, p=0.012). OS was significantly lower in the HGT cohort compared to the RCHSD cohort (3-year: 80% vs 100%, 5-year: 53.3% vs 100%, p = 0.003). PFS was not different between cohorts.

CONCLUSIONS: Despite providing access to complex neurosurgical care through the CBNP for Mexican children with craniopharyngioma, we demonstrated suboptimal survival. To address this inequity, delayed presentation and post-operative endocrine management will be addressed through infrastructure enhancements, establishment of pediatric endocrinology care at HGT, and training in early detection of alarm symptoms and post-operative care.

Barriers and Facilitators to Daily Chlorhexidine Bathing Compliance at Rady Children’s Hospital: A Qualitative Exploration of Stakeholders’ Perspectives.
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BACKGROUND: Children with cancer are at an increased risk for Healthcare Associated Infections (HAIs). Daily bathing treatments with chlorhexidine gluconate (CHG) reduce HAIs, particularly in patients requiring complex care and those immunosuppressed. However, compliance with CHG bathing is challenging. To gain a better understanding of barriers and facilitators to CHG bathing treatment compliance at our pediatric hematology/oncology inpatient unit at Rady Children’s Hospital, we conducted a qualitative exploration of diverse stakeholders’ perspectives.

METHODS: We conducted semi-structured interviews in a convenience sample of 10 stakeholders including nurses, physicians, nurse practitioners, patient care assistants (PCA), clinical educators and nursing administrators to assess barriers and facilitators to compliance with CHG bathing treatments. All audio recordings were transcribed verbatim and coded. Inductive qualitative thematic analysis was performed by three researchers (PB, BP, PA) to ensure reliability of recurrent themes.

RESULTS: Primary barriers to CHG bathing treatment compliance identified included patient refusal, gaps in patient and family education on the importance of CHG bathing treatments, and inconsistent availability of supplies for CHG bathing treatments. Key themes identified as facilitators to compliance included empowering families to autonomously perform CHG baths and emphasizing the importance of CHG bathing as a prescribed treatment. Nurses also cited fostering a culture that values and prioritizes CHG bathing as a key facilitator. Stakeholders were queried regarding potential solutions. Nursing staff suggested creating escalation protocols for non-compliant families, promoting availability of PCAs to support nurses, updating CHG treatment instructions for new diagnosis education, placing CHG treatments signage in patient rooms, and ensuring availability of supplies to families bundled in a package.

CONCLUSIONS: We identified key barriers and facilitators to compliance to CHG bathing treatments in a diverse sample of stakeholders. Findings can inform quality improvement interventions to improve compliance, including the use of escalation protocols to decrease refusals, enhancing education, and ensuring availability of supplies.
Hematology/Oncology (cont.)

RESULTS FROM THE CROSS-BORDER NEURO-ONCOLOGY PROGRAM

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BACKGROUND: Managing pediatric medulloblastoma requires an experienced, interdisciplinary team and access to sophisticated resources, usually limited in low- and middle-income countries (LMIC). The Cross-Border Neuro-Oncology Program (CBNP) between Rady Children’s Hospital-San Diego (RCHSD), US, and Hospital General-Tijuana (HGT), Mexico, was established in 2010 to provide comprehensive neuro-oncology care for children at HGT. As medulloblastoma is the most common malignant pediatric brain tumor, evaluating treatment outcomes represents a proxy of the CBNP impact.

METHODS: Children with medulloblastoma diagnosed from 2012-2021 at HGT were risk-stratified into low- or high-risk based on age, neuroimaging, and neuropathology features. Clinicopathologic profiles, extent of resection, prognostic factors, including methylation analysis, and five-year overall survival (OS) were evaluated. Kaplan-Meier was used for survival analyses.

RESULTS: Nineteen children (age 6.7±5.1 years, 37% (n=7) female, 11% (n=2) indigenous) were included in this study. Three patients (15.8%) were low-risk and 16 (84.2%) were high-risk. Patients diagnosed at HGT underwent resection at RCHSD and returned to HGT for collaborative management with chemotherapy +/- radiotherapy. Protocols were locally adapted to available agents (cisplatin, etoposide, vincristine, cyclophosphamide). Low-risk patients were treated with cumulative doses of 180mg/m² of cisplatin without evidence of long-term ototoxicity. High-risk patients received radiotherapy and higher-dose chemotherapy. Gross total resection was achieved in 68% of cases, with 5-year OS of 57.4% (95%CI 31.2-100) vs. 33.3% (95%CI 10.8-100) for sub-total resection. Five-year OS for the entire cohort was 47% (95%CI 26.2-82.6), whereas for low-risk and high-risk patients was 49.9% (95%CI 27.2-91.5) and 33.3% (95%CI 6.8-100), respectively.

CONCLUSIONS: Most patients in this cohort were high-risk, contrasting with reports from high-income countries and other LMIC. Survival, independent of risk, was notably lower compared to data from high-income countries. Although the centralized CBNP constitutes a valid model for treating children with medulloblastoma in the US-Mexico border region, collaborative strategies are urgently needed to improve survival in LMIC.

Role of Health Literacy in Caregivers’ Confidence of Knowledge in Childhood Cancer Survivorship Care Plans

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BACKGROUND: With over 400,000 childhood cancer survivors in the US, structured follow-up care is essential. Survivorship care plans (SCP) are provided to cancer survivors to help them navigate complex survivorship care. Confidence in knowledge about SCPs by caregivers may impact utilization and health outcomes. We compared confidence in SCP knowledge in caregivers of childhood cancer survivors by socio-demographics, health literacy (HL), English proficiency, and acculturation (if Hispanic).

METHODS: English or Spanish-speaking caregivers of childhood cancer survivors (&gt;2 years from end-of-therapy) aged 2-24 years from our survivorship clinic participated in the study. Caregivers completed surveys, including socio-demographics, acculturation, and to assess for objective and subjective HL with the Newest Vital Sign (NVS) and HL Self-Assessment (HLSA), respectively. Outcomes were analyzed using t-tests and Chi Square or Mann-Whitney U tests.

RESULTS: Two hundred sixty caregivers (56% female, 56.4% Hispanic) of childhood cancer survivors were enrolled. Hispanic caregivers were younger (&lt;45 years), with lower education (shigh school) and socioeconomic status (&lt;$50,000 average income). Compared to non-Hispanic caregivers, a higher proportion of Hispanics reported high confidence in SCP knowledge (p=0.022). Caregivers with lower education (p=0.015) and limited English proficiency (LEP) (p=0.010) also reported higher confidence. Caregivers with higher confidence had lower objective HL (p&lt;0.001) yet higher subjective HL (p=0.002).

CONCLUSIONS: High confidence in SCP knowledge was associated with Hispanic ethnicity, higher subjective HL, lower objective HL, lower education, and LEP. Consistent with our findings, limited knowledge may correlate with overconfidence in the perception of medical information, as reported in certain underserved populations. Therefore, high confidence alone is unlikely to predict utilization of SCP. Identifying caregivers with objectively low HL, LEP, and low education for appropriately tailored education of the SCP may improve SCP utilization. Future research should evaluate factors that predict SCP utilization and design interventions to improve long-term outcomes in childhood cancer survivors.
Role Of Social Determinants Of Health On Medication Adherence In Patients With Hemophilia

Natasha S. Bala, Bianca B. Perdomo, Paula Aristizabal, Courtney D. Thornburg.

BACKGROUND: Social Determinants of Health (SDOH) affect health outcomes and clinical progression in chronic disorders such as hemophilia. Continuous prophylaxis with intravenous clotting factor concentrates or subcutaneous bispecific antibody therapy, is the standard of care to reduce bleeding and improve quality of life in children with severe hemophilia. However, adherence to prophylaxis is a significant challenge. This study investigates the impact of SDOH, clinical, and contextual factors on adherence to prophylaxis in children with hemophilia.

METHODS: In this prospective cross-sectional study, parents of children with hemophilia (0-17 years) on prophylaxis were enrolled from 2018-2023. Adherence to prophylaxis was measured by Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (adherent= score<57). SDOH and contextual factors included socio-demographics, preferred language, health literacy, trust in provider, household material hardship, functional social support, bleeding disorder knowledge and acculturation (Hispanics only). Clinical characteristics included type and severity of hemophilia, inhibitor status, frequency and route of administration of prophylactic therapy. Associations were evaluated with logistic regression.

RESULTS: Of the 41 participants, 88% were female and 56% were Hispanic. Among the children, 87% had hemophilia A and 82% had severe disease. The mean (standard deviation) total adherence score was 32.5 (8.3) and there was no difference between Hispanics and non-Hispanics (p=0.97). Older age of child (p=0.002) and primary language as Spanish (p=0.002) were associated with lower adherence whereas those with higher trust scores had higher adherence (p=0.051). Children with prophylaxis administered via peripheral intravenous route had lower adherence as compared to central line (p=0.004).

CONCLUSIONS: Overall, adherence with prophylaxis was high in this population and associated with less burdensome route. Higher adherence in younger children could be related to parental administration of prophylaxis. Our findings can guide tailored interventions to improve adherence, including targeting older children/adolescents as they become independent in their care, language-concordant education, and measures to enhance trust in the healthcare system.

Social Determinants of Health and Post-Traumatic Stress Symptoms in Caregivers of Children with Cancer

Yvonne Yu, BSc; Shilpa Nataraj, MD; Bianca P. Perdomo, MA; Nikhil V. Kumar, MD; Christina Ruiz, MD; Paula Aristizabal, MD, MAS

BACKGROUND: Children with newly diagnosed cancer and their caregivers experience significant psychosocial distress, particularly post-traumatic stress symptoms (PTSS). Social determinants of health (SDoH) may influence a family’s ability to navigate a new childhood cancer diagnosis. The role of SDoH on PTSS in caregivers of children with cancer has not been well-studied in minoritized populations.

METHODS: Our aim was to assess the role of SDoH on PTSS in Hispanic and non-Hispanic caregivers of children with newly diagnosed cancer. Caregivers of children aged 0 to 17 years with newly diagnosed cancer (n=207) participated in this study between August 2017 and February 2022. Health literacy (HL), acculturation, sociodemographic factors and PTSS were measured using the Newest Vital Sign (NVS), Short Acculturation Scale for Hispanics (SASH), sociodemographic questionnaire, and Impact of Events Scale-Revised (IES-R), respectively. The IES-R has three subscales: intrusion, hyperarousal, and avoidance. Statistical analyses were conducted using Fisher’s exact test, Wilcoxon rank sum test, and univariable and multivariable regression.

RESULTS: Both Hispanics (n=115) and non-Hispanics (n=92) reported high levels of PTSS (mean IES-R for Hispanics=35 and non-Hispanics=28.5). Hispanic caregivers had significantly higher levels of avoidance (p=0.015), hyperarousal (p=0.011), and total PTSS (p=0.027) compared to non-Hispanic caregivers. Public insurance (p=0.054) and Spanish language used for medical communication (p=0.003) were associated with higher PTSS on multivariable analysis. HL, acculturation, marital status, and religion were not significantly associated with PTSS.

CONCLUSIONS: In this study with a high proportion of Hispanic individuals, caregivers of children with newly diagnosed cancer experienced significant PTSS. Hispanic ethnicity and adverse SDoH, such as public insurance and use of Spanish language for medical communication, were associated with increased PTSS. This study underscores the importance of early identification of caregivers at a higher risk for PTSS and the need to develop psychosocial interventions tailored to cultural and language needs.
Addressing the Need for Population-level Data in Northwestern Mexico: Results from a Cross-Border Partnership to Establish a Population-Based Cancer Registry, BajaREG, and a Pediatric Cancer Surveillance System, PACARSS

Paula Aristizabal, Yvonne Yu, Rebeca Rivera-Gómez, Gudelia Rangel, William Roberts

BACKGROUND: Population-Based Cancer Registries (PBCRs) and surveillance systems are core elements of cancer control. Given complex healthcare systems, implementation in low- and middle-income countries (LMIC), like Mexico, is challenging. We implemented the first PBCR in Northwestern Mexico, and integrated pediatric cancer real-time monitoring system, through a cross-border partnership between Rady Children’s Hospital-San Diego and Hospital General-Tijuana.

METHODS: To launch Tijuana’s PBCR, BajaREG, we established an interdisciplinary US-Mexican working group that assessed needs, adapted protocols, and conducted training on data collection, coding, and analyses.

RESULTS: In 2018, BajaREG was established and joined Mexico’s National Cancer Registry Network. Twenty data sources (5 public, 15 private) were identified. In 2020, PACARSS (Pediatric and Adolescent Cancer Registry Surveillance System) was integrated into BajaREG to monitor real-time childhood cancer outcomes. BajaREG and PACARSS implementation faced many barriers, including limited local infrastructure and funding, misinformation in the medical community, underdeveloped and inefficient information systems, and bureaucratic hurdles at public institutions. Start-up funding was obtained through Foundation-S and sustained by alliances with the Mexican government, Rady Children’s Hospital-San Diego, and Danaher Foundation. Since BajaREG inception, accurate data has been collected from 90% target sources. A total of 8231 adults and 268 pediatric (<18 years) new cancer cases were registered from 2018-2023. PACARSS has collected data in 6/6 participant institutions from 150 pediatric cases.

CONCLUSIONS: Despite challenges, including the COVID-19 pandemic, stakeholder engagement enabled success. We showcase how locally-tailored partnerships can develop sustainable PBCRs and cancer surveillance systems in LMIC. As resistance to sharing information is common in LMIC, raising awareness among health authorities involved in cancer control regarding the crucial need for comprehensive population-level cancer data to inform policy is a priority. Learnings from this binational partnership are applicable to other LMIC. This replicable model sets an important precedent in national and international collaborations in cancer registration and surveillance.
Characteristics of infants undergoing sepsis evaluation after initially successful versus unsuccessful lumbar punctures
Amanda Dube, Manaswitha Khare, Michael Levy, Michelle Edmunds, Aarti Patel, Begem Lee, Tiranun Rungruvatjarus, Elizabeth Mannino Avila

BACKGROUND: Lumbar punctures (LPs) are commonly performed as part of sepsis evaluations for febrile infants. Failures range from 12-40%. No guidance exists on management of infants in whom an LP was unsuccessful. We sought to describe characteristics of infants in whom initial LP was successful (defined as obtaining sufficient cerebrospinal fluid (CSF) for minimum necessary testing) and unsuccessful.

METHODS: This single-center retrospective chart review study at a tertiary care freestanding children’s hospital from 1/1/2019 – 12/31/2022 included patients 0-60 days old who had an LP for sepsis evaluation. We excluded patients admitted/transferred to an intensive care unit within 24h of presentation, patients with medical complexity, inpatient transfers, or with LP for reason other than sepsis evaluation.

RESULTS: Of 468 patients included, 82% had successful initial LP (n = 386) (Table 1). Of patients with unsuccessful LPs (n = 82), 44% had >/=1 repeat (n = 36). Success rate for first repeat LP was 69% (24/35). Intravenous antibiotic hours, demographics, and readmissions did not differ between groups (Table 2). Reasons for not repeating LP are listed in Table 3. LOS was longer for patients with unsuccessful LPs (p = 0.02). Elevated CRP was associated with higher likelihood of repeat LP. 66% of patients with initially unsuccessful LPs (n = 47) never had CSF obtained. None were diagnosed with bacteremia or meningitis; none had readmissions within 7 days.

CONCLUSIONS: In infants undergoing sepsis evaluation at our hospital, 56% of patients with unsuccessful LPs did not have repeat attempts. Success on initial LP was associated with LOS. No significant differences in outcomes were observed between patients with successful versus unsuccessful LP. Further investigation is needed to determine whether this represents local versus national practice pattern, and to be powered to assess for impact on rare outcomes (meningitis).

Parental Perspectives Regarding the Inpatient Discharge Process for Spanish-speaking Patients and Families
Chloe Kupelian, DO, Aarti Patel, MD, MEd, Begem Lee, MD, Elizabeth Mannino Avila, MD, Heriberto Martinez, MD, Maria Huang, MD

BACKGROUND: The transition of care from hospital to home is a complex process for patients and parents, associated with increased familial stress and uncertainty. The discharge (DC) process is particularly high-risk for Spanish-speaking patients, with increased risk for medication errors, missed follow-up (f/u) appointments, poor patient satisfaction, and reutilization. While some studies have assessed Spanish-speaking parents’ (SPP) experience with hospitalization, little is known about their perceptions regarding the DC process. The objective of this study is to explore SPP experiences with DC from the Pediatric Hospital Medicine (PHM) service. Primary aims included identifying areas for improvement in interpreter services and communication.

METHODS: SPP of children discharged from the PHM service consented and participated in a focus group, as part of a larger quality improvement initiative to improve the DC process and assess efficacy of interventions. The session was audio-recorded, transcribed in Spanish, and translated into English. Qualitative methods were used for thematic analysis.

RESULTS: One session (n = 6 parents) was held (Table 1). Most had a positive DC experience with clear verbal communication, anticipatory guidance, and consistent interpreter use. Most received translated written instructions (Table 2). Some parents noted lack of clarity regarding study results, f/u appointments, and prescriptions. Parents appreciated when health care professionals (HCP) reiterated instructions and took time to answer their questions. They felt communication with HCP and interpreters was clear and easy to understand. Parents reported significant delay between discussion of DC and ability to physically leave the hospital. Parents commented on limitations during the DC process (e.g. limited in-person interpreter accessibility and time with HCP); however, they were forgiving of these situations and reported a positive experience, despite institutional barriers.

CONCLUSIONS: Consistent interpreter use was appreciated by parents. Like previous studies, we found parents preferred in-person. Explanation of results, medications, and f/u appointments were lacking. Potential interventions include reinforcing parent preference of consistent and repeated messaging by HCP during DC teaching, educating HCP about increased transparency when discussing the DC process, and educating families about translation resources available during their child’s hospitalization. Future studies should work to formalize a process for families to request interpreter services.
Effect of COVID-19 on Prevalence and Severity of Eating Disorder Admissions in a Specialized Pediatric Inpatient Unit

Michelle Polich, MD; Shamika Seneviratne, BA; Maya Kumar, MD; Kyung E. Rhee, MD, MSc, MA

BACKGROUND: During the COVID-19 pandemic, there was an increase in eating disorder (ED) diagnoses. Our goal was to examine the change in number of ED admissions and severity of symptoms during the pandemic at a large inpatient eating disorder unit.

METHODS: A retrospective chart review of patients admitted to the Medical-Behavioral Unit (MBU) at Rady Children’s Hospital San Diego (RCHSD) from January 2019 through December 2021 was conducted (n=481). Differences in number of admissions and patient admission characteristics were compared before and after the start of the COVID-19 stay-at-home mandate. Bivariate analysis using chi-square and t-tests were performed. Logistic and linear regression models, adjusting for age and sex a priori, were created for multivariate analyses.

RESULTS: Patients were primarily female (86%), on Medicaid (59%), with a median age of 15 years. The average number of admissions per month during the COVID-19 pandemic (mean = 14.95, SD 3.62) increased by 38% from the pre-COVID time period (Pre: 10.86, SD 3.82 vs. Post: 14.95, SD 3.62, p = 0.003). No differences were noted between time periods regarding most lab values, orthostatic vital signs, readmission within 90 days, use of nasogastric tubes, and need for restraints. However, post-COVID, there was fewer percentage of patients <70% of “target weight” (pre 46.1% vs. post 26.8%, p<0.0001), and a lower proportion with hypophosphatemia (p=0.007). In the multivariate models, patients admitted post-COVID were less likely to be <70% of “target weight” and have hypophosphatemia.

CONCLUSIONS: Unexpectedly, clinical characteristics on admission were less severe during the COVID pandemic than during the pre-COVID years. Closures of many partial hospitalization or outpatient ED programs may have led to lower acuity patients being hospitalized earlier during COVID. Preserving access to robust outpatient eating disorder treatment may prevent this phenomenon from happening in future public health crises.

Dealing with Death: Health Care Professional Perspectives After Pediatric Patient Death

Maria Z. Huang, Michael Henne, Rene Roth-Bates, Ami Doshi

BACKGROUND: Pediatric health care professionals (HCPs) are at the forefront of caring for sick children and helping families cope following patient death. Yet, HCPs are often overlooked as those who experience grief and who may need support during the coping process. This study describes the variety of ways HCPs cope and the resources they utilize after a pediatric death.

METHODS: Purposeful sampling was utilized to recruit a wide range of HCPs from disciplines and clinical settings. Participants included medical decision makers, treatment implementers, and those who provide psychosocial support; they work in critical care units, medical units, emergency department, and/or outpatient. One-on-one semi-structured, audio-recorded interviews were conducted with HCPs exploring their experience after pediatric death. Interviews were transcribed verbatim. Two researchers independently coded transcripts using Atlas.ti qualitative analysis software. Discrepancies were reviewed to reach consensus on coding. Recurrent and novel themes were identified.

RESULTS: 19 HCPs completed interviews at the time of this submission. Experience ranged from 1 year to 30 years. HCPs universally described professional community as a necessary source of support. They describe a sense of purpose in fulfilling their duty toward patient families and professional colleagues with occasional burden of setting aside their own grief to address others’. Debriefs are valued by some, should be offered, inclusive, and optional. HCPs describe that having a framework for thinking about death can be helpful, tying to a desire for education on end-of-life and grief. Many institutional and unit-based support programs exist but difficulty with access is a barrier to utilization. Additionally, HCPs wish for accessible mental health, palliative care, chaplaincy, and bereavement services.

CONCLUSIONS: Findings can help leaders and institutions improve support for HCPs after pediatric death. Not only does the presence of a professional community help HCPs cope, HCPs desire more education around death and grief.
Pediatric Patients with Rhabdomyolysis at a Tertiary Academic Center: an 11-year Study  
Melissa Cameron MD, Christiane Lenzen MD, Manaswitha Khare MD, Tiranun Rungvivatjarus MD and Elizabeth Mannino Avila MD

BACKGROUND: Rhabdomyolysis is the destruction of skeletal muscle cells resulting in the release of contents into the bloodstream. Children are often hospitalized out of concern for the development of acute kidney injury (AKI). There is a paucity of evidence to guide risk evaluation of AKI, correlation with different causative etiologies, and management of children hospitalized with rhabdomyolysis.

METHODS: We conducted a retrospective chart review of subjects less than 19 years old with a discharge diagnosis of rhabdomyolysis that were hospitalized at our pediatric tertiary care hospital from 2012 to 2022. Inclusion criteria was a creatinine kinase (CK) level > 1000 U/L. For patients with multiple admissions, the index admission was used for analysis. Patients with prolonged hospitalization due to factors other than rhabdomyolysis or diagnoses that confounded diagnosis of AKI were excluded. Data was obtained through manual review after automatic retrieval from the electronic medical record with subject identification via hospital discharge diagnoses using the ICD-9 or 10 codes for rhabdomyolysis (728.88 and M62.82).

RESULTS: Of 191 patients, 11 had >1 admission for rhabdomyolysis. 79% of patients were male with an average age of 12.6 years. The average length of stay was 3.4 days with 7% (n=13) of patients requiring PICU admission. The median peak CK value was 14,562 with the median CK at discharge of 5,218 (Table 1). 43 (23%) had AKI, the majority (33, 77%) were in the activity etiology group. The activity group included patients with seizures, excessive exercise and severe agitation. On average patients in the activity group had the highest peak CK levels and 31 % in this group presented with AKI (table 2). Overall, patients with AKI had a longer LOS (5 vs 2.9 days without AKI). There were significant differences when comparing peak CK level versus etiology (Table 3). 22 patients received genetic testing, of those 6 had a genetic diagnosis identified. No patients required dialysis and there were no deaths from rhabdomyolysis, or its sequelae reported. Only 2 patients had a related readmission within 30 days, and 4 patients had a related ER visit within 30 days after discharge.

CONCLUSIONS: This is the largest reported study of hospitalized children with rhabdomyolysis in the US. Most patients with AKI were in the activity group. More evidence is needed to stratify risk groups and guide the management of children hospitalized with rhabdomyolysis.
Outsmarting Staphylococcus aureus: Breaking the Cycle of Vaccine Evasion with Innovative Immune Strategies
Irshad Ahmed Hajam, Chih-Ming Tsai, Cesia Gonzalez, Xin Du, Brian Lin, George Y Liu

BACKGROUND: Within the intricate interaction between host and microbes, pathobionts have crafted remarkable strategies to thrive alongside their hosts. However, the elusive nature of these immune evasion tactics presents a formidable barrier to vaccine development. Delving into the case of Staphylococcus aureus (SA), a notorious pathobiont that has defied all human vaccine endeavors thus far, we uncover a curious new mechanism. Herein, we illuminate a novel link between prior SA exposure and the blunting of protective SA IsdB vaccine responses.

METHODS: Mice were first exposed to SA, subsequently vaccinated, and then challenged with SA to assess how pre-existing SA immunity impacts vaccine efficacy.

RESULTS: Our investigation uncovers a pivotal role played by non-protective CD4+T cells, whose memory carries the imprint of previous SA encounters. The CD4+T cell imprint secretes abundant IL-10 cytokine that is amplified by vaccination and drives antigen-specific inhibition of vaccine protection via IL-10Ra on CD4+T cells and through the suppression of IL-17A responses. Intriguingly, IL-10 extends its suppressive influence to hinder the effectiveness of additional SA vaccines, even disrupting the synergy of combined vaccine strategies. Furthermore, we unveil a potent approach for the reversal of vaccine suppression. Adjuvants promoting robust IL-17A and IFN-γ responses, independent of IL-10, emerge as potent countermeasures, restoring vaccine efficacy of otherwise non-protective SA vaccines.

CONCLUSIONS: In summary, our findings unveil critical insight into the arms race between immunity and pathobionts. The strategic deployment of IL-10 by pathobionts like SA represents a sophisticated surveillance mechanism, poised to quash emerging threats from host immunity. Yet, the identification of adjuvants capable of circumventing pathobiont-driven suppression, paves the way toward novel vaccine strategies.

Invasive Staphylococcus epidermidis use a unique processive wall teichoic acid glycosyltransferase to evade immune recognition

BACKGROUND: Most clonal lineages of Staphylococcus epidermidis expresses glycerol-phosphate wall teichoic acid (WTA), but some healthcare-associated methicillin-resistant S. epidermidis (HA-MRSE) clones produce a second, ribitol-phosphate (RboP) WTA, resembling that of the aggressive pathogen Staphylococcus aureus. RboP-WTA promotes HA-MRSE persistence and virulence in bloodstream infections.

METHODS: For the construction of the ∆tarM(Se) mutant in S. epidermidis E73, the pBASE6-erm/lox1 shuttle vector was used according to standard procedures. Flow cytometry was used for IgG binding assay. For bacterial susceptibility, different phages were used in spot assay and transduction. Crystals of protein were obtained by hanging drop vapor diffusion. Diffraction data were collected at beamline X06DA of Swiss Light Source in Villigen, Switzerland. Structure figures were generated by PyMOL and the models were evaluated using MolProbity.

RESULTS: We report here that the TarM enzyme of HA-MRSE (TarM(Se)) glycosylates RboP-WTA with glucose, instead of N-acetylglucosamine (GlcNAc) by TarM(Sa) in S. aureus. Replacement of GlcNAc with glucose in RboP-WTA impairs HA-MRSE detection by human IgG, which may contribute to the immune-evasion capacities of many invasive S. epidermidis. Crystal structures of complexes with UDP-glucose, and with UDP and glycosylated poly(RboP) reveal the binding mode and glycosylation mechanism of this enzyme and explain why TarM(Se) and TarM(Sa) link different sugars to poly(RboP).

CONCLUSIONS: These structural data provide evidence that TarM(Se) is a processive WTA glycosyltransferase. Our study will support the targeted inhibition of TarM enzymes, and the development of RboP-WTA targeting vaccines and phage therapies.
Advancing Human Milk Analytics: Unveiling the Milk Analytics Core for Precision Profiling in Human Milk.
Gaurav Pandey, Alec Bizieff, Yan Cheung, Sydney McCune, Brock Mitts, Mitra Hooshmand, and Lars Bode

BACKGROUND: Human milk is the gold standard for newborn nutrition. The World Health Organization advocates for exclusive breastfeeding during the first six months of life based on extensive research indicating that HM confers immune protection, supports brain development, provides protection against gastrointestinal infections and necrotizing enterocolitis, and delivers a comprehensive and optimally balanced array of essential nutrients to the infant. Despite its acknowledged vitality, characterization of HM composition remains a challenge, primarily attributable to the lack of standardized methodologies. Therefore, this warrants in-depth analytical studies to bridge existing knowledge gaps effectively. The Milk Analytics Core (MAC), started as an NICHD-funded MPRINT Center of Excellence in Therapeutics core, is housed at UC San Diego’s Human Milk Institute and endeavors to elucidate the gaps in our understanding of HM components.

METHODS: In collaboration with Agilent Technologies, Inc., MAC performed a pilot experiment to compare the detection of minerals and trace minerals using two distinct digestion techniques (ambient alkaline digestion and high-temperature acid digestion), coupled with Agilent’s 7850 ICP-MS instrumentation.

RESULTS: Both methods yielded comparable results despite differences in external calibrations, indicating their suitability and effectiveness for analyzing HM samples. For quality control, the analytical performance was first validated using NIST1634f, a NIST certified reference material. Preliminary results demonstrated concentrations of Na, K, Zn, Cu, other minerals and trace elements that accurately reflect expected concentrations in HM samples.

CONCLUSIONS: In the future, these results will be validated and along with additional analyses of HM samples encompassing macronutrients, micronutrients, oligosaccharides, and other bioactive compounds. MAC aspires to evolve into a comprehensive core, equipped with advanced knowledge, expertise, analytical capabilities, and technological infrastructure, serving both the local UC San Diego and the global research community. Our goal is to improve infant nutrition and maternal and child health worldwide.

Detection of Bacteremia in Pediatric Blood Samples Using Universal Digital High-Resolution Melt (U-dHRM)
April Aralar, Tyler Goshia, Nanda Ramchandar, Shelley M. Lawerence, Aparajita Karmakar, Ankit Sharma, David Pride, Peiting Kuo, Khrissa Lecrone, Megan Chiu, Karen Mestan, Eniko Safi, Michelle Vanderpool, Sarah Lazar, Melanie Crabtree, Yordanos Tesfai, Stephanie I. Fraley

BACKGROUND: Timely identification of bloodstream infections (BSIs) is vital for optimizing treatment in septic patients, as mortality risk escalates with each hour of delay. While blood culture remains the gold standard, its lengthy turnaround time of approximately 15 hours poses significant clinical challenges.

METHODS: This study investigates the efficacy of Universal Digital High-Resolution Melt (U-dHRM) analysis for rapid and comprehensive bacterial detection, quantification, and species-level identification directly from whole blood samples.

RESULTS: Analytical validation studies demonstrate a robust correlation between U-dHRM load assessments and quantitative blood cultures, indicating high specificity in detecting viable bacteria. In a preliminary clinical study involving 17 pediatric patients undergoing concurrent blood culture tests, U-dHRM exhibited a 100% concordance rate with blood culture results and an 88% match with clinical adjudication. Additionally, U-dHRM accurately identified the causative pathogen at the species level in all cases where the organism was represented in the melt curve database. Remarkably, these outcomes were achieved with a modest 1 mL sample input and a rapid sample-to-answer time of only 6 hours.

CONCLUSIONS: Collectively, these findings underscore the potential of U-dHRM as a promising approach to diagnose bloodstream infections swiftly and accurately, addressing critical clinical needs in septic patient management.
The Role of GATA4 in Lung Hypoplasia and Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia
Betty Pham, Zhuowei Li, Nicole Talaba, Giangela Stokes, Mark Wienhold, Rebecca Hernan, Wendy Chung, David McCulley

BACKGROUND: Congenital diaphragmatic hernia (CDH) is a common and severe malformation affecting 1/2,000 births with a 10-50% mortality rate due to lung hypoplasia (LH) and pulmonary hypertension (PHN). Lung and pulmonary vascular (PV) defects in CDH are thought to originate from mechanical compression by herniated abdominal organs. However, data from fetal patients and animal models suggest that there may be primary defects in lung and PV development occurring independent of mechanical compression. These primary defects may be secondary to pathogenic genome variants directing lung and PV development. CDH genomic studies identified GATA4 as one of the most commonly implicated genes. Patients with pathogenic GATA4 loss-of-function (LOF) variants have severe phenotypes with 67% mortality. GATA4 is required for diaphragm development but has an unclear role in lung and PV development. We hypothesize that GATA4 directs lung and PV development and LOF causes LH and PHN independent of its role in diaphragm formation.

METHODS: We inactivated Gata4 expression in developing murine lung or diaphragm mesenchyme using an inducible, tissue-specific gene deletion approach. The phenotypes of Gata4 conditional deletion (Gata4 CKO) and controls were analyzed by histology, immunofluorescence staining, qRT-PCR, echocardiography, and pulmonary function testing.

RESULTS: Counter to our hypothesis, lung-specific Gata4 deletion did not impact branching morphogenesis, lung cell lineages, alveologenesis, or PV development. These Gata4 CKO mice had unaffected pulmonary function and no PHN. However, diaphragm-specific Gata4 CKO mice had pulmonary hypoplasia and abnormal airspace development.

CONCLUSIONS: Our work demonstrates that GATA4 does not have a direct role in lung or PV development. These data are significant because they suggest that the severe patient phenotype is attributable to mechanical compression during development. Our data suggest that patient genomic analysis and functional studies in mouse models could be used to identify patients who are more likely to benefit from procedures addressing mechanical compression to improve outcomes.

Unraveling Myeloid Cell Responses to Hyperoxia: Genetic Variation and Implications for Resilience Against Neonatal Lung Injury
Brandon Saiki, Sean Jansky, Yohei Abe, PhD, Fenghua Zeng, MD, PhD, Richard John, PhD, Enikő Sajti, MD, PhD

BACKGROUND: Bronchopulmonary dysplasia (BPD), a chronic lung disease, frequently complicates preterm birth, yet its development and severity vary among premature infants. The role of myeloid cells in modulating disease susceptibility remains unclear. We aimed to assess the impact of natural genetic variation on BPD severity by examining gene expression variability in myeloid cells between two mouse strains with differing susceptibility to oxidant stress.

METHODS: Bone marrow-derived macrophages (BMDMs) were generated from C57BL/6J (B6) mice (sensitive to hyperoxia) and DBA/2J (DBA) mice (resistant to hyperoxia). BMDMs were exposed to 95% oxygen for 24 hours, and transcriptomic differences were analyzed by RNA-seq. P53 expression was quantified using Western blot. Data were analyzed using HOMER and Prism.

RESULTS: Transcriptomic changes differed qualitatively between strains, with only a small fraction of genes commonly regulated. Genes upregulated in both strains were enriched in inflammatory response, cytokine production, and locomotion. To identify potentially protective gene programs, we focused on genes induced by hyperoxia in B6 but suppressed in DBA mice. Gene ontology analysis revealed enrichment of apoptotic processes and programmed cell death in this select gene group, including Bcl2l1, Trp53inp2, and Cdkn1a. Consistent with RNA-seq data, BMDMs from B6 mice exhibited higher p53 protein expression than those from DBA mice.

CONCLUSIONS: Our findings demonstrate differential responses of myeloid cells to hyperoxia exposure in sensitive and resistant mouse strains. Notably, excessive activation of the p53 axis in myeloid cells of sensitive strains may contribute to lung injury, potentially influencing BPD pathogenesis. The observed interstrain variability in gene expression post-hyperoxia suggests a basis for understanding individual differences in human BPD susceptibility.
Neonatal hyperoxia exposure derails the normal development and physiological aging of the lung

Cadence Seymour, Sean Jansky, Jason Guo, Michael Longaker, Christopher Glass, MD, PhD, Eniko Sajti, MD, PhD

BACKGROUND: Infants born premature, especially those who have developed bronchopulmonary dysplasia (BPD) are at risk for chronic respiratory dysfunction. These life-long respiratory problems are a consequence of disrupted lung development and accelerated decline in function. Exposure to hyperoxia in the neonatal period is central to the pathogenesis of BPD. However, the cellular and molecular processes that underlie the accelerated loss of healthy lung physiology in ex-preterm infants are poorly understood.

METHODS: Newborn C57BL/6 mice were exposed to 75% oxygen for 2 weeks. Lungs were harvested immediately after the hyperoxia exposure at 2 weeks or following recovery in room air at 8 weeks, 6 months, and 18 months of age. To quantify the severity of injury at these timepoints, we assessed alveolar simplification and extracellular matrix architecture measuring 147 ultrastructural features using an analysis pipeline including DDRTree on H&E and picrosirius red stained slides. We measured gene expression changes in the lung by RNAseq. Data was analyzed with HOMER.

RESULTS: Neonatal hyperoxia resulted in permanent changes in lung architecture. Hyperoxia-exposed mice had an increased MLI with a corresponding decrease in surface area that lasted into adulthood. In addition to the alveolar simplification, we found marked ultrastructural changes in the interstitium characterized by geometrically disordered and enlarged fibers. To understand the molecular mechanisms underlying these morphometric findings we measured changes in gene expression. The pulmonary transcriptome revealed distinct hyperoxia-induced changes in young and aging mice. Strikingly, the genes modulated by hyperoxia in the 2-week-old mice were downregulated in adult and aging mice. In young mice hyperoxia induced genes were related to apoptosis while in adult and aging animals to vascular smooth muscle development and extracellular matrix organization. Importantly, aging-induced gene programs were altered by hyperoxia. Compared to normal aging, hyperoxia exposed lungs showed activation of the NFkB pathway and inflammatory processes.

CONCLUSIONS: We provide novel molecular insights into the long-term effects of neonatal hyperoxia on the lung and highlight that hyperoxia induced gene programs are age and lung development specific. Of note, vasculature development related genes were downregulated in the adult and old mice suggesting that neonatal hyperoxia exposure results in a sustained suppression of these gene programs. Importantly, in addition to derailing normal lung development in the neonatal period, hyperoxia exposure resulted in altered aging. A better understanding of the aging-related changes induced by neonatal hyperoxia will aid in the development of therapies for the long-term complications of BPD.

Creation of a knock-in mouse model that synthesizes 2'-fucosyllactose in milk

Simone Renwick, Kristija Sejane, Annalee Furst, Lars Bode

BACKGROUND: Human milk oligosaccharides (HMOs) are a diverse group of complex carbohydrates that constitute the third most abundant component present in human milk. Among the 200 different oligosaccharide structures, 2'-fucosyllactose (2'FL) has garnered attention in infant nutrition due to its in vitro anti-inflammatory and immunomodulatory properties. Within the mammary gland, 2'FL synthesis is catalyzed by the enzyme fucosyltransferase 2, encoded by the FUT2 gene, which determines an individual's secretor phenotype. Synthetic 2'-FL is currently added to some infant formula in an attempt to emulate the benefits of human milk. However, our understanding of the immediate and long-term health effects of 2'FL supplementation is limited due to the absence of 2'FL in the milk of most other mammals, including rodents commonly used in preclinical research.

METHODS: To address this gap, we used the CRISPR/Cas 9 genome editing to insert the human FUT2 gene into the C57BL/6 mouse genome under the mammary gland- and lactation-specific whey acid protein promoter to produce milk containing 2'FL.

RESULTS: The knock-in mouse milk was analyzed using high-performance liquid chromatography (HPLC) and contained approximately 8 g/L of 2'FL throughout lactation, comparable to human milk concentrations. However, concentrations of 3'SL and 6'SL in knock-in milk were lower compared to wild-type mice.

CONCLUSIONS: Furthermore, we performed a cross-foster with the newly generated line and the available FUT2 knockout line to study the effects of dietary 2'FL and endogenous α1,2-linked glycans in the offspring intestine. The creation of the knock-in mouse provides a unique opportunity to explore the impact of 2'FL exposure on infant health and possible therapeutic applications.
Cord Blood Biomarkers Define Placenta-Lung Endotypes of Bronchopulmonary Dysplasia
Jiaqi (Jackie) Zhao, Janu Newar, Lillian Blank, Aliyah Abanes, Mana Parast, Karen Mestan

BACKGROUND: The placenta is an active mediator of the intrauterine environment and its influence on fetal lung development. Certain pathways of placental dysfunction predict pathogenic pathways of bronchopulmonary dysplasia (BPD). Cord blood (CB) cytokines/chemokines and growth factors circulating at birth may serve as proxies of placental dysfunction. We seek to characterize CB proteomic profiles associated with distinct placental histopathologic domains to identify distinct endotypes of BPD along pathways of inflammation and vascular dysfunction.

METHODS: We performed multiplex immunoassay (Luminex xMAP, EMD Millipore Cytokine and Human Angiogenesis Panels) on archived CB plasma from 193 infants enrolled in a Chicago-based birth cohort. Comprehensive clinical and placental data were collected using standardized study protocols, to identify patients with BPD versus no BPD (NIH Consensus Criteria) and exposure to 4 placental pathologic domains (2016 Amsterdam Workshop Criteria): acute inflammation (AI), chronic inflammation (CI), maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM). Aptamer-based proteomics (Somalogic, Boulder, CO) was conducted on a subset of 50 patients to validate the multiplex findings and explore novel proteomic pathways among 7,596 analytes.

RESULTS: Differences in protein expression were observed across all 20 analytes of the multiplex platform when stratified by placental domains. IL-6, IL-8, G-CSF, endothelin-1, HGF, FGF-2, Placental Growth Factor (PLGF) and VEGF-A were upregulated with AI (Padj<0.05). PLGF and VEGF-A were down-regulated with MVM (Padj<0.05). Proteomic analysis of 25 BPD cases and 25 non-BPD control infants confirmed differential protein expression across all 20 analytes. When further stratified by BPD, G-CSF, leptin, FGF-2 and VEGF-A were upregulated in BPD infants exposed to placental AI. G-CSF was upregulated in BPD infants with CI (P<0.01), while FGF-2 (P<0.01) was downregulated with FVM.

CONCLUSIONS: Proteomic profiles of the CB microenvironment may elucidate mechanisms of placenta-lung crosstalk that define distinct endotypes of BPD along acute/chronic inflammatory and vascular pathways of neonatal lung development.
The effects of cell-cell orientation in modeling the hallmarks of lung cancer in vitro
Andres S. Espinoza, Rachael N. McVicar, Darren Finlay, Rabi Murad, Kristiina Vuori, Bethany A. Grimmig, Anne Bush, Emily Smith, Thomas Mandel-Clausen, Heather McGee, Evan Y. Snyder, Sandra L. Leibel.

BACKGROUND: To better understand and develop treatments for lung cancer, it is important to have reliable and physiologically relevant culture models. Traditional methods of growing lung cancer cells in two-dimensional (2D) monolayers have limitations in mimicking the complex architecture and microenvironment of lung tumors in vivo, limiting their value as reliably informative disease models. In recent years, three-dimensional (3D) models have gained popularity in cancer research, as they offer a more authentic in vitro representation of the in vivo environment. We wanted to investigate if the way cancer cells are grown in different configurations, either as 2D monolayers or 3D "tumoroids," can alter cancer-related signaling.

METHODS: In this study, we utilize a new cell culture platform called "tumoroids," which involves growing HCC827 lung cancer cells in 3D configurations. By comparing transcriptional profiles of HCC827 cells grown as tumoroids versus the same cells grown in 2D monolayers, we investigate how cell-cell orientation and signaling impact the cancer-driving properties of lung cancer. We utilized bulk RNA sequencing data to compare and examine key markers associated with the hallmarks of cancer development and progression. We also measured and compared cell death in response to irradiation treatment across each model.

RESULTS: Transcriptional data revealed an increased activation of the tumor microenvironment, angiogenesis, and epithelial-mesenchymal transition (EMT) pathways in the 3D model, indicating stronger cancer-promoting signaling. Irradiation results also demonstrated differing responses across each model, with the 3D tumoroid cultures exhibiting decreased viability.

CONCLUSIONS: This data suggests that spatial configuration alone can significantly influence signaling associated with the progression of cancer and its therapeutic susceptibility. Overall, this study highlights the importance of using advanced culture models like 3D tumoroids to improve our understanding of lung cancer and facilitate the development of effective treatments.

Hyperoxia induces age-dependent transcriptomic changes in the lung
Sean Jansky; Christopher Glass, MD, PhD; Eniko Sajti, MD, PhD

BACKGROUND: Supplemental oxygen therapy is one of the most widely used interventions in the ICU. While it can be lifesaving, inhalation of high concentrations of oxygen can lead to severe hyperoxic acute lung injury (HALI) in both neonatal and adult patients. The developing neonatal lung responds in a different way to hyperoxia than the adult lung. Additionally, both patient populations exhibit significant inter-individual variability in susceptibility to hyperoxia-induced injury. However, the molecular and cellular mechanisms directing these different responses are not known.

METHODS: Newborn (postnatal 0) and adult (8 weeks) C57BL/6J (B6) sensitive and DBA/2J (DBA) mice resistant to HALI were exposed to 75% oxygen for 48 hours. Littermates raised in room air served as controls. Lungs were harvested immediately after the hyperoxia exposure and used for downstream analysis. Gene expression was measured by RNAseq. Data were analyzed with HOMER.

RESULTS: HALI in the neonatal lung was associated with the upregulation of genes related to cell division and cell cytokinesis while in adult mice to amino acid metabolic processes, apoptosis, and ferroptosis. Only 13 genes including Cdkn1a, Bax, Zmat3 involved in the p53-dependent growth regulatory pathway were commonly upregulated by hyperoxia in both age groups. Additionally, sensitive B6 mice showed significant upregulation of genes associated with apoptosis such as Nupr1 and Cdkn1a, whereas resistant DBA mice upregulated inflammation and chemotaxis related genes like Cxcl5 and Ccl9.

CONCLUSIONS: Unbiased genomic assessment reveals a divergent gene expression program in HALI in the lungs of neonatal and adult mice. Exposure of the neonatal lung to hyperoxia in the postnatal saccular and alveologenesis periods resulted in marked alteration of cell division related gene programs. Adult HALI was characterized by apoptosis and cell death. While the p53 pathway was activated in both age groups and strains in response to hyperoxia, the different downstream outcomes suggest that the timing and the magnitude of p53 activation drives alternative injury phenotypes.
The Pathogenic Role of Oxidized Phospholipid in Pulmonary Fibrosis
Wenxi Tang, Moyu Lyu, Brendan Lee, Christopher Glass, Joseph L. Witztum*, Eniko Sajti*

BACKGROUND: Increased production of oxidized phospholipids (OxPL) has been shown to have deleterious effects in acute lung injury, but its role in lung fibrosis is not known. OxPL are recognized by the IgM natural antibody (Ab) E06 and binding neutralizes their pro-inflammatory effect. We have investigated the pathogenic role of OxPL in bleomycin (BLM)-induced pulmonary fibrosis (PF) and whether neutralizing OxPL by E06 Ab would ameliorate BLM-induced PF.

METHODS: C57BL/6J(WT) and E06-scFv transgenic (E06-Tg) mice that overexpress the single-chain fragment of E06 were intratracheally instilled with BLM to induce lung fibrosis. We recorded weight change and survival rate after BLM instillation at serial time points. We measured collagen deposition in the lungs by Sirius Red staining, and measured OxPL and hydroxyproline levels by ELISA. Data were analyzed with ImageJ, Prism and Orbit Image.

RESULTS: E06-Tg mice lost less weight after BLM instillation, and had significantly higher survival rate compared to WT mice. We observed an increased accumulation of OxPL in the lungs of WT mice compared to E06-Tg mice. In addition, we measured higher collagen content in the lung homogenates of WT compared to E06-Tg mice, suggesting more fibrosis in WT mice. We also observed significantly more collagen deposition in WT mice than E06-Tg mice by Sirius Red staining.

CONCLUSIONS: BLM instillation resulted in a significant accumulation of OxPL in the lungs of WT mice. Neutralizing OxPL with E06 Ab resulted in marked improvement in the survival and significantly less lung fibrosis. These data together suggest that OxPL could be a potential target to ameliorate PF by reducing inflammatory responses and collagen deposition.
Nephrology

**POSTER #84**

**HLA-DR/DQ single molecule eplet mismatch thresholds have inferior prognostic value compared to conventional whole antigen HLA mismatch in a diverse cohort of kidney transplant recipients**

*Clarkson Crane, MD; Elizabeth Ingulli, MD; Gerald Morris, MD PhD*

**BACKGROUND:** Use of HLA Matchmaker HLA-DR/DQ single antigen eplet mismatch has been proposed to evaluate histocompatibility between kidney transplant recipients (KTR) and donors. We aim to validate previously reported thresholds with differential clinical outcomes at our center, with the hypothesis eplet mismatch will have similar or inferior prognostic value compared to conventional antigen mismatch in our cohort.

**METHODS:** Whole antigen HLA-DR/DQ and single molecule DR/DQ eplet mismatches were calculated with HLA Matchmaker (version 3.0) using high resolution HLA typing. We performed Kaplan Meier analysis for outcomes of de novo DSA and acute rejection (AR).

**RESULTS:** 431 KTR (53 pediatric and 378 adult) were included. 80 (19%) developed DSA and 49 (12%) had biopsy proven acute rejection. Using whole antigen mismatch (grouped into 0, 1-2, and 3-4), those with higher mismatch at HLA-DR or -DQ were significantly more likely to develop dnDSA (p = 0.005) and had a trend toward more AR (p = 0.2). Single antigen HLA-DR/DQ eplet mismatch at previously published thresholds demonstrated a trend toward dnDSA formation (p = 0.07) and acute rejection (p = 0.2), however this relationship was highly significant when using eplet mismatch as a continuous variable (p < 0.001 for dnDSA).

**CONCLUSIONS:** Validation of HLA-DR/DQ single antigen eplet mismatch thresholds in our cohort was inferior to traditional whole antigen assessment for clinical outcomes. The significant relationship as a continuous variable suggests a different cutoff may have prognostic utility in our cohort. This may be due to the diverse ethnic makeup and thus variation in HLA haplotype frequencies in our cohort versus those previously reported. Clinicians should exercise caution with use of molecular mismatch until there is additional evidence relating eplet mismatch to HLA biology validated in multiethnic cohorts. Future work aims to determine meaningful thresholds at our center and identify DR/DQ alleles most clinically relevant for molecular mismatch risk stratification.

**POSTER #85**

**Ambulatory Blood Pressure Monitoring in Adolescents: A Comparison of Two Classification Schemata**

*Dylan Hyatt, MD; Elliot Perens, MD, PhD*

**BACKGROUND:** Although hypertension in childhood has been linked with the development of cardiovascular disease and increased mortality in adulthood, it can be challenging to differentiate transiently elevated blood pressure measurements in the clinical setting from sustained hypertension. Ambulatory blood pressure monitoring (ABPM) allows for a more complete assessment of a patient’s blood pressure. Recently the guidelines for interpretation of ABPMs were revised. In this single center retrospective cohort study, we seek to understand the effect of changing diagnostic criteria for ABPM interpretation from the criteria endorsed by the American Heart Association (AHA) in 2014 to the criteria endorsed by the AHA in 2022.

**METHODS:** Data were collected from all subjects over 13 years of age who underwent ambulatory blood pressure monitoring (ABPM) at Rady Children’s Hospital San Diego between January 2018 and December 2020. ABPM studies with fewer than 40 measurements overall or fewer than 6 nighttime measurements were excluded. Each ABPM study was classified based on both 2014 and 2022 AHA criteria. ABPM studies were then classified into eight subgroups based on combining their categorization using both 2014 and 2022 criteria.

**RESULTS:** A total of 18.32% of the cohort changed diagnosis. The majority of subjects had their diagnosis changed from white coat hypertension to ambulatory hypertension, and these patients were on average taller than those whose diagnosis did not change. We found that a higher percentage of these subjects had evidence of left ventricular hypertrophy on echocardiogram.

**CONCLUSIONS:** These findings highlight the need for outcomes research to determine the optimal guidelines for assessment of ABPMs performed on pediatric patients.
ABSTRACTS

Drivers of Vessel Progenitor Fate Define Intermediate Mesoderm Dimensions by Inhibiting Kidney Progenitor Specification
Elliot Perens, Deborah Yelon

BACKGROUND: Proper organ formation depends on the precise delineation of organ territories containing defined numbers of progenitor cells. Kidney progenitors reside in the intermediate mesoderm (IM), bilateral stripes of cells in the posterior mesoderm. Previously, we showed that the transcription factors Hand2 and Osr1 act to strike a balance between the specification of the kidney progenitors in the IM and the laterally adjacent population of vessel progenitors. Recently, the transcription factor Npas4l/Cloche – an early and essential driver of vessel and blood progenitor formation – was shown to inhibit kidney development.

METHODS: Through genetic analyses and molecular anatomical studies, we assess how IM and vessel progenitor fates are coordinated by hand2, osr1, and npas4l.

RESULTS: Here we demonstrate how kidney progenitor specification is coordinated by hand2, osr1, and npas4l. We find that npas4l is necessary to inhibit IM formation. Consistent with the expression of npas4l flanking the medial and lateral sides of the IM, our findings suggest roles for npas4l in defining the IM boundaries at each of these borders. At the lateral IM border, hand2 promotes and osr1 inhibits the formation of npas4l-expressing lateral vessel progenitors, and hand2 requires npas4l to inhibit IM formation and to promote vessel formation. Meanwhile, npas4l appears to have an additional role in suppressing the IM fate at the medial border: npas4l loss-of-function results in excess IM generated outside of the hand2-expressing territory and enhances hand2 mutant IM defects.

CONCLUSIONS: Together, our findings reveal that establishment of the medial and lateral boundaries of the IM requires inhibition of kidney progenitor specification by the neighboring drivers of vessel progenitor fate.

Minimizing Hemodialysis Catheter Complications: A Quality Improvement Project
Jennifer Woodmansee MSN, CNS, CNN; Nadine Benador MD

BACKGROUND: Background: AV fistula is the recommended vascular access by international consensus guidelines for pediatric hemodialysis (HD) patients. However, HD catheters often need to be used due to small size of the patients and lack of local surgical expertise to create AV fistula in children. Preventing complications, which minimizes the need of HD catheter replacement, is of utmost importance for vessel preservation as they may require dialysis care multiple times during their lifetime. US News and World Reports allocates a maximum score for a vascular access rate (# of catheters/# of patients) of less than 1.5. HD catheter line infection is the leading cause of catheter loss and affects patients' morbidity and mortality.

AIM: The number of tunneled HD catheters, existing or placed during the time period of July 2022- June 2023, will be less than 1.5 accesses per unique HD patient.

METHODS: Methods: This is a Quality Improvement Initiative. The Model of improvement was used as the framework for the project. After developing our SMART aim, the multidisciplinary team utilized a “5 whys” diagram in conjunction with the Ishikawa diagram to identify root cause for the high catheter per patient rate of 1.6. The Quality improvement activities included:
1) Formalization of communication workflows between the surgical team and the nephrology team at the time of catheter placement.
2) Collaboration with central supply to allow for all HD catheter sizes to be in a central location and get a careful inventory on the catheters in the hospital.
3) Improving SCOPE BUNDLE compliance for accessing HD catheters.
4) Improving patient education around catheter care at the time of discharge and ongoing maintenance education.

RESULTS: Results: In the year prior to intervention, we had 10 unique HD patients, 6 of them required an exchange of their catheter for a rate of 1.6. In that year, we had 3 episodes of blood stream infections for a rate of 3.79 per 100 patient-months. In the year after intervention, we had 11 unique HD patients and 5 of them required an exchange of their catheter for an improved rate from the previous year to 1.45. In that year, we had no episodes of blood stream infections.

CONCLUSIONS: Conclusion: Improved collaboration with surgical services and materials management at the time of catheter insertion, along with standardization of nurse access practice and patient education, can decrease the rate of catheters per patient and improve the rate of blood stream infections.
Essential Genetic Regulators of Kidney Development Impact Vessel Progenitor Specification
Lisanne Stouthart, MS; Matthew Nunes; Deborah Yelon, PhD; Elliot Perens, MD PhD

BACKGROUND: Congenital anomalies of the kidney and urinary tract (CAKUT) are diagnosed in 1 out of 500 live births. The relatively high degree of familial aggregation of CAKUT suggests a significant genetic component, and disease-causing mutations have already been identified in at least 20 genes. Many of these genes, including the two most frequently mutated genes, PAX2 and HNF1β, have been implicated in early aspects of kidney development. The first step in kidney development is the specification of kidney progenitors within the intermediate mesoderm (IM), a pair of bilateral territories within the posterior mesoderm, flanked by tissues that give rise to vessels, blood, muscle, bone, and peritoneum. Our previous work highlighted a coupling of IM formation with the development of neighboring vessel progenitors (VPs). We demonstrated that the transcription factors Hand2 and Osr1 act in opposition to balance the specification of kidney and VPs at the lateral border of the IM. More recently we found that the transcription factor Npas4l (Cloche), an early essential regulator of VP formation, is required to inhibit IM formation at both the lateral and medial IM borders.

METHODS: Genetic analyses, molecular anatomical studies, single cell RNA-seq, genetic lineage analysis

RESULTS: First, surprisingly, our genetic analyses suggest that essential regulators of IM development – pax2a and pax8 – are required for formation of VPs at the lateral IM border while inhibiting excessive VP formation at the medial border. Second, we observe that lateral VPs co-express genes associated VP and IM fates. Third, our preliminary scRNA-seq data on IM cells (obtained by sorting cells double positive for pax2a and hnf1βa transgenes) further suggest that the IM is divided into subdomains with unique transcriptional signatures and divergent developmental potentials, including a domain capable of generating IM and VPs.

CONCLUSIONS: Together, our data further highlight intriguing genetic and lineage relationships between the IM and neighboring VPs.
Discordance Between Clinical and Pathologic Findings on Post-Induction Kidney Biopsy in Pediatric Patients with Proliferative Lupus Nephritis
Robin Miller, Clarkson Crane, Robert Sheets, Noureddin Nourbakhsh, Elizabeth Ingulli, Katayoon Shayan, Peter Yorgin, Caitlin Carter

BACKGROUND: Systemic lupus erythematosus (SLE) diagnosed during childhood is associated with higher rates of mortality and lupus nephritis (LN) compared to adult-onset SLE. Active lupus nephritis is suspected when a patient has clinical findings including proteinuria, hematuria, hypertension, or a decline in estimated glomerular filtration rate (eGFR) and is confirmed with kidney biopsy. Once a diagnosis of LN has been confirmed on initial kidney biopsy, the utility and optimal timing for subsequent biopsies in LN in has not been established. There is known discordance between the clinical parameters used to diagnose LN and the histopathologic classification. Often clinicians are uncertain about the impact of titrations in immunosuppression when relying solely on clinical parameters. In this retrospective analysis, we describe the histologic findings of LN activity on second kidney biopsy in children diagnosed with LN to explore the utility of serial kidney biopsy in guiding treatment of LN after induction therapy. In addition, we compare patients with and without complete clinical remission to determine if the standard clinical signs of kidney disease can be used to target repeat kidney biopsy procedures to the patients most likely to benefit from the information obtained.

METHODS: We performed a single center retrospective cohort study of all SLE patients who underwent kidney biopsy for lupus nephritis between January 1, 2011 and December 31, 2022 at Rady Children's Hospital, San Diego (RCHSD). Subjects were stratified based on their CARRA renal response into complete renal response (CRR) and incomplete renal response (IRR) groups at the time of the second biopsy. The groups were compared for demographic, clinical and pathologic findings at the time of each biopsy, and induction treatment. Demographic data were not distributed normally, therefore a non-parametric Wilcoxon paired t-test was used for comparison of continuous variables. The Chi squared test was used for categorical data between remission groups. Single predictor and multiple predictor linear regression models were utilized to assess the relationship between clinical factors and histologic findings on second biopsy.

RESULTS: Thirty patients met inclusion criteria for analysis, of whom 18 had achieved CARRA complete renal response (CRR) and 12 had incomplete or no response (IRR) after initial therapy. At time of second biopsy, the CRR group had lower serum creatinine and lower uPCR than the IRR group. The difference in serum creatinine between the two groups was statistically significant (p=0.01), as was the difference between eGFR (p=0.03). At time of second biopsy, both groups had lower SLEDAI scores compared to first biopsy, and CRR group had significantly lower SLEDAI scores compared to IRR group. Of the other clinical markers assessed at time of second biopsy, including age, dsDNA, serum C3, change in C3 between biopsies, and serum C4, none were found to be significantly different between the two groups. In the CRR group, 11/18 (61%) of the subjects had persistent proliferative disease on second biopsy. The remaining 7/18 (39%) showed resolution of proliferative findings. In the IRR group, 11/12 (92%) of subjects with proliferative nephritis on initial biopsy had persistent proliferative nephritis on the follow up biopsy. Only one patient in the IRR group (8%) had improvement to isolated class V LN. Using simple linear regression, only SLEDAI score at time of second biopsy was found to be associated with persistent proliferative nephritis on second biopsy (p=0.04). No other clinical factors, including individual components of SLEDAI score related to kidney function, were found to be significantly associated with persistent proliferative nephritis. No significant association was found between clinical factors (C3, C4, dsDNA, uPCR, serum creatinine, and SLEDAI score) and persistent proliferative nephritis on second biopsy, using a multiple linear regression model. Findings on second biopsy influenced immunosuppressive therapy decisions in both CRR and IRR groups. Among the 11 CRR patients with persistent proliferative disease, 1/11 (9%) had an escalation in therapy, 4/11 (36%) had therapy deescalated, and 6/11 (55%) had no change in treatment. In the CRR with resolved nephritis group, 2/7 (29%) had a de-escalation in their therapy and 5/7 (71%) of patients had no change in therapy. All 12 patients in the IRR group had an escalation in treatment based on the results of the second biopsy.

CONCLUSIONS: Currently available clinical markers of disease remission in lupus nephritis after induction therapy are insufficient to identify children with ongoing evidence of persistent proliferative nephritis. Follow up kidney biopsy is low risk and can be used to guide therapy in children with SLE and nephritis.
Accelerated Epigenetic Aging in Pediatric Onset Multiple Sclerosis
Christopher Goyne, Ashley Fair, Defne Yilmaz, Allison Schuette, Jonathan Race, Stacey Caillier, Gregory Aaen, Aaron Abrams, Leslie Benson, Charlie Casper, Tanuja Chitnis, Mark Gorman, Dimitrios Ladakis, Timothy Lotze, Lauren Krupp, Soe Mar, Jayne Ness, Mary Rensel, Moses Rodriguez, John Rose, Teri Schreiner, Jan-Mendelt Tilleman, Amy Waldman, Yolanda Wheeler, Lisa Barcellos, Emmanuelle Waubant, Jennifer S. Graves

BACKGROUND: Chronological and biological aging are associated with decreasing relapse rates but increasing disability accumulation in multiple sclerosis (MS). Both normal aging and accelerated aging from MS pathology likely contribute to observed phenotypic differences in MS. Biological aging has not been studied in pediatric onset MS (POMS) and demonstrating accelerated biological aging in this population would strongly support the role of MS pathology driving premature biological aging. We sought to measure differences in epigenetic age in POMS participants and controls to determine if epigenetic aging was accelerated in POMS.

METHODS: We performed a cross-sectional case control study, leveraging blood samples and clinical data from the US Network of Pediatric MS Centers. DNA was purified and processed using Illumina's Infinium Methylation EPIC BeadChip technology to generate quantitative methylation scores. Processed methylation scores were used to calculate epigenetic age using standard epigenetic clocks (Horvath, Hannum, PhenoAge, and GrimAge). The epigenetic age from each model was regressed on chronological age to generate an age acceleration residual (AAR), representing the deviation between epigenetic and chronological age. Age acceleration residuals were compared between cases and controls using multivariate regression analysis.

RESULTS: We analyzed samples from 164 POMS cases, and 112 pediatric controls. Age acceleration residuals were significantly greater in POMS participants compared to controls in each of the clocks applied (Horvath AAR difference = 0.85, 95% CI 0.13–1.59, p = 0.02; Hannum AAR difference = 2.36, 95% CI 0.91-3.81, p = 0.002; Phenoage AAR difference = 3.9, 95% CI 1.85-6.04, p = 0.0003; GrimAge AAR difference = 1.05, 95% CI 0.34-1.76, p = 0.004). The difference in AAR remained significant after accounting for biological sex.

CONCLUSIONS: Patients with POMS demonstrate accelerated biologic aging compared to controls as measured by epigenetic age. These data suggest the MS disease state may drive accelerated biologic aging.
Does the median time in pediatric ophthalmology clinic for retinopathy of prematurity patients decrease when patients are pre-ordered dilation drops, irregardless of insurance status?

Lauren Hennein MD

BACKGROUND: Patients who meet criteria for retinopathy of prematurity (ROP) screening are seen frequently in the pediatric ophthalmology clinic, often every few weeks until at least 40 weeks corrected age. It is ideal to minimize the time spent in a busy pediatric ophthalmology clinic to protect this vulnerable population. We hypothesized that pre-ordering dilation drops for caregivers to instill in the eyes one and a half hours prior to their ROP examinations would decrease the median time spent in clinic, irregardless of insurance status.

METHODS: The time from check in to check out at the pediatric ophthalmology clinic for ROP patients was analyzed at baseline (2/1-4/30/23). Starting 5/1/23, the ophthalmic nurse started ordering dilation drops for all ROP examinations prior to their appointments. These drops were ordered to a mail order pharmacy and patients were called to confirm that they would accept the drops being mailed to their homes. A discounted price for patients without insurance was negotiated with the mail order pharmacy. Text messages were sent to the caregivers prior to the ROP appointment to remind caregivers to instill the dilation drops one and a half hours prior to their appointment. Insurance status information was collected (i.e. commercial insurance, Medi-Cal, and TriCare). The difference in insurance status by time from check in to check out was calculated.

RESULTS: The median time from check in to check out at baseline was 81 minutes (February to April 2023; n=154). Starting 5/1/23, dilation drops were ordered for all ROP patients prior to their appointments. The median time from check in to check out from May 2023 to February 2024 decreased to 70 minutes (n=595). There was no significant difference in time from check in to check out by insurance type at baseline (February to April 2023) p=0.19. There was no significant difference in time from check in to check out by insurance type during the intervention period (May 2023 to February 2024) p=0.25.

CONCLUSIONS: The median time spent in pediatric ophthalmology clinic for retinopathy of prematurity patients decreased when patients were pre-ordered dilation drops, irregardless of insurance status. Further studies are indicated to analyze other methods to decrease time from check in to check out for ROP examinations regardless of insurance status.
ABSTRACTS

Pharmacology

Model Based Assessment of VRC07-523LS Dosing in Infants, Use of Population Pharmacokinetic-Pharmacodynamics Modeling in Adult and Infants
Dustin Huynh, Mina Nikanjam , Coleen K. Cunningham, Elizabeth McFarland, Petronella Muresan, Charlotte Perlowski, Dwight Yin, Jack Moye, Lucio Gama, Martin Gaudinski, Edmund V. Capparelli

BACKGROUND: This study developed a popPK model to understand factors affecting VRC07-523LS disposition and predict as well as linked infants’ exposure to HIV-1 sensitivities to predict PT80 and prevention efficacy (PE).

METHODS: PK data from 2 studies were utilized: HIV-exposed infants initiating therapy ≤5 days of age (IMPAACT P1112, n=21) and healthy adults (VRC605, n=25). The infant study implemented flat-fixed s.c. dosing whereas the adult study implemented weight-based dosing, via both i.v. and s.c. routes. Allometric scaling and stepwise covariate analysis were utilized. Monte Carlo simulations of the final model assessed two doses (80 mg followed by 100 mg at 12 weeks) to determine the maintenance of levels &gt;10 µg/mL. The bNAb concentration/IC80 ratio (PT80) was calculated at 8 and 12 weeks based on simulations from the final popPK model and sensitivity distribution of HIV-1 isolates. PT80 values were used to estimate PE based on a previously developed pharmacodynamic (PD) model.

RESULTS: The final popPK model is: Vss/F (L) = 12.53 x (WTKG/70)1.0 x 1.49 (if repeat dose), CL/F (L/hr) = 0.0066 x (WTKG/70)0.85 x 1.69 (if adult), D1 (duration, hours) = 36 x 2.79 (if adult). Between subject variability for Vss/F and CL/F were 35% and 29%, respectively. This model predicts an infant and adult typical CL/F 3.68 and 3.84 mL/kg/day, respectively. Concentrations exceeded 10 µg/mL in &gt;88% of virtual infants at 12 weeks and &gt;98% at 24 weeks. Median PT80 were 117 and 61 at 8 and 12 weeks, estimating HIV-1 PEs of 82.4% and 67.7%, respectively.

CONCLUSIONS: Age and repeat dosing are key factors in VRC07-523LS PK. An 80-mg SC dose of VRC07-523LS followed by 100 mg at 12 weeks rapidly achieves and maintains concentrations &gt;10 µg/mL for more than 24 weeks. This is expected to result in &gt;50% prevention efficacy in infants and supports further evaluation of VRC07-523LS during breastfeeding.

POSTER #93

Investigating the Impact of Concurrent Ototoxic Drugs on Cisplatin-Induced Ototoxicity in Pediatric Cancer
Emilie Chebat, PharmD, Julie Silva, M.A, CCC-A, Megan Paul, MD

BACKGROUND: Cisplatin is an effective chemotherapy used in the treatment of many pediatric malignancies, but it can cause ototoxicity, leading to irreversible bilateral sensorineural hearing loss in children. The associated hearing loss raises significant concerns for the cognitive and psychosocial development of young patients. Known contributing factors include the cumulative cisplatin dose &gt; 400 mg/m2, cranial radiation, and age, where younger children are at more risk of developing moderate to severe hearing loss from cisplatin than adults. More recently, sodium thiosulfate was found to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month and older, but use in our practice has been limited.

METHODS: We conducted a retrospective chart review of 178 patients who received cisplatin at Rady Children’s Hospital between January 2013 and September 2023. Data collected included baseline demographics and potentially ototoxic medications. Sodium thiosulfate administrations were collected to determine its potential to reduce the risk of cisplatin-related ototoxicity. The CHANG Scale was utilized to analyze the status of hearing evaluations, where no hearing loss was defined as Grade 0 and some hearing loss was defined as Grade ≥ 1a on the CHANG scale at the end of treatment.

RESULTS: We evaluated ototoxicity in 174 patients that received cisplatin. Hearing loss occurred at an overall incidence of 55%. Age and cranial radiation was shown to be predictive of hearing loss, which is consistent with previous studies. Notably, there was a statistically significant difference in the number of furosemide administrations between those with no hearing loss and those with some hearing loss. While we attempted to study the potential protective effects of sodium thiosulfate, our data was lacking and unable to be analyzed.

CONCLUSIONS: Our study suggests that age and furosemide may influence hearing loss in pediatric patients receiving cisplatin therapy. However, the limited use of potential protective measures like sodium thiosulfate in our practice precluded their analysis. These findings stress the need for personalized approaches to mitigate auditory complications.
**Effect of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators on Fat-Soluble Vitamin Levels in Pediatric Cystic Fibrosis Patients**

*Samantha Jalbert, PharmD; Kathryn Akong, MD; Sarah Cuevas, PharmD; Sandra Salzedo, RD; Gale Romanowski, PharmD*

**BACKGROUND:** Pediatric patients with cystic fibrosis (CF) are at an increased risk of fat-soluble vitamin deficiency and often require supplementation with CF-specific fat-soluble multivitamins to avoid complications associated with vitamin deficiencies. Since the introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies, many eligible CF patients have had significantly improved nutritional status and overall clinical outcomes. Elexacaftor, tezacaftor, ivacaftor, and ivacaftor (ETI) has improved nutritional status in some patients by restoring pancreatic function and reducing energy expenditure. However, there continues to be a lack of information surrounding the direct effect of CFTR modulators on circulating fat-soluble vitamin levels.

**METHODS:** This was a single-center, retrospective chart review of pediatric patients between 2 to 18 years old diagnosed with cystic fibrosis and initiated therapy with ETI between November 1, 2019 and August 15, 2023. The study aims to evaluate the effect of ETI on serum vitamin A, D, and E levels. Baselines vitamin levels, and the first vitamin levels post ETI initiation (range 53-569 days) were collected. As a secondary endpoint, we measured the change in percent body mass index (BMI) pre-ETI and 1 year post ETI.

**RESULTS:** A total of 62 patients were analyzed in the study with 32 patients (52%) being male. The mean age of initiation of ETI was 10.5 years old. Of the 62 patients, 11 patients were on a different CFTR modulator prior to ETI initiation. Results will be submitted with final poster.

**CONCLUSIONS:** Results will be submitted with final poster.

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**Breast Milk Transfer and Infant Exposures to DTG, TAF, and TFV: Results From IMPAACT2010/VESTED**

*Tk Nguyen, Jung-Woo Chae, Lauren Ziemba, Anne Coletti, Kevin Knowles, Benjamin Johnston, Patrick Jean-Philippe, Tsungai Mhembere, Tariro Chawana, Deo Wabwire, Violet Korutaro, Shahin Lockman, Lameck Chinula, Jeremiah Momper, for IMPAACT 2010/VESTED Protocol Team*

**BACKGROUND:** Limited information is available on breast milk transfer and subsequent infant systemic exposure to dolutegravir (DTG), tenofovir alafenamide (TAF), and tenofovir (TFV). We evaluated concentrations of these antiretroviral treatment (ART) regimens in time-matched samples (maternal plasma, breast milk, and infant plasma) from IMPAACT 2010, a randomized trial that evaluated three ART regimens in pregnancy.

**METHODS:** Pregnant women with HIV in 9 countries were randomized 1:1:1 to start open-label ART with DTG+emtricitabine (FTC)/TAF, DTG+FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF at 14-28 weeks of gestation. Matched maternal and infant samples were prospectively collected at random at Week 6 postpartum. Validated liquid chromatography-tandem mass spectrometry assays quantitated plasma and breastmilk concentrations of DTG, TAF, and TFV. The relative infant dose for DTG, TAF, and TFV was estimated by assuming an average milk intake of 150 mL/kg/day and observed breast milk concentrations.

**RESULTS:** Data were available from 192 postpartum lactating women and their 192 breastfed infants. The mean age of mothers at enrollment was 26 years old, and 85% of participants lived in Zimbabwe, Uganda, or Tanzania. Median (range) maternal plasma concentrations of DTG, TAF, and TFV were 2810 (0.0-7460), 0.0 (0.0-158), and 96.1 (0.0-353) ng/mL, respectively. Median (interquartile range) of DTG, TAF, and TFV concentrations in breast milk and infant plasma samples were 91 (67-123), 0.0 (0.0-0.0), and 8 (6-12) ng/mL and 69 (41-95), 0.0 (0.0-0.0), and 96 (73-123) ng/mL, respectively. The estimated median relative infant dose of DTG, TAF, and TFV from breastfeeding was 1.92%, 0.00%, and 0.03%, respectively.

**CONCLUSIONS:** Breast milk transfer of DTG, TAF, and TFV is low and results in minimal systemic exposure in breastfeeding infants. The clinical relevance of subtherapeutic concentrations of these ART regimens in breast milk is unknown but should be considered in the context of risk of drug resistance in infants who acquire HIV.
Evaluation of a clonidine taper protocol to manage dexmedetomidine withdrawal in critically ill neonates
Halli Helgeson, PharmD; Jeanne Carroll, MD; Amy Kimball, MD; Mark Speziale, MD; Gale Romanowski, PharmD; Nona Chamankhah, PharmD; Elaine Sim, PharmD; Jennifer Kimmel NNP-BC; Jane Kang, BSN, RN-CCRN; Amie Wong, BSN, RN-CCRN; Peggy Grimm, MS, CNS, RNC-NIC; Michael Van Gorder, MHA; Tara Glenn, MD.

BACKGROUND: Sedation and analgesia are often employed to control procedural or non-procedural pain, manage agitation, enhance ventilation, and reduce metabolic demand in term and preterm neonates with various conditions requiring intensive care. Dexmedetomidine is a centrally acting alpha-2 adrenergic agonist with favorable properties such as opioid and benzodiazepine sparing effects, decreased time on mechanical ventilation, and lower risk of delirium when compared to other commonly used sedatives in this population. However, prolonged duration and/or high doses of dexmedetomidine can increase risk of iatrogenic withdrawal syndrome when weaning. To date, a handful of studies have explored the effects of a clonidine taper on dexmedetomidine withdrawal in older children admitted to the pediatric intensive care unit; yet, to our knowledge there is no published literature on protocol-driven dexmedetomidine or clonidine tapers specific to the neonatal population. In September 2022, our institution implemented a neonatal intensive care sedation weaning protocol to guide the transition from continuous dexmedetomidine infusion to enteral clonidine, with tapering approaches stratified by withdrawal risk. The aim of this study is to summarize our experience with a dexmedetomidine to clonidine weaning protocol for prevention or management of dexmedetomidine withdrawal in critically ill neonates.

METHODS: This was a single-center, retrospective chart continued review of neonates admitted to the neonatal intensive care unit at Rady Children’s Hospital (San Diego, CA) and prescribed enteral clonidine tapers following continuous dexmedetomidine exposure of at least 72 hours. Pre-protocol patients from September 1, 2012, to August 31, 2022, were matched in a 1:1 fashion to post-protocol patients from September 1, 2022, to September 30, 2023. Patients were excluded if they received a diagnosis of Neonatal Abstinence Syndrome, transferred to another unit or facility during the taper, or expired during the taper. For this study, dexmedetomidine withdrawal was defined as the presence of agitation, hypertension and/or tachycardia, and elevated WAT-1 scores after discontinuation of dexmedetomidine. Patients were divided into low, moderate, high, and very high-risk groups based on the weaning protocol. Variables related to dexmedetomidine withdrawal will be analyzed for each risk group. Concomitant exposure to other sedatives (opioids, benzodiazepines) within these groups will be described.

RESULTS: Data was collected on baseline demographics, dexmedetomidine characteristics, clonidine characteristics, and withdrawal characteristics as indicated by the WAT-1 scoring tool.

CONCLUSIONS: Results will be submitted with final poster.
ABSTRACTS

A Patient-Centered Model for Closing Care Gaps and Addressing Social Determinants of Health: The Value of Patient Care Coordinators

Monica Angeles, MPH, Dana Patterson, Karen Arias, RN, Negin Javaheerchian, Ashlee Dagdagan, Daniela Hernandez, Zulema Ruiz, Rita Wango, Kenia Zepeda, Erin Dale MSN, RN, FNP-C, Keri Carstairs MD, MBA, FACEP, FAAP, Cassidy Boyd, MPH

BACKGROUND: Rady Children’s Health Network (RCHN), a pediatric clinically integrated network, provides patient-focused care coordination efforts to close Healthcare Effectiveness Data and Information Set (HEDIS) care gaps among children enrolled in their fully capitated Medicaid health plans. Between 2021 and 2023, RCHN was fully capitated with 5 Medicaid plans, serving more than 40,000 beneficiaries in San Diego County. HEDIS Care Gaps of focus include overdue well-child visits, childhood immunizations, lead screenings, and chlamydia screenings which were historically our most challenging. These efforts provide an extra level of support needed for children and families to successfully access care, thereby improving RCHN’s HEDIS measures.

METHODS: A Patient Care Coordinator (PCC) model was utilized to conduct telephonic outreach with the goal of closing HEDIS care gaps. A team of PCCs conducted telephone and Epic MyChart outreach to Medi-Cal members and assisted in scheduling preventative health appointments, providing education on the importance of well-childcare and vaccines, and reconciling health records to provide documentation to the health plans of completion. We worked with the families to find times that appointments met the needs of the family and provided incentives went appointments were completed. All encounters were captured in Epic and Cozeva and served as the basis for this analysis. Additionally, we know that other barriers exist for patients, so our PCCs conducted Social Determinants of Health Screenings (SDoH) and connected families to resources with the most common need to address food insecurity. These screening results were also made available to their primary care medical home.

RESULTS: Across the Medi-Cal plans, compliance for 28 HEDIS measures was improved from 2021 to 2023. Between 2022 and 2023, 18 of those HEDIS measures met or surpassed the National Committee for Quality Assurance (NCQA) 50th percentile mark. The measure with the greatest improvement for all health plans was the Well-Child Visit in the First 15 Months measure, increasing from 8.7% to 53.9% for Plan 1 members, 10.0% to 41.4% for Plan 2 members, 9.4% to 46.3% for Plan 3 members, and 5.1% to 32.1% for Plan 4 members. This is an overall 35% average increase from 2021 to 2023 across all health plans due to reconciliation and appointment efforts (Plan 1: p-value < .001, 95% CI [-0.5189, -0.3861]; Plan 2: p-value < .001, 95% CI [-0.3949, -0.2333]; Plan 3: p-value < .001, 95% CI [-0.5275, -0.2029]; Plan 3: p-value < .001, 95% CI [-0.3825, -0.1569]). Between 2021 to 2023, approximately 4000 SDOH screenings were administered to members, with 15.7% screening food insecure, 6.3% screening transportation insecure, and 14.1% screening housing insecure.

CONCLUSIONS: Utilizing a PCC model to close pediatric care gaps and improve HEDIS measures had a significant impact on our RCHN Medi-Cal population with respect to compliance with well child visits, vaccinations, and preventative screening. Additionally, we provided an added benefit of providing SDoH screening and connections to community resources when indicated. This model could be expanded to have a greater impact on members enrolled in other health plans.
A Culture of Caring: Actionable Insights in Multi-Modal Messaging (Improving Well Child Visit Rates)
Ashlee Dagdagan, Monica Angeles, MPH, Dana Patterson, Karen Arias, RN, Negin Jawaherchian, Daniela Hernandez, Zulema Ruiz, Rita Wango, Kenia Zepeda, Erin Dale MSN, RN, FNP-C, Keri Carstairs MD, MBA, FACEP, FAAP, Cassidy Boyd, MPH

BACKGROUND: Rady Children’s Health Network (RCHN), a pediatric clinically integrated network, provides care coordination efforts to close Healthcare Effectiveness Data and Information Set (HEDIS) care gaps among children enrolled in their fully capitated Medi-Cal health plans. RCHN utilizes EPIC, a cloud-based electronic medical records system along with MyChart, a web portal that allows patients and families to communicate directly with the care team, see upcoming appointments, medical bills, and more. Starting June 1, 2023, MyChart messaging was incorporated into a previously telephonic-only HEDIS outreach program to evaluate the impact on the rate of appointments scheduled and attended. HEDIS Care Gaps of focus include overdue, well-child visits, childhood immunizations, lead screenings, and chlamydia screenings. These efforts provide an extra level of support needed for children and families to successfully schedule and attend preventative care appointments and close HEDIS care gaps.

METHODS: A team of predominantly bilingual (Spanish and English) Patient Care Coordinators (PCCs) conducted telephonic and MyChart outreach with the goal of scheduling preventative care appointments and closing HEDIS care gaps. All patient families received three attempts at contact regardless of participation in Epic MyChart. Those with an active MyChart account received a phone call, a MyChart message, and a final phone call. Those without a MyChart account received three telephonic attempts to schedule an appointment to close the HEDIS care gap. Both modalities were standardized using a script for telephonic outreach and a dot phrase, an automatically generated message with customizable content and a standard subject line for MyChart messages. MyChart messages and phone calls were completed in English and Spanish. All encounters, despite modality, were captured in Epic and served as the basis for this analysis.

RESULTS: During the pilot period, June 1, 2023, to December 31, 2023, 24.9% (307/1,234) of the sent MyChart messages were read while 34.4% (2,728/7,931) of calls made a successful connection (p-value <.001, CI [-0.12, -0.069]). The average time to read the messages was 6.4 days, and 44% (135/307) read the messages in the afternoon, between 12:00 PM and 4:30 PM. Of those messages that were read, 45.2% (139/307) resulted in a preventative care appointment being scheduled while 36.1% (984/2,728) of successful telephonic outreach resulted in a scheduled appointment (p-value = .0015, CI [0.034, 0.15]). Of those appointments scheduled 76.3% (106/139) of those made over MyChart were attended while 54.5% (513/941) of those made over the telephone attended (p-value <.001, CI [0.14, 0.29]). Appointment completion is 21.8 % higher (MyChart - 106/139; Telephonic - 513/941) for those communicated with over MyChart than telephonic, resulting in statistical significance. When comparing the impact of MyChart messaging between those who listed English as their preferred language or another language, non-English speaking families are 30% more likely (Non-English MyChart Message 15/19; English MyChart Message 90/120) to schedule an appointment as a result of a MyChart message in Spanish being sent when compared to families who are English-speaking (p=.006, CI [-0.46, -0.093])

CONCLUSIONS: Effective outreach methods and communication with families and patients are the first of several key steps to closing HEDIS care gaps. By assisting with the scheduling of and ensuring that patients attend preventative care appointments with primary care providers, we can best support families to close care gaps. When compared to telephonic outreach, our approach suggests that significantly more families will schedule and complete their appointments if contacted using a patient portal such as MyChart instead of the phone, even if English is not their preferred language. This new approach has been successful, and our next steps will be to explore the impact of text messaging as another mode of communication. Utilizing a multi-modal approach for outreach and scheduling has been successful in our network and could be applied in other settings to improve HEDIS measures and successful connections to the medical home.
Discharge Education Materials for Families in the Psychiatric Emergency Department

Sijia Zhang, Christine Novotny, Ekta Patel

BACKGROUND: Youth are increasingly experiencing mental health crises with suicide rates for people aged 10-24 rising 62% from 2007 to 2021 in the United States (1). Interventions to reduce suicide risk include inpatient hospitalization or emergency department admission with development of a safety plan and follow-up with mental health providers. The post-discharge period is an especially vulnerable time for such patients with increased suicide rates and other adverse events (2). For children, post-discharge involves re-integration into their life often with significant time spent with their parents and at school. Parental relations have been identified to be the most consistent protective factor for adolescent suicide (3). Parents can support children by safety-proofing the house, de-escalating crises, and bringing their children to the emergency department in case of imminent harm. However, per scoping reviews (4, 5) and our review, there are no studies to date querying the mental health education that parents of children admitted for psychiatric treatment request at discharge.


METHODS: We designed a survey for parents of children admitted to the Rady Children Hospital of San Diego’s behavioral health emergency department (BHED). The surveys were administered at routine meetings between a BHED nurse and parent to overview discharge planning with a response rate of 100%. Based on the needs assessment survey, we created educational materials to be incorporated in the patients’ discharge instructions.

RESULTS: Our survey asked parent participants (n=37) if they would like to be provided information in the form of educational handouts about the following topics at discharge:
1. Their child’s mental health diagnoses (89% responded “yes”)
2. General parenting skills (86% responded “yes”)
3. Locking up guns and medications (62% responded “yes”)
4. Talking to kids with suicidal thoughts/de-escalation crises (97% responded “yes”)
5. Risk factors and warning signs of suicidal ideation (95% responded “yes”)

CONCLUSIONS: We provide evidence that parents of children admitted to the psychiatric emergency department would like to be supported at discharge with educational materials. Such handouts include topics such as instructions on how to safety proof, parenting skills, supportive communication during a mental health crisis, and identifying warning signs for suicidal ideation. We have incorporated these topics in the form of a discharge packet provided to parents. Further investigation is needed to better understand if such educational materials are associated with improved outcomes following discharge from the pediatric BHED. Future directions include administering a survey to assess parent satisfaction of our developed educational materials.
ABSTRACTS

Residents

Determining the Effectiveness of an ‘Outpatient Procedures and Emergencies in the Primary Care Setting’ Curriculum for Differentiated Senior Medical Students

Ani Papazian, MD; Lawrence Ma, MD; Perrie Pardee, MD; Danielle Hatt, MD; Priyanka Patel, MD; Tara Fleming, MD; Helen Wang, MD

BACKGROUND: The majority of pediatric residents will graduate and practice outpatient general pediatrics. Although pediatricians regularly treat patients with urgent conditions, only 50% feel prepared to manage common outpatient emergencies. This gap in preparedness has consequences on patient safety and quality of care, especially in areas where access to care or subspecialists are poor. Few existing Medical Education curricula focus on teaching outpatient pediatric emergency and procedure skills at both the undergraduate and graduate medical education level. Our course attempts to address this at an early stage of training, focusing on providing education to rising Pediatric, Med-Peds, and Family Medicine interns, to allow for scaffolding to occur as they progress through residency.

METHODS: Through role play and guided reflection by four trained facilitators, medical students participated in a 2 hour long experiential learning course using 9 primary care cases with 19 unique learning objectives and procedures. Cases included management of croup, hypoxia, anaphylaxis, bronchiolitis, and acute asthma exacerbation. Procedural skills included reducing a nursemaid’s elbow, practicing urinary catheterization, performing naso-aspirator/nasopharyngeal suctioning, providing supplemental oxygen, and swabbing for strep, pertussis, and influenza. Participating students completed a survey immediately before and after the session. Data was analyzed using SPSS to determine effectiveness and to refine the curriculum. Pre- and post-course mean confidence scores were compared using two-sample t-test.

RESULTS: We had a total of 23 fourth-year medical students entering Pediatrics, Med-Peds, or Family Medicine residency participate. For each of the 19 unique learning objectives, participants felt more confident in their management and procedural skills after the course. All differences were found to be statistically significant with a p-value <0.001.

CONCLUSIONS: This course increased senior medical students’ confidence in identifying and managing outpatient pediatric emergencies and in performing common outpatient pediatric procedures. The strengths of this course include its effectiveness and low implementation costs in terms of materials and facilitators. Through this curriculum, we hope to better prepare physicians, especially those practicing in low resource communities, to manage and stabilize patients who require procedures or present with emergent concerns. Future directions include: adding additional simulation scenarios, implementation at other academic institutions, and tracking the longitudinal impact on participants’ confidence levels with common outpatient procedures and emergencies as they progress through residency and beyond.

Bronchodilator Response: A Prognostic Indicator for Inhaled Corticosteroid Efficacy in Pediatric Patients with Asthma

Heriberto Martinez MD, Daniel Lesser MD, Jeremy Landeo-Gutierrez MD, MPH, Kelan Tantisira MD, MPH

BACKGROUND: Inhaled corticosteroids (ICS) are the recommended controller therapy of choice for pediatric patients suffering from mild persistent asthma. In this study, the goal was to identify which asthmatic children were more or less likely to respond to ICS, as defined by improvement in lung function, in the context of a pediatric pulmonology practice. We hypothesized that baseline bronchodilator response (BDR) is a significant predictor of an individual’s response to ICS.

METHODS: This retrospective study analyzed children between 5 and 18 years of age from the Rady Children’s Hospital San Diego pulmonary clinic from January 2019 to May 2022 who had been diagnosed with asthma. These patients had baseline pulmonary function tests (PFT) which were used to calculate a BDR before initiating ICS therapy. Follow-up PFTs obtained at least 3 weeks after initiating ICS were used to assess changes in lung function, indicating a response to therapy.

RESULTS: Among 16 patients, baseline BDR and change in FEV1% while on ICS were positively correlated, r(16) = .73, p < .05. The 6 patients who had high BDR at baseline (M = 15.7, SD = 12.8) compared to the 10 patients who had low BDR (M = 1.1, SD = 8) demonstrated significantly higher changes in FEV1%, t(16) = 2.8, p < .05, following ICS. Furthermore, patients with high BDR at baseline were 12 times more likely to have a notable lung function response to ICS.

CONCLUSIONS: Baseline BDR is associated with response to ICS in pediatric patients with asthma. As baseline BDR increases so do the changes between FEV1% in follow up visits while on ICS therapy. Furthermore, patients who have high baseline BDR have significantly higher responses to ICS. Overall, BDR may be an adequate parameter in identifying asthmatic children who could be considered responders to ICS in the real-world clinical setting.

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ABSTRACTS

Residents (cont.)

A resident education session to improve care for immigrant children
Anne Kaufman, MD; Janine Young, MD

BACKGROUND: Refugee, immigrant and migrant (RIM) children have unique healthcare needs. Pediatricians must provide comprehensive care for all patients, but most residency programs have not incorporated training on RIM health. High quality resources including CareRef and CDC Domestic Refugee Screening Guidelines, exist to guide clinicians, but many physicians are not aware of these resources.

METHODS: We developed a training session for pediatric residents (PGY2-4) on RIM health in October 2023. This four-hour session included faculty-led didactics on health screening, hepatitis B and C, HIV, tuberculosis, confidentiality, female genital cutting, and cross-border partnerships. The session concluded with a funded panel of community experts from the San Diego Refugee Communities Coalition who discussed their experiences with healthcare, language barriers, cultural practices, and reception by US medical providers. Panelists represented the following communities: Iraqi, Haitian, Karen, Burmese, Somali, and Afghan. We surveyed residents to assess their experiences with immigrant healthcare and session feedback. A follow up survey is in process.

RESULTS: The post-session survey demonstrated that most (89%, n=17) residents cared for immigrants on a daily to weekly basis. Thirty-seven percent of residents had heard of CareRef and 58% knew of CDC Domestic Refugee Screening Guidelines, but only 11% and 32%, respectively, had used these resources clinically. The community panel was the most popular component, and residents asked how to reach these cultural experts and their ethnic community-based organizations to support patients. Residents suggested further talks on immigrant statuses and services for which they qualify, common medical issues, and advocacy.

CONCLUSIONS: The new training session on RIM health emphasized the need for improved training, communication, and healthcare navigation. Given that San Diego has large immigrant communities and that UCSD is at the border, we suggest the development of a required immigrant health rotation to include evidence-based screening, essential medical diagnoses, language barriers, legal status, and advocacy.

Genetic testing in a pilot study comparing rapid whole genome sequencing and a congenital heart disease gene panel
Brianna Naumchik, Hung Nguyen, Lauren Olsen, Kasia Elsworth, Stephen Kingsmore, Nathaly Sweeney

BACKGROUND: Congenital heart disease (CHD) is the leading cause of congenital anomalies and a major contributor of infant morbidity and mortality. Whole genome sequencing (WGS) has been shown to significantly improve diagnostic yield when there is suspicion for an underlying genetic diagnosis in CHD. While an effective diagnostic tool, WGS is a costly test that should be used judiciously. Herein we performed an analysis to determine the characteristics of children with CHD referred to a genomic study comparing CHD gene panel testing and WGS.

METHODS: Presurgical patients with CHD were enrolled following consent. WGS and CHD gene panel testing was conducted on participants and parents if they opted in. Participants’ demographics, clinical history and genetic results were reviewed and recorded in a database. Rate of genetic diagnosis for both testing modalities was ascertained.

RESULTS: The majority of patients (73%) were diagnosed with a cardiac lesion prenatally. Only a few had advanced prenatal genetic testing. Overall, the average gestational age for the cohort was 37.4 weeks and only two infants had birth weights < 1500 grams. Almost half of the patients exhibited extracardiac abnormalities. This cohort had more complex cardiac lesions compared to patients with CHD hospitalized over the same time period. WGS led to a higher diagnostic yield compared to the CHD gene panel, 17% vs 10% respectively. There was a 23%% infant mortality rate in this cohort.

CONCLUSIONS: In summary, most of the patients received a prenatal CHD diagnosis, were born at term and appropriate size. The infant mortality rate for this cohort was similar to national rates for critical CHD. There was a 1.7x increase in diagnostic yield using WGS compared to a CHD gene panel. It is possible that the severity of cardiac lesions in this cohort resulted from a selection bias based on pursuing diagnosis for these critically ill children.
Factors Affecting Bony Consolidation in Craniosynostosis Patients Undergoing Cranial Distraction Osteogenesis
Hunter Faris, MD, Lucy Sheahan, MD, Mckay Reese, BS, Chelsea Rapaport, MS, Anna Hedberg, BS, Justin Ryan, PhD, Asra Hashmi, MD, Amanda Gosman, MD

BACKGROUND: Cranial distraction osteogenesis in treatment of craniosynostosis has many demonstrated benefits, however, questions remain on how to optimize outcomes. Postoperative protocols for latency, distraction, and consolidation are guided by clinical observations rather than prospective studies. This study aims to identify the effect of patient factors and postoperative protocols on consolidation formed in children undergoing distraction osteogenesis for craniosynostosis.

METHODS: A retrospective review of patients with craniosynostosis who underwent distraction osteogenesis between September 2015 and May 2023 was completed. Patients with pre-operative and post-operative CT scans were included. Mimics software was used to create 3-D reconstructions of pre- and post-operative CTs. Geomagic software was used to measure the surface area of the distraction gap between osteotomies and residual bony defects. Linear regression models were used to analyze which patient variables independently predicted consolidate formation.

RESULTS: Seventy-two patients were identified and 48 met inclusion criteria. Median age at surgery was 286 days, with 33 patients (69%) undergoing surgery prior to 1 year old. Suture involvement included 19 unicoronal, 9 unilateral lambdoid, and 20 multisuture, 9 of which were bicoronal. Seventeen patients had syndromic diagnoses. The latency period was 72 hours and distraction period was 35.7 + 10.3 days. The consolidation period as measured between start of consolidation and postoperative CT was 72.8 + 40.7 days. When controlling for other factors, only the length of the consolidation period significantly predicted higher proportion of bony consolidate within the distraction gap (B = .39, p = .01).

CONCLUSIONS: Our findings demonstrated that longer distraction periods may be beneficial. Age was determined to be a non-significant finding, which was surprising due to the loss of dural osteogenic potential as patients near 1 year old. Our findings are reassuring in that current practice patterns are not detrimental to patient outcomes, however further analysis is needed in larger, prospective cohorts.

Circulating and Placental Growth Differentiation Factor-15 are Significantly Altered in Pregnanacies Complicated by Obesity
Jonathan A. Hermel, Fenghua Zeng, Dustin D. Flannery, Sagori Mukhopadhyay, Alvaro Zevallos Barboza, Madeline Pfeifer, Sarah Lazar, Kathleen Fisch, Virginia Cheung, Mana Parast and Eniko Sajti

BACKGROUND: Obesity in pregnancy is associated with adverse outcomes for mothers and neonates. Chronic low-grade inflammation, characteristic of obesity, is thought to drive these complications. Growth differentiation factor-15 (GDF15) counterbalances excessive energy intake and facilitates adaptation to inflammation. We hypothesized that placental GDF15 gene expression and serum GDF15 protein levels are altered in obese pregnant persons and their fetuses.

METHODS: Gene expression was tested on the placenta and fetal membranes of 2 lean (pre-pregnancy BMI &lt; 25) and 2 obese (pre-pregnancy BMI &gt; 30) with otherwise uncomplicated term births. We performed single-cell RNA sequencing (scRNAseq) using the 10x Genomics platform and analyzed with the SEURAT pipeline. We additionally selected paired maternal and cord serum samples (18 lean, 18 obese) from a cohort at Pennsylvania Hospital of 4717 parturient patients and 4765 infants born full-term. Within each group, an equal number of neonates (n=6) were classified as either SGA, AGA, or LGA (Fenton 2013). A balanced distribution of sexes was maintained. GDF15 levels were measured with ELISA. Differences in mean concentrations were estimated using a linear mixed model.

RESULTS: ScRNAseq analysis revealed an increase in GDF15 gene expression in placental and fetal membranes of obese participants. Maternal GDF15 levels were more than six-fold higher than their neonates irrespective of obesity. GDF15 levels were higher in lean mothers as compared to obese mothers (15388 pg/mL vs 13482 pg/mL, p &lt; 0.05). Cord GDF15 levels did not vary with pre-pregnancy BMI or birthweight. Among lean pregnant women, greater levels of maternal GDF15 levels were associated with LGA neonates.

CONCLUSIONS: Our study is the first to compare GDF15 protein levels in maternal-fetal dyads. Our results suggest biochemical processes driving distinct GDF15 expression patterns in mothers and fetuses. Moreover, GDF15 may regulate the effects of maternal obesity on neonatal development.
Diversity of immunologic memory in human upper airways

L. Benjamin Hills, Sydney I. Ramirez, Farhoud Faraji, Paul G. Lopez, Hannah Stacey, Henry J. Sutton, Benjamin Goodwin, Hyun Jik Kim, Sara Mashoof, Carol H. Yan, and Shane Crotty

BACKGROUND: The upper respiratory tract (URT) is a major site of infection by human pathogens, yet little is known about adaptive immune responses in these tissues. Studies of human immune responses to URT pathogens have traditionally examined B and T cells from peripheral blood, largely due to sample accessibility. However, this approach fails to capture local immune responses at the primary site of infection.

METHODS: In this study, we demonstrate robust isolation of diverse T and B cell subsets from the human URT using relatively non-invasive nasal and nasopharyngeal swabs. By single cell sequencing and spectral flow cytometry, we identify populations of T and B cells critical for protection in barrier tissues including CD4 and CD8 resident memory T cells (TRM) as well as resident memory B cells (BRM) and mature plasma cells. Surprisingly, we also capture germinal center (GC) B cells and GC T follicular helper (TFH) cells from adenoids, demonstrating an effective method to study often-inaccessible responses in human secondary lymphoid organs.

RESULTS: To investigate antigen-specific immune responses, we develop and validate novel computational and experimental methods to analyze single-cell T cell receptor (TCR) and B cell receptor (BCR) repertoires in the human URT. We identify SARS-CoV-2 (SARS2)-specific T and B cells from donors with recent COVID-19 breakthrough infection, including clonally expanded SARS2-specific GC B cells and antibody secreting cells.

CONCLUSIONS: These findings have broad relevance to human immunology, infectious disease, and vaccine development. This work was supported by NIH grant CCHI AI142742.

Stenotrophomonas maltophilia colonization in the pediatric intensive care units of an academic hospital: a retrospective study

Natalie Rodriguez, Alice Pong

BACKGROUND: Stenotrophomonas maltophilia is an opportunistic pathogen that poses a significant and increasing threat as a multi-drug-resistant organism, according to the World Health Organization. The majority of research associated with S. maltophilia colonization is focused on adults. Limited studies are available for pediatric patients. This study aims to address this gap by exploring the clinical characteristics of pediatric patients colonized by S. maltophilia with a focus on respiratory sources during their stay in intensive care units (ICUs) at a children's hospital in the United States. The identification of associated risk factors can inform the implementation of effective measures to mitigate the spread of this bacteria, prevent infections, identify high-risk patients more susceptible to colonization, and inform improved management practices in pediatric ICUs.

METHODS: This is a retrospective analysis of 455 positive Stenotrophomonas maltophilia in pediatric ICUs over a 5-year period cultures of Ste from 2016-2021.

RESULTS: There were 131 first positive S. maltophilia cultures from a single source (respiratory, blood, or other body fluid) collected at least 48 hours after an ICU admission during 2016-2021 from 123 patients. The highest prevalence occurred in 2016, accounting for 22% of all cultures, while the lowest prevalence of 11% was in 2019. Overall, the CVICU (38%) had the highest prevalence compared to the NICU (27%) and PICU (35%). Of these cultures, 90% (n=118) were from a respiratory source of 118 patients (endotracheal tube, 69.5%; tracheostomy on vent, 23.7%; tracheostomy off vent, 3.4%; no artificial airway, 1.7%; bronchoalveolar lavage, 1.7%). For 92% of patients, this was their first lifetime documented positive S. maltophilia culture. Most patients (91%) had more than one chronic underlying comorbidity on admission, were on ventilatory support (91%) for 11 [5-16] days, and were treated with anti-pseudomonal antibiotics (75%) for 6 days [3-9] within the prior 14 days from culture collection.

CONCLUSIONS: Positive S. maltophilia cultures were mostly from respiratory sources and patients with more than one underlying comorbidity. Most pediatric patients were on ventilatory support, but most were not on anti-pseudomonal antibiotics for longer than 7 days within the 14 days prior to the first positive S. maltophilia respiratory culture.
Regulation of tumor inflammation by the PKA signaling pathway
Mark Fang, Sendi Adame Garcia, Valeria Burghi, Xingyu Wu, Dana Ramms, Corina Antal, Gene Yeo, Silvio Gutkind

BACKGROUND: Dysregulation of the GPCR/protein kinase A (PKA) signaling axis is now increasingly appreciated as a powerful driver in the progression many neoplasms, including bone cancers, some forms of pediatric hepatocellular carcinoma, melanoma, medulloblastoma (sonic hedgehog group), ovarian cancer, and pituitary adenomas. In recent unpublished work in the Gutkind Lab, Dr. Garcia has shown that GPCR/PKA signaling increases cyclooxygenase 2 (COX2) activity and production of inflammatory prostaglandins (e.g. PGE2). This inflammatory signaling has been shown to drive exhaustion of antitumor immune cells in the TME and allow solid tumors to escape immune surveillance. In parallel, recent unpublished work in the Gutkind Lab using mass spectrometry to study protein-protein interactions with PKA as well as differential phosphoproteomics revealed close connections with RBPs involved in RNA processing. Dr. Ramms and Dr. Burghi showed that PKA directly interacts with ADAR1, HuR/ELAV-like protein 1 (ELAVL1), DCP1A, UBAP2L, and several other RBPs associated with the splicing, translation, and degradation of RNA transcripts. These studies raise the intriguing possibility that dysregulated GPCR/PKA signaling promotes an inflammatory state in the TME of solid tumors by modulating RBPs involved in processing of pro-inflammatory RNAs. To this end, in this project I investigate how the PKA signaling pathway intersects with RNA processing proteins and how this crosstalk impacts expression of pro-inflammatory RNAs.

METHODS: My in vitro model systems: 1) Engineered HEK293 cells with doxycycline-inducible expression of either wild-type (WT) or constitutively active mutant PKA (specifically the catalytic subunit). 2) Engineered HEK293 cells expressing G3BP1-GFP that enables visualization of stress granules. I performed time-lapse immunofluorescence (IF) imaging to quantify the impact of PKA pathway activation on formation and resolution of two RNA processing bodies (stress granules/SG, processing bodies/PB). I also use IF to examine how PKA pathway activation modulates the subcellular localization of RNA binding proteins to RNA processing bodies (SGs, PBs, splice granules) or the nucleus. Doxycycline induced expression of exogenous PKA or forskolin+IBMX small molecules were used to activate the PKA pathway. In parallel, I used Western Blotting with co-immunoprecipitation to investigate whether several candidate RNA binding proteins directly interact with the PKA protein. These candidate RNA binding proteins are those that were identified in prior protein-protein interaction proteomics or differential phosphoproteomic analyses by Dr. Ramms and Dr. Burghi. I also performed RNA seq followed by qRT-PCR to examine changes in expression of genes involved in tumor inflammation and immunosurveillance.

RESULTS: I have shown that PKA pathway activation with either overexpression of exogenous PKA protein or with small molecule activation (forskolin + IBMX) inhibits stress granule formation in response to oxidative sodium arsenite stress. Additionally, overexpression of PKA protein inhibits processing body formation in response to oxidative stress, while small molecule PKA activation enhances processing body formation. PKA pathway activation also alters expression of several pro-inflammatory gene networks, including those of type I and type II interferons, several interleukins (IL2, IL15, IL21), and eicosanoid biosynthesis of inflammatory lipids such as prostaglandins.

CONCLUSIONS: The PKA signaling pathway does alter expression of inflammatory markers, which potentially occurs mechanistically via modulation of RNA processing organelles such as stress granules and processing bodies. Current continuing work aims to illuminate the details of how the PKA pathway regulates specific RNA binding proteins in RNA processing organelles and how this in turn may control RNA processing and translation.
ABSTRACTS

Implementing the Pediatric Anti-Racism Curriculum (PARC) as part of Residency Education at the University of California, San Diego (UCSD) and Rady Children’s Hospital

Melissa Campbell DO, MPH, Chandani DeZure MD, MBA, and Atim Ekpenyong MD

BACKGROUND: There has been growing recognition of racism and ensuing health inequities in the delivery of pediatric healthcare (1). Pediatric residencies play a crucial role in shaping future physicians and fostering a culture of inclusivity and equity. There is a lack of research exploring the impact of educational interventions focused on equity, diversity, and inclusion (EDI) within pediatric residencies (2,3). The Pediatric Anti-Racism Curriculum (PARC) was designed by pediatric hospitalists in 2022 to examine and address racism in healthcare (4). To date, PARC has not been studied after implementation within a pediatric residency education curriculum. The study seeks to address the need for promoting a more inclusive and equitable healthcare environment by implementing PARC within pediatric residency education and examining its effects. Study goals included: -Assessing changes in resident knowledge and understanding regarding EDI principles, cultural humility, and implicit biases. -Measuring changes in resident attitudes, perceptions, and beliefs related to racism and health inequity in healthcare. -Examining the impact of PARC on resident behaviors regarding patient care, communication, and collaboration with diverse patient populations. -Exploring resident perceptions regarding the effectiveness of PARC, relevance, and potential areas for improvement.

METHODS: The curriculum took place during resident noon conferences over 13 sessions between July and November 2023, IRB approval was granted by UCSD. An email was sent to residents with an attached consent form and links for the pre-survey (20 questions) and demographic survey (4 questions). After the last session, the post-survey (23 questions) was emailed to residents and responses gathered until 12/31/23. In addition, 2 90-minute small focus group discussions led by an independent third party took place to provide in-depth information on the impact of the curriculum. Participants were encouraged to read all PARC materials in order to participate in the focus groups. A small honorarium was given to focus group participants. Funding for the project was provided by AAP-CA3.

RESULTS: Responses to surveys: Demographic (19), Pre-Survey (25), Post-Survey (20) Number of PARC Sessions Attended: 1-2 (45%), 3-4 (40%), &gt;5 (15%) Participants in the Focus Groups: PGY1 (2), PGY2 (5), PGY3 (2) Most participants identified as White and not as first generation college graduates as seen in Figures 1 and 2. Table 1 compares responses from the PARC pre-survey and post-survey. 90% of participants were satisfied to very satisfied with their EDI education after PARC implementation compared to 56% of participants before PARC 85% of participants felt that PARC was effective to very effective at improving their knowledge and understanding of certain aspects of EDI 95% of participants were satisfied to very satisfied with the opportunities for open dialogue and discussion on EDI topics with the PARC compared to 56% of participants without PARC 100% of participants thought PARC should be included in their EDI education 4 questions were used in the Focus Groups with summaries of discussions highlighted below: What were you hoping to get from the current Pediatric Anti-Racism curricula that you haven't received in any of your past medical training? A focus on learning, self-improvement, and the application of knowledge in medical practice. There was a strong desire mentioned for practical skills, a deeper understanding of biases, and an appreciation for diverse perspectives and evidence-based learning. How has the Anti-Racism curriculum improved your ability to manage patients from diverse racial/ethnic backgrounds? Sentiments expressed are mixed, with a general trend towards increased awareness and a desire to improve patient care practices. While some participants have begun to implement changes, others feel they need more time or practice to see a significant impact. The curriculum has sparked reflection, realization, and a commitment to equitable care, but also highlighted the challenges in changing deeply ingrained behaviors and biases. Considering the knowledge and skills you've acquired from the curriculum, what resources do you now have to effectively recognize and counteract explicit biases and microaggressions that may impact your patients? The sentiments expressed indicate a journey of increased awareness and understanding of microaggressions and implicit biases, facilitated by the curriculum. The emotional responses ranged from fear and motivation to increased comfort in discussing sensitive topics, highlighting the curriculum's role in fostering a more open and reflective approach to issues of race and privilege in pediatric healthcare. Reflecting on the curriculum, what important topic or perspective do you think was absent from the discussions about racism in healthcare? The need for deeper, more diverse, and more accessible content.

CONCLUSIONS: Overall, it was statistically significant that participants were overall more satisfied with their EDI education after the implementation of PARC and all participants thought it should be included in their EDI education. Most felt the PARC was effective to very effective at improving knowledge and understanding of implicit biases, culture humility, and addressing racism in health. Most participants were very satisfied with the opportunities for open dialogue and discussion about EDI topics. The findings from the Focus Groups are represented by questions. Given the breadth of the topic there is some overlap in themes between each of the 4 questions analyzed. However, this approach was chosen in lieu of a traditional summary of the entire interview to compensate for the small sample size of the participants. Limitations: Variability in resident schedules led to inconsistency in participation in the PARC discussions and varied learning preferences were significant concerns. There was a desire for a more integrated approach that considers the diverse needs and constraints of the participants. Focus Groups had a limited sample size due to time restraints and requirement of completing all materials. The results may not adequately represent the broader group of all who attended the curriculum, thus may not capture all the perspectives of those who participated in the PARC and increases the risk of bias. This research was not intended for statistical generalizability. -Participants were more satisfied with EDI education after the implementations of PARC and felt is should continued to be implemented. -PARC delivery needs to be refined in a way that is more conducive for resident learning given the rigor of their schedules.
Exposure of breast milk to infants ≤ 34 weeks gestation after discharge from a level III NICU in San Diego
Samantha Fine, Shiyu Bai-Tong, Keriann Schulkers Escalante, Sydney A. Leibel, Sandra L. Leibel

BACKGROUND: Breast milk provides immunologic, neurodevelopmental, and nutritional benefits to infants. However, providing breast milk can be a complicated and challenging process for mothers to infants in the NICU. We examined a cohort of infants ≤34 weeks gestation from level III NICUs in San Diego to determine their monthly exposure to breast milk after NICU discharge. The objective of this study is to determine the type of nutrition (breast milk, formula, or mixture of breast milk and formula) that infants ≤34 weeks gestation receive after NICU discharge.

METHODS: Forty-four preterm infants (23-34 weeks gestation) were enrolled in the MAP (Microbiome, Atopic disease, and Prematurity) Study, which was a prospective, multi-center cohort study at level III NICUs in San Diego. Milk feeds were assessed weekly during NICU admission and monthly after discharge to determine if formula, breast milk, or mixture of breast milk and formula was used in each feed.

RESULTS: Fifty percent of infants continued to be exposed to breast milk one month post-NICU discharge. Breast milk feeds decreased to 14% by month 4 and 0% by month 5. Twenty-seven percent of infants were exposed to mixed feedings at month 1, which decreased to 11% by month 3 and 0% by month 5. By 5 months post-NICU discharge, all infants were receiving only formula.

CONCLUSIONS: The majority of infants that were discharged home on breast milk were receiving exclusive formula feeds by 5 months post-NICU discharge. It is known that breast milk is beneficial to preterm infants; however, there is a decrease in breast milk feeds post-NICU discharge in this study. This study highlights the need for greater efforts to understand why breast milk exposure decreases post-NICU discharge. We have initiated a prospective survey to better understand the barriers and supportive factors to provide preterm infants with breast milk during and after NICU admission.

Considering Renal Cell Carcinoma (RCC) in the differential for pediatric patients presenting with headaches and acute-onset cranial nerve palsy
Shadi Shams, Abigail G. Broughton, Katrina May Lambeth, Katherine Dove

BACKGROUND: Renal cell carcinoma (RCC) in pediatrics is rare, and brain metastasis occurs in only 4-11% of cases within one to five years of renal symptom onset. Patients with metastasis may exhibit atypical site-specific symptoms alongside typical urological manifestations.

METHODS: N/A

RESULTS: A 14-year-old previously healthy female presented with 3 weeks of left-sided headache, dysphagia, and left-sided tongue deviation. Review of systems was negative for weight loss, abdominal pain, and hematuria. Blood work, urinalysis, and CSF studies were normal except for an elevated ESR. Two initial brain MRIs, MRI cervical spine, and CT angiogram of the head and neck, all with and without contrast were normal. Given concern for additional cranial nerve involvement, MRI brain with and without contrast with Fast Imaging Employing a Steady-state Acquisition (FIESTA) sequence was performed, revealing an aggressive infiltrative osseous lesion on the clivus of the left occipital bone near the hypoglossal canal. MRI spine showed metastatic deposits on T3, T8, and L3 vertebral bodies and a 10-centimeter left renal mass. A biopsy of the mass confirmed TFE3-Rearranged RCC.

CONCLUSIONS: This atypical presentation of metastatic renal cell carcinoma highlights the necessity of maintaining a broad differential diagnosis, pursuing a thorough evaluation of the cranial base and foramina with high-resolution imaging in cases involving cranial neuropathies, and facilitating early oncologic intervention to improve patient outcomes.
ABSTRACTS

Increasing HIV & Syphilis Testing for Adolescents in the Emergency Department
Taylor Jarvill MD, Leah Izmirlija RN BSN, Daniel Roderick MSN RN CNL, Tatyana Vayngortin MD, Amy Bryl MD, Lukas R. Austin-Page MD

BACKGROUND: Adolescents face barriers to screening and treatment of sexually transmitted infections. Emergency departments (EDs) can provide and arrange screening, treatment, and appropriate follow-up. Our quality improvement (QI) initiative aimed to increase the proportion of ED patients aged 12 years undergoing peripheral IV (PIV) placement or phlebotomy who had HIV and syphilis screening tests done from 2.5 to 25% by May 31, 2023.

METHODS: Our QI team was comprised of ED physicians, ED nursing, hospital registration, lab, compliance, and informatics stakeholders. We constructed a key driver diagram and identified multiple interventions for implementation. Our primary measure was the weekly proportion of adolescent ED visits requiring PIV or phlebotomy that had HIV and syphilis testing performed. Process measures included the proportion of the eligible population with gonorrhea and chlamydia testing done concurrently. Outcome measures included the proportion of HIV/syphilis tests that were positive and the proportion of patients with positive tests linked to care. Balancing measures included false positive results and reported difficulties with disclosure and follow-up. Measures were analyzed using statistical process control to examine changes over time.

RESULTS: From December 2022 to December 2023, the weekly proportion of eligible adolescents tested for HIV and syphilis increased from 2.5% to 42%, with the largest increase in testing occurring and sustained after testing orders were automatically linked to PIV and phlebotomy orders in the electronic medical record. 628/1096 (57.3%) of patients tested for syphilis and HIV were concurrently tested for gonorrhea and chlamydia. There were 9 false positive HIV tests and zero confirmed positive. Syphilis testing detected 3 confirmed cases of primary syphilis, 11 false positives, and 4 patients with preliminary positive results that were lost to follow-up.

CONCLUSIONS: Using QI methodology, we successfully increased the proportion of ED patients aged 12 years old screened for HIV and syphilis, with the greatest increase after order automation.

A Descriptive Analysis of Fruit and Vegetable Point of Sale Receipt Data in the ¡Más Fresco! More Fresh Program
Claudia Ramsey, MD, Sarah Hiller-Venegas, MA, Joe Prickitt, RD, Kate Edra, Blanca Melendrez, Kyung Rhee, MD, MSc, MA

BACKGROUND: Diet related diseases are the leading cause of morbidity and mortality. Fruit and vegetable (FV) intake are associated with decreased risk of disease. However, those who experience food insecurity often lack resources to access, purchase, and consume FV. We developed the ¡Más Fresco! More Fresh Program, which provides nutrition incentives (NI) to Supplemental Nutrition Assistance Program (SNAP) recipients to purchase fresh FV at Northgate González Markets. We used store receipts to evaluate food purchasing behaviors and provide estimates of overall FV intake. Our goal was to determine if there are differences in the FV purchasing patterns of participants receiving 3 different amounts of NI ($10, $20, or $40/month).

METHODS: Point-of-Sale (POS) receipt data of participants enrolled between 2017-2020 were used for analysis. Fruit or vegetable class was determined by botanical classification, and items were further grouped by type of FV. Outcomes included units and pounds of FV purchased per participant. Number of active participants were tracked per month. ANOVA was used to compare monthly differences between groups.

RESULTS: 693, 720, and 809 participants were enrolled in the $10, $20, and $40 groups respectively. Majority of participants were female (90%), Latino (91%), and receiving $100-199/month in SNAP benefits. The monthly number of active participants was highest in the $40 group compared to other groups (ps = 0.002). The top FV purchased across all groups were bananas and tomatoes. The pounds of FV purchased per participant were significantly higher in the $40 group compared to the others (ps<0.001).

CONCLUSIONS: With utilization of innovative POS receipt data, we found that the types of FV purchased were similar between the 3 NI groups. However, significantly higher amounts of FV were bought by the $40 group. Continued research is needed to discover the health outcomes of individuals consuming increased FV via NI programs.
**ABSTRACTS**

**Respiratory Medicine**

**Cell type specific responses to hypoxia in the embryos of Drosophila melanogaster**  
*Dan Zhou, Chenxu Zhu, Jin Xue, Caitlin Marsh, Bing Ren, and Gabriel Haddad*

**BACKGROUND:** Limited oxygen supply to fetus (i.e., fetal hypoxia) may impair fetal development, increase the rate of perinatal and infant mortality and the risk of developmental disorders at later developmental stages. Several studies have shown that epigenetic modifications and programming in response to environmental stimuli are critical in achieving appropriate gene expression patterns in fetuses. Drosophila melanogaster (fruit fly) has been used as a powerful model to dissect the molecular basis regulating development for decades. Indeed, based upon evolutionary conservation, a considerable amount of knowledge regarding human health has been obtained through studies using Drosophila models.

**METHODS:** In this study, we apply a currently established high-throughput method for single-cell joint analysis of open chromatin and transcriptome (i.e., Paired-seq), which combines snRNA-seq and snATAC-seq to simultaneously determine the influence of acute hypoxia on the transcriptome and chromatin accessibility at the single nuclei level in Drosophila embryos.

**RESULTS:** We identified a total of 22 clusters of cells and detected distinct hypoxia-induced alterations in both gene expression and chromatin accessibility in early-stage embryos following hypoxic treatment, which may affect the later organogenesis and development of the neuronal, tracheal and muscular systems. In addition, we detected a dramatic hypoxia-induced reduction of germ cells, suggesting the impact of fetal hypoxia on reproduction.

**CONCLUSIONS:** Fetal hypoxia induces cell-type specific reprogramming of transcriptome potentially through rearrangement of chromatin accessibility. Such alterations may disturb embryonic development at later stages.

**Chronic fentanyl exposure decreases dopamine release in human midbrain organoids**  
*Hang Yao, Daisy Hu, Hanxiang Yin, Juan Wang and Gabriel G. Haddad*

**BACKGROUND:** The Midbrain is the major source of dopamine (DA) in the human brain and plays a critical role in the reward process, and hence it orchestrates addiction in humans. In order to understand how DA neurons contribute to the formation of opioid tolerance and dependence in the reward pathways, we have generated human midbrain organoids (hMBOs) derived from induced pluripotent stem cells (iPSCs), which harbor DA neurons.

**METHODS:** iPSCs were aggregated into the embryoid body and subsequently forming the hMBOs which grow to around 500 μm by day 30. Immunohistochemistry confirmed that hMBOs is composed of major human midbrain cell types during development, including neural stem cells that express midbrain floor plate marker FOXA2 and the transcription factor associated with patterning of ventral midbrain Otx2. We also detected the immunoreactivity of microtubule-associated protein 2 (MAP2), a postmitotic neuronal marker, thyroxine hydroxylase (TH), a marker of DA neurons, and GABA, a marker of GABA neurons in the outermost layers of the hMBOs. These data indicate that our hMBOs recapitulate the human midbrain environment, especially the development of dopaminergic system. Using Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) technology, we studied DA release in hMBOs with or without the treatment of fentanyl (FTY).

**RESULTS:** Our results show that DA release was detectable in hMBOs as early as at 30 days after embryoid body formation in hMBO under normal culture conditions. The DA release gradually increases at Days 60, 90 and 120 in hMBOs, suggesting that DA neurons mature over time during development. In the experimental groups, hMBOs were incubated with FTY for 30 days at various concentrations of 0.3, 1 or 3 μM. After that, FTY was withdrawn and hMBOs were cultured in normal culture media for the following three months. Our results demonstrate that FTY, dose-dependently, decreased DA release when measured at the end of FTY incubation (Day 30), demonstrating that FTY specifically altered the biological process of DA production and release in DA neurons in hMBOs. This DA depletion effect of FTY continues to be seen at day 60, 90 and 120, months after FTY withdrawal, although the DA release gradually recovered to normal by day 120, especially in the hMBOs treated with the lowest FTY concentration.

**CONCLUSIONS:** Our hMBOs system proves to be an appropriate and useful tool for understanding the mechanisms of opioid addiction.
Ethnic and Racial Differences in Children with Respiratory and Neurological Post-Acute Sequelae of SARS-CoV-2: An EHR-based Cohort Study from the RECOVER Program

Landeo Gutierrez, Jeremy; Ryu, Julie; Rao, Suchitra; Gross, Rachel; Lorman, Vitaly; Rhee, Kay; Tantisira, Kelan

BACKGROUND: Minority children are at greater risk for COVID infection, but it is uncertain whether this increased risk exists for certain post-acute sequelae of SARS-CoV-2 (PASC). This study aims to compare the risk of respiratory and neurologic PASC by sociodemographic and clinical characteristics.

METHODS: Retrospective cohort study of patients &lt; 21 years seeking care at PCORnet US health systems using EHR data, from February 29, 2020-August 1, 2022. Identified children with at least 2 codes known to be associated with respiratory and neurologic PASC symptoms. Associations between sociodemographic and clinical characteristics and our PASC outcomes were analyzed by multivariable logistic regression adjusted for age, site, race/ethnicity, social vulnerability index/area deprivation index, time period of entry (dominant variant time), presence of chronic respiratory/neurologic condition and healthcare utilization.

RESULTS: Among 771,725 children in the cohort, 203,365 (26.3%) had SARS-CoV-2. Of those, 41.4% were Non-Hispanic (NH) White, 15.75 NH-Black, 12.72% Hispanic White, 11.97% Hispanic Non-White. Among children with SARS-CoV-2, 3217 had respiratory PASC and 2009 had neurologic PASC. Among subjects with history of SARS-CoV-2, children &lt;5 years (OR 1.80, 95% CI 1.63-1.98), and white Hispanic children (OR 1.20, 95% CI 1.06-1.34) had higher odds of respiratory PASC. In those without SARS-CoV-2, no link between respiratory PASC and race/ethnicity were identified. Children living in regions with higher area deprivation indices (OR 1.25, 95% CI 1.10-1.42) for 60-79th percentile) and with chronic complex respiratory conditions (OR 3.30, 95% CI 2.92-3.72) had higher odds of respiratory PASC. In contrast, older (OR 1.38, 95% CI 1.17-1.62), NH-white children and those with complex neurologic conditions (OR 2.05, 95% CI 1.78-2.36) were more likely to have neurologic PASC.

CONCLUSIONS: Increased pulmonary PASC in Hispanic children was observed and may relate to sociodemographic factors, healthcare seeking behaviors and access, access to care and increased susceptibility due to genetic or comorbid factors.

Microbiota is a key player in obstructive sleep apnea-induced atherosclerosis

Jin Xue, Orit Poulsen, Jason Meadows, Dan Zhou, and Gabriel G. Haddad

BACKGROUND: Obstructive sleep apnea (OSA) is an independent risk factor for cardiovascular disease (CVD) and stroke. Moreover, most of OSA patients are obese. The basis for the increased CVD risk in OSA is the increased predilection to atherosclerosis. Although previous studies have shown that gut microbiota gets involved in atherogenesis, its role in OSA and obese-stimulated atherosclerosis remains largely unknown.

METHODS: In the current study, we dissected the contribution of the microbiota to atherosclerosis induced by OSA or obesity using germ-free (GF) mice. We compared atherosclerotic lesion magnitude in the aorta and pulmonary artery (PA) between GF and conventionally reared (CONV) ApoE/- mice following high fat high cholesterol diet (HFHC) or high fat only diet (HF), with and without intermittent hypoxia/intermittent hypercapnia (IHC, a hallmark of OSA).

RESULTS: Our data showed that HFHC diet significantly increased lesion formation as compared to regular chow (RC) in both aorta and PA. In contrast, HF diet alone (with normal cholesterol) induced a much lower level of lesions. IHC promoted atherosclerosis remarkably in the presence of HFHC which was not evident in HF. Furthermore, GF ApoE/- mice developed significantly less atherosclerotic lesions relative to CONV ApoE/- mice in the aorta (especially in the aortic trunk) under either HFHC or IHC. Of interest, unlike in the aorta, gut microbiota did not show a significant impact on the progression of atherosclerosis in PA. In addition, we found that microbiota play a role in age-related atherosclerosis, especially in the male mice.

CONCLUSIONS: Our findings demonstrated that (1) high cholesterol, not high fat, is pivotal in the development of atherosclerosis; (2) IHC acts cooperatively with HFHC to affect atherosclerosis; and (3) microbiota modulate atherogenesis, induced by either HFHC or IHC or aging, in the aorta not in PA.
Sleep Disturbance in Children with COVID
Megan R. Warner, Rakesh Bhattacharjee, Jeremy Landeo-Gutierrez, Manaswitha Khare, Julie Ryu, Natacha Akshoomoff, Almary Akerlundh, Cinthia Sanchez, Ileana Matta, Sergio Garcia Crosthwaite, Kyung Rhee, and Kelan Tantisira

BACKGROUND: Long COVID, or post-acute sequelae of COVID (PASC), refers to the persistent effects individuals endure after experiencing acute COVID-19 infection. We aim to evaluate the prevalence of sleep related PASC in pediatrics.

METHODS: We analyzed self-reported surveys from the RECOVER study conducted at the UCSD/ RCHSD study site between July 2022 and April 2024. Surveys were administered at the time of enrollment querying participants about symptoms experienced before, and four weeks after their COVID infection. For participants who had experienced COVID before enrollment, retrospective symptom recall was requested to the best of their knowledge. Sleep symptoms that persisted after their infection for more than 4 weeks were recorded as PASC. Non-infected individuals and pre-infection baseline surveys served as controls.

RESULTS: 762 participants were recruited at our site during this time; Latino/Hispanic (67.3%), and non-Hispanic (NH) White (17.1%). 623 participants indicated they had a COVID infection (age:9.9±6.2y;n=296 females) and 142 were controls age:10.1±6.2y;n=67 females). In children with a history of COVID-19, we observed substantial increases in trouble sleeping (TS) (OR:5.63, 95%CI: 3.81-8.34, p<0.0001), daytime sleepiness (DS) (OR:33.1, 95%CI: 19.8-55.3, p&lt;0.0001), daytime tiredness (DT) (OR:21.6, 95%CI: 13.2-35.6, p&lt;0.0001), and having nightmares (HN) (OR:2.7, 95%CI: 1.6-4.5, p=0.0001) during acute COVID infection compared to their baseline before the infection. These symptoms persisted in PASC compared to baseline (TS: OR:2.7, 95%CI: 1.8-4.1, p&lt;0.0001; DS: OR:5.3, 95%CI: 3.1-9.0, p&lt;0.0001; DT: OR:3.9, 95%CI: 2.4-6.8, p&lt;0.0001; HN: OR:2.3, 95%CI: 1.4-3.9, p=0.0017).

CONCLUSIONS: Our findings indicate that children with COVID-19 experience an increase in sleep disturbances during and post-infection compared to non-infected.

Deciphering the molecular mechanisms involved in polyalanine-repeat-expansion mutations of PHOX2B in Congenital Central Hypoventilation and Haddad syndromes
Tsering Stobdan, Ila Dwivedi, Vaishnavi Ventrapragada, Daniel Lesser, Gabriel G. Haddad

BACKGROUND: Congenital central hypoventilation syndrome (CCHS) and Haddad Syndrome are rare, severe and life-long genetic disorders of neurodevelopment that control breathing, i.e., brainstem, with no known cure. They are characterized by hypoventilation due to the failure of autonomic control of breathing, and an early diagnosis and treatment can only limit complications from CCHS. Haddad Syndrome includes additionally Hirschsprung's disease and often a different mutations. Besides the clinical manifestations, the diagnosis of CCHS is established with a polyalanine repeat expansion mutations (PARMs) of a transcription factor PHOX2B. Although the PARMs is characterized as a dominant-negative mutation, interfering with the normal functioning of the wild-type protein, how PARMs affect the normal functioning of PHOX2B in heterozygous patients remains unclear.

METHODS: In order to understand the underlying molecular mechanisms we have generated iPSCs and brainstem organoids (BSOs) derived from one CCHS patient and one Haddad Syndrome, both with PARMs, and family members.

RESULTS: All organoids, including organoids from the probands, constituted cells expressing PHOX2B. Although cells from the probands expressed PHOX2B, we hypothesized that its targets in these probands were abnormally regulated. To identify these targets, we utilized fluorescence-activated cell sorting (FACS) to isolate PHOX2B+ cells and plan to perform transcriptomic analysis of both probands and controls.

CONCLUSIONS: The identification of downstream targets will not only reveal critical but also potentially novel targets that underlie the basis of the cellular and molecular mechanisms of the pathobiology of such genetic diseases affecting the control of respiration and sympathetic activity.
Klinefelter’s syndrome: The first description of a synaptogenesis disease
Helen Zhao, Dan Zhou, Gabriel Haddad

BACKGROUND: Klinefelter syndrome (KS) is the most common sex chromosome disorder and occurs in about 1 per every 650 newborn boys. KS patients are born with one or more extra copies of the X chromosome, which adversely affects testicular growth and produces a reduced amount of testosterone (testosterone deficiency), among other impairments such as impaired neurocognition and language-based learning difficulties and executive function. Due to limited studies so far focused on KS brains, our understanding of KS neuropathobiology at the molecular and cellular level remains largely unknown.

METHODS: In the current study, we use iPSC-derived cortical organoids to model early neuronal development and explore the earliest cellular and molecular changes during KS fetal brain development, aiming to develop optimal therapeutic strategies for KS patients.

RESULTS: We generated cortical organoids from KS embryonic stem cells and healthy control cells and found that KS organoids were significantly smaller than control organoids even though the preparation started with the same number of cells. Further, we found that decreased organoid size was due to a decreased Ki67+ proliferation but not to an increased cell death. During neuronal differentiation, the expression of neural progenitor cells (Nestin), radial glial cells (Pax6), intermediate progenitor cells (Tbr2), and mature neuronal markers (NeuN) were compared by western blot. Nestin expression was significantly decreased in KS organoids, and differences in Pax6, Tbr2, and NeuN expression were insignificant, suggesting that abnormal neurogenesis in KS organoids occurred at the neuronal progenitor stage. RNA-seq showed that there are major transcriptomic differences from control: there were 1555 differentially expressed genes (DEGs) in KS organoids, including 630 up-regulated genes and 925 down-regulated genes. Within those genes, 80 genes were located on the X chromosome, including 58 up-regulated genes and 22 down-regulated genes. Gene ontology analysis showed that the significantly differentially expressed genes were enriched in biological processes such as nervous system development, neuron differentiation, and neurogenesis. IPS pathway analysis indicated that neuronal-related signaling pathways are significantly altered in KS organoids, especially in synaptogenesis, where SNARE, glutamate receptor, and CREB signal pathways all decreased!

CONCLUSIONS: We conclude that KS organoids had altered neurogenesis and synaptogenesis as compared with control organoids. Our data provide cellular and molecular evidence for a neurobiological defect in synaptogenesis for the first time, explaining the cognitive deficits in KS patients. Further studies are ongoing to investigate the effect of testosterone on synaptogenesis and neurogenesis during early brain development between the two groups.
ABSTRACTS

Transforming Mental Health

Characteristics of patients with completed initial evaluation in a mental health integration program

Anjali D. Sapkal, MBBS, MS; Devin P. Adams, MPH; Joshua Gibney, MD; Jason Schweitzer, MD; Kathryn A. Hollenbach, PhD, MPH

BACKGROUND: Amidst the pediatric mental health crisis, Rady Children’s Hospital-San Diego launched primary care mental health integration (PCMHI) in June 2020. PCMHI is a mental health integration program with a "Hub and Spoke" model. PCMHI embeds Integrated health therapists (IHTs) within pediatric primary care (PC) clinics to provide short-term, targeted mental health (MH) treatment. Hub clinic IHTs and psychiatrists provide services for children needing higher level of MH management. By July 2023, PCMHI was established at eight pediatric PC offices and four hub clinics.

METHODS: EPIC workbench reports were written to obtain relevant information for PCMHI patients with completed initial evaluation between 6/1/2020 and 7/31/2023. Mean and standard deviation (SD) are reported for patient’s age at initial evaluation visit. N and percent are reported for other characteristics. Descriptive analysis was conducted using STATA, 16 (College Station, TX, USA).

RESULTS: During this period, 4,208 initial evaluation appointments were conducted. Mean patient age was 12.5 years (SD = 3.5). Fifty-seven percent (n = 2,376) of the evaluated patients were female. Sixty-seven percent of the patient identified their race as Caucasian, and 54% (n = 2,262) identified their ethnicity as Hispanic or Latino. Insurance information was available for 1,775 patients, with 55% (n = 981) of the patients insured publicly.

CONCLUSIONS: These data provide a better understanding of our PCMHI patient population. These results are part of an ongoing analysis. Further steps include in-depth analysis of the diagnoses commonly evaluated through the program with focus on patients with diagnoses of anxiety and/or depression. Other characteristics that will be included are assigned treatment track at the initial evaluation, number of sessions, and duration of MH treatment. We will also examine the pre- and post-IHT measurement base care parameters including GAD-7 for anxiety, PHQ-9 for depression, and clinical global impressions (CGI) scores as indicators of patient improvement.

Differences Between an Established Behavioral Health First Contact Method and A Telemedicine Alternative for Patient Scheduling Outcomes

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BACKGROUND: A primary care behavioral health integration program located within pediatric clinics utilizes warm hand-offs to help facilitate a patient’s referral to the mental health therapist. An alternative workflow was developed that utilizes a centralized access and triage (CAT) team for patients who are unable to receive a warm hand-off. The CAT team reaches out to patients by phone to explain the services provided and offers a brief telemedicine assessment. This study aimed to further evaluate the association between these two first contact methods and initial appointment scheduling outcomes.

METHODS: All patients referred for mental or behavioral health services in an eight-month period were included. Data was collected through electronic health records and manual chart abstraction was completed to collect more information around each patient’s specific first contact experience. Only patients who receive a warm hand-off or were contacted by the CAT team will be included for final analysis using STATA 16 (College Station, TX).

RESULTS: A total of 786 referrals were found within the review period that matched inclusion criteria. 531 (67.6%) patients received a warm hand-off, 101 (12.8%) received a call from the CAT team, and 154 (19.6%) received neither. No statistically significant differences were detected between the two groups with regards to scheduling (P=.121), rescheduling (P=.431), or completing initial appointment (P=.548).

CONCLUSIONS: The effectiveness of the warm hand-off in comparison with the centralized access and triage team did not show any significant differences in the scheduling pathway of our patients. Blocked time for warm hand-offs is not always utilized, is not billable, and does not always coincide with when a pediatrician wants to conduct the warm hand-off. Given the effectiveness of our CAT team, behavioral health practitioners workflows can become more flexible allowing for greater sustainability for the program.
**ABSTRACTS**

**Transforming Mental Health (cont.)**

**Abstract: Early Identification of Pediatric Behavioral Health Concerns: Should We Be Doing More than Screening for Depression?**

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**BACKGROUND:** Pediatric mental and behavioral health (MBH) concerns are steadily increasing and practices routinely screen adolescents for depression and/or self-harm. Children’s Primary Care Medical Group (CPCMG) screens for depression (PHQ-9) beginning at 12 years. We sought to determine whether pediatric patients would benefit from additional screening for anxiety.

**METHODS:** In January 2023, we began anxiety screening using the GAD-7. We extracted patient demographic characteristics, MBH screening results, and evidence of prior MBH history from EHR for all 12-year well checks from January 1 through November 30, 2023. Screening scores were categorized and comparisons between PHQ-9 and GAD-7 scores were made among patients with no prior MBH history. Data were analyzed using STATA 16 (College Station, TX).

**RESULTS:** 6286 patients had a 12-year well check and completed screenings at a CPCMG clinic. 18.2% of patients screened positive for depression and 21.5% screened positive for anxiety. Among patients with no evidence of depression (PHQ-9 screening or prior medical history), anxiety symptoms at the 12-year well check were: 8.2% (n=427) mild; 1.8% (n=95) moderate, and 0.9% (n=47) severe.

**CONCLUSIONS:** Validated tools are widely used to screen adolescent patients for depression risk and/or self-harm. This only provides a partial picture of our patient experience. Without GAD-7 screening, we would have missed 11% (n=569) of patients with measurable anxiety symptoms without depression. Screening for anxiety is quick, and efficient and can be completed by patients prior to their appointment. We feel that all patients should be screened for both anxiety and depression when easy to administer, validated screening tools become available which coincides with the 12-year well check.