Weill Cornell Medicine
Pediatrics
Drukier Institute for
Children's Health

Third Annual Pediatrics Research Day

May 22, 2024 | 8 am - 7 pm |
Belfer Research Bldg 2nd and 3rd floor

3rd Annual Pediatric Research Day
May 22 2024

8:00 – 8:45 am
Pediatrics Research Day Registration and Breakfast

8:45 – 11:30 am
Trainee Lightning Round Oral Presentations*
Moderator: Dr. David Lyden

*All lightning round presenters will have posters available for viewing at 5:00 pm in Poster Session 2.

11:30 – 12:45 pm
Lunch and Poster Session 1

12:50 – 1:00 pm
Welcome Address from Dr.'s Virginia Pascual and Sallie Permar

1:00 – 1:45 pm
Keynote Address
Joshua Milner, MD
Professor of Pediatrics; Director, Division of Pediatric Allergy, Immunology and Rheumatology; Chief of Allergy, Immunology and Rheumatology Services for New York Presbyterian Morgan Stanley Children Hospital
New York Presbyterian/Columbia University Irving Medical Center

1:45 – 2:00 pm
Break

2:00 – 2:15 pm
Overview of Research in the Department of Pediatrics and Drukier Institute for Children's Health - Sujit

2:15 – 3:15 pm
Clinical & EQ oral presentations
Moderator: Dr. Hamieh

3:15 – 3:30 pm
Break

3:30 – 5:00 pm

Translational and basic science oral presentations
Moderator: Dr. Juan Pascual

5:00 – 6:30 pm
Reception and poster session
Awards announced at 6:15

Weill Cornell Medicine
Continuing Medical Education

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CONTINUING MEDICAL EDUCATION
GENERAL INFORMATION

3RD ANNUAL PEDIATRICS RESEARCH DAY

May 22, 2024 8 am – 6:30 pm
Weill Cornell Medical College
Belfer Research Building, 2nd and 3rd Floors, 413 East 69th Street, New York, NY 10021
Genevieve Fouda, MD, PhD, Course Director, Chani Traube, MD, Course Co-Director

IDENTIFIED PRACTICE GAPS/EDUCATIONAL NEEDS

The clinical and research communities are rarely presented with the chance to share and review each other's work outside of professional society meetings, or to form new interdisciplinary teams. This event provides an opportunity for the members of the pediatrics and immunology communities to foster new relationships in the collective goal of advancing care for children. Additionally, it provides the opportunity to foster mentoring and networking across career levels and between WCM and affiliated institutions.

TARGETED AUDIENCE

This course is targeted towards primary and specialty care physicians, medical students, graduate house staff, psychologists, advanced practice providers and basic scientists interested in the diagnosis and treatment of the pediatric community, and with interest in immunology.

OBJECTIVES/DESIRED OUTCOMES

It is intended that this Weill Cornell CME activity will lead to improved patient care, including improvements in knowledge, competence, or performance. At the conclusion of this activity, participants should be able to:

1. Have the opportunity to form multidisciplinary research collaborations
2. Become familiar with the most cutting-edge diagnostic and treatment methodologies in the care of pediatric patients, and in immunology
3. Become familiar with the current research in the fields of pediatrics, and immunology, and be aware of opportunities for research collaboration.

DISCLOSURE OF RELATIONSHIPS/CONTENT VALIDITY

It is the policy of Weill Cornell Medical College to adhere to the ACCME Criteria, Policies and New Standards for Integrity and Independence in Accredited Continuing Education and to ensure all content is valid in order to ensure fair balance, independence, objectivity, and scientific rigor in all its provided activities. All speakers, Course Directors, Co-Course Directors, planners, reviewers, and staff members participating in provided activities are expected to disclose relevant financial relationships pertaining to their contribution to the activity. Relationship information is analyzed to determine whether conflicts of interest exist. All conflicts of interest are resolved prior to participation in the planning or implementation of this activity. Presenters and authors are also expected to disclose any discussion of (1) off-label or investigational uses of FDA approved commercial products or devices or (2) products or devices not yet approved in the United States.

WCMC CME activities are intended to be evidence-based and free of commercial bias. If you have any concerns, please call the Office of Continuing Medical Education at 646-962-6931 to anonymously express them.

Course Director, Planner

Genevieve Fouda, MD, PhD

- Has no relevant financial relationship with ineligible companies to disclose.
- Will not be discussing the off-label or investigational use of products or services

Course Co-Director, Planner

Chani Traube, MD

- Has no relevant financial relationship with ineligible companies to disclose.
- Will not be discussing the off-label or investigational use of products or services

Course Faculty

Joshua Milner, MD

- Scientific advisory board: Blueprint Medicine
- Research grant recipient: Pharming
- Will not be discussing the off-label or investigational use of products or services
- All of the relevant financial relationships listed for this individual have been mitigated.

Virginia Pascual, MD

- Consultant: GlaxoSmithKline and Regeneron
- Advisor: Moderna
- Royalties: Novartis
- Research Grant: Sanofi
- Will not be discussing the off-label or investigational use of products or services
- All of the relevant financial relationships listed for this individual have been mitigated.

Sallie Permar, MD, PhD

- Consultant: Merck, Moderna, Dynavax, Pfizer
- Institutional Sponsored Program: Merck and Moderna
- Will not be discussing the off-label or investigational use of products or services
- All of the relevant financial relationships listed for this individual have been mitigated.

The following presenters have the following disclosures:

- Has no relevant financial relationship with ineligible companies to disclose.
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Ahsan Uddin, MD
Tal Dror Cohen, MD
Wei Wei, MD
William Patten, MD
Jennifer Shenker, MD
Zenna Solomon, MD
Jordan Leith, BS
Lulu Guo, PhD
Nell Borys, BS
Nicole Palmer, BS
Isabella Kong, PhD
Zeynep Bahadir, MD
Isabella Richter
Christian Binuya, BS
Elliott Gordon, MD
Michelle Foley, MD
Justin Kotliar, MD
Yafa Davydova, MD
Allison Pressimone, MD
Jheel Pandya, MD
Theresa Scott, DO, MS
Jiayi Sun, PhD
Kanza Baqai
Yasmine Issah, ScM
Preetha Balsubramanian, PhD
Joshua McGrath, PhD
Nicole Soo
Rui Yang, MD
Vanja Cabtic, MD
Hannah Major-Monfried, MD
Rebecca Miller, MD
Hera Mahmood, MD
Nicole Kelly, MD
Melanie Dubois, MD, MPH
Claire Otero, PhD
Kelly Banks, MD, PhD
Hana Flaxman, BS
Hannah Federman, phD
Suhong Sun, PhD
Omar Hayatt, BS
Kenneth Vuong, BS

Planning Committee

Lisa Roth, MD

- Consultant – fees paid to WCM – Merck
- Consultant - Roche
- Will not be discussing the off-label or investigational use of products or services
- All of the relevant financial relationships listed for this individual have been mitigated.

Sujit Sheth, MD, MSc

- Consultant: Agios, BMS/Celgene, Forma, Chiesi and Bluebird Bio
- Investigator in Clinical Trials: Agios, BMS/Celgene and Forma
- Clinical Trial Steering Committee: Vertex
- Will not be discussing the off-label or investigational use of products or services
- All of the relevant financial relationships listed for this individual have been mitigated.

Taylor Jackvony, MD

- Has no relevant financial relationship with ineligible companies to disclose.
- Will not be discussing the off-label or investigational use of products or services

Sharleen So

- Has no relevant financial relationship with ineligible companies to disclose.
- Will not be discussing the off-label or investigational use of products or services

Veronika Hostiuk

- Has no relevant financial relationship with ineligible companies to disclose.
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- Royalties: Novartis
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Course Coordinator
Vanessa L. Dudley, MSHS
- Has no relevant financial relationship with ineligible companies to disclose.
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CME Staff
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ACCREDITATION AND CREDIT DESIGNATION STATEMENTS

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Weill Cornell Medical College designates this live activity for a maximum of 8.75 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

EVALUATION

The CME Evaluation Form is included in your syllabus. Completed forms will be collected at the door at the end of this activity. We encourage you to complete the Evaluation Form as this will allow us to assess the degree to which the activity met its objectives. It will also guide the planning of future activities and inform decisions about improving the educational program.

WCMC is accessible for individuals with disabilities or special needs. Participants with special needs are requested to contact the Office of CME at 646-962-6931.

Revised June 2021

LR: LIGHTNING ROUND ORAL PRESENTATIONS
8:45 am – 11:30 am

LR-01 TR
EPITOPE SPECIFICITY OF NEUTRALIZING ANTIBODIES IN LONGITUDINAL SAMPLES FOR CHILDREN LIVING WITH HIV WHO DEVELOP NEUTRALIZATION BREADTH

Vuong Kenneth, Bahadir Zeynep, Dennis Maria, Fouda Genevieve G., Nelson Ashley

INTRODUCTION: As of 2022, 1.5 million children (0-14 years) are living with HIV globally, according to the UNAIDS report. There has yet to be a cure for HIV or an established regimen to prevent HIV acquisition; however, eliciting broadly neutralizing antibodies (bnAbs) is the goal in engineering a successful vaccine strategy. BnAbs are unique in that they can target conserved binding sites, also known as epitopes, on the HIV envelope (env) and can neutralize multiple HIV strains. Such epitopes on the HIV env include the CD4-binding site (CD4bs), V3-glycan, V2-glycan, and gp120-gp41 interface. Recent studies have shown that bnAbs display significant breadth and potency and indicated that bnAbs are developed earlier in children living with HIV compared to adults. Moreover, some studies have found that bnAbs are detectable as early as the first year of life. In comparison to adults, children develop bnAbs in plasma targeting the same principal epitopes on the HIV env. Studies from our group and others have suggested that children's plasma neutralization activity may be polyclonal, targeting multiple epitopes on the HIV env. This is interestingly unexpected as adults tend to have bnAb responses targeting a distinct epitope. We previously attempted to map the epitope specificity of bnAb responses in a cross-sectional cohort of children living with HIV and were only able to map about thirteen percent (n = 5 of 38) of them to a single epitope. Together, these data suggest that different mechanisms may be driving neutralization breadth development in children versus adults living with HIV.

OBJECTIVE: To evaluate the epitope specificity of neutralizing antibodies in longitudinal samples of children living with HIV who develop HIV-1 neutralization breadth.

METHODS: ART-naïve longitudinal samples of children living with HIV (1-3 years old, n=12) were initially screened using a standard neutralization assay with TZMbl cells against a global parent HIV panel of 10 viruses. The samples of the 1 to 3-year-olds that demonstrated high neutralization titers having an ID50 greater than 120 were screened against a panel of mutant viruses from the parent strain. Neutralization responses are reported in ID50, the dilution of plasma resulting in a 50% reduction in luminescence compared to that of virus control wells. For this study, we will assess a panel of 25710-2.43, BJOX002000.03.2, and TRO.11 mutants and map the epitope specificities that bnAbs are known to target on the HIV env. Epitope specificity was assigned by the reduction in ID50 of greater than 3-fold compared with the parent strain.

RESULTS: When evaluating epitope specificity by age, we found that specificity could not be determined in any samples screened at 1 year of age (n=4), while 50% (n=4 of 8) of samples screened at 2 years mapped to at least one epitope, and a similar trend was observed at age 3 years. Overall, epitope specificity was mapped to at least one epitope in 40% (n=8 of 20) longitudinal samples screened, with each demonstrating epitope specificity to the V3-glycan region. We also observed the potential evolution of the bnAb response in 5 pediatric samples, as evident by changes in epitope specificity over time. For instance, infant S0063B1 had plasma neutralization Abs (nAbs) that mapped to both gp120-gp41 (N88A) interface and V3-glycan at age 2; however, at age 3, their nAbs mapped to a different epitope (N625A) at the gp120-gp41 interface and maintained V3-glycan. Interestingly, infant S0016B1 had epitope specificity to only the V3-glycan at age 2 but developed specificity to two epitopes (V3-glycan and gp120-gp41) at age 3. In contrast, for infant S1051B1 epitope specificity could not be determined at age 2 but mapped to multiple ones at age 3.

CONCLUSION: Our results demonstrated that plasma nAb responses in the majority of these longitudinal pediatric samples did not map to a single epitope, suggesting that the nAb responses target multiple epitopes on the HIV envelope. This supports previous observations from our group and others, suggesting that HIV neutralization breadth in children is mediated by a polyclonal neutralizing antibody response. Future approaches will focus on understanding the B cell responses in children who develop breadth and assess how the virus is evolving in these children.

LR-02 CL
GROWTH HORMONE THERAPY AND QUALITY OF LIFE IN CHILDREN WITH CHRONIC KIDNEY DISEASE COMPLICATED BY SHORT STATURE: THE PEDIATRIC NEPHROLOGY RESEARCH CONSORTIUM LONGITUDINAL STUDY

Baqai Kanza, Borova Dajana, Noziere Akeem, Singer Pamela, Kallash Mahmoud, Mahan John D. ,Kogon Amy, Akchurin Oleh.

INTRODUCTION: Short stature is a common complication of chronic kidney disease (CKD) in children. Recombinant human growth hormone (GH) injections effectively improve growth velocity in children with CKD. Interestingly, studies that assessed whether GH improves quality of life (QoL) in children with idiopathic short stature were inconclusive. Whether GH improves QoL in children with CKD-induced short stature, remains unknown. OBJECTIVE: Determine the change in QoL in children

with CKD and short stature 6 months after GH therapy initiation compared to baseline and assess families' overall satisfaction with GH therapy.

DESIGN/METHODS: This is a multicenter study with 4 participating tertiary medical centers. QoL was assessed by Pediatric Quality of Life Inventory (PedsQL, parental version) in 4 domains: physical, emotional, social, and school at GH therapy initiation (baseline) and then again at 6 months. After 12 months of GH therapy, treatment satisfaction was assessed via a survey. Paired t-test was used for statistical analyses.

RESULTS: We enrolled 24 patients (22 boys, age 8.1±4.9 years, 58% Caucasian and 25% African American, baseline eGFR 49.6±40.6 mL/min/1.73 m2). Height z-score was -2.3±1.1 at enrollment and -1.8±1.3 at 6-month follow-up (p=0.017). Body mass index (BMI) z-score was normal and did not change after 6 months of GH therapy (-0.06±0.9 at baseline and 0.015±1.0 at follow-up). PedsQL of children from our cohort was lower compared to published reference values for both healthy children and children with CKD and normal height in all domains. None of the PedsQL domains correlated with height z-score, BMI z-score, or eGFR. At follow up, QoL improved in the physical, social, and school domains by 8-10 points ($p<0.05$). The GH satisfaction survey was filled out by 21 parents; among them, 85.7% indicated that they would recommend the use of GH to other children and 80.9% reported that they would use GH therapy again. Pain and discomfort from GH injections was not considered a problem by 47.6% parents whereas 33.3 % parents considered it to be a minor problem, and none considered it a major problem. When asked about side effects, 71.4% parents reported no side effects associated with GH treatment.

CONCLUSION(S): This is the first study demonstrating improvement of QoL in children with CKD and short stature after GH therapy. Parents overall reported high level of satisfaction with GH therapy despite daily subcutaneous injections.

LR-03 TR
THERAPEUTIC VACCINE REPAIRS SHIV-INDUCED GUT MICROBIAL DYSBIOSIS IN ORALLY-INFECTED PEDIATRIC RHESUS MACAQUES

Nicole Soo, Alexander Grier, Isaac R. Cinco, Veronica Obregon-Perko, Zain Gohar Siddiqi, Gloria Mensah, Bhrugu Yagnik, Diane G Carnathan, Chiamaka A. Enemuo, Julia T. Ngo, Genevieve G. Fouda, Sallie R. Permar, Guido Silvestri, Rama R. Amara, Ilhem Messaoudi2, Ann Chahroudi, and Ria Goswami.

BACKGROUND: Each year 130,000 infants are newly infected with HIV. Viral infection is associated with gut microbial dysbiosis, leading to systemic immune activation and inflammation. While antiretroviral therapy (ART) can efficiently control disease progression, it cannot clear established HIV reservoirs, resulting in adherence to therapy for life. Importantly, ART does not successfully restore gut microbial dysbiosis-mediated immune activation levels, a factor that impacts HIV persistence on therapy. Hence, strategies that can clear HIV reservoirs, as well as repair gut bacterial dysbiosis, will be needed to reduce HIV persistence and achieve drug-free HIV control in the pediatric population. In this project, we used an infant rhesus macaque (RM) model of oral simian/human immunodeficiency virus (SHIV) infection, to determine i) whether the timing of ART initiation controls gut dysbiosis levels and ii) whether an immune cell-engaging therapeutic vaccine ameliorates virus-induced microbial dysbiosis.

METHODS: Fecal samples were obtained from uninfected (n=40) pediatric RMs or age-matched orally SHIV.C.CH505-infected pediatric RMs, who initiated ART at 0.6 weeks (early, n=7), or 2 weeks (intermediate, n=9) or 8 weeks (late, n=14) post-infection. Additionally, feces were obtained from 8 RMs who initiated ART late (8 weeks) and received a SHIV DNA/MVA/SOSIP-based HIV therapeutic vaccine. 16s rRNA sequencing was performed to profile gut bacterial taxa and the microbiome was correlated with intestinal HIV cell-associated RNA (CA-RNA).

RESULTS: The gut microbiome of RMs who received ART early was most similar to the microbial profile of an uninfected RM. However, intermediate and late ART initiation was associated with significant differences in bacterial taxa compared to the uninfected group. More importantly, even after long-term ART (48-56 weeks), bacterial dysbiosis was not restored to the level of uninfected animals, when ART was initiated at an intermediate and late stage. Interestingly, while a SHIV DNA/MVA/SOSIP-based therapeutic vaccine on ART was not able to reduce viral reservoir size, it restored the microbial profile almost to the level of uninfected monkeys. Finally, after correcting for therapy-based differences, we identified bacterial species Sarcina ventriculi, Lactococcus lactis, and Treponema succinifaciens to be associated with elevated intestinal SHIV CA-RNA levels and bacterial species Eubacterium hallii, Ruminococcus bromii, and Terrisporobacter mayombei to be correlated with decreased SHIV CA-RNA.

CONCLUSION: In this novel study that evaluates HIV-induced gut microbial dysbiosis in a physiologically relevant preclinical model of breastfeeding HIV transmission and therapy, we emphasize the need for the incorporation of adjunctive strategies to restore HIV-induced gut microbial dysbiosis. Additionally, gut microbiome was found to be associated with HIV persistence in the gut, highlighting the importance of microbial modulation in early life to a phenotype that

reduces viral persistence to achieve ART-free HIV suppression in children living with the virus.

LR-04 BS
MUTABILITY AND HYPERMUTATION ANTAGONIZE IMMUNOGLOBULIN CODON OPTIMALITY

McGrath, Joshua; Park, Juyeon; Troxell, Chloe; Chervin, Jordan; Li, Lei; Kent, Johnathan; Changrob, Siriruk; Fu, Yanbin; Huang, Min; Zheng, Nai-Ying; Wilbanks, Dewey; Nelson, Sean; Sun, Jiayi, Inghirami, Giorgio; Madariaga, Maria Lucia; Georgiou, George; Wilson, Patrick C.

BACKGROUND: Human antibody repertoires encode massive variable region sequence diversity in order to protect against microbial infection and other antigenic threats. In addition to germline variation among IG gene variants, and combinatorial diversity generated through V(D)J recombination, post-activational targeting of highly mutable “hotspot” motifs in V(D)J DNA facilitates somatic hypermutation (SHM) to further diversify B cell clones in the periphery. While beneficial for polyclonal immunity, the existence of such extreme repertoire heterogeneity begs the question as to how the molecular underpinnings of immunoglobulin diversity (germline variability, mutability hotspots, stochastic SHM) have evolved alongside another more ubiquitous feature of protein-coding DNA – codon optimality.

OBJECTIVE/METHODS: In the current study, we address this knowledge gap by analyzing germline IG genes and natural V(D)J repertoires using multiple optimality metrics.

RESULTS: We found that germline V genes exhibit variability in optimality similar to other multigene families. Furthermore, analysis of pseudogenes suggests that optimality is maintained by selective pressures associated with functionality. Germline IGHV optimality scores positively correlated with IGHV usage within serum IgG from influenza vaccinees. V gene optimality inversely correlated with germline mutability (mutation potential), and SHM caused a load-dependent deoptimization of IGH repertoires within human tonsils, lymph nodes, and bone marrow, as well as whole zebrafish and mouse splenocytes. Clonal deoptimization was also observable within large SARS-CoV-2 spike-specific IGH clonal families. In vitro, transfection of hIgG1 plasmids with synonymous amino acid sequences but suboptimal V(D)J codon usage elicited significant expression loss.

CONCLUSION: Overall, our data provide context as to how the immunoglobulin biosystem has evolved to promote variable region diversity within the landscape of codon optimality.

LR-05 TR
BROADLY NEUTRALIZING ANTUBODY (bNAb) ESCAPE HIV ENVELOPE MUTATIONS IN ORALLY SHIV-INFECTED INFANT RHESUS MACAQUES RECEIVING TRIPLE bNAb-BASED PASSIVE IMMUNIZATION

Binuya Christian R, Giorgi Elena E, Omonije Olusola, Phan Caroline, Carnathan Diane G, Yagnik Bhrugu, Enemuo Chiamaka A, Obregon-Perko Veronica, Amara Rama R, Silvestri Guido, Chahroudi Ann, Permar Sallie R, Fouda Genevieve G, Goswami Ria

BACKGROUND. In 2019, approximately 1.7 million children were living with HIV, and <500 acquired the virus every day. While antiretroviral therapy (ART) can control plasma viral load, it does not eliminate viral reservoir established immediately following early-life infection, resulting in life-long drug adherence. Therefore, alternative strategies that can reduce HIV reservoir size are needed. Passive immunization with a single bNAb can temporarily control viral replication upon ART interruption. However, HIV’s rapid evolutionary capacity allows for the development of virus variants that escape bNAb-mediated neutralization, resulting in eventual viral rebound. Our group recently identified a novel triple bNAb combination comprising of 3BNC117, PGDM1400, and PGT151 that mediates robust HIV neutralization and non-neutralizing effector functions. In this study, using an oral SHIV challenge model of infant rhesus macaques (RMs), we will determine if HIV develops escape mutations against the passively immunized triple bNAb combination and additional well-known HIV bNAbs.

METHODS. Ten infant RMs were challenged orally with SHIV.C.CH505 and ART was initiated at 8 weeks post-infection (wpi). Animals were passively immunized with a combination bNAb targeting specific HIV-env epitopes: 3BNC117 (CD4bs), PGDM1400 (V2 glycan), and PGT151 (gp120-gp41 interface) at 8 and 49 wpi. ART was interrupted at 49 wpi, and RMs were monitored for viral rebound thereafter. HIV env genes from the rebounding virus were amplified using single genome amplification (SGA) and HIV env variants were aligned with the challenge virus to identify mutations that can result in escape from the three passively immunized bNAbs, as well as other well-known HIV bNAbs.

RESULTS. All infant RMs showed a steady drop in viral load immediately after ART initiation and passive bNAb infusion at 8 wpi. Upon ART interruption, the median time to viral rebound was 49 days, with a range of 21 days to 70 days. Sequence analysis of the rebound viruses showed that, compared to the CH505 SHIV challenge, 3/10 RMs developed V2-bNAb resistant mutations: one animal lost the N160 glycan (targeted by V2 bNAbs) and together with two other animals, carried the E170K mutation, also associated with V2 bNAb resistance. Two animals lost the N230 glycan, while a third one carried

T750S, and both changes are associated with resistance to some V3 bNAbs. Interestingly, 9 animals showed neutralization resistance against the passively infused bNAb, 3BNC117. Additionally, 4/10 animals developed N334S mutation, which filled the N332 glycan loss in V3, that was missing from challenge virus. By comparing the Env sequences with and across animals and accounting for unique escape mutations, 16 envs were selected for assessment of in vitro neutralization by corresponding bNAbs.

CONCLUSION. Using a pediatric preclinical model of oral HIV infection, we mapped HIV-env mutations associated with neutralization resistance against well-known HIV bNAbs. Establishing knowledge on how these specific Env mutation motifs affect neutralization response will guide the development of future therapeutic regimens such as passive and active immunization strategies to minimize HIV viral escape, leading to ART-free HIV control in the pediatric population.

LR-06 BS
THE ROLE OF SOCS1, TNFAIP3, AND B2M IN HODGKIN LYMPHOMA

Sun, Suhong, Kong, Isabella; Trukillo-Alonso-Vicenta; Azrak, Griffin; Roshal, Michail; Nam, Seung; Cesarman, Ethel; Melnick, Ari; Giulino-Roth, Lisa

BACKGROUND: Hodgkin lymphoma (HL) is a prevalent form of lymphoma that has a peak incidence in adolescents and young adults. Despite advances in chemotherapy and immunotherapies, relapses and refractory conditions continue to pose challenges for patients. However, the rarity of malignant Hodgkin and Reed Sternberg (HRS) cells in HL limits our ability to study this disease. Previous studies from our team have identified several gene mutations in HRS cells, including SOCS1, TNFAIP3, and B2M. Nevertheless, an appropriate mouse model to investigate the mechanisms underlying these gene mutations in HL remains elusive.

OBJECTIVES: The objectives of this study are twofold: 1) to elucidate the role of these genes in the development of HL; and 2) to establish a mouse model for HL.

METHODS AND RESULTS: To achieve these aims, we have utilized the Cre/Loxp system to knock out genes of interest in CD30+ B-cells, the cell type suspected to be the cell-of-origin for HL. To date we have isolated bone marrow (BM) and spleen from B2M flox/flox, SOCS1 flox/flox mice, followed by in vitro culture of B cells using a pan B cell kit. We then utilized flow sorting to isolate B220+CD30+ cells. We have confirmed successful knockout of SOCS1 and B2M in B220+CD30+ cells through RT-PCR analysis of SOCS1 and flow cytometry for MHCI expression respectively. Next, we transplanted these B220+CD30+ cells into MuMT mice (Ighmtm1Cgn/J), which lack mature B cells due to a mutation in the immunoglobulin have chain IgM. On day 7 post-transplantation, PCR analysis revealed the presence of the B2M flox allele and flow analysis identified both B220+IgM+ and B220+CD138+ B cell populations in BM, suggesting successful engraftment.

CONSLUSION: In conclusion, we have successfully knocked out SOCS1 and B2M in CD30+ murine B cells and transplanted these cells into MuMT mice. This model will now allow us to investigate the role of these genes in HL development and may lead to the first murine model of HL.

LR-07 TR
IMMUNOGENICITY OF GERMLINE-TARGETING BG505 SOSIP TRIMER IMMUNIZATION IN INFANT AND JUVENILE RHESUS MACAQUES

Issah, Yasmine, Nelson, Ashley N., Hu, Xintao, Isaac, John, Shen, Xiaoying, Ozarowski, Gabriel, Sewell, Leigh, Zhang, Shiyu, Ward, Andrew B., Montefiori, David C., Sanders, Rogier W., Moore, John P., Van Rompay, Koen K.A., De Parish, Kristina, Permar, Sallie R.

HIV is a highly mutable virus, therefore a vaccine that induces protective, broadly neutralizing antibodies (bnAbs) before sexual debut is critical to eliminate the ~410,000 new infections annually among adolescents worldwide. Recent work has established that children living with HIV develop bnAbs earlier and at a higher frequency than adults. In this study we compared a germline-targeting BG505 SOSIP trimer immunization strategy to induce precursor bnAbs in infant and juvenile rhesus macaques (RM).

Infant (n=5) and juvenile (n=4) RMs received 3 immunizations of the germline-targeting BG505 GT1.1 SOSIP trimer (50mg) with the 3M-052-SE adjuvant 6 weeks apart. All RMs were then boosted 12 weeks later with the BG505.664 WT SOSIP trimer 3 times in 6-month intervals. After an over one-year follow-up, all animals received a mixed Clade B nanoparticle boost. Vaccine-elicited antibody responses were monitored through 2.5 years.

BG505 GT1.1 SOSIP trimer immunization consistently induced higher magnitude antigen-specific IgG binding responses in infants compared to juvenile RMs. However, plasma tier 2 autologous virus neutralization responses were similar between the groups, yet the infant response targeted more epitopes. Notably, by weeks 54 and 80, three of five GT1.1 SOSIP-immunized infants exhibited a plasma neutralization signature indicating CD4 binding site-specific (CD4bs) bnAb precursor development, while only one of four juvenile RMs had developed this response. By week 150, however, we saw an additional infant develop the CD4bs bnAb precursor response while the one juvenile was not able to maintain that same response. Those same four infants and one juvenile

exhibited modest heterologous tier 2 neutralization activity while only 2 juveniles show similar heterologous neutralization responses.

Our data indicates that sequential immunization with germline-targeting BG505 SOSIP trimers may induce neutralizing antibodies and CD4bs bnAb precursors more frequently in infants compared to juveniles. Our results support observations in humans suggesting the infant immune environment may be better suited for induction of plasma HIV bnAb responses.

LR-08 QA
LOW REPRESENTATION AND HIGH QUALITY: A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL OF PEDIATRIC GUIDELINES FOR CHEST PAIN

Palmer Nicole R, Pasumarthi Tejanth, O'Connell Joe, Lee Brandon, Yu Tiffany, Kothapudi Venkata N, Patel Shama, Morgan Rebecca L

INTRODUCTION: Chest pain is potentially life-threatening and requires quick and accurate evaluations. This symptom can arise in all populations with a variable differential depending on their age and risk factors. Our primary aim is to describe the quality of guidelines related to the evaluation and diagnosis of acute, undifferentiated chest pain. Guidelines that are applicable to pediatric populations are additionally evaluated for prevalence and quality.

OBJECTIVES: To describe the quality of guidelines related to the evaluation and diagnosis of acute, undifferentiated chest pain and assess the prevalence and quality of guidelines applicable for pediatric populations.

METHODS: Systematic review with a critical assessment of the guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool; this tool included six domains for the assessment of each guideline quality: 'Scope and Purpose', 'Stakeholder Involvement', 'Rigor of Development', 'Clarity of Presentation', 'Applicability', and 'Editorial Independence'. A rating of the overall guideline quality was also provided. Inter-rater reliability was calculated using an intraclass correlation coefficient. Statistical significance was defined as a 2-tailed p-value of 0.05, as measured by Excel 2019.

RESULTS: The initial search revealed 8611 records. After screening, we assessed the quality of the 30 applicable guidance documents published between 2000 and 2022 that provided recommendations regarding the evaluation and diagnosis of undifferentiated chest pain. The intraclass correlation coefficient for this study was of "excellent reliability" (0.93). The average AGREE II scaled domain scores ranged from 33% to 75% with a mean value of 53%.

One of the included studies provided recommendations specific to pediatric populations. This guideline was statistically significant ($p<.05$) for a greater level of quality than the remaining 29 guidelines over all of the seven domains of quality.

CONCLUSIONS: There exists a wide variety of quality in documents that provide recommendations for the evaluation and diagnosis of chest pain. The one guideline that provides recommendations for pediatric populations was of a statistically significant greater quality than those that did not.

LR-09 BS
TARGETING LATENCY SWITCH FOR THE TREATMENT OF EBV+ LYMPHOMA

Kong Isabella Y, Whitehouse Rebecca, Trezise Stephanie, Alonso Vicenta T, Zanetti Giorgia, Clark Sarah, Azrak Griffin, Zappasodi Roberta, Inghirami Giorgio G, Gewurz Benjamin, Cesarman Ethel, Roth Lisa G

INTRODUCTION: Epstein-Barr virus (EBV) infection contributes to the development of a significant subset of human lymphomas. EBV-infected lymphoma cells exist in three latent states: latency I, II or III. Latency II and III infected cells express immunogenic viral proteins such as EBV latent membrane protein 1 or 2 (LMP1/2) and EBV nuclear antigen 3 (EBNA3) that can be recognized by cytotoxic T cells (CTLs). As such, EBV-specific T cell immunotherapy is being developed for the treatment of latency II and III EBV+ lymphoma. However, these proteins are not expressed in latency I EBV+ lymphoma, rendering these tumors resistant to EBV-specific T cell therapies.

To address this, we investigated the use of pharmacologic agents to convert latency I Burkitt lymphoma (BL) tumors to the latency II/III program, rendering these cells to be susceptible to T-cell therapies. We found that hypomethylating agent decitabine induces the latency II/III program in BL tumors and renders tumors susceptible to killing by EBV-specific CTLs. We revealed that decitabine-induced latency conversion is regulated through the inhibition of DNMT1 and validated this by showing that DNMT1 inhibitor, GSK032 potently induces latency I to latency II/III conversion of BL cells.

Despite our promising findings of tumor growth inhibition in response to decitabine-induced latency conversion followed by EBV-CTL therapy, there are key gaps in knowledge that will be essential to the ultimate clinical translation of this approach: 1) little is known about the immune cells required for the clearance of latency-switched tumors and if allogeneic T-cells are needed or if the intact immune response is sufficient; 2) how to overcome the resistance of the EBV+ latency-I lymphomas that do not undergo latency conversion in

response to decitabine. Understanding mechanisms of resistance will allow for the development of approaches that maximize conversion to latency II/III.

To study the human immune response to latency-converted EBV+ lymphomas, we developed a humanized mouse model of BL. SGM3-NSG mice (NOD.Cg-PrkdcscidIl2rgtm1WjlTg (CMV-IL3, CSF2, KITLG)) are transplanted with human cord blood CD34+ cells and then engrafted with an HLA-matched latency I EBV+ BL tumor, prior to treatment with decitabine. We found that decitabine treatment of humanized mice with BL increases T cell infiltration to the tumor, suggesting a robust T-cell response in the absence of allogeneic EBV specific CTLs.

To examine the epigenetic machinery that may contribute to the mechanism of decitabine-induced latency switch, we performed ChIP-qPCR, ATAC-sequencing and bisulfite-sequencing. ChIP-qPCR data revealed that cells resistant to decitabine and GSK032 induced latency conversion has an elevated level of histone repressive marks H3K27me3 and H3K9me3. We showed that the addition of Ezh2 inhibitor, which targets H3K27me3, to decitabine or GSK032 increases latency conversion, indicating a compensatory role of histone repressive marks on resistance to decitabine induced latency conversion.

In summary, our work has identified DNMT1 as a key regulator of latency restriction and revealed the potential use of DNMT1 inhibitors to sensitize latency I EBV+ lymphomas to T-cell mediated tumor clearance. Future studies using our newly developed latency-I BL humanized mouse model will help identify the key immune effectors that respond to latency converted cells. This along our findings on the resistance mechanisms will guide the development of rational combination therapies to improve the treatment of otherwise immune refractory EBV+ latency-I lymphomas.

LR-10 CL
VARIATION IN ASSESSMENT AND DISPOSITION OF PATIENTS EVALUATED BY PSYCHIATRY ACROSS A MULTISITE HOSPITAL SYSTEM BY RACE

Flaxman BA, Hana R; Arnesen MD, Rachel; Samuels MD, Susan

INTRODUCTION: Previous research has demonstrated racial bias in the field of pediatric psychiatry, such as the overdiagnosis of conduct disorder and underdiagnosis of ASD and ADHD among BIPOC patients. More recent studies highlighted the increasing rates of pediatric mental health concerns during the COVID-19 pandemic and suggest that racial disparities in psychiatric care disproportionately affect minority children. Uncovering and building awareness of these disparities is essential, especially given the recently high rates of poor mental health among this country's youth.

OBJECTIVES: Our study's primary objective is to examine race-based differences in assessment and disposition of pediatric patients who underwent psychiatric evaluation in the hospital between March-December of 2019 prior to the COVID-19 pandemic and in 2020 during the early months of the COVID-19 pandemic. Secondary objectives include characterizing the demographics of the pediatric population requiring psychiatric evaluation at a large, multisite hospital system. METHODS: Data was collected through retrospective chart review by making a request through the Tripartite Request Assessment Committee (TRAC). Information collected included age, sex, race, city of residence, chief complaint/reason for evaluation, primary medical comorbidities, disposition, COVID-19 status, length of stay, visit number, living situation, characteristics of current mental health care, and MRN of pediatric patients evaluated in the hospital by psychiatry between March-December of 2019 and 2020. Chief complaint/reason for evaluation was determined by research staff through careful analysis of each patient's psychiatric evaluation note and reported patient assessments as recorded in their electronic health record (EHR). Chi-squared analysis was used to assess whether there was a significant association between assessment or disposition and patient racial group (Asian, Black or African American, white non-Hispanic, Hispanic). Data for patients without racial or demographic information specified in their EHR were excluded from data analysis, as was data for American Indian, Alaska Native, or Native Hawaiian identifying patients given comparatively very low numbers of patients identifying as such.

RESULTS: The total sample size for this study was 1,503. Recorded racial and ethnic identities were 47.6% white (Hispanic and non-Hispanic), 16.7% Black or African American (Hispanic and non-Hispanic), 16.4% Other or Declined/Unknown (non-Hispanic), 12.0% Other or Declined/Unknown (Hispanic), 6.5% Asian (Hispanic and non-Hispanic), 0.5% Native Hawaiian, and 0.3% American Indian or Alaskan Native (Hispanic and non-Hispanic). Average age among the entire sample was 15.8 (standard deviation 3.4), with the average age of each racial or ethnic group falling within 1 standard deviation of the sample average. Gender identities were recorded as 52.0% female, 44.8% male, 1.2% transmale, 1.0% nonbinary, and 0.7% transfemale. Following psychiatric evaluation, an assessment of "disruptive behavior, aggression, or running away" was made in 35.5% of Black/African American patients; compared to 6.1% of Asian, 20.7% of white non-Hispanic, and 22.8% of Hispanic patients, with a $p<0.01$ for association between race and this assessment. Disruptive behavior was the most common assessment made when evaluating Black/African American patients. White and Asian patients were most frequently admitted or

transferred to a psychiatric care unit, with 49.8% and 44.9% receiving higher level care, respectively. 36.7% of Hispanic patients and 34.4% of Black/African American patients were provided with higher level care following evaluation, with a $p<0.01$ for association between race and discharge status. Notably, for patients displaying psychotic symptoms, suicidal ideation, or those presenting following a suicide attempt, 62.5% of white patients (N= 349) received higher-level care, compared to 53.7% of Black or African American patients (N=95), 51% of Asian patients (N=49), and 48.8% of Hispanic patients (N=82) with a $p=0.064$ for this association.

CONCLUSIONS: Preliminary analysis suggests Black or African American and Hispanic patients are more likely to be assessed as having "disruptive behavior, aggression, or running away" as the reason for presentation to the psychiatric emergency room compared to white and Asian patients of a similar age-range. Data also suggests that white and Asian patients are more likely to be admitted or transferred to a psychiatric care unit than Black or African American and Hispanic patients, even among patients displaying psychotic symptoms, suicidal ideation, or those presenting following a suicide attempt. The root cause of these disparities is an important area for further research; previous studies hypothesize that systemic and unconscious bias may play a role. Uncovering and bridging disparities in care within the field of pediatric psychiatry continues to be essential, especially in the wake of the COVID-19 pandemic and the repercussions it has had on the mental health of youth in this country.

LR-11 TR
ANALYSIS OF LIVE URINARY CELLS BY FLOW CYTOMETRY IN CHILDREN WITH CKD: A NOVEL APPROACH TO "LIQUID BIOPSY"

Federman, Hannah G., Campbell, Chantalle A., El-Sayed, Heba. Akchurin, Oleh.

BACKGROUND: Chronic Kidney Disease (CKD), driven by kidney fibrosis, affects 10-15% of Americans, including 200,000 children. CKD currently has no cure and few interventions to slow disease progression exist. One of the barriers to improving outcomes in children with CKD is a lack of tools to assess kidney fibrosis non-invasively on a cellular level. While it has been acknowledged that most, if not all, kidney cell types can be found in the urine, utilization of urinary cells as a tool to get insight into cellular events within the injured kidney and to guide management remains very limited.

OBJECTIVE: Our overarching objective is to develop and validate a flow cytometry and cell sorting protocol that can serve as a reproducible approach to the characterization of key cell populations of kidney tissue-derived urinary cells.

METHODS: In this ongoing project, we use human urine samples collected from children with CKD in WCM pediatric nephrology clinic and from healthy controls (as part of an IRB-approved WCM pediatric CKD registry study) as well as unilateral ureteral obstruction (UUO) mouse model of kidney fibrosis. Human urine samples are kept at 4^{o}C for up to 4 hours upon collection and processed in daily batches. Samples are passed through 70 µm filters, cells are washed, counted, stained with fluorescently-tagged antibodies, and immediately processed for flow cytometry. Mice are sacrificed 7 days after UUO, urine is collected from the dilated kidney / ureter above the ligation and processed in a similar manner to that of human urine. Kidneys are collagenase-digested and single cell suspensions are processed for flow cytometry immediately and in one batch with the corresponding urine samples.

RESULTS: On average, we obtained 500,000 – 1,500,000 human urinary cells per 50 ml of urine, 70-80% of them remaining alive by the time of flow cytometry. In mice, we obtained 500,000 – 2,500,000, 20-50% of them alive, depending on strain. Currently, we are validating identification of urinary proximal tubular epithelial cells (pTEC), the key cell population implicated in kidney fibrosis. pTECs were defined as CD45-CD10+CD13+ cells and constituted 0.5-1.5% of human urinary cells. Validation experiments include cross-staining of nephrilysin (CD10) and membrane alanyl aminopeptidase (CD13) positive cells with other established tubular markers such as prominin-1 (CD133) and megalin (LRP2 = GP330). Interestingly, cellular iron status of human urinary cells assessed by ferroorange, a fluorescent probe labeling labile iron pool, and by transferrin receptor 1 (CD71) appeared to be distinct between human urinary pTECs and mouse kidney pTECs.

CONCLUSIONS Urinary cells appear to consistently contain a sizable population of proximal tubular epithelial cells amenable for downstream analyses in children with CKD and in healthy controls. Our ongoing work is focused on delineating functional properties of urinary tubular cells in comparison with kidney tubular cells and linking these properties with clinical characteristics of CKD patients.

LR-12 BS
EVALUATING HIV-1 SPECIFIC NEUTRALIZING AND NON-NEUTRALIZING ANTIBODY FUNCTIONS IN CHILDREN LIVING WITH HIV

Bahadir Zeynep, Vuong Kenneth, Dennis Maria L, Nelson Ashley, Fouda Genevieve G

BACKGROUND: Broadly neutralizing antibodies (bnAbs) have shown promise due to their high potency and breadth against a diverse range of HIV-1 strains. Typically, bnAbs develop slowly and present in the latter course of the infection in adults. We previously demonstrated an early bnAb response in a cohort of 212 ART-Naïve children living with HIV (aged 1-3 years) when

compared with chronically infected adults. Given these distinct immune characteristics, the early-life immune landscape may be more favorable for bnAb development. In addition to their neutralizing functions, bnAbs also show non-neutralizing effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These non-neutralizing antibody effector functions play a significant role in decreasing the viral load, leading to partial and potentially total protection against viral transmission. With this study, we aim to establish an association between the development of neutralization breadth and polyfunctional antibody responses in children living with HIV. Thus, investigating HIV-1 specific neutralizing and non-neutralizing antibody functions in children living with HIV is crucial to understanding the different immune characteristics of antibody development in early life.

OBJECTIVE: Investigate HIV-1 specific neutralizing and non-neutralizing antibody functions in children living with HIV.

METHODS: We obtained plasma samples from ART-naive children living with HIV-1 transmitted in utero or at the time of delivery from the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) repository. born to women living in the United States. A two-phase screening approach was implemented to assess neutralization breadth and potency. We evaluated plasma from children at 4 (n=13) and 5 (n=20) years of age against 5 viruses from a global HIV-1 panel representing various clades. Samples that neutralized ≥ 3 of 5 viruses are currently being further tested against 5 additional global panel viruses. Samples that neutralized ≥ 5 of 10 viruses in the panel were defined as having neutralization breadth. Non-neutralizing antibody functions of the samples will be evaluated by antibody-dependent cellular phagocytosis (ADCP) and Fc-gamma receptor (FcR)-binding assays.

RESULTS: The majority of children screened at 4(n=12 of 13) and 5 years (n=14 of 20) of age neutralized ≥ 3 of 5 viruses in the first phase of screening, with a combined frequency of ~79%. In comparison, we previously showed only 60% of 1-year old children and 76% of 2-year-old children were able to neutralize 50% of the viruses and overall, 69% children aged 1-3 neutralized ≥ 3 of 5 viruses. Plasma samples from these children will also be screened for non-neutralizing antibody functions such as, ADCP.

CONCLUSION: These results contribute to previous studies suggesting that children develop potent broadly neutralizing antibody responses earlier than adults and that their neutralization breadth increase with age. Our future work will focus on mapping the epitope specificity of the neutralization response.

LR-13 BS
ENHANCED TLR5 EXPRESSION IS LINKED TO DECREASED SUPPRESSION CAPACITY OF NAÏVE TREGS FROM CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Balaji Uthra, Santos Marina, Smitherman Cynthia, Walters Lynette, Miller Thomas, Baisch Jeanine, Wright Tracey, Gu Jinghua, Caielli Simone, Pascual Virginia

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a breakdown of tolerance to nucleic acids and a high Type I Interferon (IFNs) signature in the blood. Regulatory T cells (Tregs) play a crucial role in maintaining self-tolerance by suppressing the activation and expansion of autoreactive effector T cells. Previous studies described an expansion of dysfunctional Tregs in SLE. In this study, we employed single-cell RNA sequencing (scRNA-seq) to analyze purified CD4+ T cells from the blood of 12 children with SLE and 8 matched healthy controls, totaling 195,763 cells. Our analysis confirmed the expansion of blood naïve and memory Tregs in pediatric SLE patients, especially those diagnosed with Lupus Nephritis. SLE Naïve Tregs exhibited an upregulation of TLR5 at both the RNA and protein levels and were less suppressive compared to those from healthy controls. Furthermore, incubation with flagellin, a TLR5 ligand, further reduced their suppressive function. Interestingly, SLE serum induced TLR5 expression in iTregs (in vitro induced Tregs). Understanding the underlying mechanisms of Treg dysfunction, especially in the context of TLR5 modulation, and the potential connection with microbiome-derived signals could pave the way for targeted therapeutic interventions aimed at restoring immune balance and ameliorating the symptoms.

LR-14 BS
REPLICATING NEONATAL DIGESTION PHYSIOLOGY FOR IN VITRO MODELING OF NUTRIENT-HOST INTERACTIONS

Hayatt Omar, Birdinc Serena, Brown Joanne, Olagoke Olawande, Woodbine Maria Jose Hernandez, Mandalaywala Divya, Liu Martha, Liu David, Moncada Figueroa Denisse, Breber Emma, Revilla Jhoanny, Freedman Steven D, Martin Camilia

INTRODUCTION: Animal studies have provided crucial insights into nutrient digestion and assimilation, as well as nutrient-host interactions. However, limitations arise due to the incomplete equivalence of animal models with human systems. In vitro modeling using human cells and tissue presents a solution but removes the digestive process from the system, often resulting in the direct application of undigested nutrient substrates. We hypothesized that this practice could lead to erroneous conclusions in nutrient-host interactions.

OBJECTIVES: Our objective was to establish a human in vitro model of nutrient-host interactions using pre-digested nutrients to simulate the immaturity of the preterm gut.

METHODS: A pre-digestion protocol was applied to a Docosahexaenoic acid (DHA)/ Arachidonic acid (ARA) fatty acid supplement, involving stepwise exposures to porcine salt and lipase addition, rotating incubation at 37°C, and pH maintenance with NaOH and HCl. Hydrolysis was estimated using TLC and confirmed by GCMS analysis. CACO-2 cells were incubated with the final digesta for 72 hours, and viability was assessed using an LDH assay. Fatty acid incorporation into cell membranes was quantified by GCMS.

RESULTS: The pre-digestion process achieved a total lipid hydrolysis rate of 60%. During 72-hour incubations with the final digesta, overall CACO-2 cell viability was 80%. Fatty acid incorporation into cell membranes at 24 hours for the key select polyunsaturated fatty acids of ARA and DHA increased by 509% and 874%, respectively when exposed to the digested fatty acid supplement compared to the undigested supplement.

CONCLUSION: We successfully applied a pre-digestion protocol mimicking neonatal in-vitro conditions to a dietary supplement. Exposure to digested supplement was well tolerated in culture and resulted in differential fatty acid incorporation of key fatty acids during exposure to digested versus undigested enteral substrate. Our in vitro model of pre-digestion holds promise for precisely studying nutrient-host interactions and mechanisms with human derived cells without bypassing the process of digestion. Next steps include using fetal/infant derived intestinal cell lines and enteroids to elucidate the roles of ARA and DHA in augmenting intestinal development and mitigating intestinal injury.

LR-15 TR
LIPID NANOPARTICLE-MEDIATED DELIVERY OF SYNTHETIC CO-STIMULATORY MOLECULES TO ENHANCE ANTI-TUMOR IMMUNE RESPONSE

Richter Isabella, Perea Del Angel AM, Sadelain M, Heller DA, Hamieh M**

Immunotherapies based on CAR T-cells and Immune Checkpoint Blockade (ICB) have revolutionized cancer treatment. Despite clinical successes, therapeutic resistance often develops due to factors including antigen escape, lack of T-cell persistence, and immune suppression in the tumor environment. To improve T-cell persistence, we have engineered a synthetic co-stimulatory molecule by fusing the ectodomain of CD80 with the endodomain of 4-1BB (termed 80BB; Dobrin et al. 2024). Capitalizing on CD80's binding to the co-stimulatory molecule CD28 and the inhibitory molecule CTLA-4, 80BB activates the 4-1BB co-stimulatory endodomain upon binding to both molecules. Stable co-expression of 80BB with an HLA Independent TCR (HIT), an antigen-specific TCR, and most importantly patient-derived tumor infiltrating lymphocytes (TILs) with endogenous TCRs, extended survival and sustained effective anti-tumor response in mice. These findings prompted us to hypothesize that in situ delivery of 80BB to T-cells would improve anti-tumor function without ex vivo processing. To this end, we leveraged mRNA-encapsulating lipid nanoparticles (LNPs) to target T-cells and safely and efficiently deliver 80BB in vivo. We achieved one step-integration of a glycolipid into LNPs (gLNPs) that binds L-selectin (CD62L), exploiting its selective expression on immune cells, mainly naïve and memory T-cells. Addition of the glycolipid to LNPs containing the ionizable lipid MC3 resulted in a 10-20-fold increase in transfection efficiency of Jurkat and primary T-cells compared to conventional LNPs. Further optimization of this gLNP formulation will elucidate its potential for providing in situ delivery of mRNA for 80BB to improve survival and anti-tumor efficacy for patients.

PO1: POSTER SESSION 1
11:30 – 12:45 pm

PO1-01 BS
EPIGENETIC INHERITANCE OF DYSREGULATED METABOLIC PHENOTYPES IN Khdc3-null MICE AFTER SERUM TRANSFER EXPERIMENT

Phillips, Katie

INTRODUCTION: The obesity epidemic greatly affects our pediatric population, affecting 19.7% of children in the US1 and associated with an increased risk of comorbidities such as asthma, diabetes mellitus, hypertension, dyslipidemia, and sleep apnea. There is a strong inherited contribution to the risk of obesity and other metabolic diseases, yet less than 5% of that heritability can be explained by genetic mutations or polymorphisms2. Epigenetic changes can be induced in response to environmental exposures, and in this manner one's diet can influence the risk of obesity and metabolic disease in their descendants by epigenetic changes to the sperm and eggs that are inherited at the time of fertilization, providing a potentially significant contributor to heritability of obesity4. Small RNAs are emerging as an important mechanism of these cross-generational epigenetic changes that drive obesity and metabolic disease.

OBJECTIVES: The purpose of our study is to further delineate the mechanisms of non-genetic, epigenetic inheritance of metabolic phenotypes through investigation of the mammalian germ cell gene Khdc3. Mice lacking the Khdc3 gene have abnormal small RNA profiles in germ cells that is associated with dysregulated metabolic phenotypes in wild type offspring of Khdc3-mutant mice.

We hypothesize that Khdc3 regulates small RNA composition in germ cells in response to environmental exposures, through regulation of uptake of circulating small RNAs in serum, and thus alters gene expression patterns and phenotypes for future generations. To examine the role of Khdc3 in this somatic-germ cell communication, we performed a serum transfer experiment, in which wild type mice females injected with the serum from Khdc3-null mice, and Khdc3-null females were injected with serum of wild type mice. These females were then mated to wild type males, and their offspring were examined for hepatic metabolic dysregulation by RNA-Seq.

METHODS: Serum was isolated from wild type and Khdc3-null mice, and then 180uL was injected into recipient mice every 12 hours for a total of 3 injections. These mice were bred with wild type males, and the livers of the resultant female offspring were examined for evidence of metabolic dysregulation using RNA-Seq.

RESULTS/CONCLUSIONS: The RNA-Seq has been performed and is currently being processed by our bioinformatics team. We expect to have the final results in the next few weeks.

Sources:
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PO1-02 BS/TR
PROTEIN CORONA ENGINEERED LIPID NANOPARTICLE (PRO-LNP) FOR TARGETED MACROMOLECULAR DRUG DELIVERY

Major-Monfried, H, Wang, N, Luo, Danmeng, Kentsis, A

Current lipid nanoparticle systems enable the delivery of versatile cargos, but are limited by their liver and reticuloendothelial system uptake, which has confined their clinical applications exclusively to diseases of the liver. The long-term goal of this proposal is to develop a modular LNP based platform for safe, efficient, cell type specific delivery of peptidomimetics and other macromolecular drugs, including synthetic tumor suppressors for cancer treatment, like CRYBMIM, a second generation of peptidomimetic inhibitor, specifically disrupting the interaction between master hematopoietic cell regulator MYB and its co-activator CBP/P300 which is required for AML leukemogenesis. The objective of this proposal is to engineer LNPs that have attenuated hepatic and reticuloendothelial system uptake through rational LNP corona protein modification and cell type specific delivery through decoration with both decoy lipoproteins and targeting ligands. Our central hypothesis is that cell specific LNP delivery of macromolecular agents, like CRYBMIM, can be achieved by first, disrupting ApoE:LDL-R uptake in the liver by installing a decoy ApoE on the LNP surface that has reduced affinity for the LDL receptor, and second, directing LNP tissue fate through decoration with novel targeting molecules. Successful completion of this project is expected to yield a LNP macromolecular drug delivery platform, and a specific PRO-LNP-CRYBMIM optimized for effective AML therapy. While this study is focused on treatment of refractory leukemias, cell type specific LNPs with reduced liver and reticuloendothelial system uptake represent a platform technology that can be broadly applied for cancer therapy and and genome editing enzymes for somatic gene therapy.

PO1-03 BS
DECODING THE TOLEROGENIC IMMUNE LANDSCAPE IN PEDIATRIC CANCER

Cabric, Vanja

Immune checkpoint inhibition has revolutionized the treatment of adult cancers yet its success in pediatric cancer is limited to a few tumor types. At the heart of an anti-tumor immune response are antigen-presenting cells (APCs), master regulators of the immune system that are uniquely poised to initiate the activation of T cells and regulate the balance between effector immune responses and immune tolerance. Current immunotherapy aims to unleash an anti-tumor immune response by blocking inhibitory interactions between APCs and T cells. However, lack of data on the APC landscape in children hampers the rational design of immunotherapeutic strategies aimed at targeting these key cell types and associated inhibitory molecules. To this end, we recently uncovered a novel lineage of APCs (Thetis cells; TCs), encompassing four subsets (TC I-IV). A striking feature of TCs was their enrichment in lymph nodes in both mouse and humans during early life. Our work thus far has established a critical role for TC IV in peripheral regulatory T (pTreg) cell differentiation and tolerance to both dietary and commensal antigens. Furthermore, we found that TC IV are specifically enriched at sites of pTreg generation and tolerance induction, notably gut and hepatic lymph nodes. While this layered ontogeny ensures enhanced representation of tolerogenic APCs during key windows when the developing immune system first encounters harmless dietary and microbial antigens, we hypothesize that the same cell types prevent effective immune responses to tumors that arise during early life. In preliminary work using orthotopic models of malignancy, we have found that TCs are enriched in tumor draining lymph nodes (TDLN). This increase in TCs is associated with a parallel increase in immunosuppressive Tbet+ Treg

cells in the TDLN of pediatric but not adult mice. Previous studies established a critical role for Tbet+ Treg cells in suppressing anti-tumor immunity. We hypothesize that the increased abundance of TCs in pediatric tumor draining lymph nodes, drives the differentiation or expansion of T-bet+ Treg cells upon presentation of tumor antigens, and that the profound enrichment of TCs during early life underlies the immunosuppressive landscape of pediatric tumors.

Using state of the art single-cell profiling to identify rare but critical cell types within tumor and tumor draining lymph nodes, alongside novel genetic models to interrogate critical molecules underpinning the tolerogenic program of TCs, we will determine the role of TCs in mouse and human hepatoblastoma. We anticipate these studies will reveal novel targets for pediatric cancer immunotherapy and provide a roadmap for future studies addressing the role of early antigen-presenting cells in pediatric cancer.

PO1-04 BS
ELUCIDATING POST-TRANSCRIPTIONAL REGULATION OF ONCOGENIC DRIVERS/DEVELOPMENTAL TRANSCRIPTION FACTORS BY MUSASHI RNA BINDING PROTEINS IN NEURBLASTOMA

Wei Wei, Xie Xueqin, Baali Ilyes, Kharas Michael

Neuroblastoma, a tumor of the peripheral sympathetic nervous system, displays a diverse spectrum, ranging from spontaneous regression to highly aggressive cancer. However, the genomic landscape of neuroblastoma is comparatively less complex, suggesting disturbances of developmental and oncogenic pathways extend beyond genomic and epigenomic changes. Post-transcriptional regulation enhances proteome abundance and diversity, with RNA binding proteins (RBPs) serving as central arbiters of this process. RBP MUSASHI1 (MSI1) and MUSASHI2 (MSI2) are members of highly conserved two-protein family that has been demonstrated to play a role in proliferation and lineage commitment in neural and hematopoietic stem cells as well as cancer stem cells. MSI family proteins emerge as key players in orchestrating RNA stability and translation, governing cell fate determination and asymmetric cell division- a conserved mechanism pivotal for stem cell renewal and cellular diversity. The aberrant expression of MSI disrupts transcriptional patterns and signaling pathways, contributing to tumor initiation, progression, and drug resistance across varied cancer typeS. In neuroblastoma patients, we have identified correlations between high expression of either MSI1 or MSI2 and worse survival. Notably, neuroblastoma cell lines are the most sensitive cell lines to depletion of MSI1 or MSI2 among the cancer cell lines assessed in the DepMap genome-wide CRISPR-Cas9 screen database. We have validated that depletion of MSI by shRNA inhibited the proliferation of neuroblastoma cell lines and reduced the protein abundance of MYC or MYCN, in MYC-driven or MYCN-amplified neuroblastoma cell lines, respectively. The presence of exogenous MSI2 can partially rescue the reduction in proliferation and MYC/MYCN protein abundance caused by MSI-shRNA mediated depletion. MSI inhibitor Ro 08-2750 (Ro) demonstrated effectiveness in suppressing both MYCN-amplified and MYC-driven neuroblastoma cell lines. The Ro treatment resulted in a reduction in MYCN protein levels in MYCN-amplified neuroblastoma cells, consistent with the MSI depletion experiment. In addition, both MSI1 and MSI2 directly bind to MYCN mRNA and enhance the its translation, confirming that MYCN is one of the targets of MSI proteins in neuroblastoma. We hypothesize that MSI proteins post-transcriptionally regulate crucial neuroblastoma oncogenic drivers, leading to an altered translational program that drives or facilitates neuroblastoma tumorigenesis. This study elucidate the function of MSI proteins in neuroblastoma, and uncover critical posttranscriptional regulatory mechanisms by MSI RBP networks, which may result in novel therapeutic strategies.

PO1-05 CL
TRANSITION TO A NON-INVASIVE REJECTION SURVEILLANCE PROTOCOL WITH DONOR-DERIVED CELL-FREE DNA (dd-cfDNA) IN PEDIATRIC HEART TRANSPLANT RECIPIENTS

Bravo Stephen, Akabas LH, Barry OM, Hsiao WC, Richmond ME, Lytrivi ID

BACKGROUND: Acute allograft rejection (AR) is a leading morbidity for pediatric heart transplant (HT) recipients, detected in up to 30% of subjects in the first-year post-HT. While endomyocardial biopsy (EMB) remains the gold standard for detection of AR, the limitations and invasive nature of this procedure have led many pediatric programs to utilize adjunctive non-invasive methods of rejection surveillance. Our program adopted donor-derived cell free DNA (dd-cfDNA) as the main surveillance method on 07/01/2022.

OBJECTIVE/HYPOTHESIS: This study aims to compare the procedural burden between a biopsy-based protocol and a predominantly non-invasive surveillance protocol, as well as the detection and severity of AR episodes.

METHODS: Patients who underwent HT before age 18 followed at our center from 2019-2023 were retrospectively reviewed. Two time periods were compared, Era 1 (01/2019-03/2020, biopsy based) and Era 2 (07/2022-06/2023, dd-cfDNA based). Patients with multi-organ transplants, post-transplant lymphoproliferative disorder, and bone marrow transplants were excluded.

RESULTS: Biopsies, anesthesia, and intubations had a statistically significant decrease in Era 2, with a 44% reduction in biopsies per patient-year in Era 2. When screening with dd-cfDNA in Era 2 there was a significant increase in the number of positive biopsies (32/312, 10.1%), compared to 19/745 (2.6%) positive biopsies found in Era 1 ($p < 0.001$). Cases of rejection were significantly more likely to be associated with a positive biopsy (72.9% in Era 2 vs. 45.9% in Era 1) and less likely to present as clinical rejection ($p = 0.017$).

CONCLUSION: We were able to significantly reduce surveillance EMB and related procedures without a significant change in allograft rejection detection when utilizing dd-cfDNA. We were also able to significantly increase the diagnostic yield of EMB testing by screening with dd-cfDNA. Given the increase in positive biopsies, decrease in clinical rejection, and trend towards decreased AR with hemodynamic compromise, our limited experience suggests that integrating dd-cfDNA may also lead to earlier detection of rejection in pediatric populations. Future studies will allow us to determine if dd-cfDNA protocols are superior in the detection of early rejection and can decrease HR in pediatric patients.

PO1-06 CL
NEONATES BORN TO COVID-19 POSITIVE MOTHERS AMONG DIFFERENT WAVES – AN OBSERVATIONAL COHORT STUDY

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BACKGROUND: This neonatal database was created in 2020 to follow neonates born to SARS-CoV-2 positive mothers, and to elucidate trends in infection and demographic data over the course of the various COVID-19 waves.

OBJECTIVE: Our study aimed to understand neonatal infection rates and demographics during the COVID waves.

METHODS In this observational cohort study, we identified all neonates born between 03/2020 and 10/2022, at 4 NewYork Presbyterian Hospitals in New York City (USA) to mothers positive for SARS-CoV-2 at delivery. Neonates were tested for SARS-CoV-2 via PCR at 24h, with recommended follow up for testing at 5-7 days (d), and 14 d of life. We recorded demographics, birth data, neonatal testing and follow up. Descriptive statistics were used for demographic (D) and clinical factors of interest (CFI). Categorical variables are represented as n (%) and continuous variables are represented as mean (M) with standard deviation (SD). Fisher's exact test and one-way ANOVA were used to examine the association between D/CFI and COVID-19 wave. Seven COVID-19 waves were identified – Wave 1 (W1) (03-06/2020), Wave 2 (W2) (07/2020-06/2021), Wave 3 (W3) (Delta, 06-12/2021), and Waves 4 (W4) (combined 4 Omicron waves, 12/21-current).

RESULTS A total of 1534 neonates born to mothers positive for SARS-CoV-2 were identified; 52% were male. 38% were White, 14% Black, 8.9% Asian, 39% declined to answer or unknown. 15% were Hispanic/Latino origin and 33.8% declined to answer or unknown. There was no statistical difference among the different waves for gestational age (GE), birth weight (BW), length (L) and head circumference (HC) with M GE 38.5 (SD 1.95), M BW 3228g (SD 552), M L 50.12 cm (SD 2.94) and M HC 34.04 cm (SD 1.82). There was a significant difference in the distribution of birth PCR result across the 4 COVID-19 waves ($p < 0.001$). 16 (1%) of all neonates were PCR positive at 24 hours of life, of which 14 (2.7%) were positive in W4, compared to 1 (0.3%) in W1, 1 (0.2%) in W2 and 0 (0%) in W3. When analyzing separately all the 7 Waves, the highest positive result at birth was during W5 with 5 (6.8%) newborns testing positive. Follow up at 5-7d and 14d decreased over time.

CONCLUSION: Among Waves there was no statistically significant difference for standard birth variables (GE, BW, L, HC), however there was significant difference in distribution of positive PCR at birth across COVID-19 Waves, with highest transmissibility from mother to newborn in W4 (during the various Omicron variants). Follow up data collection was limited due to decreased parental fear of COVID-19 with subsequent lack of follow up.

PO1-07 CL
THE EFFICACY OF ANTIFIBRINOLYTICS IN CHILDREN UNDERGOING CRANIOFACIAL SURGERY

Morgan Smith, Katherine Schertz Hickey, Oliver Karam, David Faraoni, Michelle Demetres, Vincent Duron, Yeu Sanz Wu, Marianne E. Nellis

INTRODUCTION: Surgery, including repair of craniofacial defects, is one of the most common causes of clinically relevant bleeding in the pediatric population. Antifibrinolytic therapies have been studied in pediatric cardiac surgery and have been shown to reduce blood loss and decrease the need for transfusions. A recent systematic review suggests that antifibrinolytics, such as tranexamic acid (TXA) and aminocaproic acid (EACA) also reduce blood loss in non-cardiac pediatric surgery.

OBJECTIVE: The objective of this study is to determine if intraoperative administration of antifibrinolytics, including TXA, EACA, or aprotinin, decreases blood loss and/or the

need for transfusion in pediatric patients undergoing craniofacial surgery.

METHODS: We conducted a systematic review and meta-analysis of three databases from inception to April 2023. Adult-only studies (mean age >21 years), non-human studies, and case series were excluded. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. The estimated blood loss in the operating room and post-operative transfusion of blood components were evaluated.

RESULTS: A total of 38 studies including 7,063 patients were analyzed. When compared to controls, administration of TXA resulted in a mean decrease in estimated blood loss of 14.6 mL/kg (95% CI 6.8-22.4 mL/kg), p<0.001. Studies looking at the blood loss in patients receiving EACA and aprotinin were limited and did not achieve statistical significance. Administration of TXA compared to control resulted in a mean decrease in intraoperative red blood cell (RBC) transfusion of 7.5 mL/kg (CI 95% 5.1-9.9 ml/kg), p<0.001. Administration of aprotinin compared to control resulted in a mean decrease in RBC transfusion of 20.0mL/kg (CI 95% 9.8-30.2mL/kg), p<0.001. Administration of EACA compared to control was limited to two studies and did not achieve statistical significance. Administration of TXA compared to control resulted in a mean decrease in intraoperative plasma transfusion of 6.2 mL/kg (CI 95% 2.4-9.9 mL/kg), p<0.001.

CONCLUSIONS: TXA demonstrates potential for decreasing intraoperative blood loss and blood product requirements in pediatric patients undergoing craniofacial surgery. Further studies are needed to evaluate the effects of other antifibrinolytics and to determine the best dosing regimen of TXA that maximizes hemostasis with the lowest risk of side effects.

PO1-08 CL
POLYSOMNOGRAPHY FINDINGS IN CHILDREN'S INTERSTITIAL LUNG DISEASE (chILD)

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RATIONALE: Children's interstitial lung disease (chILD) is an umbrella term encompassing a heterogeneous group of complex, rare, diffuse lung diseases affecting infants and children. As sleep related breathing disorders can impact health, development, and growth, early diagnosis is important for better prognosis of individuals with chILD. Previous studies have evaluated sleep disordered breathing within individual chILD diagnoses such as Neuroendocrine Cell Hyperplasia of Infancy (NEHI). The aim of this study was to describe findings on overnight polysomnography (PSG) in a cohort of patients with chILD.

METHODS: We performed a single center retrospective chart review under an Institutional Review Board approved protocol. We queried the Weill Cornell electronic medical record to identify children 0 – 21 years old who ever received diagnostic ICD-10 codes for chILD from 2012-2022. Retrospective validation protocol was performed independently by two pediatric pulmonologists to confirm patient cohort. Those who underwent PSG were identified and demographic information, chILD diagnosis, symptoms, reason for referral and polysomnography data were recorded and analyzed. Obstructive sleep apnea (OSA) was defined as AHI >1/hr, and sleep related hypoxemia as >5min below SpO2 90%.

RESULTS: Fourteen children out of 52 with chILD underwent a full night polysomnography. Of these, four (28%) had chILD associated with rheumatologic disease, 4 (28%) bronchiolitis obliterans, 2 (14%) ABCA3, 2 (14%) chILD of unknown etiology, 1 (7%) NEHI, and 1 (7%) pulmonary interstitial glycogenosis. Of those who were referred for PSG, 4 (29%) patients were referred for hypoxemia, 7 (50%) for snoring, and 3 (21%) for both. Of those who underwent PSG, 8 (57%) children met the diagnosis for OSA and 3 (21%) for sleep related hypoxemia (Table 1). Overall, the prevalence of OSA in this tested population with chILD was 53%.

CONCLUSION: A high prevalence of sleep related breathing disorders was found in a cohort of children with chILD. The rate of OSA is higher than in the general population, which previously was thought to be uncommon in children with chILD. Early screening and low threshold for referral for polysomnography are recommended for early diagnosis and treatment. Larger, multicenter studies are necessary to fully understand the prevalence and impact of sleep disordered breathing in patients with chILD.

Table 1

n	**14**
Age (years)	8 (0.1 – 19)
Gender (male)	10 (71%)
BMI (kg/m2)	18.8 (12 - 32.3)
TST (min)	418 (252 - 549)
Sleep Efficiency (%)	81 (45 - 98)
REM(%)	16.4 (5.8 - 28.9)
Arousal Index (events/hr)	12.2 (4.2 - 33.1)
AHI (events/hr)	1.5 (0 - 14.1)
OAHI (events/hr)	0.9 (0 - 11.2)
CAI (events/hr)	0.3 (0 - 2.9)
Mean SpO2 (%)	97.7 (92.6 – 99.8)
Minimal SpO2 (%)	91.5 (79 – 96)
Minutes below 90%	0 (0 – 30)

Maximal PetCO2 (mmHg)	48.7 (41.6 – 52.2)
PLMI (events/hr)	0.8 (0 – 71.5)
OSA n(%)	8 (57%)
CSA n(%)	0
Hypoxemia n(%)	3 (21%)
Poor sleep efficiency (<85%)	8 (57%)
PLMD n(%)	2 (1.4%)

*PSG performed on oxygen

Abbreviations: TST: total sleep time; REM: rapid eye movement; AHI: apnea-hyponea index; OAHI: obstructive apnea hypopnea index; CAI: central apnea index; SpO2: oxyhemoglobin saturation; PetCO2: end-tidal carbon dioxide; PLMI: periodic limb movement index; OSA: obstructive sleep apnea (AHI>1); CSA: central sleep apnea (CAI>5); PLMD: periodic limb movement disorder (PLMI>5)

PO1-09 CL
THROMBOPROPHYLAXIS IN CHILDREN TO PREVENT CENTRAL VENOUS CATHETER ASSOCIATED THROMBOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND: Central venous catheters (CVC), which are frequently used in children in both inpatient and outpatient settings, are strongly associated with increased risk of deep vein thrombosis (CADVT). It remains unclear if pharmacologic thromboprophylaxis is effective in preventing CADVT in children.

OBJECTIVE: To determine the effectiveness of pharmacologic thromboprophylaxis in reducing the risk of CADVT in children.

DESIGN/METHODS: We conducted a systematic review and meta-analysis of several databases including Ovid MEDLINE, Ovid Embase and Cochrane Library from inception to July 2022. We included observational and interventional studies in which unfractionated heparin, heparin-bonded CVCs, low molecular weight heparin, vitamin K antagonists, direct thrombin inhibitors, antiplatelet agents and direct oral anticoagulants were administered. Studies were excluded if they did not include our primary outcome of radiologically confirmed deep vein thrombosis (DVT), contained data on pre-term infants or adults (<21 years) only, focused on patients requiring extracorporeal membrane oxygenation (ECMO), or reported non-human data. Patient demographics, characteristics of the CVC, name and dosing of the prophylactic agent, and radiologic method used to detect DVT were abstracted.

RESULTS: A total of 15 studies met eligibility criteria and included 1,480 patients. Anticoagulants used in the studies included low molecular weight heparin (LMWH), utilized in eight studies; unfractionated heparin (UFH) in four studies; vitamin k antagonists in five studies; urokinase in one study; nitroglycerin in one study; and heparin bonded catheters in two studies. Catheter type varied among studies but included tunneled and non-tunneled catheters as well as peripherally-inserted and Hickman catheters. Thirteen percent (81/613) of patients who received pharmacologic thromboprophylaxis developed CADVT and 16% (143/871) of patients who did not receive pharmacologic thromboprophylaxis developed CADVT. Risk ratio of CADVT with pharmacologic thromboprophylaxis was 0.71 (95% confidence interval, 0.48-1.05).

There was significant heterogeneity observed amongst the studies (I2 = 48%). Subgroup analysis of studies using LMWH showed a benefit with a risk ratio of CADVT using LMWH of 0.43, (95% confidence interval, 0.22-0.85). Subgroup analyses based on patient pathology showed a benefit in patients with gastrointestinal pathology with a risk ratio of CADVT using pharmacologic thromboprophylaxis of 0.11 (95% confidence interval). Benefit was not seen in other subgroups such as in oncology patients.

CONCLUSION(S): Pharmacologic thromboprophylaxis was not associated with reduced risk of CADVT in mixed populations of children. However, subgroup analyses show benefit in specific populations and when using low molecular weight heparin compared to other pharmacologic agents.

PO1-10 CL
INSIGHTS FROM AN ANOMALOUS AORTIC ORIGIN OF A CORONARY ARTERY (AAOCA) REGISTRY: A SINGLE CENTER EXPERIENCE IN ADULTS AND CHILDREN

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INTRODUCTION: Anomalous aortic origin of a coronary artery (AAOCA) is a rare congenital anomaly associated with sudden cardiac death. The true natural history is unclear with wide variation in clinical practice.

OBJECTIVE: We aim to better characterize management and outcomes at our center in patients who did and did not undergo surgical repair.

METHODS: Patients were identified from our surgical and local imaging databases, electronic health record query, and notification by primary cardiologist between Jan 2001

and Sept 2023. We conducted a retrospective review to document demographics, clinical evaluation, surgical intervention, and follow up.

RESULTS: A total of 316 patients were identified. Median age at diagnosis was 14 years (IQR 7-44). Diagnoses via either echocardiogram or CT included anomalous left coronary from right sinus (ALCA) n=63, anomalous right coronary from left sinus (ARCA) n=183, left coronary from non-coronary sinus n=10, single right coronary (S-RCA) n=25, or single left coronary (S-LCA) n=3, while 25 were inconclusive and 7 discrepant. The most common referral reason was symptoms (58%). Surgery was performed on 138/316 patients: (49/63) 78% of ALCA, (72/183) 39% of ARCA, (4/10) 40% of left coronary from non-coronary sinus, and (12/25) 48% of S-RCA. Median age at surgery was 16 years (IQR 12-42). There were 7 patients (5%) with discrepant pre-operative imaging and surgical diagnoses. Surgical outcomes had no mortalities nor stroke with rare complications such as aortic insufficiency n=4 (3%), early re-operation n=1 (0.7%), and late re-operation n=3 (2%). Of patients who did not undergo surgery (n=178) the distribution was: ALCA (16/178, 9%), ARCA (112/178, 63%), left coronary from non-coronary sinus (7/178, 4%), S-RCA (13/178, 7%), and S-LCA (1/178, 0.6%); remainder were inconclusive or discrepant. There were no documented deaths at current state of follow up.

CONCLUSIONS: In this cohort of adult and pediatric patients diagnosed with AAOCA, there were no reported mortalities. In those who underwent surgery, complications were rare. Imaging played a central role in diagnosis. Our experience highlights the importance of a collaborative approach for decision making in these patients.

PO1-11 CL
ASSOCIATION BETWEEN ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AND PLASMA COTININE LEVELS IN CHILDREN AND ADOLESCENTS WITH ASTHMA

Brady K, Thomas C, Gerber LM, Permaul P

BACKGROUND Plasma cotinine (nicotine metabolite) levels correlate with smoke exposure. Primary and secondary smoke exposure increase cotinine levels and asthma exacerbations. We hypothesized that asthma severity is positively correlated with smoke exposure as determined by detectable plasma cotinine levels.

METHODS: The NewYork-Presbyterian (NYP) Pediatric Asthma Cohort Study enrolled patients, ages 2-20 years with and without asthma, from outpatient clinics. A physician diagnosis of asthma was used to identify asthma versus control. Plasma cotinine levels were assessed, and a survey completed.

RESULTS: 190 predominantly Black (29%) or Hispanic (56%) patients were included in analyses, 112 asthma and 78 control. Cotinine was detected in 26 (14%) of patients. Of patients who had detectable levels, 71% had household incomes $45,000 while of those with undetectable levels, 42% had incomes $45,000(p=0.012). Patients with detectable levels had a higher median age (16 vs. 14 yrs; p=0.037). Cotinine levels were detected in 10% of participants who were never/rarely exposed, 0% exposed several times a month, and 35% exposed several times a week/daily(p=0.013). Cotinine levels were detected in 57% of patients with primary and secondary smoke exposure, 0% with primary, 23% with secondary, and 10% with no exposure (p=0.006). Cotinine levels were detected in 14% of control patients, 10% with intermittent/mild persistent asthma, 19% with moderate/severe persistent asthma(p=0.4).

CONCLUSIONS: Differences in cotinine detection were seen based on household income, age, and the type and frequency of smoke exposure. Although detectable cotinine levels were highest in patients with severe asthma, it did not reach statistical significance.

PO1-12 CL
MASSIVE TRANSFUSION IN CHILDREN WITH CANCER/HEMOPOIETIC STEM CELL TRANSPLANT

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BACKGROUND: Management of life-threatening bleeding (LTB) in children has been extrapolated from studies of bleeding adults. Only recently have there been pediatric studies investigating the optimal management of LTB in children. However, management of LTB in pediatric cancer and hematopoietic stem cell transplant recipients (HSCT) patients, whose bone marrow is clearly different than their non-cancer counterparts, has not yet been investigated.

OBJECTIVE: We sought to characterize the epidemiology of LTB in children with cancer and/or HSCT. In addition, we sought to characterize the utilization of blood products and antifibrinolytic therapy in children with cancer and/or HSCT with LTB and to define hemostatic resuscitation principles that are associated with improved outcomes.

METHODS: We conducted a multisite retrospective cohort study involving 23 participating centers in the US and Europe from 2017-2022. Patients were included if they: (A) were 0-21 years of age; (B) received chemotherapy within the last 6 months or HSCT within the last 12 months; and (C) received >40 mL/kg of blood components in < 24 hours OR died from hemorrhage before receiving that volume of blood products. Children supported by extracorporeal membrane oxygenation were excluded. Descriptive statistics was used to

characterize the study sample with respect to clinical and demographic factors of interest.

RESULTS:132 cancer and/or HSCT pediatric patients with LTB were identified. The median (IQR) age in months was 7.2 (2.2-14.1) years. Of the 132 patients, 54 were female and 78 were male. 58% received >40 ml/kg of blood products <24 hours, 39% received >40 ml/kg of blood products <6 hours, and 3% died from exsanguination before blood products could be given. Of the 117 patients with an oncologic diagnosis, 28% had ALL and 17% had AML. Gastrointestinal bleeding was the most common source (56%), followed by pulmonary (20%). The children in the cohort had significant thrombocytopenia prior to their bleeding event (median (IQR) platelet count 50 (24-115) x109/L). The RBC:plasma:platelet ratio given for resuscitation was roughly 2:1:1 in the 24 hour bleeding group and 3:1:1 in the 6 hour bleeding group. There was a relatively low use of antifibrinolytics (20% for <24 hour group, 12% for <6 hour group), a relatively high use of cryoprecipitate (31% for <24 hour group, 35% for <6 hour group) and prothrombin complex (PCC) (21% for <24 hour group, 6% for <6 hour group). Twenty-nine children (23%) died of exsanguination despite resuscitative measures.

CONCLUSIONS: Despite thrombocytopenia going into their LTB events, children with cancer and/or HSCT are resuscitated with relatively low ratios of platelet transfusions. Even though antifibrinolytics have reduced mortality in non-cancer cohorts of bleeding children, they are not frequently used in this cohort of bleeding children. The mortality rate from exsanguination is high. Further analyses will investigate the independent associations of resuscitative measures on mortality.

PO1-13 CL
EXPERIENCES OF FAMILIES AFTER SURGICAL PLACEMENT OF ENTERAL FEEDING TUBES: A QUALITATIVE STUDY

Pressimone Allison G Banker Sumeet L Lakhaney Divya

INTRODUCTION/BACKGROUND: Families of children with medical complexity (CMC) and technology assistance report higher rates of financial and social hardships as well increased unmet needs with respect to the Social Determinants of Health (SDoH). At the hospital where this study was conducted, there is bedside training for management and troubleshooting enteral feeding tubes; however, there is no structured or intentional discussion about how this technology will impact finances, employment, childcare, and other factors. (i.e., SDoH). There are limited studies about the intersection of CMC, medical technology, and SDoH within the pediatric population.

OBJECTIVES: The primary objective of this study is to explore the relationship between medical technology (enteral feeding tubes) and families' SDoH during their transition from hospital to home.

DESIGN/METHODS: This is a prospective qualitative study using semi-structured interviews to explore family perspectives after being discharged home with new enteral feeding tubes. An interview guide was developed to explore the following domains: school and childcare, employment, finances, and housing. Eligible participants included any parent or caregiver over 18 years who has a child with a surgically placed enteral feeding tube and whose preferred language was English. Participants were recruited from an outpatient pediatric surgery clinic. Data were analyzed with deductive and inductive coding based on an existing framework of pediatric hospital to home transition. Transcripts were reviewed independently by the research team, and codes were iteratively revised using the constant comparison methodology. Codes were then generalized into common themes.

RESULTS: We have conducted 8 in-depth interviews with caregivers of children who have enteral feeding tubes. All participants were mothers. 50% identify as white, 33% as Black or African American, 17% as Hispanic or Latino. 66% of children had other assistive technology in addition to the enteral feeding tube, including central lines and speech devices. The interviews were conducted over Zoom and averaged 60 minutes in length. During analysis, several key themes emerged: Parent identity, navigating systems within and outside of healthcare, importance of support structures within the community and medical system, and availability of resources. Caregivers shared their struggles to balance their role in their child's life. This was represented in their recognition of having to be not only a parent, but also nurse, medical assistant, pharmacist, social worker, etc. Families frequently discussed the challenges of navigating multiple systems to meet the needs of their child, including the medical system and education system. Both positive and negative experiences were described depending on the background and prior experiences of the caregivers. Support structures were identified both within the healthcare system—knowledgeable, consistent medical teams and the assistance provided by social workers—and external to the hospital, such as online forums, peer groups, and extended family members. Finally, families shared perspectives on how availability of resources could make caring for their child more or less difficult. This included access to home nursing, transportation for school, and occupation, physical, and speech therapists. Please see examples of representative quotations below.

CONCLUSIONS: This study provides insight into the areas where families of children with enteral feeding tubes may need more support than what is currently provided.

These findings support a holistic approach to care by anticipating families' needs and addressing the complexities that come with feeding tubes both prior to placement of the tube and during the discharge process, with particular attention paid to the impact this technology can have on SDoH. Further studies should explore populations with other medical technologies, as well as with families with a preferred language for care other than English.

THEME: Parent Identity 1. Key Concept: Parent as Nurse --Representative Quotation: I don't have a home nurse. So like, who's doing his care? I'm just me and Dad. At this point we're nurses. At this point, we're full time nurses and we still have to go to work and do everything else so. It's just what it is at this point. Just have to take what it is. 2. Key Concept: Parent as Parent --Representative Quotation: So I think it will be helpful to get the home health aide and we could kind of focus more so on being present and making memories more so than, OK, get everything in. 3. Key Concept: Parent as Advocate --Representative Quotation: But I again, I went in the Medicare office until I found someone, a supervisor that was really kind to help me because I was told a lot of things there. That's a dog pound. They shouldn't have people like that working there to tell you the truth. So I went and I got in they were like, no, no, he qualifies, he was born here and he has special needs. --Representative Quotation: Some people, I guess, will hate me, some love me, but it's just the way you have to be and and you know, sometimes I feel like I tell people how it is and they get offended and they're like, no, no--You're advocating, and that's a good thing. So I learned from the same people that I told them of, that it's a good thing to speak up and you're not being rude or feisty because you know you could get confused with advocating from being rude. You have to learn how to advocate without trying to offend people. Theme: System Navigation 1. Key Concept: Education system --Representative Quotation: But now when he goes to kindergarten, I'm, now I have no idea about schooling, of where to send him. I barely know how to. I'm Jamaican, so I barely know how the schooling system works. So that's my issue right now, I'm actually looking. Into the only school that I did found it was a private school. But then the tuition for that is like 28,000 dollars a semester 2. Key Concept: Medical system --Representative Quotation: That was a struggle with the speech because as soon as we get one person, they're like, oh, they're moving me to somewhere else. I'm not gonna be working [there] anymore. Then we have to wait months again for another speech therapist. And then he already forgot what he remembered from one speech therapist. And then by time we get the other speech therapist, they're not using the same technique. So now he's using another technique and then that person says I'm not going to be working in [there] anymore. They're moving. So it was just never like consistent. It's not a consistent thing. Theme: Support Network 1. Key Concept: Medical team --Representative Quotation: I would say the most helpful medical provider would be [his] pulmonologist. It's like, you know, they're not just pulmonologists. They're like pediatricians. They like, know it all. So they treat [him] for his pulmonary issues. But if I were to call her and say, oh, you know, [he] is throwing up--what should I do? She'll, like, prescribe medications for me or tell me what to do. 2. Key Concept: Spousal support --Representative Quotation: Even my husband, he's got into medical and now he changes his G-TUBE. He changes his ostomy bag. He done, he's learned everything. And because, you know, I said at one time I got sick and we realize what happens if I'm gone. So I'm like, I need you to step in and then he did. 3. Key Concept: Social work assistance --Representative Quotation: [He] was never approved for Medicaid because of our income. So I had, someone at the hospital advocated for me and told me how to do this through a different way where they don't look at income. Obviously, [he] should be approved, then should qualify for all the benefits. 4. Key Concept: Family support --Representative Quotation: So I received 100% help from my mother, so my mother cares for [him] and she's been, I would say my right hand man. --Representative Quotation: So we have we have family close by, but family is so scared to learn because he's so fragile. Well, they think he's so, I guess he is, medically fragile. Nobody else wants to learn, so if something happens to me and Dad today, I don't know who's gonna take care of [him]. Theme: Resource Availability 1. Key Concept: Online forums --Representative Quotation: It didn't really click until I got home and I started going on Facebook and seeing other people's experience and stuff like that and I was getting. I got most of my help from my Facebook group. 2. Key Concept: Home services --Representative Quotation: Home nursing: And now the thing is that I have nursing, but they don't really know how to do stuff… I have to take care of his central line and then they do help me with the G-tube and the ostomy. It's hard—they won't learn how to change it. There's one—his main nurse has been with us for 11 years, but she already knows how to do everything. So she's my backup person to go to. Like, if something happens, she knows everything about [him]. --Representative Quotation: Paid family assistance: My mom, she I got her to start working for freedom care. So she does come over four nights a week and we did that only because at the time [my son] used to scratch at his dressing a lot, his broviac line so we got no sleep.

PO1-14 CL
ARRHYTHMIAS DURING PEDIATRIC CARDIAC EXTRACORPOREAL CIRCULATORY SUPPORT: A SINGLE CENTER RETROSPECTIVE COHORT STUDY

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OBJECTIVE: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a form of mechanical circulatory support in cardiac failure and can be utilized

for pediatric patients with congenital or acquired heart disease. These patients are at risk for arrhythmias while supported on ECMO, however, data are limited regarding the incidence and types of arrhythmias, and their association with adverse outcomes. We present our single center experience of arrhythmia on pediatric cardiac ECMO support, and the association with a composite poor outcome measure, defined as death, need for ventricular assist device (VAD) or heart transplantation.

DESIGN: Retrospective, single-center study. Setting: Cardiac neonatal ICU and cardiac PICU in urban, quaternary care center. Patients: Pediatric patients requiring ECMO for cardiac indications including extracorporeal cardiopulmonary resuscitation (eCPR), cardiogenic shock, hypoxemia secondary to lack of pulmonary blood flow or inability to wean from cardiopulmonary bypass (CPB). Interventions: None.

MEASUREMENTS AND MAIN RESULTS: There were 83 cannulations across 74 patients included in the final study cohort. Arrhythmias occurred during 27 (33%) of ECMO runs, including ventricular arrhythmias in 14 (16%) runs. Arrhythmia on ECMO was associated with our composite poor outcome (HR 3.40, P=0.01), and that association was more pronounced with ventricular arrhythmias (HR 7.8, P=0.01). Arrhythmia on ECMO was associated with longer ECMO duration (278 vs 121 hours, P<0.0001), as were ventricular arrhythmias (387 vs 129 hours, P<0.0001).

CONCLUSIONS: In this single center study, the incidence of arrhythmias in pediatric cardiac VA-ECMO was substantial (33%). Arrhythmias, particularly ventricular arrhythmias, were associated with prolonged ECMO duration and worse transplant and VAD-free survival.

PO1-15 CL
DIAGNOSTIC AND PROGNOSTIC UTILITY OF QRS-T ANGLE IN PEDIATRIC MYOCARDITIS

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INTRODUCTION: Myocarditis is defined as inflammation of the myocardium. Clinical diagnosis is usually made using troponin and inflammatory markers, echocardiography, cardiac MRI (cMRI), and electrocardiography (ECG). The angle between the spatial QRS and T axes (QRS-T angle) on the ECG is an indicator of the myocardial depolarization-repolarization relationship. In adults with myocarditis, a wider QRS-T angle has been associated with late gadolinium enhancement on cMRI. QRS-T angle has not yet been studied in children with myocarditis.

METHODS: After IRB approval, a single-center retrospective review was conducted. ICD-10 codes that included “myocarditis” were used to search the electronic medical record for children ≤ 18 years of age from 2018 to 2023. Only patients diagnosed by an attending pediatric cardiologist were included. Patients with major congenital cardiac malformations, a history of cardiomyopathy, and without an available ECG were excluded. The initial ECG at our institution at presentation for each study subject was used for analysis. ECGs of age- and sex- matched healthy children who had normal echocardiograms were used as controls. All ECGs were read in a blinded fashion and manual measurements were taken to calculate the QRS-T angle using the Kors’ regression-related transform. Mann-Whitney U test was used for statistical analyses. P-value <0.05 was considered significant.

RESULTS: There were 21 study subjects with a median age of 8.4 years (IQR 1.7 – 15.7). There were 13 (62%) females. Patients with myocarditis had a greater QRS-T angle than control subjects with a median of 55.8 degrees (IQR 46.3 – 116.6) and 17.9 degrees (IQR 11.2 – 30), respectively (p<0.01). Seven patients had cMRI with 5 showing enhancement. Those with enhancement on cMRI had greater QRS-T angle than those without enhancement with a median of 51.6 degrees (IQR 48 – 55.8) and 18.8 degrees (IQR 15.1 – 22.6), respectively (p = 0.05). Four patients required mechanical circulatory support, one required a transplant, and one patient died. There was no significant difference in QRS-T angle between the composite of these negative outcomes and the rest of the study subjects (p = 0.65).

CONCLUSIONS: QRS-T angle may be a useful tool to help in the diagnosis of myocarditis. Among children with myocarditis, a wider QRS-T angle may correlate with presence of fibrosis, as detected by cMRI, however a larger sample size is needed to better elucidate this relationship.

PO1-16 CL
THE CLINICAL RELEVANCE OF DIFFERENT ANTIPHOSPHOLIPID ANTIBODY PROFILES IN PEDIATRIC RHEUMATOLOGY PATIENTS

Pandya Jheel, Erkan Doruk, Onel Karen

BACKGROUND: The clinical relevance of different antiphospholipid antibody (aPL) profiles, including low level anticardiolipin (aCL) and anti-β2-glycoprotein-I (aβ2GPI) antibodies, is ill defined in the pediatric population. Our purpose is to describe the demographic, clinical, and laboratory characteristics of aPL positive pediatric patients based on different aPL profiles.

FINDINGS: In this single center retrospective cohort study, based on the screening of our pediatric (age <18)

rheumatology electronic medical records (2016-2022), we identified patients who had at least one “positive” aPL (lupus anticoagulant [LA], aCL IgG/M, or aβ2GPI IgG/M) result. Patients were grouped into high- (LA positive and/or aCL/aβ2GPI IgG/M; 40U [ELISA]) and low-risk (LA negative and aCL/aβ2GPI IgG/M 20-39U) aPL profiles; those with persistently positive aPL were descriptively analyzed for demographic and clinical characteristics. Of 57 included patients, 34 (59%) had initial high- and 23 (40%) had initial low-risk profiles. Based on subsequent aPL results available in 42/57 (74%) patients, 25/27 (93%) in the high-, and 7/15 (47%) in the low-risk groups remained still positive. Of these 32 patients with persistently positive aPL, moderate-to-large vessel or microvascular thrombosis occurred in nine (28%) patients with high-risk and in none with low-risk aPL profiles; non-thrombotic aPL-related manifestations were reported in 15 (47%) patients with persistent aPL positivity.

CONCLUSION: An initial high-risk aPL profile was persistent in approximately 90% of our cohort, a third of whom had thrombosis, and half had non-thrombotic aPL manifestations. Our results underscore the need for a large-scale effort to better characterize aPL-related manifestations in pediatric patients with persistent high-risk aPL-profiles.

PO1-17 CL
NEOBEAT DETERMINATION OF HEART RATE (HR) INDICATES OCCULT BRADYCARDIA IN LATE PRETERM INFANTS WHEN SUBJECTED TO RESPIRATORY INTERVENTIONS AND/OR DEEP SUCTIONING

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BACKGROUND: HR is an important indicator of neonatal well-being, and is critical in driving management decisions during neonatal resuscitation. Specifically, effective positive pressure ventilation (PPV) is associated with a rapid increase in HR. The literature is devoid of early HR changes in late preterm infants who require respiratory support in the delivery room. The Neobeat is a novel device that uses dry electrode technology to facilitate early detection of HR at birth.

OBJECTIVE: To compare HR responses during neonatal resuscitation of late preterm infants of gestational age (GA) 34 - 36 6/7 weeks delivered via C-section who only require routine resuscitation to those that require respiratory support during the first 5 minutes of life.

METHODS: This was an observational, prospective single center study that utilized the Neobeat to detect HR, either alone or in concert with wet EKG and pulse oximetry (PO), if indicated for HR detection. Late preterm infants delivered via C-section were eligible for the study. Parental consent was obtained prior to delivery. The NeoBeat was placed over the infant's abdomen with the acquired HR blinded to the clinician. Infant management including wet EKG and PO placement was at the discretion of the responsible clinical provider. Data obtained included prenatal characteristics (Table 1), time for infant to reach warmer, time to NeoBeat placement, time to initial HR acquisition (Table 2), placement of PO and wet EKG leads where applicable. Neobeat data was continuously acquired after placement and available for subsequent review. The HR response to respiratory interventions were noted. All data is presented as a mean ± standard deviation. Data was analyzed with student and paired T-Tests.

RESULTS: 18 infants of birth weight of 2702 ± 482 g, and GA of 35.2 ± 6 weeks were recruited; one infant was excluded with a subsequent diagnosis of tracheal agenesis. Prenatal characteristics are shown in Table 1. Nine infants received no respiratory support, five received PPV ± CPAP, and three only CPAP. One of 17 infants had an initial HR <100 bpm. The times for the infant to reach the warmer, device placement and initial HR acquisition are shown in Table 2. The initial HR for infants without intervention (n=9) was significantly ↑ versus those that received PPV ±CPAP (n=8) i.e. 157 ± 15 vs 131 ± 22 bpm respectively (p=0.007). HR significantly ↓pre versus post PPV/CPAP by 90 ± 12 bpm (p=0.003 [paired T-Test]), and ↓ pre versus post suctioning by 45 +/- 32 bpm (p=0.07). Individual HR tracing for infants not requiring respiratory intervention revealed a beat-to-beat variability pattern shortly after data acquisition. (Figure 1). Examples of an acute reduction of HR in response to PPV/ CPAP or deep suctioning application is shown in Figures 2-4.

CONCLUSIONS: The initial HR observed immediately following birth in late preterm infants in this report is consistent with published data in term infants using the NeoBeat1. The beat to beat variability in HR observed in infants without respiratory interventions, suggests an intact automatic response and parallels the normal intrapartum variability associated with uncomplicated labor6. The significant reduction in some infants with PPV or CPAP as well as with deep pharyngeal suctioning suggests a vagal response, and may complicate cardio-respiratory transition. Since the NeoBeat HR was blinded to the clinician, they were unaware of these cardiovascular changes since wet EKG and PO placement occurred later. The NeoBeat provides a simple and rapid method of detecting occult changes in HR, and if promptly recognized, may facilitate corrective measures and minimize unnecessary interventions.

PO1-18 HS
PROVIDER PERCEPTIONS OF COMMUNIATION WITH FAMILIES OF LOW SOCIOECONOMIC STATUS AND/OR LIMITED ENGLISH PROFICIENCY IN A LEVEL IV NEONATAL INTENSIVE CARE UNIT

Sun Vicki, Rose Ramile, Muftu Serra, Krieger Julia, Elachi Dina

BACKGROUND: The practice of family-centered care (FCC) is becoming increasingly prevalent within the neonatal intensive care unit (NICU). FCC allows for improvement of family psychosocial well-being, empowers families to be participating members of the care team, and encourages collaborative relationships between patients, their families, and the health care team.1,2 Race-, ethnicity-, and socioeconomic status-based outcome disparities remain present in the NICU, and it remains crucial to consider these additional challenges when practicing FCC to ensure equitable care.3,4 Furthermore, the literature reveals that parent-provider communication is an important determinant for parental well-being and satisfaction with care.5 However, provider perceptions and mind-set may impact implementation of FCC.6,7 The NewYork Presbyterian Weill Cornell NICU is a 60-bed Level IV NICU that sees around 700 admissions annually. While many disciplines interface with families, a significant amount of communication occurs between patient families and frontline providers.

OBJECTIVE: This hypothesis generating study explores the perspectives of NICU frontline providers on communication between the medical team and families of NICU patients with low socioeconomic status (SES) and/or limited English proficiency (LEP) through the lens of familycentered care as defined by the American Academy of Pediatrics in a Level IV NICU.

METHODS: This is an ongoing qualitative study among NICU frontline providers, including neonatal nurses, nurse practitioners, and neonatal-perinatal fellows, to identify prevailing themes regarding communication between staff and families. Participants were recruited via emails and flyers and received compensation for their time. Sixty-minute focus group sessions were conducted over Zoom to explore communication methods, resources, barriers to communication, and differences in communication specifically between NICU staff and families with low SES and/or LEP. Qualitative transcripts were assessed by members of the study team to identify key concepts and areas of need regarding FCC in the NICU. Data analysis and coding was performed using the Dedoose platform.

RESULTS: In November 2023, three focus groups were conducted with 2 to 5 participants in each group. The participants include 5 nurses, 4 nurse practitioners, and 2 neonatal-perinatal fellows. Eleven parent-themes emerged from qualitative analysis: collaboration, empowering families, flexibility, information sharing, listening and respect, presence of family, time spent with family, quality of healthcare delivery, social work, social determinants of health, and quality improvement. Parent-themes were then further divided into 48 additional child-codes. Notable themes identified in the transcripts included barriers to information sharing (111 excerpts), interpretation services/tools used (73 excerpts), modes of communication (85 excerpts), and discharge readiness (53 excerpts).

CONCLUSIONS: Focus groups conducted with NICU staff members show strong themes including barriers to information sharing, discharge readiness, and variable interpreter utilization which are critical to address when developing a simulation-based communication curriculum. The study team is conducting structured interviews with NICU families to assess similar themes regarding communication and FCC in the NICU. Key concepts identified will be used to develop a pilot-based curriculum aimed to improve perceived gaps in care and disparities in communication in the NICU for families with low SES and/or LEP.

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PO1-19 HS
BENEFITS, CHALLENGES, AND PREFERENCES FOR PEDIATRIC TELEHEALTH VISITS SUBSEQUENT TO COVID-RELATED TELEHEALTH EXPANSION

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Childhood obesity is a major health problem in the United States, affecting approximately 1 out of every 5 children. Childhood obesity continues to be a public health crisis that has only worsened during the COVID-19 pandemic. It is imperative to determine best approaches to patient care to control rising obesity rates and prevent long-term consequences. New guidelines from the American Academy of Pediatrics have encouraged increased patient encounters when addressing pediatric obesity. Previous studies have found that telehealth is an effective tool for providing weight management for children and adolescents with obesity and that telehealth was equal or better at improving obesity outcomes such as BMI, and feasibility and convenience seemed to be higher in the telehealth groups. The use of telehealth may impact the overall points of contacts. Previous research has shown that increased number of points of patient contact is associated with improved outcomes. It is essential to identify strategies to increase the points of contact in order to work towards improved outcomes in obesity management.

Health for Life (HFL) is an intensive health behavior and lifestyle treatment program for children and adolescents 4-21 years of age who are overweight or have obesity. This study will assess adolescent patient and parent preferences, ease of use, benefits, and challenges that come with telehealth use in the HFL clinic. It will also determine whether there is an association between access to telehealth and total number of patient contacts/encounters in the HFL clinic, and to look at the relationship between the frequency of patient contact and clinical outcomes of interest. The study population includes patients and parents of the HFL clinic who speak either English or Spanish. It will also assess the use of translator services during in-person and telehealth visits. This information will help guide decision-making on telehealth use in similar clinics.

The primary aim of this project is to assess patient and parent preferences, ease of use, benefits, and challenges that come with telehealth use in the HFL clinic. The secondary aims of this project are to determine whether there is an association between access to telehealth and total number of patient encounters, as well as, to evaluate if the frequency of encounters is associated with changes in outcome measures, including changes in BMI percentile and other biometric measures.

PO1-20 HS
COMPARING THE EPIDEMIOLOGY AND DISEASE COURSE OF PEDIATRIC VIRAL ILLNESSES DURING THE "TRIPLE-DEMIC" VIRAL SURGE IN 2022-2023 TO PRE-PANDEMIC VIRAL SEASONS (2017 – 2020)

Jonas, Jennifer A.; Acker, Karen; Thomas, Charlene; Yen, Steven; Grinspan, Zachary; Levine, Deborah

BACKGROUND: Pediatric hospital admissions for viral illnesses decreased significantly during the COVID-19 pandemic due to societal restrictions and masking. While children were only a small percentage of those affected by the pandemic, there was a surge of pediatric admissions for RSV and other viral infections in the 2022-2023 viral season, colloquially referred to as the "triple-demic". Literature to date has not fully described how this post-pandemic surge compared to previous viral seasons.

OBJECTIVE: To describe the epidemiology and hospital course of pediatric patients with acute viral infections during the recent post-pandemic year and compare to a pre-pandemic viral period.

METHODS: This observational study examines EMR data for children aged 0-18 who presented to the pediatric emergency department (ED) at an urban academic tertiary care center and received viral testing during the post-pandemic (2022-2023) or pre-pandemic (2017-2020) viral seasons. Primary outcomes: rate of hospitalization, step-down or intensive care (ICU) admission, highest level of respiratory support (invasive and non-invasive ventilatory support, oxygen therapy) and hospital length of stay (LOS). Secondary outcomes include rate of co-occurring viral infections, pneumonia, and patient demographics.

DATA ANALYSIS: Pre-and post-pandemic rates of hospitalization and highest level of respiratory support were compared using two-sample test of proportions. Continuous variables such as age and LOS were compared using two-sample t-tests. Multi-variable regression analysis was used to control for demographic factors.

RESULTS: The number of admissions for patients with positive viral panels almost doubled post-pandemic compared to pre-pandemic seasons with increases ranging from 92-97%. The increase in the percent of those who presented to the ED who were admitted was significant (5.6% vs 3.2%, $p<0.0001$). Of those who were admitted, there was a significant increase in the percent who required either step-down or PICU-level care (69% vs 50%, $p<0.0001$) and a significant increase in the percent who required a higher level of respiratory support such as high flow nasal canula (HFNC), non-invasive

positive pressure ventilation (NIPPV) or mechanical ventilation (33% vs 23%, p<0.0001).

CONCLUSION: More children with viral illnesses required hospitalization and higher levels of care in the post-pandemic viral season compared to 3 pre-pandemic seasons. Future studies will need to examine whether these findings are transient or sustained in subsequent seasons.

Tables 1:

	2022-2023		2017-2020	
	#	%	#	%
Total ED visits	13,796		37,379	
ED visits with Viral Swabs	6,037	44%	5,523	15%
Limited viral swab	3,467	57%	1,410	26%
Positive	1,073	31%	643	46%
Full RPPs	2,570	43%	4,113	74%
Positive	1,779	69%	2,859	70%
Multiple Co-occurring	363	14%	546	13%
Total Positive Viral Panel	2,852	47%	3,501	63%
Admitted to hospital	770	27%	1,202	34%

Table 2:

	2022-2023		2017-2020	
	#	%	#	%
Total Admitted to hospital	770		1,202	
Location of Care:				
Floor	236	31%	597	50%
Step-down unit	317	41%	229	19%
PICU	217	28%	376	31%
Highest level respiratory care:				
HFNC	157	20%	170	14%
NIPPV (CPAP or BIPAP)	84	11%	76	6%
Mechanical Vent	13	2%	38	3%
Multiple co-occurring viruses	144	19%	215	18%
Superimposed PNA	147	19%	167	14%
Hospital LOS:				
Average	2.97		3.06	
Median	2.01		2.07	
IQR	1.3-3.3		1.3-3.2	
Readmissions				
Total Visits	44	6%	61	5%

Table 3: Demographics of Admitted Patients

	2022-2023	2017-2020
Age (Years):		
Average	3.3	3.1
Median	2.1	1.7
IQR	0.9 - 4.3	0.6 - 4.0
Gender:		
Male	444 (58%)	690 (57%)
Female	326 (42%)	512 (43%)
Race:		
White, Non-Hispanic	398 (52%)	489 (41%)
Black, Non-Hispanic	62 (8%)	105 (9%)
White, Hispanic	39 (5%)	47 (4%)
Black, Hispanic	16 (2%)	25 (2%)
Other	136 (18%)	208 (17%)
Declined	119 (15%)	328 (27%)
Insurance Type:		
Commercial	524 (68%)	755 (63%)
Public	218 (28%)	383 (32%)
Other	28 (4%)	50 (4%)
Unknown	0	14 (1%)

Table 4: Distribution of Viral Illnesses Among Admitted Patients

Virus	2022-2023	2017-2020
Rhinovirus/Enterovirus	340 (44%)	555 (46%)
Respiratory Syncytial Virus	242 (31%)	380 (32%)
Coronaviruses	54 (7%)	134 (11%)
SARS-CoV-2	53 (7%)	NA
Influenza A or B	51 (7%)	121 (10%)
Adenovirus	64 (8%)	82 (7%)
Metapneumovirus	69 (9%)	72 (6%)
Parainfluenza	56 (7%)	76 (6%)
Other	4 (1%)	23 (2%)

PO1-21 HS
THE USE OF ANTIFIBRONOLYTICS DURING PEDIATRIC EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT

Burke, Kilian; An, Anjile; Seiss, Christopher; Nellis, Marianne

BACKGROUND: Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy for pediatric intensive care unit (PICU) patients with cardiac and pulmonary failure, yet it is associated with significant bleeding. Antifibrinolytic agents such as tranexamic acid (TXA) and aminocaproic acid (EACA) are used anecdotally to manage bleeding in pediatric ECMO patients, but the epidemiology of their use and efficacy is unclear.

METHODS: We conducted a retrospective observational study of pediatric ECMO patients from the Pediatric Health Information System (PHIS) database, from 2012-2022. Children were included if they were less than 18 years of age and received ECMO support. Patients who were hospitalized for less than 1 day or were receiving ECMO support for a second course during their admission were excluded. We extracted information on patient age, gender, race, geographic region, and comorbidities, receipt of TXA or EACA, blood product usage, ECMO duration, hospital length-of-stay, thrombotic events (based on ICD9/10 coding) and mortality rates. Descriptive analyses and regression models were performed to compare those who did and did not receive antifibrinolytic agents. The Mann-Kendall trend test was used to evaluate trends in usage over time.

RESULTS: 14,409 children received ECMO support during our study period. Forty-six percent (6582) were female with a median (IQR) age of 0 (0-2) years. Forty-one percent (5883) received at least one dose of antifibrinolytic during their ECMO course. The number of children receiving any antifibrinolytic increased significantly during the eleven years studied (tau=0.782, p=0.001). Notably, the proportion of children on ECMO receiving TXA over the ten years increased substantially (tau=0.745, p=0.002), while there was a trend toward decreased use of EACA (tau=-0.455, p=0.062). Ninety-six percent of children received at least one RBC transfusion with those who received any antifibrinolytic also receiving

more RBC transfusions (mean number 13+/-12 versus 7+/- 8, p<0.001). Eleven percent (1594) of children had thromboses. Usage of antifibrinolytics was independently associated with a higher risk of developing thromboses (OR 1.33, 95%CI 1.17-1.50), higher expected count of RBC transfusions (IRR 1.46, 95%CI 1.41-1.51) and higher expected count of any blood components (IRR 1.46, 95%CI 0.41-1.50).

CONCLUSIONS: Through analysis of this large national cohort, we demonstrate the increased usage of antifibrinolytics, particularly TXA, in children supported by ECMO. While there appears to be increased clotting and blood component exposure in children receiving these hemostatic therapies, prospective studies are needed to prove causation rather than the use of antifibrinolytics as a marker of hemostatic imbalance.

PO1-22 HS
NEONATAL NEURODEVELOPMENTAL FOLLOW UP CLINIC: WHO FOLLOWS UP?

Lubor, Brienne; Vernov, Mary

BACKGROUND: Racial, ethnic, and socioeconomic disparities in maternal and neonatal health outcomes are evident from an increased risk of preterm delivery, neonatal mortality and morbidity, and neurodevelopmental impairment (Linsell et al., 2015). The American Academy of Pediatrics recommends that high-risk patients be enrolled in a program that specializes in neurodevelopmental assessment. Despite the benefits of high-risk infant follow-up (HRIF), long-term attendance is challenging (Tang et al., 2018). Infants of a single parent, infants born to Black mothers, families residing further from clinic, and families from under-resourced neighborhoods are less likely to follow up (Ballantyne et al., 2014; Fraiman et al., 2022).

OBJECTIVE To examine the medical and socio-demographic factors impacting referral patterns, rates of follow-up and attrition from a single center level IV NICU to HRIF clinic.

DESIGN/METHODS This is a retrospective review of all patients admitted to the level IV NICU at our home institution between January 2021 and December 2022. Patients qualifying for referral to HRIF (gestational age (GA) </= 32 weeks, birth weight (BW) </= 1500 grams, encephalopathy, stroke, seizures, congenital infection, etc.) are included in the analysis. Medical factors (GA, BW, sex, morbidities e.g. chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis) and socio-demographic factors (race, ethnicity, primary language) will be evaluated for association with likelihood of referral to HRIF clinic, attending initial visit, and sustained follow-up. The data will be summarized using descriptive statistics (means and standard deviations for continuous variables and frequencies for categorical variables). We will perform bivariate analysis using Student's t-test for continuous variables and Fisher's Exact Test for categorical variables. Logistic regression analyses will be conducted, taking into account maternal and neonatal characteristics and socio-economic determinants of health, to determine predictors of referral to HRIF and clinic attendance. This study is IRB approved.

RESULTS Total n=1319 patient charts reviewed. Data analysis divided into three classification groups: 1) patients indicated for clinic, successfully referred, and successfully followed up, 2) patients indicated for clinic, successfully referred, but lost to follow up to clinic, and 3) patients indicated for clinic but not referred, never followed up. Total patients indicated for clinic N=411 patients. For group 1 (G1, successful follow up with clinic) n=250, 61%. For group 2 (G2, lost to follow up with clinic) n=94, 23%. For group 3 (G3, indicated but not referred, LTFU) n=67, 16%. Of the 250 patients who followed up, 117 patients followed up in 2021, compared to 133 patients who followed up in 2022. Among groups, 191 patients (76%) in G1 had private insurance, 49 patients (52%) in G2 had private insurance, 47 (70%) in G3 had private insurance (p<0.001). For those who identified a race/ethnicity on Epic, most patients in all three groups identified as white, not Hispanic/Latino (G1 40%, G2 43%, G3 40%). Significant difference in registration and active enrollment in Weill Cornell Connect online portal rates (G1 93%, G2 72%, G3 70%, p<0.001). For all follow up visits, majority of visits were in person (97%) vs video visit (3%).

CONCLUSIONS, LIMITATIONS, AND FUTURE PLANS Multiple medical and socio-demographic factors affect and impact patient referral, rates of follow up, and attrition from our HRIF clinic, including insurance type and access to online patient portal. Our HRIF serves a diverse clinic population of NICU graduates and families. Patients who successfully followed up were more likely to receive referrals to services. Limitations and considerations for this dataset include that this study involves retrospective chart review; our data is limited to what is collected in the EMR, and our data set has to be continuously updated as patients follow up for clinic at different time points, all in the context of a worldwide pandemic, which affected all outpatient follow up access for patients of our clinic and beyond. We will continue to collect data and analyze clinic referral, follow up, and attrition for years to come. Future directions may include QI cycles addressing various barriers to clinic.

PO1-23 HS
SOCIAL DETERMINANTS OF HEALTH AND ADHERENCE OF OUTPATIENT ENDOSCOPIES IN A PEDIATRIC POPULATION

Tung, Shouli; Thomas, Charlene; Turkish, Aaron; Rose, Melissa

BACKGROUND: Disparities in healthcare access and patient outcomes have been extensively documented within the realm of pediatric healthcare, particularly when addressing complex chronic conditions like inflammatory bowel disease (IBD). Previous research studies have highlighted that children from lower-income backgrounds are not only more likely to utilize healthcare services at a higher rate, but also face an elevated risk of surgical interventions, especially in the case of Crohn's disease (Benchimol et al.) In the context of outpatient endoscopies, studies in the adult population have identified non-adherence issues, notably a substantial 20% no-show rate. (Badurdeen et al.) Encouragingly, quality improvement initiatives in the pediatric population have shown promise by implementing interventions that significantly reduced the endoscopy no-show rate from 7% to 2% (Mani et al.) Despite these strides in improving outpatient endoscopy adherence among adults, there remains a significant gap in research regarding the influence that social determinants of health (SDH) may have on pediatric patient adherence to outpatient endoscopies. This research gap is especially pronounced in low-income and ethnically diverse pediatric populations.

OBJECTIVE: To explore the relationship between social determinants of health and adherence to outpatient endoscopies in a low-income pediatric population.

METHODS: This was a retrospective chart review from a pediatric gastroenterology group within a large urban hospital. Data were collected from June 2021 to June 2022. Variables including primary language, zip code, ethnicity, age, gender, procedure status (completed or not completed), day of the week for scheduling and completion, family history of gastrointestinal illness, and bowel prep quality were analyzed. Using zip code, patients were stratified into low, medium and high risk socioeconomic (SES) populations. Patients with completed procedures within 3 months of the order date were considered adherent. Procedures completed as inpatients were excluded from the analysis. Patients that had adequate documentation of symptom improvement or labs normalizing as a reason for why endoscopy was not completed were also excluded. Patients who did not have adequate documentation regarding adherence were also excluded. A total of 438 patients were included in the statistical analysis.

RESULTS: Patients aged 6-17 had the highest endoscopy completion rate at 89%, compared to patients 18 and older at 86% and patients 5 and younger at 74%. Patients with primary languages of Spanish and Chinese had a 94% rate of endoscopy completion, patients with English as a primary language had an 86% completion rate, and patients with “other” languages had an 82% completion rate. When comparing risk levels and completion of endoscopies, high-risk SES population had an odds ratio of 0.88 (95% CI, 0.42 to 1.88) compared to medium-risk SES population of 1.57 (0.79 to 3.15).

CONCLUSIONS: There are variations in endoscopy completion rates based on demographic factors such as age, primary language, and socioeconomic status. Our data revealed that patients aged 5 and younger had the lowest completion rate while patients aged 6-17 had the highest completion, possibly due to differences in patient cooperation, understanding of the procedure, or other factors that may vary by age group. Additionally, we found that patients with primary languages of Spanish and Chinese had higher completion rates than patients with English as a primary language, possibly due to various trust levels in their clinicians. Furthermore, our findings suggest that SES may play a role in endoscopy completion rates with medium-risk SES patients having a slightly higher completion rate. This may be due to differences in access to healthcare resources, support systems, or other factors related to SES that could impact a patient’s ability to follow through with the procedure. Overall, our study highlights the importance of considering demographic factors when assessing and addressing barriers to endoscopy completion. Further research is needed to explore these relationships in more depth and develop targeted strategies for increasing endoscopy completion rates across diverse patient populations.

PO1-24 HS
EPIDEMIOLOGY OF INTRACRANIAL HEMORRHAGE (ICH) IN CHILDREN SUPPORTED BY EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Mahmood Hera, Alexander Peta, Vogel Adam, Thomas Charlene, Bembea Melania, Norton Bridget, Schmoker Jennifer, Rasmussen Lindsey, Haileselassie Bereketeab, Tzanetos Deanna, Furlong-Dillard Jamie, Lee Amie, Boville Brian, Meimanis Mara, Viamonte Heather, Hefley Glenda, Niebler Robert, Loftis Laura, Nellis, Marianne

INTRODUCTION: Children supported by extracorporeal membrane oxygenation (ECMO) are at significant risk for intracranial hemorrhage (ICH). Associated risk factors and temporal patterns of bleeding events are not clearly defined. We sought to describe the use of head imaging and the prevalence of ICH in children supported by ECMO. Methods: A retrospective analysis of the Pediatric

ECMO Outcomes Registry (PEDECOR) was performed. Patients 0 to 24 months of age supported by ECMO at twelve centers in the United States from 1/1/2014 to 6/30/2022 were identified. Patients with prior ECMO support, ICH prior to the start of ECMO, and those children with no head imaging during or after ECMO support were excluded.

RESULTS: Of 1094 children ages 0-24 months supported by ECMO during the study period, 460 (42%) had at least one head image performed (total of 524 images). Fifty-one percent (235/460) of the patients were male, and the median (IQR) age was 0.8 (0.1-4.0) months. Seventy-six percent (348/460) of ECMO support was veno-arterial. The majority of images were ultrasounds (434, 94%) followed by CTs (87, 19%) and MRIs (3, <1%). 111 children (29%) were found to have ICH. Eighty-four percent (93/111) of ICH were identified within the first five days of ECMO. Children with ICH were younger, median (IQR) age 0.4 (0-2.4) months, as compared to those without ICH, 1.3 (0.2-4.5) months, p<0.001. There were differences in platelet count between the two groups; the median (IQR) platelet count prior to the bleeding event was 86 (62-108) x109/L for children with ICH as compared to 56 (36-77) x109/L for children without ICH, p<0.001. Children with ICH were more likely to die during their ICU admission (ICU mortality 64% as compared to 43% in children without ICH, p<0.001). Of those who survived, children diagnosed with ICH were more likely to have a new neurologic disorder (74% as compared to 25% in children without ICH, p <0.001).

CONCLUSIONS: ICH in children receiving ECMO is common, occurs early in the ECMO course, is associated with younger age, but not the degree of thrombocytopenia. Given the associated morbidity and mortality of ICH, this patient population may benefit from evidence-based protocol development to decrease variability in obtaining head imaging.

PO1-25 HS
INPATIENT BURDEN OF PEDIATRIC SOMATIC SYMPTOM AND RELATED DISORDERS IN THE US: A RETROSPECTIVE NATIONAL DATABASE STUDY

Kelly Nicole, An Anjile, Abramson Erika

INTRODUCTION: Pediatric somatic symptom and related disorders (SSRDs) are associated with negative impacts on education, development, and overall quality of life and can lead to inpatient admission when symptoms become severe. There have been no national studies examining prevalence and healthcare utilization associated with US pediatric SSRD admissions.

OBJECTIVES: Our primary objective was to characterize pediatric SSRD admissions from 2015 through 2023 using the Pediatric Health Information System (PHIS) database, which contains data from over 50 US children's hospitals. Secondary objectives were to describe patient demographics, markers of healthcare utilization (length of stay (LOS), cost, and readmission) and characteristics associated with higher utilization.

METHODS: We included inpatient encounters for patients 5-21 years old with an admitting or primary SSRD ICD-10 code. Inclusion criteria were validated using patients from our institution. We used descriptive statistics to summarize patient- and encounter-level variables. Multivariable logistic regression with gender, age, race, insurance, diagnosis count, anxiety/depression, and hospital region was used to identify factors independently associated with higher healthcare utilization.

RESULTS: There were 6,884 encounters from 46 hospitals, representing 6,369 unique patients. There were over 850 admissions per year between 2016 and 2022, with a peak of 1076 in 2019. Most patients were 12 or older (n=5121, 80%), 74% were female (n=4682), and 55% were non-Hispanic white (n=3486). There was a near equal mix of commercial and public insurance (47%, n=2977 and 49%, n=3135, respectively). Patients carried a median of 7 diagnoses (IQR 4, 10) and 22% (n=1,395) had a complex chronic condition. Median LOS was 2 days (IQR 1, 4) and ranged from 1 to 377 days. Median cost was $7751 per encounter (IQR 4580, 13569) with a range of $54 to $1,075,730. 418 patients (6.6%) had multiple admissions during the study period. In the multivariable regression, odds of having a LOS < 5 days were lower for those with public insurance (OR 0.83, 95%CI 0.73-0.96) compared to commercial, higher for those with < 7 diagnoses (OR 3.23, 95%CI 2.82-3.69), and higher for those with anxiety (OR 1.27, 95%CI 1.08-1.49) compared to those without anxiety or depression. Hospitalization in the Northeast was associated with higher LOS, cost, and readmission.

CONCLUSIONS: PHIS represents 15% of national pediatric admissions, therefore thousands of children are likely hospitalized each year for SSRDs, at a high cost to the healthcare system. Pediatric patients with SSRDs are geographically, demographically, and clinically diverse. Strategies to reduce the inpatient burden of SSRDs are critical to improve care for patients and families and reduce healthcare system utilization.

PO1-26 QA
MILESTONES MATTER: A QUALITY IMPROVEMENT INITIATIVE TO PROMOTE PROVIDER AND PARENTAL RECOGNITION OF DEVELOPMENTAL DELAYS

Scaglione, Christine

BACKGROUND: For children with developmental delays (DD), early identification and initiation of services through Early Intervention (EI) is key to improved outcomes. Historically, children of low socio-economic status (SES) and non-English speaking families have longer time to diagnosis and lower EL referral rates. SMART AIM: In our resident-led primary care clinic in Manhattan, NY, we aimed to increase the percentage of developmental screens completed and acted upon through the launch of our Milestones Matter Initiative.

DESIGN/METHODS: This Quality Improvement (QI) study, conducted from August 2022 through May 2023, utilized The Model for Improvement. Our key drivers centered on improving clinic workflow and education initiatives for providers and families (Figure 1). We tested our interventions via six Plan-Do-Study-Act (PDSA) cycles including editing of our electronic medical record note templates, creating an EI referral process flowchart, handing out developmental milestone cards to families at well visits in four languages (English, Spanish, Bengali and Arabic) and resident-focused educational activities. Our measures included EI referral rate and evaluation results (main primary outcomes), screening and documentation of DD (process) and parent-reported anxiety about their child's development (balancing). We used P charts to analyze and display data and applied Associates in Process Improvement (API) rules to detect special cause variation.

RESULTS: Of 809 patients, we increased screening and documentation of DD from 74 % to 95% and 79% to 95% respectively (Figure 2A and 2B). We identified 232 patients with DD (28% of sample) of whom 72% met criteria for EI referral (n=168). Of referred patients, 70% were evaluated by EI (n=118) and 79% of those met criteria for services (n =118). We noted an improvement in the percent of English-speaking families who had an EI referral (from 58% to 80%), while there was no change among non-English speaking families (64%) (Figure 3). There was no significant increase in parent-reported anxiety.

CONCLUSION: We successfully implemented a resident-led program to identify DD in early childhood and initiate referral to EI for evaluation. Impactful interventions include the incorporation of an electronic note template and the distribution of "Milestone Cards" in patients' primary languages. We noted a disparity in the rate of EI assessments for non-English speaking families. Future efforts will include addressing this disparity, expansion of "Milestone Cards" in more languages, and incorporating an EI navigator to assist families.

PO1-27 QA
PEDIATRIC EMERGENCY MEDICINE PHYSICIANS' PERSPECTIVES OF CONCUSSION IN YOUNG CHILDREN

Julia Gombar

STUDY OBJECTIVE: Traumatic brain injury (TBI) during early childhood (before 6 years) is prevalent, accounting for rising rates of emergency department visits. These injuries may lead to post concussive symptoms, which may be subtle and difficult to diagnose in young children. Prolongation of post concussive symptoms may lead to developmental delays. We aimed to explore pediatric emergency medicine (PEM) physicians' perspectives on "concussion" terminology, diagnosis, and management, specifically in a young child with mild TBI.

METHODS: We conducted semi-structured interviews involving a hypothetical scenario with pediatric emergency physicians. We recruited by a snowball sampling method. Interviews were recorded, transcribed, and analyzed by a research team consisting of a PEM physician, pediatric resident, and medical students. Using a phenomenology approach, we developed and refined codes and derived themes until reaching thematic saturation. Peer debriefing with an expert collaborator aided with revisions of themes.

RESULTS: A single researcher interviewed 13 participants. Three primary themes emerged: 1. Role of guidelines and tools in the diagnostic work-up 2. Difficulties and inconsistencies in the approach to diagnosis of concussion; 3. Difficulty in providing clear discharge instructions to parents.

CONCLUSION: Variability exists among PEM physicians in diagnosis and management of concussions in young children. Discomfort with lack of reliability of symptoms and underappreciation of typical early childhood characteristics may account for findings.

Educational initiatives, age-appropriate clinical tools and treatment-guided outcomes research are needed to guide PEM physicians in the care of young children with head injuries.

PO1-28 QA
SIXTY GOLDEN MINUTES: A GOLDEN HOUR BUNDLE FOR HIGH-RISK PRETERM INFANTS

Kotliar, Justin MD; Priyanka, Tiwari MD; Davydova, Yafa MD; Lubor, Brienne MD; Karotseris, Christine MSN; Taikina, Jane BSN; Connolly, Cailinn BSN; Farra, Elizabeth MSN; Milless, Laura MSN; Yap, Vivien MD; Blatt, Lauren MD

INTRODUCTION: The "Golden Hour" (GH) refers to the first sixty minutes after birth in neonates, and practice of evidence-based interventions within GH is associated with reduction in morbidity and mortality.

OBJECTIVE: The outcome measures were to improve the rates of hypothermia, time to antibiotic administration, time to intravenous fluid (IVF), and use of non-invasive ventilation (NIV) at 24 hours of life by 25% by July 2023. The process measure was to increase overall adherence to the elements of the GH bundle to 50% by July 2023.

METHODS: A multidisciplinary quality improvement (QI) team performed sequential interventions through 5 PDSA cycles in inborn newborns <32 weeks or ≤1500 grams in a level IV NICU. Balance measures included hyperthermia, pneumothorax, and admission temperature in excluded newborns. Baseline data was collected from January 2020 to November 2021, and control charts (p and X-bar/S charts) were used to analyze data. A survey was issued to staff to assess for knowledge and perceived barriers.

RESULTS: A total of 332 infants were included (163 pre-GH bundle, 169 post-GH bundle). Pre- and post-GH bundle mean gestational age was 29 3/7 and 29 6/7 weeks (P=0.11) and mean birth weight 1189 and 1281 grams (P=0.02), respectively. The adherence to the GH bundle was 88%. For the outcome measures, there were center line changes for severe hypothermia (<36°C) from 25% to 0%, mild hypothermia (<36.5°C) from 40% to 15%, mean time to antibiotics from 132 to 77 minutes and IVF within GH from 30% to 86%. There was no center line change for NIV at 24 hours of life. For the balance measures, there were no increased rates of hyperthermia, pneumothorax, or hypothermia in excluded newborns. For the survey (n=75), the average score for knowledge-based questions was 77%. 48% of respondents had <5 years of training and 90% had a favorable view regarding the initiative. Common themes included improved teamwork and communication, but alongside increased stress.

CONCLUSION: A multidisciplinary QI team demonstrated adherence to the GH bundle and subsequently improved the rates of hypothermia, time to antibiotic administration and IVF initiation. Although no special cause variation was seen with rates of NIV at 24 hours of life, there was a trend towards improvement. Survey results illustrate favorable education and support of the initiative, but with increased stress. Future PDSA cycles will include ventilation guidelines and better workflow incorporation to reduce stress.

PO1-29 QA
EXPLORING THE ROLE OF TRADITIONAL AND TECHNOLOGY-ASSISTED TRANSLATION DURING THE DISCHARGE OF HIGH RISK NICU INFANTS OF PARENTS WITH LIMITED ENGLISH PROFICIENCY (LEP) IN A LEVEL IV NICU

Pérez Cynthia, Lame Maria, Mejia Dianna, Gonzalez Christopher, Howell Joy

TEXT OF ABSTRACT PENDING

PO1-30 QA
TEAM KIPOW! (KID POWER!) CORNELL: STUDYING THE IMPACT OF A SERVICE-LEARNING OPPORTUNITY ON MEDICAL STUDENTS' SELF-EFFICACY IN LIFESTYLE COUNSELING

Buirkle Julia, Xie Amy, Lee Nancy, Narayanan Nisha

BACKGROUND The Team Kid Power! (Team KiPOW!) Cornell program implements health policy at a local elementary school to improve dietary and exercise practices through evidence-based methods. Trained Weill Cornell medical students visit P.S. 083 Luis Muñoz Rivera elementary school weekly to teach an interactive health curriculum, eat a healthy snack with the children to model healthy behaviors, and lead them in active play.

Lifestyle counseling and motivational interviewing are critical clinical skills that allow for more comprehensive, patient-centered care. Studies show medical students are lacking confidence in this domain, particularly in pediatric nutrition counseling. Understanding whether this service-learning program increases self-efficacy in patient counseling will demonstrate a way medical students can practice these skills beyond the traditional classroom and clinical environments.

OBJECTIVE To determine the impact that participation in Team KiPOW! Cornell sessions has on medical student mentors' skills and confidence in lifestyle counseling.

DESIGN/METHODS The Childhood Obesity Prevention Self-Efficacy Survey (COPS-E) is a validated, 18-item questionnaire that assesses the clinician's confidence in areas such as describing to a child what a healthy diet should include, assessing their readiness for change, and helping them overcome barriers to change. The COPS-E survey was distributed electronically via RedCap to medical students before participation in the KiPOW program, and the same survey was distributed again after attending mentor orientation and at least one after school

session. Goal sample size was 80. IRB exemption was obtained.

RESULTS Anonymous responses were collected between September 2023 and February 2024. A total of 65 responses were collected: 32 responses from students prior to attending any school sessions, 9 students who attended 1-2 sessions only, and 24 students who attended 3 or more sessions.

Unpaired t-tests were performed comparing responses in students who have not yet attended any sessions to students who have attended one or more sessions. Among the 18 questions asked in both surveys, 10 questions showed a significant increase ($p<0.05$) in students' confidence levels in lifestyle counseling. Specifically, students reported great confidence in describing to a child how to choose healthy foods to consume ($p=0.0001$; Figure 1), describing to a child how to increase fruit and vegetable consumption ($p=0.0004$; Figure 2), and how to use motivational interviewing to guide a child to make lifestyle changes ($p=0.0347$; Figure 3).

To further examine the correlation between number of sessions attended and overall confidence in lifestyle counseling, the average of the 18 COPS-E question responses was calculated for each participant. Response averages were then compared in students who completed 0 sessions, 1-2 sessions, or 3+ sessions. Performing a Spearman's rank-order correlation, a positive correlation was found between average confidence level in the 18 COPSE survey questions and the number of sessions attended (Rho= 0.455, p = 0.0002; Figure 4).

CONCLUSION Medical student mentors gained confidence across multiple subdomains of pediatric lifestyle counseling, and their level of confidence was directly related to amount of time spent as a mentor in the program. The results from this study, despite our small sample size, illustrate the benefits of integrating service learning into the medical student curriculum. Further developing the medical student orientation training sessions and integrating follow-up sessions throughout the year would strengthen this service-learning opportunity even more. Ideally, these skills in motivational interviewing and lifestyle counseling could be more directly tested through clinical simulations. As the KiPOW! Cornell program grows we hope ultimately to expand to other medical schools and public grade schools across New York City.

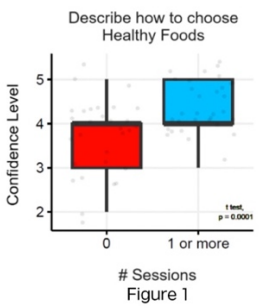

Figure 1

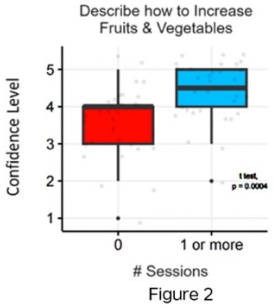

Figure 2

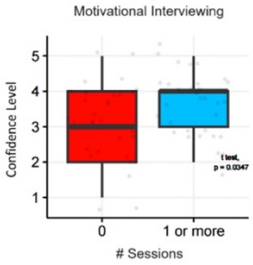

Figure 3

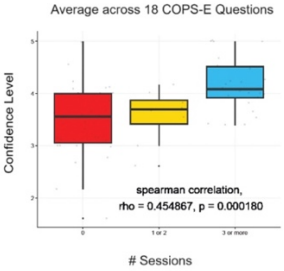

Figure 4

PO1-31 QA
IMPROVING CARE FOR NEWBORNS WITH JAUNDICE IN CONCORDANCE WITH THE AMERICAN ACADEMY OF PEDIATRICS (AAP) HYPERBILIRUBINEMIA MANAGEMENT GUIDELINES

Cynthia Isedeh, DO; Abie Iyare, MD; Nicole Zambelletti, PA-C; Lauren Garcia, PA-C; Allie Knowles, PA-C; Taylor Kaplan, PA-C; Narissa Williams, MD; Jennifer Gigliotti, PA-C; Gabriella Gagliardi, PA; Megan Schwarz, PA-C; Melanie Wilson-Taylor, MD; Snezana Nena Osorio, MD MS

BACKGROUND Most newborns (80%) will have jaundice requiring careful monitoring and appropriate therapy because high level of bilirubin can lead to bilirubin encephalopathy. The newest AAP guidelines provide an avenue to achieve a balance in providing adequate therapy while eliminating harm to newborns with jaundice.

OBJECTIVE: To increase the percent of Well-Baby Nursery newborns with jaundice age ≥ 35 weeks' gestation who receive management consistent with AAP-guidelines to 90% by May 2025. We define AAP-guideline consistent management as providing phototherapy when the newborn meets or is above recommended phototherapy threshold, obtaining rebound bilirubin for infants who received phototherapy < 48 hours of life, had a positive DAT, or had known or suspected hemolytic disease, and who received G6PD screening prior to discharge. Methods: This is an ongoing observational study using sequential planned experimentation to improve care for newborns with jaundice. An interdisciplinary quality improvement (QI) team including physician assistants, pediatric hospitalists, pediatric resident, and a quality improvement specialist met monthly to design project aims and measures. Staff awareness, IT support, and unit culture were identified as

key drivers. Using electronic medical record (EMR) review we collected the following process measures: the % of newborns receiving phototherapy at or above recommended threshold, % newborns receiving phototherapy and subsequently having rebound bilirubin checked, and % newborns having G6PD screening after phototherapy. Balancing measures were escalation of care to NICU and hospital readmission within 4 days of phototherapy discontinuation. Interventions were tested via four PDSA cycles (Figure 1). We analyzed data using Shewhart "P" chart and applied API rules to detect special cause variation.

RESULTS: Out of 149 newborns ≥ 35 weeks' gestational age, 24% were treated with phototherapy at or above recommended phototherapy threshold (Figure 1) and 48% patients received appropriate rebound bilirubin testing. Recommended G6PD screening increased from 93% to 100% (Figure 2). We also found that 59% of newborns received phototherapy based on bilirubin rate of rise ≥ 0.2 mg/dL/hour. There was no change on readmission rate for phototherapy.

CONCLUSIONS: We surpassed our aim in G6PD screening largely due to state-mandated testing and our institutional efforts at providing equitable care. Adherence to current phototherapy guidelines were not achieved, highlighting the importance of identifying providers' barriers and workflow optimization to reach outcome goals.

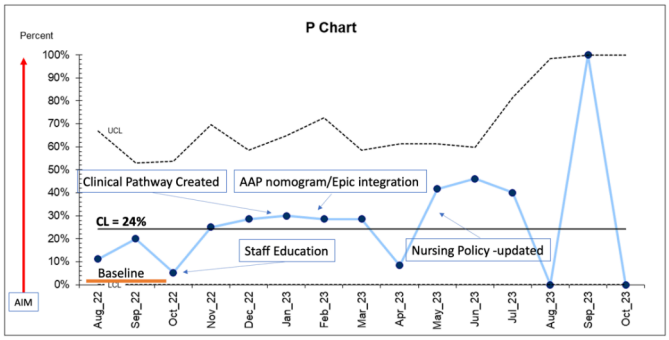

Figure 1. Eligible newborns who received phototherapy at or above recommended phototherapy threshold

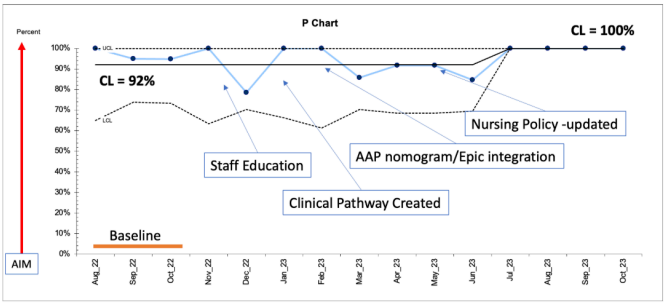

Figure 2. Eligible newborns who received G6PD screening based on the AAP guidelines. New York State mandate to screen for G6PD started in June 2022.

PO1-32 TR

IDENTIFYING MICROBIOLOGIC MECHANISM WHICH MAY BE IMPLICATED IN IRON DEFICIENCY IN QUIESCENT PEDIATRIC CROHN'S DISEASE

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ABSTRACT: Iron deficiency anemia (IDA) is the most common extra-intestinal complication seen in patients living with inflammatory bowel disease (IBD), Oral and intravenous iron replacement therapies uniquely alter the gut microbiota in patients with IBD. Studies of iron absorption capacity in patients with quiescent disease reveal that patients do have the ability to absorb iron; yet it is known that 20% of patients in disease-free remission may still have some measure of iron deficiency anemia on laboratory examination. Therefore, there is an urgent need to understand the etiology of IDA in quiescent pediatric IBD to optimize treatment.

There is a lack of research evaluating the microbial, inflammatory, and immunologic factors implicated in iron malabsorption and metabolism in patients with quiescent Crohn's disease (qCD). Given decades of research linking the pathogenesis of IBD to disruptions in the microbiome, it is hypothesized there are differences in the microbiota and immunologic response in patients with qCD that explain the pathogenesis of IDA. We evaluated the impact of the microbiome and immune status on iron regulation in pediatric qCD, seeking to understand if altered compositions in intestinal microbiota or immune phenotypes may explain the etiology of, or mechanism for, IDA in this cohort.

METHODS: We utilized both cross-sectional, descriptive, and analytical study designs to evaluate stool and serum samples stored in a Live Cell Bank (LCB). 365 samples met the initial inclusion criteria, with an additional 222 sets excluded due to absence of stored stool or due to active disease on histopathologic evaluation. Study participant characteristics were collected. 143 stored samples were included for initial 16S microbiome analysis from 56 male (39.2%) and 87 female (60.8%) study participants, aged three to twenty one years, with biopsy confirmed, quiescent Crohn's disease. 80 samples were selected for metagenomic analysis. Comparator groups included similarly matched quiescent Crohn's disease study participants without IDA as well as healthy pediatric study participants, all of whom were represented in the LCB.

RESULTS We applied Next Generation Sequencing (NGS) and Shotgun Metagenomic Analysis to stool samples. Samples were analyzed for taxonomic composition, alpha diversity, beta diversity, and differential abundance. We measured hepcidin and interleukin 6 (IL6) levels in a subset of 40 stored serum samples. Results obtained were compared against

reference datasets for healthy gut microbiome as well as that associated with iron deficiency anemia without concomitant IBD.

CONCLUSIONS To our knowledge, this is the first study to utilize microbiome and immunologic analysis in quiescent pediatric Crohn's disease with concomitant IDA, identifying pathogens and pathways that may broaden the understanding of IDA in this cohort and may serve as targets for IDA management.

PO1-33 TR
ENHANCING THE PERSISTENCE AND ANTI-TUMOR EFFICACY OF CAR-T AND CAR-NK CELLS FOR PEDIATRIC MALIGNANCIES THROUGH GENETIC DISRUPTION OF DEATH RECEPTORS

Cohen TD, Yi F, Zimmerman N, Dündar F, Zumbo P, Eltilib R, Brophy E, Arkin H, Feucht J, Gormally M, Hackett C, Chandran SS, Park JH, Hsu KC, Sadelain M, Betel B, Klebanoff CA

BACKGROUND: Chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment of relapsed hematologic malignancies. However, it is estimated that 30-60% of patients relapse, with inferior outcomes correlating with poor persistence. The FAS-L/FAS death receptor signaling pathway governs endogenous lymphocyte homeostasis, but whether this pathway also limits CAR persistence remains unknown.

PURPOSE: This study aimed to determine 1) which cell-types express FAS-L in cancer patients 2) whether FAS-L/FAS regulates CAR-T/NK cell survival 3) the impact of CAR-T/NK derived FAS-L and FAS on tumor killing.

METHODS: Single cell transcriptome analysis from patient samples with diverse cancer types was used to generate a single-cell atlas characterizing the cellular subsets expressing FASLG. RNA scope multiplex fluorescent assays were used to evaluate endogenous bone marrow FASLG expression in patients who have undergone CD19 directed CAR-T therapy. Competitive fitness assays were conducted with human T and NK cells that were transduced with vectors encoding either 1) a CD19 targeting CAR, a FAS dominant negative receptor (ΔFAS),and truncated epidermal growth factor receptor (tEGFR) suicide switch, or 2) identical CAR and truncated low-affinity neuronal growth factor (tLNGFR). The ratio of tEGFR:tLNGFR by flow cytometry at 1 month post adoptive transfer was used to compare persistence of CAR lymphocytes with or without ΔFAS. Anti-tumor efficacy with and without ΔFAS was evaluated in vitro using Incucyte and in vivo in NOD/SCID/gc-/- (NSG) mice bearing Nalm6 (pre-B ALL) or Raji (non-Hodgkin Burkitt lymphoma). Finally, CRISPR/CAS9 knock-out of FASLG in human CAR-T and NK cells was used to elucidate the role of FAS-L on adoptively transferred lymphocyte persistence and anti-tumor efficacy.

RESULTS: We found that FASLG expression is primarily restricted to endogenous T cells, NK cells, and CAR-T cells, whereas tumor and stromal cells express minimal FASLG. Competitive fitness assays comparing persistence of CAR-T/NK cells with or without DFAS in vivo demonstrated relative enrichment of DFAS expressing CAR-T and CAR-NK cells (tEGFR/tLNGFR ratio 131.1 in bone marrow). This phenotype could be rescued with FASLG knockout of FAS WT CAR-T/NK cells (tEGFR/tLNGFR ratio 11.6 vs. 1.7 in FASLG WT vs KO CAR-T cells in bone marrow), suggesting that CAR-T/NK derived FAS-L auto-regulates cell survival. With this enhanced persistence, we also found that adoptively transferred DFAS CAR-T/NK cells yielded superior antitumor efficacy in vitro and in vivo against Nalm6 and Raji cells ($p<0.05$ for all in vivo comparisons) compared to CAR-T/NK cells alone. However, FASLG was expendable for tumor killing as there was no change in survival of Nalm6 bearing mice injected with FASLG WT vs KO CAR-T cells ($p=0.5634$).

CONCLUSIONS: Taken together, these findings reveal that CAR-engineered lymphocyte persistence is mediated by a FAS-L/FAS auto-regulatory circuit. Furthermore, impairment of FAS in CAR-T/NK cells establishes a potential novel, ex-vivo, gene therapy strategy to enhance the persistence and antitumor efficacy of cellular immunotherapies for childhood cancers.

PO1-34 TR
SPHINGOLIPID PROFILE AS AN EARLY PREDICTOR OF BRONCHOPULMONARY DYSPLASIA

Solomon Zenna, Worgall Tilla, Worgall Stefan, Heras Andrea

INTRODUCTION: Bronchopulmonary dysplasia (BPD), the lung disease associated with premature birth, is a significant health problem often with long-term consequences such as impaired lung growth, airway hyperreactivity, and early development of chronic obstructive pulmonary disease. However, the mechanisms for the development of BPD are incompletely understood and effective therapies do not exist. There is increasing evidence that sphingolipids are critical for lung development and the repair processes that follow early lung injury, and sphingolipid dysregulation has been implicated in various respiratory diseases.

OBJECTIVES: We hypothesized that disordered sphingolipid homeostasis is a critical factor in the development of BPD. Our primary aim was to investigate whether variations in the respiratory and systemic sphingolipid composition of premature infants is associated with development of BPD. Our secondary aims were to determine the contribution of (1) the

respiratory and gut microbiome, (2) pre-eclampsia and prenatal steroid exposure, and (3) social and environmental factors on sphingolipid composition and BPD development.

METHODS: We evaluated premature neonates (less than 32 weeks gestational age) who were admitted to the neonatal intensive care unit (NICU) and receiving invasive mechanical ventilation for the management of respiratory distress syndrome. Tracheal aspirates, blood (in the form of dry blood spots), and stool was collected every day for the first week of life and then once a week until 1 month of life. To comprehensively assess sphingolipid synthesis, thirty-two sphingolipids were analyzed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Retrospective chart review was conducted to obtain demographic data as well as information regarding clinical outcomes. Patients were stratified into BPD Grade I, II, III, IIIa, and non-BPD using the NICHD severity-based definition of BPD at 36 weeks postmenstrual age. Comparison between BPD and non-BPD was conducted by unpaired t-test. Subjects were enrolled across two New York City NICUs capturing wide ethnic, racial, and socioeconomic diversity.

RESULTS: BPD, extreme prematurity (<28 weeks gestation), and extremely low birth weight (birthweight <1000g) were associated with lower levels of systemic structural sphingolipids (e.g. sphingomyelins) and cell mediators (e.g. sphingosine 1-phosphate) in the first days of life. Systemic sphingolipid levels increased with increasing gestational age and birth weight up to 27 weeks gestation and 1000g respectively. Premature infants that went on to develop BPD demonstrated a further decrease in systemic sphingolipids during the second week of life, including sphingosine-1-phosphate.

CONCLUSIONS: Blood sphingolipids distinguished neonates with BPD, extremely low birth weight, and extreme prematurity from their premature counterparts. These results can be informative of sphingolipid dysregulation in the development of BPD and its consequences on lung health, lung growth, and lung outcomes of BPD. Studies evaluating the association between blood and airway sphingolipids, respiratory and gut microbiome, and the influence of social/environmental factors are ongoing.

Acknowledgements: This research was supported in part by NIH T32 HL134629-Martinez

PO1-35 TR

RADIATION IMPROVES CD19 CART EFFICACY THROUGH INCREASED EXPANSION, PERSISTENCE, AND TRAFFICKING IN LARGE B-CELL LYMPHOMA

Michelle Foley, Mohammad Alhomoud, Mayumi Sugita, Leandro Martinez, Takahiro Yamazaki, Olivier Boyer4, Lorenzo Galluzzi, Koen Van Besien, Renier Brentjens, Silvia Formenti, Jeremie Martinet, Monica L Guzman

INTRODUCTION: Multiple anti-CD19 chimeric antigen receptor T-cell (CART19) have been approved to treat relapsed/refractory lymphoma and leukemias in both adults and children. However, there continues to remain high rates of relapse after CART19 therapy. Radiation has long been used to maintain disease control particularly in non-Hodgkin lymphoma. We sought to determine the impact of low dose total body irradiation (LDTBI) on cytotoxicity of CART19 cells in a DLBCL model.

METHODS: The effect of radiation on CART19 cell cytotoxicity was first tested in vitro on two different human DLBCL cell lines. DLBCL cells were irradiated at 1Gy and co-cultured with CART19. The viability of the DLBCL cells was evaluated 16 hours later by flow cytometry (FC). Next, we assessed the activity of CART19 cells in vivo using a syngeneic mouse model. Mouse CART19 (mCART19) were constructed using mouse T-cells transduced with SFG-m1928z-CD40L vector. Animals were lymphodepleted using cyclophosphamide (Cy) administered 24 hours before CART19 treatment. LDTBI was delivered 4 hours before CART19. In addition to evaluating the benefit of LDTBI prior mCART19, we delivered a second dose of LDTBI 9 days after mCART19 treatment. Thus, we evaluated 6 cohorts as follows: (1) Untreated n=4, (2) Cy/LDTBI n=5 (3) Cy/LDTBI/LDTBI n=3, (4) Cy/mCART19 n=5, (5) Cy/LDTBI/ mCART19 n=5, (6) Cy/LDTBI/ mCART19/LDTBI n=5. Mice were monitored using IVIS imaging system, peripheral blood draws and bone marrow aspirates. We also assessed mCART19 trafficking into the tumor tissues in vivo by establishing new cohorts of (1) Cy/mCART19 n=4, (2) Cy/LDTBI/ mCART19 n=4 and harvesting tumor-infiltrated spleen and liver at day 3 post treatment. To further assess the mechanism of LDR on CART19 cytotoxicity, we explored the role of Fas/FasL signaling apoptosis pathway through measuring changes of Fas expression by FC and RT-qPCR in response to 1 Gy of radiation in human DLBCL cell lines.

RESULTS: In vitro, a one-way ANOVA was performed to compare viability of irradiated cells to non-irradiated cells. In both cell lines, we observed that 1Gy radiation treatment significantly improved CART19 cytotoxicity (OCI-Ly10; p-value=0.009; SU-DHL-4 cell line p-value=0.048). In vivo, adding LDTBI to Cy had a minor improvement compared to untreated controls (median overall survival (OS)= 21 days vs 16.5 days; p-value=0.009). As expected, Cy/mCART19 improved the

median OS when compared to controls (median OS= 35 day; p-value=0.003). Strikingly, 8/10 of the mice treated with Cy/LDTBI/mCART19 remained in complete remission (CR) at 6 months post-treatment (p-value <0.001), Figure 1. Since one dose of LDTBI prior to mCART19 was very effective, adding the second dose of LDTBI did not result in additional survival benefit. Mechanistically, in vivo we observed a 2.8-fold increase of mCART19 expansion in Cy/LDTBI/mCART19 cohort when compared with Cy/mCART19 cohort (p-value <0.001) at day 9 post treatment in peripheral blood as well as sustained bone marrow B-cell aplasia in 7/8 mice (Cy/LDTBI/mCART19 cohorts) which suggests mCART19 persistence. Mice that received Cy/mCART19 with no LDTBI showed evidence of B-cell reappearance 7 days prior to overt relapse. In regards to mCART19 trafficking, flow cytometry revealed that the LDTBI cohort had significant increase in the amount of mCART19 in the spleen and the liver (1.9-fold; p-value=0.041, and 2.1-fold; p-value=0.012, respectively) compared to Cy/mCART19 cohort, suggesting that LDTBI improves mCART19 tumor-trafficking ability. Lastly, in vitro we observed consistent upregulation of Fas in all irradiated DLBCL cell lines compared to non-irradiated controls (i.e., mean Fas fold change 0 to 1Gy; OCI-Ly10: FC 1.87, RT-qPCR 3.76; SUDHL-4: FC 1.19, RT-qPCR 1.77, n=3) suggesting that radiation upregulates this pathway to promote CART cytotoxicity.

CONCLUSIONS: In conclusion, our results show a novel and efficacious approach to harnessing LDTBI with CART19. Based on our findings, the combination of LDTBI and CART19 enhances the efficacy of CART19 leading to improved survival in a syngeneic mouse model. Mechanistically, radiation improves CART19 efficacy by boosting CART19 expansion, persistence, trafficking into tumor sites, and upregulation of Fas in tumor cells; suggesting an increased and translatable benefit in the clinical setting.

PO1-36 TR
WORK-IN-PROGRESS: USE OF STEROID GLUCOCORTICOID RECEPTOR MODULATORS (SGRMs) TO REVERSE WEIGHT GAIN SECONDARY TO GLUCOCORTICOID DYSREGULATION

Uddin Ahsan, Agas Agnieszka, Teruel Mary

INTRODUCTION: Supraphysiologic glucocorticoid (GC) exposure has been known to cause weight gain. We have additionally shown a 'flattened' GC rhythm, a hallmark of chronic stress and sleep dysregulation, is associated to obesity (Tholen et al, Cell Reports 2022; Bahrami-Nejad et al, Cell Metabolism 2018). Our in vitro studies have also demonstrated the existence of a bistable switch mechanism linked with clock proteins affecting the proliferation and differentiation of pre-adipocytes (Bahrami-Nejad et al, Cell Metabolism 2018; Zhang et al, PNAS 2022). This supports a time-dependent exposure effect driving adipogenesis. The suppression of GC signaling using compounds inhibitory to the action of the glucocorticoid receptor may restore rhythms and override the obesogenic effects of GC flattening.

OBJECTIVES: 1. To demonstrate the ability of selective glucocorticoid receptor modulators (SGRMs) to suppress GC signaling for fixed intervals 2. To determine whether SGRMs can be used to prevent weight gain induced by GC flattening.

METHODS: 8-week-old male mice will be used under standard housing with ad lib access to food and standard chow. GC flattening will be achieved by implantation of a 21-day sustained-release corticosterone pellet subcutaneously. Negative control animals will have sham pellet implantation. Two SGRMs will be studied: relacorilant and exicorilant, administered by oral gavage once daily at onset of mouse rest period at 30-60 mg/kg/day dose. Oral gavage with saline will be used as a sham procedure for control groups. Pilot study to determine the effect of SGRMs on hypothalamic-pituitary-adrenal (HPA) axis will be conducted for 5-day exposure time. This will also provide pharmacodynamic effects of each SGRM. As corticosterone level would be affected by the implanted pellet, we will measure adrenocorticotropic hormone (ACTH) level, using ELISA, to confirm a rise in ATCH levels as surrogate for inhibited GCR activity. After determining the optimal dose and timing of relacorilant and exicorilant to give to the mice, we will perform the main experiment using 4 groups of mice: negative control, positive control, relacorilant-treated and exicorilant-treated, with 5 mice per group and undergoing daily treatment for total of 14 days. We will measure weight gain every other day, as well as body composition by EchoMRI at 0, 7, and 14 days. At the end of this period, mice will be euthanized and liver, inguinal fat depot, abdominal fat depot, pancreas and extensor digitorum longus muscle will be harvested, fixed in formalin and stored for histologic analysis.

HYPOTHESIS/EXPECTED RESULTS: Our previous research has shown that timing of steroid exposure is critical to inducing obesity, which raises suspicion that the obesogenic effects of GC flattening may be heavily influenced by the disruption of the diurnal trough phase. We hypothesize that inhibition of GC activity during the rest phase for mice may re-create this trough and counter the effect of flattening.

IMPORTANCE: Relacorilant and exicorilant are in phase II and phase III trials for the treatment of a variety of oncologic and metabolic conditions. Demonstration of their ability to reverse the obesogenic effects of GC flattening would indicate potential utility for treatment of subtypes of obesity related to chronic stress and GC dysregulation.

PO1-37 ED
EVALUATING THE IMPACT OF BRIEFING ON COMPLEX NEONATAL RESUSCITATION PERFORMANCE AND WORKLOAD

Miller Rebecca, Elachi Dina, Perlman Jeffrey M, Thomas Charlene, Chang Catherine

BACKGROUND: The Neonatal Resuscitation Program (NRP) recommends briefing prior to deliveries. While role delegation & equipment checks are standard elements, "discussion of the clinical context" may be variable. Limited studies describe the impact of pre-delivery briefing, & it's different components on performance & workload

OBJECTIVE: To assess the impact of expanded briefing (ExpB) on time to performance of critical skills, performance of the NRP algorithm & individual workload compared to limited briefing (LimB)/no briefing (NoB) prior to simulated scenarios of neonatal resuscitation.

METHODS: 10 teams were recruited to participate in 3 delivery room scenarios utilizing a SimNewB manikin (Laerdal Medical) (Figure 1, Table 1). In scenario A, no history was provided. In scenarios B & C, performance of a "critical skill" could be anticipated from the history [B: paracentesis; C: laryngeal mask airway (LMA) & needle thoracentesis]. In scenario A, no teams briefed. In scenario B, both groups performed a scripted briefing (Group 1:ExpB & Group 2:LimB). In scenario C, groups crossed over. Time to performance of scenario specific critical skill(s) & overall performance were recorded. The NASA Task Load Index (NASA TLX) was used to assess workload. Wilcoxon rank-sum was utilized.

RESULTS: 59 participants of similar experience were recruited. In scenario A (NoB) there were no differences in performance between groups. In scenario B, the ExpB group performed paracentesis faster than the LimB group (8min 33sec vs 11min 32sec; p=0.3). In scenario C, the ExpB group placed an LMA faster than the LimB group (2min 39sec vs 7min 46sec; p=0.019). Needle thoracentesis was performed faster in the ExpB vs LimB group (7min 35sec vs 11min 34sec; p=0.11). There was a reduction in workload when any briefing was performed (scenario B vs A) (NASA TLX score 48/100 vs 62/100; p=0.002). Additionally, ExpB reduced workload compared to LimB in scenario C (NASA TLX score 49/100 vs 58/100; p=0.021), with a notable reduction in mental demand (65/100 vs 78/100; p=0.043) and frustration (30/100 vs 50/100; p=0.016). Moreover, ExpB reduced workload compared to a LimB and NoB for all three scenarios (NASA TLX score 48/100 vs 54/100 vs 61/100; p=<0.001), with a notable reduction in mental demand (68/100 vs 75/100 vs 80/100; p=0.003), temporal demand (63/100 vs 65/100 vs 80/100; p=<0.001) and effort (60/100 vs 65/100 vs 73/100; p=0.001).

CONCLUSION: Any pre-delivery briefing expedites performance of the NRP algorithm & critical interventions in simulated neonatal resuscitations. Performing an ExpB reduced average workload, with a noteworthy reduction in mental demand, temporal demand and effort, which may impact resuscitation performance. Development of a standardized template for facilitating discussion of the clinical context for any resuscitation is essential, particularly in cases where additional/rarely performed interventions may be required.

OP1: ORAL PRESENTATIONS SESSION 1
Clinical Research and Education
Moderator: Dr. Juan Pascual
2:15 – 3:10 PM

OP1-01 CL
EVALUATING FOR TUBERCULOSIS INFECTION AND DISEASE IN ADOLESCENTS WHO ARE EXPOSED UNINFECTED AND HIV-UNEXPOSED UNINFECTED IN BOTSWANA

Dubois, Melanie M.; Schenkel, Sara; Jao, Jennifer; Kgole, Samuel; Masesa, Gosego; Ngwaca, Martha; Phale, Boitshepo; Sharma, Tanvi; Fitzgerald, Daniel; Mathad, Jyoti; Mupfumi, Lucy; Maphorisa, Comfort; Mohammed, Terence; Moyo, Sikhulile; Kgathi, Coulson; Masheto, Gaerolwe; Makhema, Joe; Powis, Kathleen

BACKGROUND: Botswana has high HIV and tuberculosis (TB) prevalence. Over 25% of adolescents ages 10 to 15 were exposed in utero to HIV but remained HIV uninfected. Importantly, prevalence of adolescent TB has not been well-described, particularly in the population of adolescents HIV-exposed uninfected (HEU). Adolescents who are HEU may be a high-risk group for TB, as they live in HIV-affected households with higher risk of exposure to TB, have poorer growth and health outcomes, mental health concerns, and socioeconomic risk factors compared to their HIV-unexposed uninfected (HUU) counterparts. We describe prevalence of TB infection and disease among adolescents by HIV exposure status.

METHODS: Adolescents participating in the Botswana-based FLOURISH study were separately assented with parental consent to participate in a sub-study evaluating for TB symptoms within the last two weeks, household TB contact within the last year, and results of QuantiFERON-TB Gold Plus (QFT-Plus) to assess for TB infection. All adolescents underwent HIV testing at enrollment and were found to be HIV-uninfected. Referral to local health clinics for TB evaluation occurred if a participant screened positive by symptoms, household contact, or was QFT-Plus positive. Fisher's exact test was used to assess for prevalence differences in TB infection/disease by HIV exposure status.

RESULTS: From February to August 2023, 50 adolescents were enrolled in the TB sub-study, 50% of whom were HEU. Median age was 11 years (Interquartile range 11, 12) and was similar between groups. Males accounted for 40% of adolescents HEU and 52% of HUU (p=0.57). No participant had a history of TB infection or disease, or reported a household TB contact in the last year. A total of 3 adolescents had a positive QFT-Plus test, all of which were HEU (12%; p=0.23). One adolescent HEU who was QFT-Plus positive also reported TB symptoms. Three additional adolescents reported TB symptoms, including 2 who were HEU. All 6 adolescents, including 5 who were HEU, were referred to a government health facility for evaluation. The participant with TB symptoms and positive QFT-Plus testing was started on TB treatment, while no other adolescent was deemed to have TB disease.

CONCLUSIONS: In the FLOURISH cohort, adolescents who are HEU were found to have a higher prevalence of TB infection using QFT-Plus testing compared to their HUU counterparts. While this result was not statistically significant, larger studies are needed in high burden HIV and TB settings to validate our findings, as adolescents who are HEU may benefit from routine TB screening and treatment or preventative therapy.

OP1-02 CL
ESTIMATING SUBNATIONAL CARDIAC SURGICAL NEED IN AFRICA DUE TO RHEUMATIC HEART DISEASE USING GEOGRAPHIC DISTRIBUTION OF SURGEONS: MORE THAN JUST A NUMBERS GAME

Jordan Leith, Kevin An R., Lamia Harik, Camilla Sofia Rossi, Gianmarco Cancelli, Giovanni Soletti Jr., Robert Peck N., Castigliano Bhamidipati M.

OBJECTIVE: Previous needs assessments examining workforce requirements of adult cardiac surgeons across Africa have utilized a ratio of countries' surgeons to their population. We investigated rheumatic cardiac surgical need at the subnational level across Africa incorporating subnational population, incidence, and geographic data.

METHODS: Subnational population data (administrative region 1 i.e. state/province equivalent) for adults and youth was collected from each African country's most recent census. The incidence of rheumatic heart disease (RHD) was collected for each country using the Institute of Health Metrics and Evaluation Global Burden of Disease instrument. Location and number of cardiac surgeons were collected using CTSnet as in prior studies. QGIS 3.32 was used to create a subnational map of Africa. A nearest neighbor analysis was conducted using QGIS 3.32 to determine the location and distance of each subnational regions nearest cardiac surgical center. Equation 1 was used to estimate subnational surgical need and construct a choropleth map.

RESULTS: 779 subnational regions from 54 countries were included in this analysis. Africa was estimated to have 509 cardiac surgeons located in 74 subnational regions with 1,027,811 incident RHD cases annually. After considering the average annual case load per surgeon, derived from previous STS/AATS taskforce surveys, the ratio of incident RHD to total surgical case capacity was 10.6, suggesting that <10% of potential cardiac surgical cases due to RHD could be met by current surgeons if operating solely on RHD. At the regional level, the ratio of cases to capacity ranged from 0.04 for regions served by Tunis, Tunisia to 447.30 for regions served by Luanda, Angola. Figure 1 displays a choropleth map of surgical need stratified into deciles for all subnational regions, with neon-green lines linking each to its nearest surgical center. The highest surgical need existed in central Africa and the Horn of Africa with many of these subnational regions exhibiting both the highest incident cases of RHD and furthest distance from surgical centers. Conversely, subnational regions in North Africa and South Africa displayed the lowest surgical need due to their proximity to and number of surgeons. Across the continent, the average distance a patient would need to travel to see a surgeon, weighted by population, was 312 kilometers. The region with the furthest distance a patient would travel to see their nearest surgeon was Dar es Salaam, Tanzania at 770 kilometers. However, this is skewed by Dar es Salaam being the nearest region with surgeons for much of Madagascar. For contiguous Africa, the region with the furthest distance a patient would travel to see their nearest surgeon was Luanda, Angola at 638 kilometers.

CONCLUSIONS: While there is a shortage of cardiac surgeons across Africa, disparities in the distribution of surgeons exist requiring patient to travel great distances, especially in Central Africa and the Horn of Africa. Although more surgeons are being trained and surgical capacity is being built, it may be beneficial in these areas to facilitate locally initiated/led medical missions, patient transport networks, and support of strep A surveillance/treatment programs.

OP1-03 ED
DEVELOPING VALIDITY EVIDENCE FOR A NOVEL PEDIATRIC TELEMEDICINE ASSESSMENT TOOL (PTAT) FOR PEDIATRIC RESIDENTS

Scott, Theresa E; Paradise Black, Nicole; Li, Su-Ting; Abramson, Erika

OBJECTIVES: Rates of pediatric telemedicine use rapidly increased during the SARS-CoV-2 pandemic, including in pediatric residency clinics. Pediatric telemedicine training curricula and best practices were subsequently published, building a body of evidence for a discrete set of pediatric telemedicine skills. Despite its growing importance, there is limited information on how to assess these skills, including lack of a robust assessment tool.

Our work seeks to fill this gap by designing and building validity evidence for a novel pediatric telemedicine assessment tool, the PTAT.

METHODS: Candidate behaviors were identified through a literature review and refined through a national Delphi panel. The PTAT was created and reviewed by a local group of pediatric telemedicine physicians. A Standardized Patient (SP) script for a pediatric telemedicine case was developed and pediatric residents performed a single telemedicine encounter that was recorded for future assessment using the PTAT. Two SPs were trained on a single pediatric case and 21 residents and five faculty were recruited. The faculty underwent a 15-minute pre-recorded training on how to use the PTAT. To provide initial feedback, two faculty scored six encounters, resulting in the addition of a free text comment box. Three faculty raters then scored the remaining 15 encounters. Residents were surveyed on their telemedicine training, experience, and comfort level. Descriptive statistics and interrater reliability (intraclass correlation (ICC)) were calculated.

RESULTS: The PTAT consists of 16 items among three domains (visit setup, conducting a virtual visit, and clinical telemedicine skills) and scored on a four-point rating scale; it also includes a five-point overall global skills assessment (GSA). Compared to post-graduate year-1 (PGY-1) residents, PGY-2-4 residents had more telemedicine experience (92% vs. 25%, p=0.003) and higher PTAT (1.54 vs 1.21, p=0.007) and GSA scores (1.67 vs. 1.00, p=0.002). There was no difference in formal telemedicine training rates or comfort level between PGY training levels. The PTAT items had moderate overall interrater reliability (ICC=0.558 (95% CI=0.461-0.643)).

CONCLUSIONS: The PTAT is a reliable tool with good content validity for assessing pediatric resident performance in simulated telemedicine encounters and may be used to structure formative feedback. Future studies are underway to collect additional validity evidence for PTAT use in real-time clinical encounters, thus refining it to create a much needed tool for assessing pediatric telemedicine skills.

OP1-04 EQ
TREATMENT OF ACUTE MYOCARDITIS IN HOSPITALIZED CHILDREN IN THE UNITED STATES: A PEDIATRIC HEALTH INFORMATION SYSTEM STUDY

Kanyo, Istvan; Haque, Kelly; An, Anjile; Siess, Christopher; Nellis, Marianne

BACKGROUND: Cases of acute fulminant myocarditis in children frequently require care in the intensive care unit and may require extracorporeal therapies. Few studies have examined the association of medications used with outcomes, including use of ECMO (extracorporeal membrane oxygenation).

OBJECTIVE: To describe the epidemiology of acute myocarditis in hospitalized children in the United States from 2012-2022 including the use of steroids and intravenous immunoglobulin (IVIg). To analyze the association of medication administration with mortality and ECMO use.

DESIGN/METHODS: We conducted a retrospective cohort study of hospitalized patients using data obtained from the Pediatric Health Information System (PHIS) database. Patient encounters (ages 0-17 years) coded with a diagnosis of myocarditis from January 1, 2012, to December 31, 2022, were included. Patients with an ICD-10 diagnosis of COVID-19 infection or COVID-19 pneumonia were excluded in final analysis. Associated data regarding demographics, complex chronic conditions, and use of extracorporeal therapies were included. Administration of steroids and IVIg during hospitalization was recorded, as was receipt of vasopressors and anti-arrhythmic medications. Patients were grouped into 4 categories; group 1 received no IVIg or steroids, group 2 received steroids without IVIg, group 3 received IVIg without steroids, and group 4 received both IVIg and steroids. Descriptive statistics were used to characterize medication use over time. The Mann-Kendall trend test was used to assess medication usage over time. Multivariable logistic regression was performed to determine the independent association between medication use, mortality, and ECMO cannulation.

RESULTS: There were 3239 patients included from 52 hospitals within the PHIS database. The median age was 12 years (IQR 2, 16), 65% were male. The median length of stay was 7 days (IQR 3, 18). The mortality rate was 6% (n=193) and 14% (n=461) required support by extracorporeal membrane oxygenation (ECMO). Pharmacy data was available for 2294 patients. 189 (8%) of children were included in Group 1, 450 (20%) in Group 2, 578 (25%) in Group 3, and 1077 (47%) in Group 4. The trend test showed proportion of patients that received IVIg without steroid administration (group 3) significantly decreased over the study period (tau = -0.527, p = 0.029).

Multivariable analysis was used to account for sex, race, hospital region, admit age, length of stay, need for ICU admission, presence of a complex chronic condition, and use of anti-arrhythmic medication. The receipt of IVIg alone (OR 0.24, 95% CI 0.13-0.42) or the combination of IVIg and steroids (OR 0.60, 95% CI 0.42-0.87) was independently associated with decreased mortality compared to steroid use alone.

The receipt of IVIg (OR 0.38, 95% CI 0.24-0.59) or treatment without steroids or IVIg (OR 0.38, 95% CI 0.20-

0.68) was independently associated with decreased ECMO use compared to steroid use alone.

CONCLUSIONS: The need for ECMO support and mortality from acute myocarditis remains significant. The use of IVIg without steroids in treatment of acute myocarditis has decreased over time. The use of IVIg is independently associated with decreased mortality and decreased ECMO use in children with acute non-COVID myocarditis compared to utilization of steroids alone.

OP2: ORAL PRESENTATIONS SESSION 2
Translational and Basic Science
Moderator: Dr Bernard Kuhn
3:25 – 5:00 pm

OP2-01 TR
ADDITION OF HUMAN CYTOMEGALOVIRUS VIRAL FCY RECEPTORS TO GB SUBUNIT VACCINE IMPROVES ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS RESPONSE IN A RABBIT IMMUNOGENICITY MODEL

Otero Claire, Gross Mackensie, Herbek Savannah, Connors Megan, Mitchell Libby, Kolb Philipp, Permar Sallie

Congenital cytomegalovirus (CMV) is a leading cause of neurologic birth defects, but there is no licensed CMV vaccine. Recent evidence suggests that neutralizing antibodies are not sufficient for protection and that Fc mediated effector functions associate with protection from vertical CMV transmission. Human CMV encodes three viral Fcγ receptors (vFcγRs: gp34, gp68, or gp95) that have demonstrated in vitro interference with Fc-mediated effector functions through binding to the IgG Fc region and preventing activation of host Fcγ receptors. We hypothesized that adding vFcγRs to a CMV vaccine would improve Fc-mediated effector functions by eliciting vFcγR-targeting antibodies that block the immune evasion function. We utilized a rabbit immunogenicity model (n=4 per group) to assess immune responses against a three-dose series, each four weeks apart, of protein subunit glycoprotein B (gB) adjuvanted with squalene emulsion with or without one of the vFcγRs. Co-immunization with the gB+gp34 significantly improved FcγRI activation over the gB-only vaccine as measured by a reporter cell assay using Week 10 plasma against CMV-infected fibroblasts (ANOVA p=0.0017, Dunnett's p=0.0009). This result was mirrored by the downstream functional output of FcγRI, as the gB+gp34 vaccine group demonstrated the highest antibody-dependent cellular phagocytosis (ADCP) function. The four groups demonstrate remarkably similar gB-specific IgG responses and FcγRI binding against gB-targeting antibodies, suggesting that the observed improvement in ADCP function is not a result of stronger antibody responses against gB or better engagement of FcγRI by those antibodies but instead a result of antibodies targeting the vFcγR. Work is ongoing to define vFcγR-targeting antibody responses and evaluate the impact on other Fc-mediated effector functions, like antibody-dependent cellular cytotoxicity (ADCC). Given the implication of these antibody functions in preventing vertical CMV transmission, a vaccine that improves Fc-mediated immunity by targeting vFcγRs has immense potential to be effective in preventing congenital CMV.

OP2-02 BS
THE IMPACT OF ANTIRETROVIRAL INITIATION TIMING ON THE DYNAMICS OF HIV-SPECIFIC ANTIBODY GENERATION AND ANTIVIRAL FUNCTIONS IN AN ORAL INFANT SHIV INFECTION MODEL

Lulu Guo, Stella J. Berendam, Caroline Phan, Emily Uffman, Veronica Obregon-Perko, Amit Kumar, Guido Ferrari, Guido Silvestri, Sallie R. Permar, Ann Chahroudi, Genevieve G. Fouda

INTRODUCTION: The optimal timing of antiretroviral therapy (ART) initiation is a critical factor with profound implications for HIV-1 treatment outcomes. Early and precise administration of ART not only suppresses viral replication but also plays a pivotal role in shaping the immune response against HIV-1. The delicate interplay between the timing of ART initiation and its immunomodulatory effects underscores the need for a comprehensive exploration of these dynamics, particularly in the context of pediatric HIV-1 infections. This research aims to deepen our understanding of how the timing of ART initiation influences the kinetics of HIV-specific antibody development and broader antiviral functions within the unique framework of an oral infant Simian-Human Immunodeficiency Virus (SHIV) infection model. Such insights hold promise for refining treatment strategies, optimizing health outcomes, and advancing our overall ability to address the multifaceted challenges posed by HIV.

METHODS: Three groups of ten infant Indian rhesus macaques were enrolled, excluding Mamu-B08+ and Mamu-B17+ animals. The animals were infected with SHIV.C.CH505.375H.dCT at 4 weeks of age and subsequently treated with a three-drug ART regimen at varying time points post-infection: early ART (4-7 days post-infection), intermediate group (two weeks post-infection), and late ART (eight weeks post-infection). The ART formulation included Tenofovir disoproxil fumarate (TDF), Emtricitabine (FTC), and Dolutegravir (DTG). Following a minimum of 52 weeks on ART, analytical treatment ATI was conducted. HIV-specific antibody responses were measured by ELISA and Binding Antibody Multiplex Assay (BAMA), Neutralization in TZM-BL cells, ADCP, and ADCC activity against the autologous virus were also assessed.

RESULTS: The early ART group, initiated four to seven days post-infection, demonstrated transient viremia with a subsequent decline following ART, and only two out of ten infants developed detectable gp120-specific antibody responses that were no longer detectable at ATI. The intermediate ART group, treated two weeks after infection, showed higher antibody levels that rapidly declined, with 5 out of 8 infants maintaining detectable antibodies after 52 weeks. In the late ART group, treated eight weeks after infection, all animals developed robust antibody responses peaking at 8-10 weeks post-infection, and antibody levels remained detectable after 52 weeks. Slight differences in binding breadth and epitope specificity of the Env-specific antibodies were observed between groups. The late ART group exhibited sustained ADCP activity while on ART, suggesting that a small fraction of antibodies could mediate robust phagocytosis. Furthermore, autologous neutralizing antibodies developed in the late ART group, but not in the other animal groups indicating a potential association with delayed ART initiation. Notably, the rebound virus in animals with autologous neutralization was less sensitive to plasma neutralization than the challenge virus, suggesting a role of autologous neutralization in the selection of rebound viruses. Following treatment interruption, virus rebound occurred in varying proportions across groups. Interestingly the animal from the late ART group with the highest level of autologous neutralization did not experience viral rebound.

CONCLUSION: Overall, our findings underscore the complex interplay between ART timing, antibody responses, and viral dynamics in the context of pediatric HIV infection.

OP2-03 BS
INITIAL EXPOSURE SHAPES MEMORY B CELL RESPONSE TO SUBSEQUENT INFLUENZA VIRUS INFECTION IN CHILDREN

Sun J, Troxell C, Jo G, Fu Y, Chervin J, Wilbanks D, Zheng N, Huang M, Nelson S, Neumann G, Han J, Meade P, Campredon L, Sliger E, Thomas P, Kawaoka Y, Ward A, Krammer F, Gordan A, Wilson P

INTRODUCTION Numerous studies have suggested memory responses to the initial exposure of influenza virus during early childhood play important roles on shaping antibody responses to subsequent exposures, a phenomenon known as ‘immune imprinting’. In 2016, Gostic et al. found that people who experienced first infections with seasonal H3 viruses (group 2) were less susceptible to avian influenza H7N9 viruses (group 2), whereas older individuals who were initially exposed to H1 or H2 viruses (group 1) were less susceptible to avian H5N1 viruses (group 1), suggesting potent protection against future infections via childhood imprinting. Despite the great importance of imprinting on antibody response to influenza virus, its underlying biology remains elusive.

OBJECTIVES We aim to investigate how initial exposure shapes memory B cell responses to subsequent influenza virus infections in children. To do that, we characterize memory B cells elicited after primary H3N2 and subsequent H1N1 infections in children under 4 years of age, as well as in H1N1-infected adults as control.

METHODS We have established high-throughput assays to analyze memory B cell differentiation and Ig repertoire at single-cell level. For this, we conjugate streptavidin with distinct molecular barcodes to major influenza antigens, hemagglutinin (HA) and neuraminidase (NA), and use them as probes to isolate thousands of antigen-specific B cells in multiple functional subsets. Using probes from multiple strains or subtypes, we can identify and quantify cross-reactivity of antigen-specific B cells. By pairing fluorescence-activated cell sorting and 10xGenomics single cell sequencing, we can determine the antigen-specificity (probe score), expression of cell surface markers (CITE-seq), VDJ sequences, and transcriptomes of each individual antigen-specific B cell. The integrated datasets can then be correlated with clinical features including age, immune-history, and exposure type (vaccination versus infection). Most importantly, we can map B cell receptor sequences to antigen specificity for thousands of antigen-specific B cells.

RESULTS In this study, we isolated hundreds of HA-specific B cells from adults and children from which we expressed over 100 monoclonal antibodies (mAbs). Importantly, we found the predicted antigen specificities of these B cells determined by probe score are positively correlated with the actual antigen specificities of mAbs determined by ELISA, confirming the accuracy of our approach. Compared to adults, we found the expansion of H1-reactive B cells following H1N1 infection is less efficient in H3-imprinted children, suggesting immune memory bias or imprinting. Moreover, we identified broadly neutralizing antibodies (bnAbs) that neutralize H1N1 and H3N2 viruses in both adults and children. Structural analysis showed that they target a highly conserved cross-group stem epitope with various approaching modes and molecular interactions. Interestingly, we found the bnAbs isolated from children are less broad and potent than those from adults, and they belong to unique lineages that utilize VH3, unlike the multidonor lineages that utilize VH1-69, VH6-1, and VH1-18 . Together, our data provide evidence of immune imprinting and shed new light on how initial exposure shapes memory B cell repertoire.

OP2-04 BS
SEX DIFFERENCES IN THE PRETERM GUT MICROBIOME UNDERLIE ENHANCED GASTROINTESTINAL IMMUNITY IN PREMATURE FEMALE NEONATES

Banks Kelly, Rager Stephanie, Jin Jenny, Sanidad Katherine, Ahmad Mehrose, Ananthanarayanan Aparna, Perlman Jeffry, Zeng Melody

INTRODUCTION: Preterm birth occurs before 37 weeks of gestation and comprises 10.9% of all births in the United States. Preterm infants are exceptionally vulnerable to infection and inflammation which are central to the common causes of morbidity in this population including necrotizing enterocolitis, bronchopulmonary dysplasia, respiratory infections, and sepsis. Interestingly, multiple studies have demonstrated a sex advantage for female premature neonates over their male counterparts with reduced morbidity and mortality. Bacterial colonization of the gut in newborns is a critical driver of the maturation of the gut and the development of the immune system.

OBJECTIVE: This work aims to define how the gut microbiome in preterm neonates contributes to sex differences in gastrointestinal immunity and outcomes for premature neonates.

METHODS: We created a biobank by collecting stool samples from infants in the NICU or newborn nursery, for these experiments, all stool samples included in our studies were from late preterm infants (babies born between 33 and 36 6/7 weeks gestation) who had never been treated with antibiotics. These samples were sequenced using shotgun metagenomic sequencing to see the frequency of bacterial species and compare between genders. Further, samples were cultured to isolate individual bacterial strains to understand their impact. Stool samples were used for functional assays in coculture with murine bone marrow derived macrophage (BMDMs) followed qPCR to assess cytokine expression. Coculture with murine colon organoids was also performed followed by qPCR, Ki67 assay for proliferation and assessing permeability by injecting FITC dextran into the organoids. In addition, we used in vivo models, pooling 3 female or 3 male late preterm microbiome samples together and using oral fecal matter transplantation (FMT) to colonize germ-free mice. We performed bulk RNA sequencing on colon from FMT mice to determine transcriptional changes induced by male vs female FMT. We then exposed these mice to enteric pathogens, including Citrobacter rodentium (C. rod), a murine model of enterohemorrhagic E. coli (EHEC) or to a dextran sulfate-sodium (DSS)-induced colitis model.

RESULTS: We performed metagenomic shotgun sequencing of 27 preterm stool samples (11 female, 16 male), which yielded 2 species significantly increased in abundance in female samples, Staphylococcus Haemolyticus and Staphylococcus Hominis. In addition, we found increased expression of the proinflammatory cytokine Il-6 in murine macrophages induced by individual heat-killed female stool microbiome samples over male samples. Using in vivo models, we observed reduced colony forming units (CFU) of C. rod in the spleens and livers of mice given female- FMT, which was characterized with robust recruitment of neutrophils to the colon of mice receiving F-FMT. Similarly, we observed protection from a dextran sulfate-sodium (DSS)-induced colitis model in F-FMT mice compared that in M- FMT mice, demonstrated by significantly less weight loss and longer colons at day 8 of DSS treatment.

We bulk sequenced RNA from colons of mice 3 weeks after female or male FMT as well as germ-free (GF) controls. PCA analysis showed that transcriptional profiles clustered based on the gender of stool transplanted. Further, GSEA analysis revealed upregulation of cytokine signaling downstream of TNFa, TGFb, and Il-2, which are known to be important not only for immune regulation but also gut maturation. In the mice with F-FMT, we found an increase in both estrogen and WNT signaling, the latter of which positively regulates intestinal stem cell proliferation.

CONCLUSIONS: Together, our results thus far show that there are components of the female gut microbiome that confer protection against enteric infection and inflammation that may play a role in why female premature neonates have lower morbidity and mortality compared to male premature neonates. Our future work is focused on identifying the mechanism behind this protection. We will test our hypothesis that preterm female gut microbiome is enriched with gut bacteria that express GUS enzymes which can recycle estrogen from its glucuronidated form, and these bacteria enhance gut immune and barrier maturation in preterm female neonates.

OP2-05 TR
ASTHMA-ASSOCIATED GENETIC VARIATIONS OF SPHINGOLIPID DE NOVO SYNTHESIS ALTER EPITHELIAL CELL GROWTH

Borys N, Gomi R, Gomi K, Worgall S

This project evaluates the effects of common asthma-risk genetic variations that are known to decrease sphingolipid synthesis on cell proliferation to provide further insight into the pathophysiological mechanisms underlying childhood asthma.

Asthma, the most common chronic respiratory disease in children, has a strong genetic predisposition through variations at the 17q21 locus which alter the expression of several genes, including ORMDL3, a key regulator of serine-palmitoyl transferase (SPT) in the de novo

sphingolipid synthesis pathway, and gasdermin B (GSDMB), a regulator of pyroptosis and inflammatory responses. The T allele of the 17q21 rs7216389 single-nucleotide polymorphism (SNP) is strongly associated with the risk of childhood asthma and reduced sphingolipid synthesis. While decreased sphingolipid synthesis leads to increased airway reactivity in mice, there is a gap in knowledge on how cellular sphingolipid metabolism is functionally linked to human asthma pathogenesis. We posit the genetic decrease in sphingolipid synthesis will affect cell growth, proving further insight into asthmatic airway remodeling.

To further understand the role of rs7216389 on a cellular level, we created model cells using two cell lines, human embryonic kidney (HEK293) cells and human Small Airway Basal Cells immortalized (hSABCi) cells, homozygous for the asthma risk (TT) and non-risk (CC) alleles with CRISPR Cas9 genome editing. For each cell line, relative gene expression of ORMDL3 and GSDMB was determined using TaqMan qPCR (quantitative polymerase chain reaction), and relative sphingolipid synthesis levels were measured using mass spectrometry. The effect of rs7216389 on cell growth was assessed using the ibidi Wound Healing Assay and FastTrack AI software to quantify the cell-free gaps and determine the areas covered by cells (μm2) over time (15 – 48 hours).

HEK293 TT cells demonstrated increased ORMDL3 expression, decreased de novo sphingolipid synthesis, and lower cellular sphingolipid levels in comparison to HEK293 CC cells. In contrast, the TT hSABCi cells notably had increased GSDMB expression compared to hSABCi CC cells. HEK293 TT cells showed faster growth compared to the CC cells ($p<0.001$) over 18 hours and shifted the gap closure curve to the left ($p<0.0001$). This effect could be partially induced through chemical inhibition of sphingolipid synthesis by pre-treating HEK293 TT cells with the SPT-inhibitor myriocin for 4 hours ($p<0.05$). To a lesser degree than the HEK293 cells, hSABCi-NS1.1 TT cells also showed faster growth and cell-free gap closure compared to the CC cells ($p<0.05$) over 12 hours.

These results suggest that asthma-associated 17q21 genotypes can enhance cellular proliferation in HEK293 and small airway epithelial cells, implying an effect of the asthma-risk allele independent of ORMDL3 and/or GSDMB expression and sphingolipid synthesis. These findings can have implications for further understanding the pathways involved in airway remodeling in asthma and the identification of novel therapeutic targets.

OP2-06 BS
AUTOSOMAL RECESSIVE T-BET AND ROR γT DEFICIENCY UNDERLIES MYCOBACTERIAL SUSCEPTIBILITY

Yang, Rui

Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by selective, inherited predisposition to clinical disease caused by weakly virulent mycobacteria, such as *M.bovis* BCG vaccines and environmental mycobacteria (EM). Twenty MSMD-causing genes have been identified. Their mutations affect IFN-γ-related immune circuits by impairing either the production of, the cellular response to IFN-γ, or both. T-bet and RORγT are transcription factors that govern the lineage commitment of two different T helper lineages, T_H1 and T_H17 cells, respectively, in mice. Surprisingly, both autosomal recessive (AR) T-bet and RORγT deficiencies in humans underlie mycobacterial susceptibility. Here we summarize the molecular, cellular, and clinical features of a recently identified patient with AR T-bet deficiency and three new patients with AR RORγT deficiency. Human AR T-bet deficiency underlies mycobacterial disease by preventing the development of innate (NK) and innate-like adaptive lymphocytes (iNKT, MAIT, and $Vδ2^+$ γδT cells) as well as IFN-γ produced by them. It also underlies peripheral eosinophilia and recurrent upper respiratory inflammation due to excessive production of T_H2 cytokines, particularly IL-5 and IL-13, by $CD4^+$ αβT cells. Although humoral immunity in inherited T-bet deficiency remains grossly intact, T-bet is required for the *in vivo* and *in vitro* development of a distinct subset of human B cells in humans resembling murine “age-associated B cells” that are associated with infection and autoimmunity. We also identified three new patients with AR RORγT deficiency that underlies both mycobacterial and fungal susceptibility. Inherited RORγT deficiency abolishes the development of iNKT and MAIT cells, two IFN-γ-producing innate-like adaptive T cell subsets, and impairs the production of IFN-γ by $Vδ2^+$ γδT cells in response to mycobacterial stimulation. The production of IFN-γ by purely adaptive αβT cells remains largely intact upon mycobacterium-specific stimulation. The development of T_H17 cells and the production of T_H17 cytokines are abolished in inherited RORγT deficiency, thereby underlying susceptibility to *C.albicans*. Collectively, impaired development of and defective production of IFN-γ by MAIT, $Vδ2^+$ γδT cells, and iNKT cells are sufficient to cause mycobacterial susceptibility, whereas the contribution of purely adaptive αβT cells to antimycobacterial immunity, at least against *M.bovis* BCG or EM, is probably inconsequential.

PO2: POSTER SESSION 2
5:00 – 6:30 PM

***Lightning Round posters will be displayed at this time. Abstracts are listed under LR-01 through LR-15.**

PO2-01 BS
A COMPARISON OF HUMORAL IMMUNE RESPONSES INDUCED BY INFANT HIV BG505 GERMLINE-TARGETING SOSIP ENVELOPE TRIMER VACCINATION ACROSS IMMUNOGEN PLATFORMS

Ramos, John, Issah, Yasmine, Nelson Ashley N, Shen, Xiaoying, Ozorowski, Gabriel, Sewell, Leigh, Zhang, Shiyu, Ward, Andrew B, Montefiori, David C, Shattuck, Robin, Sanders, Rogier W, Moore, John P, Van Rompay, Koen K.A, De Paris, Kristina and Permar, Sallie R.

BACKGROUND: mRNA-based vaccines encoding immunogenic antigens have proven safe and effective in triggering long-lasting immunity. They provide immense potential for rapid antigen design and production for a variety of pathogens, including HIV vaccines designed for engagement of broadly neutralizing antibody (bnAb) B cell lineages. Additionally, the encapsulation of mRNA in lipid nanoparticles (LNP) is self-adjuvating, a property which protein-based vaccines lack. In this study, we sought to determine effective priming strategies to develop an HIV vaccine that induces protective bnAbs in early life to prevent the ~410,000 new infections that annually occur among adolescents worldwide.

METHODS: In this study, groups of infant rhesus macaques (RMs) were immunized with matched antigen-design HIV Env BG505 germline-targeting (GT)1.1 SOSIP trimer using three different vaccine platforms: 50mg of protein-only trimer adjuvanted with 3M-052-SE (n = 5), 5mg of saRNA-LNP (n = 5), and 15mg of mRNA-LNP (n = 6). Each group received their respective vaccine at weeks 0, 6, and 12 followed by several boosters. All groups received a booster either BG505.GT1.1 SOSIP or BG505.664 SOSIP at weeks 24 or 26, 52, and 78.

RESULTS: Across platforms, BG505 GT1.1 SOSIP trimer protein immunization elicited higher plasma IgG binding responses following the 2nd immunization compared to the saRNA and mRNA-immunized RMs. Furthermore, the median autologous tier 1 and 2 neutralization titers elicited by protein-based vaccine were a log higher-($p<0.05$) at weeks 14 and 28. Notably, by week 28, two of five protein-immunized infants exhibited a plasma neutralization signature indicating CD4 binding site-specific (CD4bs) bnAb precursor development, while none of the saRNA or mRNA-immunized RMs had developed this response.

CONCLUSION: Our data indicates that protein-based priming immunization with germline-targeting SOSIP trimers may induce higher-magnitude vaccine-specific antibodies and induce CD4bs bnAb precursors at a higher rate than sequence-matched mRNA and saRNA-based vaccination in early life. Future work includes the optimization of antigen design and intermediate germline-targeting immunogens that can enhance the development of bnAb B cell lineages.

PO2-02 BS
DROSOPHILA MUSCLE COFILIN MAINTAINS NEUROMUSCULAR JUNCTION STRUCTURE FOR PROPER NEUROTRANSMISSION

Christophers B, Leahy SN, Soffar D, von Saucken V, Broadie K, Baylies M.

Muscle cofilin alters neuromuscular junction postsynaptic development to strengthen functional neurotransmission. bioRxiv. November 22, 2023. doi: 10.1101/2023.11.21.568166

INTRODUCTION: Nemaline myopathy (NM) is a skeletal muscle disease with an incidence of 0.22 per 100,000 children. NM is hallmarked by muscle weakness and, on histopathology, an obvious presence of actin accumulations in disrupted muscle. Cofilin-2, an actin severing protein, is linked to NM and is the predominant cofilin isoform in postnatal and mature skeletal muscle. Previously, our lab has shown that muscle-specific knockdown of Drosophila cofilin (DmCFL) leads to a progressive decline in larval muscle structure and function similar to that seen in NM.

OBJECTIVE: Examine other defects in muscle development in the DmCFL knockdown NM fly model.

RESULTS AND CONCLUSIONS: RNA sequencing analysis showed upregulation of genes associated with the neuromuscular junction (NMJ). The NMJ is the site of communication between the presynaptic motor neuron and postsynaptic muscle membrane. DmCFL is enriched at the postsynapse, and its loss leads to progressive disorganization of F-actin in this region. Surprisingly, no significant changes in gross presynaptic Bruchpilot active zones or overall postsynaptic glutamate receptor levels were found. However, DmCFL knockdown results in mislocalization of glutamate receptors containing the GluRIIA subunit in more deteriorated muscles and neurotransmission strength is strongly impaired. These findings expand our understanding of cofilin's roles in muscle to include NMJ structural development and suggest that NMJ defects may contribute to NM pathophysiology.

PO2-03 BS
SPATIAL MOLECULAR PROFILING OF THE KIDNEY OF CHILDREN WITH LUPUS NEPHRITIS

Rodriguez-Alcazar Juan, Balaji Uthra, Troncoso Leanna, Reid Amanda, Hamon Pauline, Houghton Sean, Walters Lynnette, Smitherman Cynthia, Baisch Jeanine, Santos Marina, Larosiliere Owen, Robinson Lauren, Wright Tracey, Caielli Simone, Merad Miriam, Gu Jinghua, Pascual Virginia

Childhood-onset lupus nephritis (cLN) affects 80% of pediatric systemic lupus erythematosus patients. Classified based on histological renal features, cLN is treated with immunosuppressive agents that trigger side effects. Despite the need for targeted therapies, little is known on the molecular pathways causing cLN and their variability across patients. We employ spatial transcriptomics and proteomics approaches to profile kidney biopsies of cLN patients and define cellular and molecular endotypes across clinical traits. We found that distinct spatial organization of the renal immune compartment classified cLN biopsies according to histological classification. Myeloid cells with phagocytic and highly inflammatory transcriptional programs, including the expression of S100A9, infiltrate glomeruli of proliferative cLN. A subset of these patients also presents glomerular inflammasome-competent myeloid cells expressing IL-1β. Tubulointerstitial and periglomerular immune hubs characterize a subgroup of membranous and mixed cLN. Immune hubs' cell composition varies across patients and tissue lesions and can be skewed towards specific lymphoid populations, including T, B, or plasma cells with different isotype specificity. Our results highlight the importance of understanding the spatial organization and heterogeneity of the renal immune compartment in cLN. The prognostic value of these findings and their relevance to target disease is being currently explored.

PO2-04 BS
SMALL EXTRACELLULAR VESICLES AND PARTICLES (EVPs): NOVEL BIOMARKERS FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) DISEASE ACTIVITY AND ORGAN INVOLVEMENT

Zurong Wan, Juan Rodriguez Alcazar, Oleh Akchurin, Lauren Robinson, Jeanine Baisch, Cynthia Smitherman, Lynnette Walters, Irina Matei, David Lyden, Virginia Pascual

Systemic lupus erythematosus (SLE) is a lifelong autoimmune disease with a wide range of clinical manifestations. SLE patients who frequently experience periods of heightened disease activity have greater chance of having permanent organ damage. Biomarkers for SLE disease activity and organ involvement would allow for closer monitoring and preemptive treatment. Exosomes are secreted into plasma by all kinds of live cells, thus have the potential of reflecting immune status. Proteomic analysis was performed on plasma exosomes from 2 dependent cohorts of pediatric SLE patients isolated by a protocol newly developed by a collaborative project with Lyden lab. Among the exosomal proteins that were positively correlated with SLE disease activity were plasma cell-related proteins including immunoglobulin isotype IgA, IFITM2 and FCLR5. Urine exosomes were analyzed in search for biomarkers of lupus nephritis (LN), one of the most severe organ manifestations of SLE. As expected, an array of exosomal proteins originated from liver, renal tubular epithelial cells or immune cells distinguish SLE patients with LN from patients without, regardless of disease activity. More strikingly, is even an exosomal signature unique to SLE patients without LN. Most importantly, this study identified exosomal proteins associated with the frequency of disease flares. In summary, these findings suggest that the proteome of exosomes from plasma or organ-specific fluids can reflect SLE disease activity, organ involvement, and may even help predict prognosis.

PO2-05 BS
IRON SEQUESTRATION IN MYELOID CELLS CONTRIBUTES TO THE DEVELOPMENT OF ANEMIA IN CHRONIC KIDNEY DISEASE

Campbell Chantalle, Elsayed Heba, Matthews-Balcombe Jade, Patino Edwin, Federman Hannah, Choi Mary, Akchurin Oleh

INTRODUCTION: Anemia is a common complication of pediatric chronic kidney disease (CKD). Anemia reduces the quality of life and is associated with poor growth in children with CKD. Anemia of CKD is driven in part by the functional iron deficiency due to hepcidin induction. While it is known that hepcidin acts by blocking iron exporter ferroportin (Fpt), the exact cellular targets remain poorly understood in CKD. Specifically, the relative contribution of hepcidin's action on enterocyte Fpt (leading to iron malabsorption) vs. macrophage Fpt (leading to iron sequestration) in the development of anemia during CKD remains unclear.

OBJECTIVES: Elucidate the contribution of myeloid iron sequestration to renal anemia development using a mouse model of CKD and myeloid-specific (LysM-Cre) Fpt knockout (KO) mice.

METHODS: A high-adenine diet was used to induce CKD in 8-week-old wild type (WT) and KO mice for 8 weeks. Iron content was assessed in the bone marrow, liver, and spleen by a colorimetric method and by Perls' Prussian blue stain. Blood was collected at euthanasia for complete blood counts and serum chemistries.

RESULTS: Adenine diet effectively induced CKD which was confirmed by kidney histology, serum creatinine, and blood urea nitrogen. There were no differences in the

kidney function and systemic inflammation (assessed by the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios) between WT and KO CKD mice. CKD mice developed anemia, which was more severe in the KO (hemoglobin 11.8±0.6 vs. 9.6±0.2 g/dL, p<0.001 and hematocrit 39.1±1.9 vs. 30.9±1.8%, p<0.001). This corresponded to ferric iron accumulation in the bone marrow, liver, and spleen of WT CKD mice despite low serum iron. Iron sequestration was notably more severe in KO CKD mice compared to WT CKD. Thus, myeloid Fpt deletion enhanced iron sequestration and worsened anemia in CKD mice, independent of kidney function and systemic inflammation.

CONCLUSIONS: Iron sequestration in myeloid cells critically contributed to the development of anemia in this mouse model of CKD. The hepcidin-ferroportin axis appears to be a promising but underexplored therapeutic target for the treatment of renal anemia.

PO2-06 BS
WHOLE-GENOME DEEP SEQUENCING OF RHESUS CYTOMEGALOVIRUS FROM PRIMARY INFECTION DURING PREGNANCY

Crooks, Chelsea M, Mirza, Anne, Lammi, Stephen, Manuel, Tabitha D, Kaur, Amitinder, Kowalik, Timothy F, Permar, Sallie R

INTRODUCTION & OBJECTIVE Human cytomegalovirus (HCMV) is a herpesvirus that is a leading cause of birth defects that result from infection during pregnancy. Despite the high disease burden, there are no licensed vaccines for the prevention of vertical transmission of CMV. Rhesus CMV (RhCMV) is highly homologous to HCMV and is used to study RhCMV vertical transmission in a rhesus macaque model. This model provides an excellent opportunity to study viral determinants of CMV pathogenesis and immunology to inform development of vaccines and therapeutics. Here we use viral deep sequencing to characterize infection dynamics in a cohort of seronegative dams challenged with RhCMV.

METHODS Twelve RhCMV seronegative dams were challenged intravenously with 1x106 PFU each of a full-length, infectious RhCMV BAC clone, FL-RhCMV, and a passaged isolate, UCD52, simultaneously at 8 weeks of gestation. Plasma and amniotic fluid samples were collected weekly for the duration of gestation. Fetuses were delivered via c-section near term, approximately 80 days post-infection (dpi), and placental, fetal plasma, and fetal tissues were collected. All samples were tested for RhCMV DNA via qPCR. DNA was isolated from 4, 7, and 14 dpi plasma and all DNA+ amniotic fluid and tissue samples in preparation for Illumina-based deep sequencing. Using a set of 96 overlapping primer pairs designed for RhCMV, we performed whole-genome, Illumina-based deep sequencing on 68 samples from this cohort. We used the Qiagen CLC Genomics Workbench to perform sequencing analysis by modifying the SARS-CoV-2 ARCTICv3 workflow to reproducibly perform trimming, mapping, and variant calling. Using the approximately 4,296 nucleotide positions at which UCD52 and FL-RhCMV differ in their coding regions, we will calculate the percentage of reads that contained each nucleotide at these sites and average these percentages across the genome to determine the approximate proportion of each virus in each sample. This analysis focuses on a single macaque that had two RhCMV DNA+ amniotic fluid timepoints and was the only macaque that had a fetus with extensive DNA+ tissues.

RESULTS & CONCLUSIONS Whole-genome sequencing of samples from a single macaque revealed that FL-RhCMV was the dominant strain in plasma by 4 dpi. FL-RhCMV remained the dominant strain in amniotic fluid collected 77 and 82 dpi, suggesting that FL-RhCMV has a competitive fitness advantage over UCD52 in vivo. Current analysis is focused on determining the approximate proportion of each virus in each sample and determining how this may or may not change over the course of gestation and across the placental barrier into fetal tissues. Future analyses will focus on the full cohort to determine whether specific variants are associated with vertical transmission and whether there is any evidence of a population bottleneck at the placental interface.

PO2-07 BS
THE ROLE OF KHDC3 AND SMALL RNAs IN THE EPIGENETIC INHERITANCE OF OBESITY AND METABOLIC DISEASE

Cullen, Sean M, Senaldi, L, Ventura, A, Smith-Raska, M

Childhood obesity is a worsening public health epidemic in the United States. Based on current rates of increasing incidence, fifty percent of children are predicted to meet clinical criteria for obesity by 2050. Obesity is a multifactorial disease, but it exhibits strong familial inheritance. There is a large gap in understanding of how obesity is inherited, and mouse models show a significant role for sperm small RNAs.

We hypothesize that KHDC3, strongly expressed in germ cells, is the key regulator for integrating external signals and environmental exposures into changes in sperm small RNA expression patterns, which impacts the inheritance of obesity & metabolic disease. We will utilize a Khdc3-null (KO) mouse model and obesity from a high fat diet (HFD) to study these changes and determine how small RNAs lead to weight & metabolic alterations in their genotypically wild-type (WT) progeny named WT* mice.

KO, WT, & WT* male mice were fed a HFD or control diet (CD) for 12 weeks. Males bred to WT females to generate WT progeny (WT*) were exposed to some combination of ancestral deletion of Khdc3 and/or a HFD. Males had their sperm small RNA isolated & sequenced. Weight gain was

monitored weekly and glucose tolerance tests (GTTs) were administered, and tip-tail base length was noted.

Unsurprisingly, all mice on a HFD gained significantly more weight than their CD counterparts. KO males on CD are significantly larger in weight and length than WT males. WT* males do not weigh more than WT males but are significantly longer. When examining the sperm small RNA components of KO & WT males exposed to either HFD or CD, there are significantly up- & down-regulated small RNAs from multiple small RNA classes, including several small RNAs involved in glucose & lipid metabolism. KO mice fed a CD experience a blunted response to GTT, compared to WT mice. Interestingly, WT* mice with a KO grandfather fed a HFD weigh more, when fed either a HFD or CD, than WT mice generated from WT grandfathers fed a HFD. In addition, WT* mice with a KO grandfather fed a HFD who are also fed a HFD themselves, exhibit the worst glucose dysregulation of the 10 experimental conditions studied.

Khdc3-null mice have an observable phenotype of both larger size and improved glucose homeostasis, compared to WT mice. They also exhibit significant sperm small RNA dysregulation whether exposed to a HFD or not. Their genotypically WT progeny, however, whether exposed to a HFD or CD themselves, exhibit worse glucose dysregulation than their WT controls. This suggests a heritable change in sperm of KO mice fed a HFD that impacts progeny multiple generations away from the original exposure. Future experiments will examine metabolic tissues of WT* males and the ability of sperm small RNAs from KO males (exposed to either CD or HFD) to directly impact the size and glucose metabolism of otherwise WT progeny.

PO2-08 BS/CL
ALAGILLE SYNDROME IS DRIVEN BY DEFECTS IN HEPATOCYTE TO CHOLANGIOCYTE REPROGRAMMING

Huppert Kari, Rendeiro Andre F, Subramanian Sanjay, Chetal Kashish, Peters Anna L, Chandar Vasuretha, Sinha Saloni, Bram Yaron, Salomonis Nathan, Elemento Olivier, Stacey S Huppert, Schwartz Robert E.**
**Co-Corresponding Author*

The liver is alone among solid organs in its ability to fully regenerate its mass and function following extensive injury. Mouse studies using genetic reporters to trace the hepatocyte or cholangiocyte (biliary epithelial cell) lineages reveal no evidence of contribution from a reserve stem cell population for hepatic cell homeostasis or liver regeneration. An alternative process to stem cell-mediated regeneration is transdifferentiation or adaptive cellular reprogramming by which a cell changes its identity. Using a mouse model of severe bile duct loss, we have demonstrated that transdifferentiation of hepatocytes to cholangiocytes in the liver can build a biliary system that failed to form during development. The hepatocyte-derived biliary system enables resolution of cholestasis and reversal of fibrosis. Unfortunately, the process of hepatocyte to cholangiocyte transdifferentiation is impaired in patients with Alagille syndrome (ALGS) wherein a characteristic feature is bile duct paucity. Alagille syndrome (ALGS) is a multisystem developmental disorder caused by autosomal dominant mutations in JAGGED1 (95%) or NOTCH2 (1-2%), which encode key components of the Notch signaling pathway. Our single cell transcriptomic data in a Jagged1 haploinsufficient mouse experimental model of ALGS reveals that hepatocytes partially enter the cholangiocyte transcriptional program but are unable to fully implement the cholangiocyte transcriptional program. We are using the Resolve spatial transcriptomic platform to assess 100 transcripts in the liver of both the Jagged1 haploinsufficient mouse experimental model of ALGS and human ALGS patients. Spatial transcriptomics will allow us to assess the spatial relationship of niche and hepatocyte to cholangiocyte transdifferentiating cells and to computationally infer required receptor-ligand interactions as well as transcriptional regulators.

PO2-09 BS/TR
ASSESSMENT OF NEUTRALIZATION AND VIRUS DEVELOPMENT FOLLOWING NATURAL INFECTION IN HIV POSITIVE INFANTS

Memon Saad, Byrd Alliyah, Phan Caroline, Uffman Emilie, Dennis Maria, Fouda Genevieve, and Nelson Ashley

BACKGROUND. The rapid mutation of HIV has made it incredibly challenging to develop a vaccine against this virus, evidently seen by the absence of a viable solution even after three decades into the HIV epidemic. Given the great diversity of HIV, a vaccine will need to induce broadly neutralizing antibodies (bnAbs) to high levels in order to achieve protection against most virus strains. Interestingly, infants living with HIV are more capable of developing bnAbs than adults are and have been shown to develop them as early as 1-2 years post-infection. This makes early childhood an optimal time for implementation of an HIV vaccine displayed by the enhanced capacity to develop effective immune responses during this time. Understanding how broad neutralization develops during natural infection is critical to guide vaccine development efforts. Therefore, the purpose of this study is to extract and amplify the HIV viral genome in two infants displaying HIV neutralization responses against multiple virus variants, to highlight the path of mutations in the virus that may contribute to antibody mutation and potential development into bnAbs.

METHODS. We are using archived plasma samples from the NICHD Mother and Infants Cohort study. Longitudinal plasma samples from children living with HIV were previously screened and 2 children who displayed broad

neutralization at different time points were selected for this pilot study. Plasma samples were available from the two infants at four distinct time points spanning years 1 to 4. TZM-bl cell-based Neutralization against a global HIV panel containing 10 viruses was assessed when the children were aged 1-3 years. Single Genome Amplification (SGA) was then performed using PCR for the age 4 samples to extract and amplify the viral envelope genome. PCR amplicons were sequenced and analyzed. Partially overlapping sequences from each amplicon were assembled and edited using Sequencher (Gene Codes, Inc). Sequences with double peaks per base read were discarded. Highlighter mutations plots were created using a highlighter tool freely available from the Los Alamos National Laboratory HIV Sequence Database.

RESULTS. Both infants developed and displayed neutralization breadth to the HIV viral global panel. Child 1 (PTD E0020B1) displayed neutralization breadth at age 1 and maintained breadth in years 2 and 3. Child 2 (PTD S0016B1) showed neutralization breadth at age 2 and developed stronger breadth at age 3. Furthermore, highlighter plots for Child 1 showed substantial mutations within the viral envelope genome at 4 years of age. The analysis of the sequences from Child 2 is ongoing, and additional time will be needed to gain proper insight into viral evolution.

CONCLUSION. Overall, both infants displayed neutralization responses to the different variants of HIV and mutations in their viral envelopes suggesting co-evolution of the viral envelope and HIV-specific antibodies of the infants.

PO2-10 CL
INPATIENT KANGAROO CARE EXPLAINS SES-RELATED DISPARITIES IN DEVELOPMENT AT OUTCOMES IN INFANTS BORN PRETERM

Lazarus Molly F., Marchman Virginia A., Feldman Heidi M., Scala Melissa, Travis Katherine E. a

INTRODUCTION: Very preterm birth (PT, <32 weeks gestational age) is associated with short- and long-term neurodevelopmental delays, effects that are exacerbated in children from lower socioeconomic status (SES). Kangaroo care (KC), a skin-to-skin care practice, has been shown to benefit cognitive development, especially in PT infants. PT children from lower-SES backgrounds are less likely than their higher-SES peers to experience KC during their NICU stays.

OBJECTIVE: To investigate whether the rate of KC during in-patient NICU hospitalization serves as a mechanism through which SES impacts cognitive outcomes at 6 and 12 months of age in PT infants.

METHODS: Participants were infants (N=202) born very PT at Lucile Packard Children's Hospital. Minutes/day of family-administered KC (adjusted for length of hospital stay) were recorded by medical staff as part of routine charting. Insurance status (public vs. private) was the proxy for SES. Cognitive outcomes were age-adjusted 6- and 12-month Cognitive-Adaptive Test (CAT) scores (Capute Scales) collected as part of High-Risk Infant Follow-up. We used mediation models test the hypotheses that relations between SES and outcomes are explained by indirect effects of inpatient KC. Covariates included gestational age at birth, health acuity (a composite based on diagnosis of IVH, Sepsis, NEC, and/or BPD during NICU stay), and experience of hospital stay during COVID-19 (birthdate after 3/08/2020). (Table 1 describes the sample).

RESULTS: Figures 1 and 2 show the results of the mediation models. PT infants from lower (vs. higher) SES backgrounds had lower cognitive scores (c path) at 6 months (B = -6.02, p = .014) and 12 months (B = -5.90, p = .006). Lower-SES infants experienced lower rates of KC (a path; 6 months: B=-.35 p < .001; 12 months: B= -.35, p < .001). Higher KC rates were associated with higher cognitive scores (b path; 6 months: B = 8.40, p < .001; 12 months: B = 8.00, p < .001). The indirect effect (c-c') was significant; SES was no longer significantly associated with cognitive scores (6 months: B = -2.81, p = .269; 12 months: B = -3.13, p = .153). Thus, KC rates fully explained the relation between SES and cognitive scores at both ages.

CONCLUSION: In this study, variation in child cognitive outcomes was due to variation in KC suggesting that family involvement in KC mitigates the adverse impacts of SES-related factors in PT infants. Encouraging family involvement in NICU care and implementing KC-based interventions may be valuable strategies for improving cognitive outcomes in at-risk populations.

PO2-11 CL
RELATIONS BETWEEN KANGAROO CARE AND NEONATAL WHITE MATTER CONNECTIVITY IN INFANTS BORN VERY PRETERM

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INTRODUCTION: Kangaroo Care (KC), or skin-to-skin care, is a developmental care method beneficial to health outcomes in preterm infants. Children born very preterm (VPT <32 weeks gestational age (GA)) are at-risk for white matter injuries and abnormal white matter development1. Aberrant white matter development is linked to adverse neurodevelopmental outcomes in VPT children2. KC is often encouraged in the neonatal intensive care unit as a neuroprotective strategy, yet

evidence linking hospital-based KC practices to neonatal structural brain development is limited.

OBJECTIVE: The present study examined relations between KC and brain white matter connectivity from near-term diffusion MRI (dMRI) scans.

METHODS: We performed a retrospective cohort study of male and female VPT infants (N=100). Infants underwent diffusion MRI scanning prior to hospital discharge as part of the standardized near-term imaging protocol. Post-menstrual age (PMA) at scan was 34.4 - 41.2 weeks. White matter connectivity was assessed with mean diffusivity (MD) and fractional anisotropy (FA) measured from four fronto-limbic white matter tracts (superior frontal corpus callosum (CC), cingulate, anterior thalamic radiation, uncinate). Medical staff recorded daily minutes of parent-administered KC in the electronic medical record. We expressed KC as duration (minutes of KC / instance). We performed hierarchical linear regressions to assess the unique contribution of KC to white matter connectivity of each pathway after controlling for GA, socio-economic status (SES), health acuity and PMA at scan.

RESULTS: KC predicted cingulate (B = .002; p =.005) and anterior thalamic (B = .002; p = .043) mean MD over and above GA, SES, health acuity, and PMA at scan. KC marginally predicted superior frontal CC MD (B =.001, p = .097) and did not predict uncinate mean MD or mean FA from any of these tracts.

CONCLUSION: Variations white matter brain development in VPT infants related to the duration of KC instances lasted during hospitalization. These associations suggest that the experience of KC may be a unique contributor to fronto-limbic white matter connectivity. These findings also indicate that longer durations of KC instances beyond the minimum recommended time of 60-90 minutes may be important for brain development. Ongoing analyses will explore whether fronto-limbic white matter connectivity mediates relations between KC and long-term neurodevelopmental outcomes.

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PO2-12 CL
ASSESSING NON-NEUTRALIZING IMMUNE RESPONSES VIA ANTIBODY-DEPENDENT PHAGOCYTOSIS IN INDIVIDUALS WITH ACUTE PRIMARY HCMV INFECTION DURING PREGNANCY

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INTRODUCTION & OBJECTIVE Human cytomegalovirus (HCMV) is the most common congenital infection affecting newborns and is a leading cause of neurological birth defects and hearing loss in infants who experience in utero infection. Despite the high prevalence of HCMV impacting newborns, there are still no effective vaccines which prevent the spread of CMV from mother to child. We hypothesize that non-neutralizing antibody responses such as antibody-dependent cellular phagocytosis (ADCP) play a critical role in the prevention of vertical transmission of HCMV.

METHODS In this project, we are using plasma samples from a cohort of 185 study participants who were determined to have primary, acute CMV infection during the first half of pregnancy as a part of a clinical trial to test the efficacy of a hyperimmune globulin. Our goal is to study immune responses from these samples to characterize differences in the immune responses between transmitters or non-transmitters. We currently are in the process of collecting and analyzing data and are blinded to the transmission status of these participants. The viremia status of each of these participants at the time of sample collection was previously determined and we will be using this status to compare immune responses as this was a risk factor for transmission of HCMV in a previous secondary analysis of the trial. Here we used a flow based ADCP assay to quantify the plasma antibody-mediated phagocytosis of CMV in a monocyte cell line.

RESULTS/CONCLUSIONS We were able to successfully measure ADCP responses in all participants tested with a range of responses in the group. We found that there is not an association between viremia status at the time of sample collection and ADCP (unpaired t-test, p=0.4317). When we are unblinded from the transmission status of the participants, we will compare the ADCP responses between these groups to gain a better understanding of the factors that correspond with transmission. These results have important implications for creating an effective vaccine against HCMV as they help us gain a better understanding of the mechanisms through which the maternal immune system protects against congenital CMV infection.

PO2-13 CL
ESTIMATING SUBNATIONAL CONGENITAL CARDIAC SURGICAL NEED IN AFRICA USING GEOGRAPHIC DISTRIBUTION OF SURGEONS, MORE THAN JUST A NUMBERS GAME

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WITHDRAWN

PO2-14 HS
ANTIBODY EFFECTOR FUNCTIONS ELICITED BY A STABILIZED, PREFUSION-LIKE GLYCOPROTEIN B VACCINE AGAINST HYMAN CYTOMEGALOVIRUS

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BACKGROUND: Congenital Cytomegalovirus (cCMV) is the most common non-genetic cause of hearing loss and neurodevelopmental delays in infants worldwide, affecting 0.5 to 2% of all live births. There is an urgent need for a licensed, effective CMV vaccine to elicit maternal immunity to prevent congenital transmission. The viral envelope fusion protein glycoprotein B (gB) has been the leading vaccine candidate, but vaccines targeting the postfusion form of gB have failed to elicit robust neutralizing responses. The most effective vaccine trial to date is the gB/MF59 vaccine which utilized postfusion gB, yet advanced clinical trials that resulted in 50% efficacy for prevention of CMV acquisition were seen as inadequate for vaccine licensure. For some viruses, such as RSV, the prefusion conformation of the fusion protein elicits more potent neutralization than the postfusion form. Yet, our team recently reported that a prefusion-like form of the gB protein did not result in more potent neutralization of CMV infection of fibroblast cells. Interestingly, the protection observed from the postfusion gB/MF59 vaccine was previously linked to non neutralizing antibody function and has recently also been linked to a newly discovered region on gB, antigenic domain 6 (AD-6). Antibodies targeting AD-6 may prevent cell-associated spread of CMV. Thus, we aimed to define the antibody specificity and effector functions elicited by a stabilized, prefusion-like CMV gB in mice. Methods: We immunized Balb-c mice with 2ug prefusion-like or postfusion gB adjuvanted with CpG 1018® adjuvant and aluminum hydroxide. Plasma was collected at baseline and after three vaccine doses. Plasma IgG binding to soluble and cell-associated gB, as well as antigenic domains of gB (AD 1-6) were measured. Fc-mediated effector antibody responses were also measured.

RESULTS: Both pre- and postfusion gB immunization elicited strong antibody binding to gB, while binding to cell-associated gB was significantly higher in postfusion gB immunized mice. IgG induced by both vaccines mapped to three antigenic domains of gB (AD-4, AD-5, AD-4+5, AD-6). Binding to AD-6 was not significantly different between pre- and post-fusion immunized animals. No detectable responses were elicited against the AD-2 region, a target of potently-neutralizing anti-gB antibodies. Rates of antibody dependent cellular phagocytosis (ADCP), an important Fc-mediated effector function, were significantly higher for mice immunized with postfusion gB than prefusion-like gB. Conclusion: HCMV stabilized, prefusion-like gB is immunogenic in mice. The prefusion-like gB antigen did not elicit binding or nonneutralizing functions superior to postfusion gB. Our work suggests that improved gB antigen design strategies remain to be elucidated in order to identify an improved CMV vaccine.

PO2-15 TR
OPTIMIZATION OF AN HIV GLOBAL PANEL SOSIP BAMA FOR ASSESSMENT OF BINDING BREADTH

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BACKGROUND: An HIV vaccine that can achieve protective immunity prior to sexual debut is critically needed to prevent the estimated 590,000 new HIV infections that occur yearly in young adolescents and adults. This vaccine will need to be able to elicit antibodies able to recognize and block entry of a broad range of different strains of HIV into healthy cells called broadly neutralizing antibodies (bnAbs) during childhood. As elicitation of bnAbs through vaccination has proven difficult, a better understanding of the pathways leading to HIV neutralization breadth during natural infection is significant for informing vaccine development. An initial step in the pathway to bnAb development is the recognition of heterologous HIV envelope proteins by plasma antibodies. This study will be utilizing longitudinal samples from children living with HIV to determine if binding breadth correlates with the eventual development of neutralization breadth.

OBJECTIVE: Develop a multiplex assay to assess antibody binding breadth across various HIV trimers Methods: Luminex beads were coupled with 6 native-like HIV envelope trimeric SOSIP proteins (TRO11, 246 F3, BJOX2000 , CH119, CNE55 , 25710). In preliminary data, the beads were tested for binding of against a panel of broadly neutralizing antibodies and binding was compared to neutralization. Based on these preliminary data VRC01 (CD4 bs-specific) and PGT128 (V3 glycan-specific) were selected as positive controls. The assay was then applied to measure binding responses in 113 Plasma samples from two cohorts of ART-naïve children living with HIV aged 1-3 years. These samples have been

previously tested for neutralization against the corresponding pseudoviruses.

RESULTS: A total of 34 samples from the 1-year time point,38 from 2 year of timepoint and 41 from the three years of timepoint were tested. Overall, 19/34 of the one-year-old samples, 30/41 of the 2 years old samples demonstrated binding to all 6 envelopes trimers, and 33/41 of the 3-year-old samples demonstrated binding to all 6 envelope trimers. Of the 82 samples that showed binding to all six envelope trimers, 44 also neutralized the six corresponding pseudoviruses.

CONCLUSION: Our results indicates that binding breadth against Env trimers from the global panel increases with age, similar to observations reporting an increase in neutralization breadth from 1 to 3 years of age. Ongoing analyses will determine if there is a correlation between the binding breadth that was tested in BAMA and with the neutralization breadth development across this pediatric cohort.

PO2-16 TR
NEUTRALIZATION PHENOTYPE OF BREASTMILK HIV-1 VIRUSES

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BACKGROUND: In 2022, there were ~1.3million new HIV infections worldwide with more than 130,000 infections among children under 15 years of age that are mainly due to vertical transmission. Breastmilk transmission continues to be an important mode of vertical HIV-1 transmission despite the availability of ART. There is a critical need to develop novel strategies to complement antiretroviral-based interventions. One of the most promising strategies is the use of broadly neutralizing antibodies (bnAbs) to passively immunize infants. Implementing bnAb prophylaxis for infants known to be HIV-exposed could potentially reduce cumulative HIV incidence to 0.3-2.2%. The results from previous clinical studies have demonstrated the potential of bnAbs prophylaxis in adults and highlighted the need for combination of bnAbs to increase efficacy. Importantly, while clinical studies have shown the safety of some bnAbs in infants (e.g., VRC01 and VRC07), the sensitivity of HIV-1 variants isolated from breastmilk to these bnAbs, especially to combinations of bnAbs has been understudied.

OBJECTIVES: This project aims to assess the sensitivity of breastmilk HIV-1 viruses from infected mothers to a large panel of bnAbs and to combination of bnAbs in order to guide the clinical development of bnAbs passive immunization as a strategy to prevent breastmilk transmission.

METHODS: The ability of bnAbs to neutralize breast milk viruses will be measured using pseudotyped viruses in TMZ-bl cells. Briefly, we will measure the ability of the bnAb to reduce virus infection of TMZ-bl cells via reduction of luciferase reporter gene expression after a single round of infection. We will test a panel of 15 bnAbs targeting different regions of the HIV envelope against a panel of approximately 30 viruses isolated from breastmilk (including viruses transmitted to babies). Single and combination bnAbs will be tested.

RESULTS: In preliminary experiments, we tested the sensitivity of 8 breastmilk transmitted/founder (T/F) viruses against 10 bnAbs targeting major HIV envelope epitopes: CD4 binding site (VRC01, VRC07, 3BNC117), V3-glycan (PGT121. PGT128. 10-1074), V2-glycan (PG9, PGT145, PGDM1400), and gp120-gp141 interface (PGT151). Five of the viruses were sensitive to the majority of the tested bnAbs, whereas three of the viruses were resistant to most of the bnAbs when tested individually. The viruses were generally resistant to V3-glycan dependent bnAbs with 5/8 viruses resistant to three V3 targeting bnAbs in our panel. All the viruses were sensitive to PG9, a V2-glycan specific bnAb. Two clinically relevant triple bnAb combination were also tested against 7/8 viruses. In prior work, we observed that the combination 3BNC117/PGDM1400/PGT151 demonstrated robust and broad neutralization as well as non-neutralizing functions, and the combination VRC07/PGDM1400/PGT121 is a leading candidate bnAb combinations proposed for adult clinical trials. 3BNC117/PGDM1400/PGT151 neutralization 6/7 viruses at a median IC50 of 0.03 ug/ml and VRC07/PGDM1400/PGT121 neutralized 5/7 viruses at a median IC50 of 0.04 ug/ml.

CONCLUSION: Our preliminary data suggests that breastmilk T/F viruses are generally sensitive to bnAbs and that combination bnAbs can neutralize most breastmilk viruses with high potency. In coming months, we plan to test more breastmilk viruses against a larger panel of bnAbs and bnAbs combinations. Ultimately, we will determine which combination of bnAbs provide high coverage and potency against breastmilk viruses and assess if some combinations are synergistic or antagonistic. With the data generated, we hope to identify combinations that could be pursued in clinical trials.

PO2-17 TR
IgG, IgM, IgA BINDING RESPONSE IN RELATION TO VIREMIA STATUS IN PRIMARY ACTUTE HUMAN CYTOMEGALOVIRUS INFECTED INDIVIDUALS DURING PREGNANCY

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BACKGROUND AND OBJECTIVES Human Cytomegalovirus (HCMV), a type of herpes virus, is the most common cause of birth defects in the United States with 1 in 200 babies are born with congenital CMV (cCMV). For about 1 in 5 of those babies, cCMV will result in long term health issues including sensorineural hearing loss, vision loss, and developmental, growth and motor delay. There are currently no vaccines available to prevent CMV, however the development of a vaccine that can prevent vertical transmission has the potential to greatly reduce risk of long-term disability in infants. One challenge in the development of a vaccine is the lack of correlates of protection for the prevention of cCMV. We aim to understand antibody binding to HCMV in primary, acute infections in pregnant women, with a focus on the relationship between IgG, IgM and IgA binding and viremia status at the time of sample collection. METHODS A cohort of 399 pregnant women was identified from screening over 200,000 pregnancies for primary, acute CMV as part of a clinical trial to test a CMV hyperimmune globulin. 78 participants were identified as having transmitted CMV to their infant. Samples were collected for immune analysis prior to the administration of the treatment or placebo. Participants were then 1:2 matched transmitters to non-transmitters based on maternal age, gestational age, race, ethnicity, parity, and treatment group, resulting in final subset study cohort of 185 plasma samples. We are currently blinded to transmitter status and have analyzed data to date using concurrent viremia at the time of sample collection to compare binding antibody responses, since this was a factor associated with a risk of transmission in a previous secondary analysis of this trial.

A Binding Antibody Multiplex Assay (BAMA) was used to measure IgM, IgG, and IgA antibody binding to two panels panel of CMV antigens in our cohort of 185 participants. The first panel consists of entry glycoproteins: (gB, gH/gL/gO, and the pentameric complex (PC)). The second panel consists of tegument proteins (pp65, pp71, and pp150), immune evasins (UL16 and UL141) and three gB antigenic domains (AD; AD-1, AD-4, AD-5 and AD-4+5). Due to their size, we could not include gB AD-2 and AD-6 in our BAMA panel and instead screened IgG antibody responses to these antigens via ELISA.

RESULTS AND CONCLUSIONS We were able to successfully measure antibody responses to a variety of HCMV antigens in all participants in our cohort, with the highest responses observed against the entry glycoproteins and pp150. Using an unpaired t-test, we saw no significant difference (p>0.05) in IgA binding to any of the antigens between individuals that did and did not have concurrent viremia at the time of sample collection.

Future analyses will assess difference in IgG and IgM binding by viremia status, as well as assessing the correlation between transmission status and binding of all three isotypes to CMV antigens. Antibody binding response is vital for vaccine development, and this study provides insight into which antigens play key roles in driving antibody response to building long term immunity against HCMV infection.

PO2-18 TR
THE ROLE OF MATERNAL BROADLY NEUTRALIZING ANTUBODY ACTIVITY IN PERINATAL TRANSMISSION OF HIV-1

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BACKGROUND: Despite increased availability to antiretroviral therapy (ART), up to 5% of women living with HIV (WLH) still transmit the virus to their infants. While broadly neutralizing antibodies (bNAbs) are the immunologic goal of HIV-1 vaccine candidates, we have demonstrated escape of infant HIV variants in the presence of bNAbs targeting a single, dominant epitope in postnatal transmitters. We hypothesize that WLH with bNAbs responses against single epitopes of the HIV envelope are at higher risk of perinatal transmission due to viral escape, and this impacts the development of a bNAb response in infants.

METHODS: Plasma was acquired around delivery from 15 perinatal transmitters and 47 non-transmitters with HIV from the US-based, pre-ART era Mother-Infant Cohort Study (MICS), matched 1:3 on CD4+ T-cell counts, maternal age, delivery type. Plasma from paired infants with HIV was acquired at 1- 3 years of age. Maternal and infant plasma was screened for neutralization against a global HIV-1 panel, with breadth defined as neutralizing ≥ 5 out of 10 viruses with an ID50≥40. For transmitters with breadth, plasma was screened against HIV-1 pseudoviruses with epitope mutations, and a two-fold reduction in neutralization compared to wild-type was considered as mapping to an epitope. Antibody dependent cellular cytotoxicity (ADCC), was assessed against cells infected with a transmitted/founder subtype B virus (WITO).

RESULTS: A greater proportion of perinatal transmitters (7 out of 15, 47%) had neutralization breadth compared

to non-transmitters (15 out of 47, 32%); these responses mapped to the V2/V3 glycan region for 4 out of 6 (67%) transmitters with neutralization breadth tested so far. Maternal transmitters also trended towards higher ADCC against WITO compared to non-transmitters. Finally, infants seemed to frequently a develop a bNAb response between ages 1 - 3 irrespective of maternal bNAb status, as infants of both transmitters with bNAb activity (4 of 5, 80%), and without (7out of 7, 100%), exhibited bNAb activity.

CONCLUSIONS: Our findings support the existence of increased bNAb activity in transmitters that is frequently specific to a single epitope, which could lead to emergence of bNAb-resistant viral variants that can be transmitted perinatally to the infant, which in turn may contribute to endogenous bNAb responses. Thus, bNAb-based pediatric HIV prevention and treatments that are synergistic with ART will likely need to be multi-specific to effectively eliminate and cure pediatric HIV.

PO2-19 TR
THE IMPACT OF MATERNAL ANTIBODY ON INFANT SARS-CoV-2 VACCINE RESPONSES

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INTRODUCTION: Infants under six months of age are at increased risk for severe disease outcomes due to viral infections. Young infants account for a large number of child hospitalizations due to COVID-19. In 2023 the Food and Drug Administration approved use of two SARS-CoV-2 mRNA-LNP vaccines for children 6 months of age or older. This age cutoff is partially due to unknown interactions between maternal antibody and SARS-CoV-2 mRNA derived Spike and the impact on infant de novo humoral responses. Maternal antibodies are associated with “blunting” infant immune responses to some vaccines. Mouse models using mRNA- lipid nano particle vaccines have demonstrated that this platform facilitates vaccine-specific immune responses in the presence of vaccine-specific maternal antibody, indicating that this widely used vaccine platform may facilitate overcoming maternal antibody inhibition. To assess the potential of maternal antibody inhibition of infant SARS-CoV-2 mRNA-LNP immunization, we developed a mouse model to investigate the impact of maternal antibody on vaccine responses at two stages of development, 1) in weanling mice when maternal antibody is waning and 2) at seven days of life when suckling pups have high titers of maternal antibody in circulation.

OBJECTIVES: To determine whether SARS-CoV-2 mRNA-LNP vaccine responses are impacted by maternal antibody inhibition.
METHODS: Adult female mice were immunized with 5ug of beyond use date (BUD) of Moderna mRNA-1273 (n=5) or PBS (n=5) and paired with a male to yield a litter. The resulting pups were immunized with 5ug of BUD mRNA-1273 at day seven of life or at weaning. Seven-day old mice were immunized by intradermal injection into the pinna of each ear. Weanling and adult mice were immunized by intramuscular injection. SARS-CoV-2 Spike specific serum IgG levels were measured by ELISA on days 0,3,7,14,21,28,35 post pup immunization. Splenocytes were harvested to determine the proportion of Spike specific B cells in lymphoid tissues. Results: Maternal antibody was detectable up to 35 days post mock immunization in weanling pups. Naïve weanling pups with no maternal antibody present develop robust anti-Spike serum IgG levels comparable to adults. In pups exposed to maternal antibody, Spike-specific serum IgG levels are detectable up to 35 days post pup immunization at levels similar the maternal antibody only controls. While we detected variation in vaccine specific antibody levels, there was no statistical difference between groups two weeks after pup immunization, indicating that weanling pups can overcome potential maternal antibody inhibition.

CONCLUSIONS: This data demonstrate that mice are an adequate species to model transfer of vaccine elicited maternal antibody to offspring. We demonstrate that the mRNA-LNP platform is capable of eliciting robust humoral responses in the context of waning maternal antibody even after a single dose. These findings indicate that immunization with a SARS-CoV-2 mRNA-LNP vaccine may be a viable strategy for the prevention of severe COVID19 in early life. Studies of B cell responses in lymphoid tissue and neonatal pup immunizations are ongoing.

PO2-20 TR
SARS-CoV2 ANTIBODY RESPONSES ACROSS THE AGE SPECTRUM

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BACKGROUND: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) led to 180 million infections and about 3.8 million deaths around the world. Pediatric and adult participants develop neutralizing antibodies against ancestral strains (Garrido et al., 2021). We hypothesize that pediatric participants generate IgG binding breadth and neutralizing antibodies to SARS-CoV-2 variants comparable to adults.

OBJECTIVE: Compare antibody neutralization in convalescent or vaccinated pediatric participants and adults. We will also compare the magnitude of IgG binding of convalescent or vaccinated pediatric and adult participants.
METHODS: Serum samples were collected from convalescent or vaccinated pediatric and adult

participants, which were used to test against SARS-CoV-2 variants Omicron and D614G. Our cohort consisted of 16 infants, 28 prepubescents, 30 pubescents, 46 adults (n= 120). We used a luciferase reporter SARS-CoV-2 Spike pseudovirion assay to compare levels of neutralization in adults and pediatric patients 1-month post-infection for both Omicron and D614G variants. We measured IgG breadth by a binding antibody multiplex assay (BAMA) to establish the magnitude of IgG binding to SARS-CoV-2 spike variants. Our cohort consisted of serum samples collected 1-month post SARS-CoV-2 infection or 1-month post SARS-CoV-2 vaccination. The convalescent serum samples were collected from children ages 5-11 (n=15), adolescents ages 12-17 (n=20), and adults (n=8). The vaccinated serum samples were collected from children ages 5-11 (n=16), adolescents ages 12-17 (n=10), and adults (n=10). We compared our inhibitory dilution (ID50) data to overall magnitude of binding breadth.

RESULTS: Neutralization titers between children and adult participants for Omicron and D614G variants showed no significant differences in ID50 (p-value >0.05). These findings demonstrate that children develop effective neutralization responses comparable to that of adults. Our BAMA results detected IgG binding breadth for each spike protein and for omicron subvariants in all participants. Vaccinated children and adolescent elicited greater levels of antibody binding compared to convalescent children and adolescents. Convalescent or vaccinated adults presented higher levels of spike specific IgG binding than convalescent or vaccinated children and adolescents.

CONCLUSION: Antibody neutralization titer and magnitude of binding shows that children and adults can develop antibodies across SARS-CoV-2 variants. Here we show that children in the BRAVE cohort have a lower magnitude of IgG binding breadth, while maintaining neutralizing antibody levels similar to adults. These findings indicate that the pediatric immune response may make SARS-CoV-2 neutralizing antibodies more efficiently than their adult counter parts. Analysis of neutralization titers in vaccinated children and adults is going.